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PATENT & TRADEMARK OFFICE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.	7,767,206
Issued:	August 3, 2010
To:	Kirin-Amgen, Inc.
For:	Neutralizing Determinants of IL-17 Receptor A and Antibodies that Bind Thereto

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

HAND DELIVERY

Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandra, VA 22314

Madam:

The Applicant, Kirin-Amgen, hereby applies for extension of the term of United States Patent No. 7,767,206 under 35 U.S.C. §156 and provides the following information in accordance with 37 C.F.R. §1.740.

Kirin-Amgen, Inc. is the assignee of the entire interest in and to U.S. Patent No. 7,767,206 (the '206 patent), and the chain of title is recorded in the USPTO assignment records as follows:

1. Assignment from inventors Joel Tocker, Christopher Mehlin, Ai Ching Lim to Amgen, Inc., recorded at Reel 020799, Frame 0697;
2. Assignment from Amgen, Inc. to Kirin-Amgen, Inc., recorded at Reel 030045, Frame 0876.

A Power of Attorney and Statement under 37 C.F.R. §3.73(b) appointing the attorney associated with customer number 105263 to transact all business in the USPTO in connection with the '206 patent is filed concurrently herewith. Copies of these documents are provided as Exhibit L.

As explained herein, Amgen, Inc. (Amgen) began the first clinical investigation of brodalumab. On August 13, 2015, Amgen transferred ownership of the investigational new drug exemption to AstraZeneca UK Ltd. (AstraZeneca). AstraZeneca was the original marketing authorization applicant for SILIQ ™ (brodalumab). On April 1, 2016, AstraZeneca transferred the Biologics License Application for SILIQ ™ (brodalumab) to Valeant Pharmaceuticals Luxembourg S.a.r.l (VPL) and Valeant Pharmaceuticals North America LLC (VPNA) as the U.S. agent (collectively, Valeant). Copies of letters from each of

Amgen, AstraZeneca and Valeant authorizing Applicant to rely upon their activities before the U.S. Food and Drug Administration (FDA) are provided in Exhibit M.

1. **Identification of the Approved Product (37 C.F.R. § 1.740(a)(1))**

The name of the approved product is SILIQ™. The active ingredient in SILIQ™ is brodalumab. Brodalumab is a human IgG2 monoclonal antibody that binds to human interleukin-17 receptor A (IL-17RA) and blocks the biological activities of IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer and IL-25. Brodalumab contains heavy chain and light chain variable regions containing complementarity-determining regions (CDRs) that bind to IL-17RA. Brodalumab was developed using Abgenix Xenomouse® hybridoma technology, which generates fully human antibodies. The heavy chain variable region of brodalumab contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO:14 and the light chain variable region of brodalumab contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO:40.

The heavy chain variable region of brodalumab contains CDRs 1, 2 and 3. CDR1 of the heavy chain variable region contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID No. 146. CDR2 of the heavy chain variable region contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO: 147. CDR3 of the heavy chain variable region contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO: 148.

The light chain variable region of brodalumab contains CDRs 1, 2 and 3. CDR1 of the light chain variable region contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO: 224. CDR2 of the light chain variable region contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO: 225. CDR3 of the light chain variable region contains the amino acid sequence identified in U.S. Patent NO: 7,767,206 as SEQ ID NO: 226.

2. **Federal Statute Governing Regulatory Approval of the Approved Product (37 C.F.R. § 1.740(a)(2))**

Regulatory approval of the approved product was governed by the Public Health Service Act (42 U.S.C. § 201 *et seq.*) and the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355 *et seq.*).

3. **Date of Approval for Commercial Marketing (37 C.F.R. § 1.740(a)(3))**

SILIQ™ was approved for commercial marketing and use under section 351(a) of the Public Health Service Act on February 15, 2017 (Exhibit A).

4. **Identification of Active Ingredient and Statements Related to Commercial Marketing of Approved Product (37 C.F.R. § 1.740(a)(4))**

a. The active ingredient in SILIQ™ is brodalumab. Brodalumab is a human IgG2 monoclonal antibody that binds to human interleukin-17 receptor A (IL-17RA). Brodalumab contains heavy chain and light chain variable regions that are based on CDRs that binds to IL-17RA. The heavy chain variable region of brodalumab contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO:14 and the light chain variable region of brodalumab contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO:40. The amino acid sequences of the

heavy and light chains of brodalumab were registered with Chemical Abstracts Service (CAS) and assigned CAS Registry No. 1174395-19-7. A copy of the record under CAS Registry 1174395-19-7 is provided as Exhibit E.

The heavy chain variable region of brodalumab contains CDRs 1, 2 and 3. CDR1 of the heavy chain variable region contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID No. 146. CDR2 of the heavy chain variable region contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO: 147. CDR3 of the heavy chain variable region contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO: 148.

The light chain variable region of brodalumab contains CDRs 1, 2 and 3. CDR1 of the light chain variable region contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO: 224. CDR2 of the light chain variable region contains the amino acid sequence identified in U.S. Patent No. 7,767,206 as SEQ ID NO: 225. CDR3 of the light chain variable region contains the amino acid sequence identified in U.S. Patent NO: 7,767,206 as SEQ ID NO: 226.

b. Applicant states that SILIQ™ has been approved for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. SILIQ™ was approved for commercial marketing and use under Department of Health and Human Services U.S. Biologics License Application No. 761032 to Valeant, under the provisions of section 351(a) of the Public Health Service Act (See SILIQ™ approval letter and product label; Exhibits A & B).

c. Applicant states that brodalumab has not been previously approved for commercial marketing under the Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act, either alone or in combination with other ingredients.

5. **Statement Regarding Timelines of Submission of Patent Term Extension Request (37 C.F.R. § 1.740(a)(5))**

Applicant states that this application for patent term extension is being timely submitted within the sixty day statutory period specified in 35 U.S.C. § 156(d)(1). The last day that this application may be timely submitted is April 15, 2017.

6. **Complete Identification of the Patent for Which Extension is Being Sought (37 C.F.R. § 1.740(a)(6))**

a. Names of inventors: Joel Tocker, Christopher Mehlin, Ai Ching Lim
b. Patent Number: 7,767,206
c. Date of Issue: August 3, 2010
d. Date of Expiration: December 18, 2027

7. **Copy of the Patent for Which an Extension is Being Sought (37 C.F.R. § 1.740(a)(7))**

A copy of U.S. Patent No. 7,767,206 is provided in Exhibit C.

8. **Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate (37 C.F.R. § 1.740(a)(8))**

a. The '206 patent is subject to a terminal disclaimer over U.S. Patent No. 7,939,070. However, U.S. Patent No. 7,939,070 is terminally disclaimed over the '206 patent. However, the '206 patent also received 82 days of PTA. Thus, the expiration date of the '206 patent is December 18, 2027.

b. A certificate of correction has not been issued for the '206 patent.

c. The maintenance fee for the '206 patent that was due 3.5 years after grant was timely paid (Exhibit D). The 7.5 and 11.5 year maintenance fees are not currently due.

d. The '206 patent has not been the subject of a reexamination proceeding.

9. **Statement Regarding Patent Claims Relative to Approved Product (37 C.F.R. § 1.740(a)(9))**

a. Claims 1-6 of the '206 patent claim the approved product or the approved use of the approved product.

b. Pursuant to 37 CFR § 1.740(a)(9) and MPEP § 2753, the following explanation is provided which demonstrates the manner in which claims 1-6 read on the approved product, and the manner in which claims 1-6 read on the manner of using the approved product. These comments do not make any representation about the scope of coverage of the other claims within the meaning of 35 U.S.C. § 156.

i. Description of the approved product

SILIQ™ (brodalumab) for injection is described in section 11 of the approved label for SILIQ™ as follows:

> Brodalumab is a human monoclonal IgG2κ antibody directed against human interleukin-17 receptor A (IL-17RA). It is expressed in a Chinese Hamster Ovary (CHO) cell line. Brodalumab is comprised of 1312 amino acids and has an estimated molecular mass of 144,000 Daltons.
> SILIQ (brodalumab) Injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution, delivered via subcutaneous injection. A few translucent to white, amorphous particles may be present. SILIQ is supplied in a single-dose 2.25 mL syringe made from type 1 glass with stainless steel 27G x ½" needle. Each SILIQ single-dose prefilled syringe delivers 1.5 mL of solution containing 210 mg of brodalumab formulated in glutamate (6.5 mg), polysorbate 20 (0.15 mg), proline (36 mg), and Water for Injection, USP at pH 4.8.

See, Exhibit B at section 11.

The amino acid sequences of the heavy and light chain of brodalumab were submitted to CAS, and assigned CAS Registry No. 1174395-19-7, to obtain "brodalumab" as the United States Adopted Name (USAN/International Non-proprietary Name (INN)) for the human monoclonal antibody that is the active ingredient in SILIQ™. Copies of the USAN/INN application and CAS record demonstrating that the amino acid sequences submitted to CAS have been assigned the USAN/INN brodalumab and CAS Registry No. 1174395-19-7 are provided in Exhibits E and F.

ii. Demonstration of the manner in which claims 1-6 of U.S. Patent No. 7,767,206 reads on the approved product.

Claims 1-6 of the '206 patent read as follows:

Claims of the '206 Patent	Demonstration of the manner in which each claim reads on the approved product
1. An isolated monoclonal antibody, comprising a first isolated monoclonal antibody, or IL-17RA-binding fragment thereof, that specifically binds to IL-17RA and competes for binding with a second isolated monoclonal antibody, wherein said second isolated monoclonal antibody, or IL-17RA-binding fragment thereof, comprises a light chain CDR1 (SEQ ID NO:224), CDR2 (SEQ ID NO:225), CDR3 (SEQ ID NO:226) and a heavy chain CDR1 (SEQ ID NO:146), CDR2 (SEQ ID NO:147), CDR3 (SEQ ID NO:148).	Sequence alignments of light chain CDR1, CDR2, CDR3 of brodalumab with SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226 and heavy chain CDR1, CDR2, CDR3 of brodalumab (CAS registry 1174395-19-17) with SEQ ID NO:146, SEQ ID NO:147 and SEQ ID NO:148 of U.S. Patent No. 7,767,206 are provided in Exhibits G and H. These sequence alignments show that the amino acid sequences of the brodalumab light chain CDR1, CDR2, CDR3 are the same as SEQ ID NO: 224, SEQ ID NO: 225, and SEQ ID NO: 226 of the '206 patent, respectively, and that the amino acid sequences of the brodalumab heavy chain CDR1, CDR2 and CDR3 are the same as SEQ ID NO:146, SEQ ID NO:147 and SEQ ID NO:148 of the '206 patent, respectively. All of the limitations in claim 1 are met by brodalumab.
2. The first isolated monoclonal antibody of claim 1, wherein said first isolated monoclonal antibody is selected from the group consisting of: a. a human antibody; b. a humanized antibody; c. a chimeric antibody; d. a single chain antibody; e. a diabody; f. a triabody; g. a tetrabody; h. a Fab fragment; i. a F(ab')2 fragment; j. an IgD antibody; k. an IgE antibody; l. an IgM antibody;	Brodalumab is a human antibody as described in CAS registry 1174395-19-17. Claim 2 is dependent on claim 1. As mentioned above, all of the limitations in claim 1 are met by brodalumab. As a result, all of the limitations in claim 2 are met by brodalumab.

Claims of the '206 Patent	Demonstration of the manner in which each claim reads on the approved product
m. an IgG1 antibody; n. an IgG2 antibody; o. an IgG3 antibody; and p. an IgG4 antibody.	
3. The first isolated monoclonal antibody of claim 2, wherein said antibody inhibits human IL-17A from binding to human IL-17RA.	Example 5 of the '206 patent describes an antibody that has the sequence of brodalumab (CAS registry 1174395-19-7) and inhibits human IL-17A from binding to human IL-17RA. All of the limitations in claim 3 are met by brodalumab.
4. The first isolated monoclonal antibody of claim 3, wherein said antibody inhibits human IL-17A and human IL-17F from binding to human IL-17RA.	Example 5 of the '206 patent describes an antibody that has the sequence of brodalumab (CAS registry 1174395-19-7) and inhibits human IL-17A and IL-17F from binding to human IL-17RA. All of the limitations in claim 4 are met by brodalumab.
5. The first isolated monoclonal antibody of claim 2, wherein said antibody inhibits human IL-17A or human IL-17F from binding to human IL-17RA.	Example 5 of the '206 patent describes an antibody that has the sequence of brodalumab (CAS registry 1174395-19-7) and inhibits human IL-17A or IL-17RF from binding to human IL-17RA. All of the limitations in claim 5 are met by brodalumab.
6. An isolated monoclonal antibody, comprising a first isolated monoclonal antibody, or IL-17RA-binding fragment thereof, that specifically binds to IL-17RA and competes for binding with a second isolated monoclonal antibody, wherein said second isolated monoclonal antibody, or IL-17RA-binding fragment thereof, comprises a light chain variable domain sequence comprising SEQ ID NO:40 and a heavy chain variable domain sequence comprising SEQ ID NO:14.	Sequence alignments of the heavy chain and light chain variable regions of brodalumab (CAS registry 1174395-19-7) with SEQ ID NO:14 and SEQ ID NO:40 of U.S. Patent No. 7,767,206, respectively are provided in Exhibits G and H. These sequence alignments show that the amino acid sequence of the brodalumab light chain variable region is the same as SEQ ID NO. 40 of the '206 patent , and that the amino acid sequence of the brodalumab heavy chain variable region is the same as SEQ ID NO:14 of the '206 patent.. All of the limitations in claim 6 are met by brodalumab.

10. **Relevant Dates under 35 U.S.C. § 156 for Determination of Applicable Regulatory Review Period (37 C.F.R. § 1.740(a)(10))**

U.S. Patent No. 7,767,206 issued on August 3, 2010. The following information is provided pursuant to 37 C.F.R. § 1.740(a)(10)(i)(A)-(C).

a. The effective date of the investigational new drug application (IND) and the IND number. 37 C.F.R. § 1.740 (a)(i)(10)(A)

The investigational new drug application (IND) became effective on September 26, 2009 and the IND number is 104671 (See Exhibit I). Amgen was the original IND applicant for SILIQ ™ (brodalumab). Amgen transferred the IND to AstraZeneca on August 13, 2015.

b. The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number. 37 C.F.R. § 1.740 (a)(10)(i)(B)

A Biologics License Application (BLA) was initially submitted by AstraZeneca to the FDA on November 16, 2015. The BLA was accepted for filing by the FDA on January 21, 2016. The BLA was assigned number BLA 761032. A copy of the letter dated January 21, 2015 from the FDA notifying AstraZeneca that the BLA has been filed is provided in Exhibit J.

On April 1, 2016, AstraZeneca transferred the BLA for SILIQ ™ (brodalumab) to Valeant.

c. The date on which the NDA was approved or the Product License issued. 37 C.F.R. § 1.740 (a)(10)(ii)(C)

The FDA approved BLA 761032, authorizing the marketing of SILIQ™, on February 15, 2017. SILIQ™ (brodalumab) was approved under Department of Health and Human Services U.S. Biologic License Application No. 761032 (see Exhibit A).

11. Summary of Significant Events During Regulatory Review Period (37 C.F.R. § 1.740 (a)(11))

Amgen submitted to FDA an IND for a human IgG2 monoclonal antibody that binds to human interleukin-17 receptor A (IL-17RA) on August 27, 2009. The antibody was developed as a potential new therapeutic for treating adults suffering from moderate-to-severe plaque psoriasis.

On September 4, 2009, FDA notified Amgen that IND 104671 had been received. As of September 25, 2009, Amgen had not received any notice from the FDA that the studies proposed under IND 104671 were under a clinical hold, so the studies under IND 104671 were commenced on September 26, 2009 (*see* Exhibit I).

Following commencement of human clinical trials in the United States under IND 104671, Amgen and AstraZeneca collectively conducted three (3) Phase I comparative bioavailability and bioequivalence studies, two (2) Phase I healthy subject pharmacokinetic and initial tolerability studies, one (1) Phase Ib/2a patient pharmacokinetic and initial tolerability study, one (1) Phase I intrinsic factor pharmacokinetic study, one (1) Phase I extrinsic factor pharmacokinetic study, and two (2) Phase II and three (3) Phase III controlled clinical studies pertinent to the claimed indication. In addition to these studies, the applicants conducted another ten (10) Phase II and Phase III uncontrolled and other studies.

On November 16, 2015, AstraZeneca submitted the BLA for brodalumab for the treatment of patients with moderate-to-severe plaque psoriasis (Exhibit J).

On November 25, 2015, FDA acknowledged receipt of the complete BLA via letter (Exhibit K) and assigned number BLA 761032 to the BLA.

On January 21, 2016, the FDA notified AstraZeneca that BLA 761032 had been accepted for filing (Exhibit K).

SILIQ™ was approved on February 15, 2017 for commercial marketing and use under Department of Health and Human Services U.S. Biologics License Application No. 761032, under the provisions of section 351(a) of the Public Health Service Act (Exhibit A). Approval of the BLA was issued to Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL) and Valeant Pharmaceuticals North America LLC (VPNA) as the U.S. agent.

The activities undertaken by the marketing applicants during the regulatory review period are provided in Exhibits N (IND Period) and O (BLA Period).

12. Statement Concerning Eligibility for and Duration of Extension Sought Under 35 U.S.C. § 156 (37 C.F.R. § 1.740 (a)(12))

a. In the opinion of the Applicant, the '206 patent is eligible for an extension of patent term under 35 U.S.C. § 156 and 37 C.F.R. § 1.720 because:

i. One or more claims of the '206 patent claim the approved product or a method of using the approved product. 35 U.S.C. § 156(a) and 37 C.F.R. § 1.720(a).

ii. The term of the '206 patent has not expired before the submission of this Application 35 U.S.C. § 156(a)(1) and 37 C.F.R. § 1.720(g).

iii. The term of the '206 patent has not been extended under 35 U.S.C. § 156. 35 U.S.C. § 156(a)(2) and 37 C.F.R. § 1.720(b).

iv. This Application is submitted by the owner of record of the '206 patent and in compliance with 35 U.S.C. § 156 and 37 C.F.R. § 1.720. 35 U.S.C. § 156(a)(3) and 37 C.F.R. § 1.720(c), 1.730(b).

v. The approved product, SILIQ™ (brodalumab), was subject to a regulatory review period before its commercial marketing or use. 35 U.S.C. § 156(a)(4) and 37 C.F.R. § 1.720(d).

vi. The permission for commercial marketing or use of the approved product after regulatory review is the first permitted commercial marketing or use of the approved product. 35 U.S.C. § 156(a)(5) and 37 C.F.R. § 1.720(e).

vii. The application for patent term extension is submitted within the 60-day period beginning on the approval date of the approved product. 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.720(f).

viii. The term of no other patent has been extended pursuant to 35 USC § 156 based on the same regulatory review period for the product, SILIQ™ (brodalumab). 35 U.S.C. § 156(c)(4) and 37 C.F.R. § 1.720(h).

b. Period of request extension and explanation of how the length of extension was calculated.

i. Applicant requests that the term of the '206 patent be extended by 1156 days.

ii. The requested period of extension of the term of the '206 patent corresponds to the regulatory review period that is available for extension under 35 U.S.C. § 156, based on the facts

and circumstances of the regulatory review of the approved product, SILIQ™ (brodalumab). The requested period of extension is based on the regulatory review and issue date of the '206 patent and was determined as follows:

1. The relevant dates for determining the period of patent term extension are:

IND became effective:	September 26, 2009
U.S. Patent No. 7,767,206 issued:	August 3, 2010
BLA for SILIQ™ (brodalumab) was submitted:	November 16, 2015
BLA for SILIQ™ (brodalumab) was filed:	January 21, 2016
BLA was approved:	February 15, 2017

2. The '206 patent issued **during** the period specified in 35 U.S.C. § 156(g)(1)(B)(i). The regulatory review period thus includes a period based on the time between the day the '206 patent issued and the date the BLA was submitted. This period is 1932 days. Pursuant to 35 U.S.C. § 156(c)(2) the calculated regulatory review period includes one-half of the time in the period specified in 35 U.S.C. § 156(g)(1)(B)(i). Accordingly, the regulatory review period includes 966, days (one-half of 1932 days).
3. The '206 patent issued prior to the start of the period specified in 35 U.S.C. § 156(g)(1)(B)(ii). The regulatory review period thus includes a period equal to the number of days from the day the BLA was submitted and the day the BLA was approved. This period is 458 days.
4. The period of patent term extension for the approved product, SILIQ™ (brodalumab), determined according to 35 U.S.C. § 156(b), (c)(2) and (g)(1), and in view of the calculated regulatory review periods set forth above, is 1424 days (966 days plus 458 days)
5. The 14-year limit pursuant to 35 U.S.C. § 156(c)(3) applies to this application for the following reasons: (a) The '206 patent will expire on December 18, 2027 and the date that is 14 years after the date of approval of the approved product is February 15, 2031. The period from the date the patent expires to the end of the 14-year period is 1156 days, which is shorter than the calculated period of patent term extension.
6. The '206 patent issued after the enactment of 35 U.S.C. § 156, therefore, the period of extension on the basis of regulatory review may not exceed 5-years pursuant to 35 U.S.C. § 156(g)(6)(A). **The requested period of extension is 1156 days, which is approximately 3.2 years.** Accordingly, the 5-year limit under 35 U.S.C. § 156(g)(6)(A) does not apply to this extension.

13. **Statement Pursuant to 37 C.F.R. § 1.740(a)(13)**

Applicant acknowledges the duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

14. **Applicable Fee (37 C.F.R. § 1.740(a)(14))**

The fee for this application prescribed in 37 C.F.R. § 1.20(j) is $1,120.00. Please charge the fee, and any fees associated and due in this application to our Deposit Account No. 13-3080, referencing the number: 208689-9015.

15. **Name and Address for Correspondence (37 C.F.R. § 1.740(a)(15))**

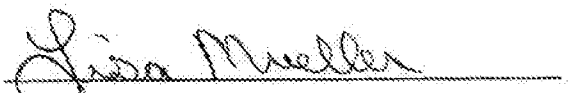
Please direct all inquiries and correspondence relating to this application for patent term extension to:

Lisa L. Mueller
MICHAEL BEST & FRIEDRICH LLP
444 W. Lake Street, Suite 3200
Chicago, Illinois 60606
312.222.0800 (main)
312.596.5812 (direct)
312.222.0818 (fax)

16. **Copies of this Application (37 C.F.R. § 1.740(b))**

Pursuant to 37 C.F.R. § 1.740(b), two additional copies of this application are filed concurrently herewith.

Respectfully submitted,



Lisa L. Mueller
Registration No. 38,978

Please recognize our Customer number 105263 as our correspondence address

MICHAEL BEST & FRIEDRICH LLP
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312.222.0800 (main)
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Exhibit A

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761032

BLA APPROVAL

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
c/o Valeant Pharmaceuticals North America LLC
Attention: Karen M. Krstulich
Executive Director Regulatory Affairs
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Ms. Krstulich:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Siliq (brodalumab).

We acknowledge receipt of your major amendment dated October 18, 2016, which extended the goal date by three months.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2053 to Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL), Grand Duchy of Luxembourg, Luxembourg, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Siliq (brodalumab). Siliq is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture brodalumab drug substance at [redacted]. The 210 mg/1.5 mL drug product will be manufactured at [redacted], and packaged and labeled at [redacted]. You may label your product with the proprietary name, Siliq, and market it in a 210 mg/1.5 mL pre-filled syringe.

DATING PERIOD

The dating period for Siliq shall be 12 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b)(4) months from the date of manufacture when stored at (b)(4).

We have approved the stability protocols in your license application for the purpose of extending the expiration dating periods of your drug substance and drug product under 21 CFR 601.12. Data supporting extension of the expiration dating period should be submitted to the BLA Annual Report.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Siliq to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Siliq, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Medication Guide and Instructions for Use). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on December 13, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 761032.**" Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages < 6 years because necessary studies are impossible or highly impracticable. This is because the prevalence of psoriasis in the 0 to less than 6 years age group is low (with the highest published prevalence of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

We are deferring submission of your pediatric studies for ages 6 to <18 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected. Based on the immunomodulatory mechanism of action for brodalumab, pediatric studies in population 6-17 years of age with moderate to severe psoriasis will likely be deferred at least until after adult studies have been completed and a determination of safety and efficacy has been made for adult psoriasis subjects.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

3164-1 Open-label study to determine PK of a single dose of brodalumab in 16 children (6 to < 18 years old) with severe plaque psoriasis.

Final Protocol Submission:	06/17
Study Completion:	01/19
Final Report Submission:	06/19

3164-2 Double-blind, active comparator-controlled, multicenter study with brodalumab to determine the safety and efficacy in adolescent subjects (12 to < 18 years old) with severe plaque psoriasis.

Final Protocol Submission:	04/19
Study Completion:	01/24
Final Report Submission:	06/24

3164-3 Open label, single arm study with brodalumab to determine safety and efficacy in children (6 to <12) with severe plaque psoriasis.

Final Protocol Submission:	04/24
Study Completion:	01/29
Final Report Submission:	06/29

Submit the protocols to your IND 104671, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of maternal, fetal and neonatal toxicity as well as an unexpected serious risk of malignancy, opportunistic infections, and neutropenia.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3164-4 Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women with a diagnosis of psoriasis exposed to brodalumab versus a non-brodalumab systemic medication exposure cohort. The outcomes will include major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age births. This study may use multiple data sources in order to obtain a sufficient sample size as women with

psoriasis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.

The timetable you submitted on December 22, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/17
Study Completion:	12/22
Final Report Submission:	06/23

3164-5 Conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women with the diagnosis of psoriasis exposed to brodalumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on December 22, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/17
Study Completion:	06/30
Final Report Submission:	06/31

3164-6 Conduct a prospective, observational study to assess the long-term safety of Siliq (brodalumab) compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study's primary outcome is malignancy. Secondary outcomes include, but are not limited to, opportunistic infections (e.g., tuberculosis [TB], opportunistic mycoses) and neutropenia. Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to brodalumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a prespecified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the brodalumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period, including any exclusion and inclusion criteria. Enroll patients over an initial 4 year period and follow for a minimum of 8 years from the time of enrollment.

The timetable you submitted on December 23, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission	08/17
Final Protocol Submission:	03/18
Study Completion:	11/30
Final Report Submission:	11/31

Submit the protocols to your IND 104671, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3164-7	Submit final study report for LC/UV/MS analysis using appropriate control samples to confirm the capability of this method to detect volatile compounds in the presence of brodalumab drug product.

The timetable you submitted on December 22, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission:	03/17

Submit chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any

changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Siliq (brodalumab) to ensure the benefits of the drug outweigh the risk of observed suicidal ideation and behavior (SIB) in subjects treated with Siliq.

Your proposed REMS must include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that Siliq (brodalumab) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of observed suicidal ideation and behavior (SIB) in subjects treated with Siliq that is listed in the labeling. The elements to assure safe use (ETASU) are intended to ensure that prescribers are informed about the risk of SIB observed with Siliq therapy and the need to counsel patients about this risk. The ETASU are also intended to ensure that patients are informed about the risk of SIB observed with Siliq therapy and the need to seek medical attention should they experience manifestations of suicidal thoughts and behavior, new onset or worsening depression, anxiety, or other mood changes.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers who prescribe must be specially certified.
- Pharmacies that dispense the drug are specially certified.
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions.

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies that dispense the drug be specially certified, and the drug be dispensed to patients with documentation of safe-use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

Your proposed REMS, submitted on February 13, 2017, and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Siliq (brodalumab) into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

1. Siliq Stakeholder data (prescribers, pharmacies, patients, and distributors) per reporting period and cumulatively:
    a. Numbers of each certified/enrolled stakeholder, status of certification, and method of certification including:
        i. Number of certified prescribers by medical degree, prescriber specialty, and method of certification (email, fax, online)
        ii. Number of certified pharmacies by pharmacy type (inpatient, outpatient chain, outpatient independent) and method of certification (email, fax, online)
        iii. Number of authorized distributors and wholesalers
        iv. Number of enrolled patients and their demographics (age, gender, race)
    b. Listing and categorization of reasons enrollment is incomplete for each stakeholder category.
2. Utilization Data, per reporting period and cumulatively: Number of Siliq prescriptions (new and refills) dispensed stratified by:
    a. pharmacy type
    b. method of dispensing authorization (on-line versus phone)
    c. prescriber specialty
    d. patient demographics (age, gender, race)
3. Compliance Metrics, per reporting period:
    a. Report of annual audit findings from a representative sample of 25% of certified pharmacies or one, whichever is greater, for audits conducted during the reporting period, including:
        i. What processes and procedures the REMS and distributors/wholesalers have in place to verify, prior to dispensing Siliq, that the pharmacies are certified
        ii. Any corrective actions taken to address findings of non-compliance
        iii. The status of corrective actions,
        iv. Any resulting preventative actions taken.
    b. Report of findings from an audit of 25% of the certified pharmacies or one, whichever is greater, within 90 calendar days after the pharmacy places its first order of Siliq to ensure that all processes and procedures are in place and functioning

i. This report is to include any corrective actions taken to address findings, the status of corrective actions, and any resulting preventative actions taken

c. Number of Siliq prescriptions dispensed that were written by non-certified prescribers and the actions taken to prevent future occurrences.

d. Number of Siliq prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences.

e. Number of times a Siliq prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, to include a description of how the events were identified and any corrective actions taken.

f. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences.

g. Number of prescribers, pharmacies and distributors de-certified and reasons for decertification.

h. The number of and reasons for rejected prescription authorizations.

i. Failures of Rx dispensing authorization due to calls to the REMS for authorization when the Call Center was closed or when the prescriber/patient verification portion of the website was down.

j. The numbers of the most frequently asked questions to the Call Center organized by topic.

4. REMS Program implementation (to be provided in the 12 month assessment only)

a. Product Launch Date

b. Date when the Siliq REMS website went live

c. Date healthcare providers could become certified online, by email, or by fax

d. Date when the REMS Program Website & Call Center are fully operational, including the online confirmation of patient authorization functionality and the availability of REMS materials

5. Evaluation of knowledge via Knowledge, Attitude and Behavior (KAB) surveys

a. Prescribers

i. An evaluation of knowledge of certified prescribers of the potential risk of suicidal ideation and behavior observed with Siliq therapy.

ii. An evaluation of prescriber practice or behavior with regards to counseling patients about the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

iii. An evaluation of certified prescriber knowledge of Siliq REMS requirements and processes.

b. Patients

i. An evaluation of knowledge of patients of the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

ii. An evaluation of patients' recall of counseling by prescriber, pharmacist, or both, on the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

iii. An evaluation of patient receipt of the wallet card.

c. Pharmacies

i. An evaluation of knowledge of authorized representatives and staff pharmacists in certified pharmacies of the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

ii. An evaluation of knowledge of authorized representatives and staff pharmacists in certified pharmacies of the Siliq REMS requirements and processes.

6. With respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified (Section 505-1(g)(3).

We remind you that, in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification,* provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 761032 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 761032 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 761032/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761032/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761032/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761032/ S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR BLA 761032

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email REMS_Website@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
02/15/2017

Exhibit B

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SILIQ safely and effectively. See full prescribing information for SILIQ.

SILIQ™ (brodalumab) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: SUICIDAL IDEATION AND BEHAVIOR

See full prescribing information for complete boxed warning.

- **Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. (5.1, 6.1)**
- **Prior to prescribing, weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior. (5.1)**
- **Patients with new or worsening suicidal thoughts and behavior should be referred to a mental health professional, as appropriate. (5.1)**
- **Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes. (5.1)**
- **SILIQ is available only through a restricted program called the SILIQ REMS Program. (5.2)**

INDICATIONS AND USAGE

SILIQ is a human interleukin-17 receptor A (IL-17RA) antagonist indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. (1)

DOSAGE AND ADMINISTRATION

- Administer 210 mg of SILIQ by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks. (2.1)

DOSAGE FORMS AND STRENGTHS

- Injection: 210 mg/1.5 mL solution in a single-dose prefilled syringe. (3)

CONTRAINDICATIONS

- Crohn's disease (4)

WARNINGS AND PRECAUTIONS

- Infections: Serious infections have occurred. Consider the risks and benefits prior to initiating SILIQ in patients with a chronic infection or a history of recurrent infection. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinue SILIQ until the infection resolves. (5.3)
- Tuberculosis (TB): Evaluate patients for TB infection prior to initiating treatment with SILIQ. (5.4)
- Crohn's Disease: Crohn's disease occurred during clinical trials. Discontinue SILIQ if patient develops Crohn's disease while taking SILIQ. (5.5)
- Immunizations: Avoid using live vaccines concurrently with SILIQ. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥1%) were arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and tinea infections. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-888-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

WARNING: SUICIDAL IDEATION AND BEHAVIOR

Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. Prior to prescribing SILIQ, weigh the potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior. Patients with new or worsening suicidal ideation and behavior should be referred to a mental health professional, as appropriate. Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes *[see Warnings and Precautions* (5.1)*]*.

Because of the observed suicidal behavior in subjects treated with SILIQ, SILIQ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SILIQ REMS Program *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

SILIQ™ is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended SILIQ dose is 210 mg administered by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks.

If an adequate response has not been achieved after 12 to 16 weeks of treatment with SILIQ, consider discontinuing therapy. Continued treatment beyond 16 weeks in patients who have not achieved an adequate response is not likely to result in greater success.

2.2 Tuberculosis Assessment Prior to Initiation of SILIQ

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SILIQ *[see Warnings and Precautions (5.4)]*.

2.3 Important Administration Instructions

Administer SILIQ subcutaneously. Each prefilled syringe is for single-dose only.

Instruct patients to review the Medication Guide before use (see Medication Guide). SILIQ is intended for use under the guidance and supervision of a healthcare professional. Patients may self-inject SILIQ when deemed appropriate by a healthcare professional and after proper training in subcutaneous injection technique using the prefilled syringe.

Advise patients who are self-administering to inject the full dose and to read the Instructions for Use before administration (see Instructions for Use).

Do not inject SILIQ into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis.

2.4 Preparation of SILIQ Prefilled Syringe

- Allow SILIQ prefilled syringe to reach room temperature (approximately 30 minutes) before injecting. Do not warm in any other way. Do not remove the gray needle cap on the prefilled syringe while allowing it to reach room temperature.

- Visually inspect SILIQ for particles and discoloration prior to administration. SILIQ is a clear to slightly opalescent, colorless to slightly yellow solution. A few translucent to white, amorphous proteinaceous particles may be present. Do not use SILIQ if it is cloudy or discolored or if foreign matter is present.
- Instruct patients to use the prefilled syringe and to inject the full amount (1.5 mL), which provides 210 mg of SILIQ, according to the directions provided in the Instructions for Use *[see Instructions for Use]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 210 mg/1.5 mL solution in a single-dose prefilled syringe. SILIQ is a clear to slightly opalescent, colorless to slightly yellow solution and may contain a few translucent to white, amorphous particles .

4 CONTRAINDICATIONS

SILIQ is contraindicated in patients with Crohn's disease because SILIQ may cause worsening of disease *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Ideation and Behavior

Suicidal ideation and behavior, including 4 completed suicides, occurred in subjects treated with SILIQ in the psoriasis clinical trials. There were no completed suicides in the 12-week placebo-controlled portion of the trials. SILIQ users with a history of suicidality or depression had an increased incidence of suicidal ideation and behavior as compared to users without such a history *[see Adverse Reactions (6.1)]*. A causal association between treatment with SILIQ and increased risk of suicidal ideation and behavior has not been established.

Prescribers should weigh the potential risks and benefits before using SILIQ in patients with a history of depression or suicidality. Patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate. Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation and behavior, new onset or worsening depression, anxiety, or other mood changes. Prescribers should also re-evaluate the risks and benefits of continuing treatment with SILIQ if such events occur.

Because of the observed suicidal ideation and behavior in subjects treated with SILIQ, if an adequate response to SILIQ has not been achieved within 12 to 16 weeks, consider discontinuing therapy.

SILIQ is available only through a restricted program under a REMS *[see Warnings and Precautions (5.2)]*.

5.2 SILIQ REMS Program

SILIQ is available only through a restricted program under a REMS called the SILIQ REMS Program because of the observed suicidal ideation and behavior in subjects treated with SILIQ *[see Warnings and Precautions (5.1)]*.

Notable requirements of the SILIQ REMS Program include the following:

- Prescribers must be certified with the program.
- Patients must sign a Patient-Prescriber Agreement Form.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive SILIQ.

Further information, including a list of qualified pharmacies, is available at www.SILIQREMS.com or by calling the SILIQ REMS Program Call Center at 855-511-6135.

5.3 Infections

SILIQ may increase the risk of infections. In clinical trials, subjects treated with SILIQ had a higher rate of serious infections than subjects treated with placebo (0.5% versus 0.2%) and higher rates of fungal infections (2.4% versus 0.9%). One case of cryptococcal meningitis occurred in a subject treated with SILIQ during the 12-week randomized treatment period and led to discontinuation of therapy *[see Adverse Reactions (6.1)]*.

During the course of clinical trials for plaque psoriasis, the exposure-adjusted rates for infections and serious infections were similar in the subjects treated with SILIQ and those treated with ustekinumab.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SILIQ. Instruct patients to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a serious infection or is not responding to standard therapy for the infection, monitor the patient closely and discontinue SILIQ therapy until the infection resolves.

5.4 Risk for Latent Tuberculosis Reactivation

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SILIQ. Do not administer SILIQ to patients with active TB infection. Initiate treatment for latent TB prior to administering SILIQ.

Consider anti-TB therapy prior to initiation of SILIQ in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Closely monitor patients receiving SILIQ for signs and symptoms of active TB during and after treatment.

5.5 Crohn's Disease

In psoriasis trials, which excluded subjects with active Crohn's disease, Crohn's disease occurred in one subject during treatment with SILIQ and led to discontinuation of therapy. In other trials, exacerbation of Crohn's disease was observed with SILIQ use.

SILIQ is contraindicated in patients with Crohn's disease.

Discontinue SILIQ if the patient develops Crohn's disease while taking SILIQ.

5.6 Immunizations

Avoid use of live vaccines in patients treated with SILIQ. No data are available on the ability of live or inactive vaccines to elicit an immune response in patients being treated with SILIQ.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of labeling:

- Suicidal Ideation and Behavior *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.3)]*
- Crohn's Disease *[see Contraindications (4), Warnings and Precautions (5.5)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The overall safety population included 4558 subjects (3066 SILIQ, 613 ustekinumab, 879 placebo) in controlled clinical trials and open-label extension studies. The majority of subjects were male (69%), white (91%), and aged 40-64 years old

(58%). One-third of subjects reported previous biologic use prior to enrollment. Across the clinical development program, 4464 subjects received at least one dose of SILIQ; 3755 subjects were exposed to SILIQ for at least 1 year.

Weeks 0 to 12:

Data from one multicenter, randomized, placebo-controlled trial (Trial 1), two multicenter, randomized, placebo- and active-controlled trials (Trials 2 and 3), and one dose-finding trial (Trial 4) in plaque psoriasis were pooled to evaluate the safety of SILIQ (210 mg weekly at Weeks 0, 1, and 2, followed by treatments every 2 weeks [Q2W]) compared to placebo for up to 12 weeks after treatment initiation.

During the 12-week, randomized treatment period, about 1% of the subjects in the treatment groups (SILIQ, ustekinumab and placebo) discontinued treatment because of adverse events. Adverse events leading to discontinuation of SILIQ included neutropenia, arthralgia, and urticaria. The proportion of subjects who developed serious adverse events was similar among the SILIQ, ustekinumab, and placebo groups.

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the SILIQ 210 mg Q2W group than in the placebo group during the 12-week randomized treatment period of the pooled trials.

Table 1: Adverse Reactions Occurring in ≥ 1% of Subjects in the SILIQ Group and More Frequently than in the Placebo Group in Plaque Psoriasis Trials through Week 12

Adverse Reactions	Placebo (N=879) n (%)	SILIQ 210 mg every 2 weeks[a] (N=1496) n (%)	Ustekinumab (N=613)[b] n (%)
Arthralgia	29 (3.3)	71 (4.7)	15 (2.4)
Headache	31 (3.5)	64 (4.3)	23 (3.8)
Fatigue	10 (1.1)	39 (2.6)	16 (2.6)
Diarrhea	10 (1.1)	33 (2.2)	5 (0.8)
Oropharyngeal pain	10 (1.1)	31 (2.1)	8 (1.3)
Nausea	10 (1.1)	28 (1.9)	6 (1.0)
Myalgia	3 (0.3)	26 (1.7)	4 (0.7)
Injection site reactions (pain, erythema, bruising, hemorrhage, pruritus)	11 (1.3)	23 (1.5)	12 (2.0)
Influenza	4 (0.5)	19 (1.3)	7 (1.1)
Neutropenia	4 (0.5)	15 (1.0)	5 (0.8)
Tinea infections (tinea pedis, versicolor, cruris)	2 (0.2)	15 (1.0)	3 (0.5)

[a] subjects receiving 210 mg of SILIQ at Weeks 0, 1, and 2, followed by treatment every two weeks during the 12-week period

[b] Trials 2 and 3 included the active comparator, ustekinumab.

Adverse reactions that occurred in less than 1% of subjects in the SILIQ group through Week 12 were conjunctivitis and candida infections (including oral [0.2%], genital [0.1%], and esophageal [0.1%] versus none in the placebo group).

Week 0 to End of Trial:

Through Week 52, exposure-adjusted rates of serious adverse events were similar between subjects treated with SILIQ and those treated with ustekinumab. Through the end of the trial, the exposure-adjusted rates of treatment-emergent serious adverse events were similar to those seen in the 52-week period in the subjects treated with SILIQ.

Specific Adverse Reactions:

Suicidal Ideation and Behavior

During the 12-week randomized treatment period in the pooled trials, one subject in the SILIQ group attempted suicide and none in the placebo or ustekinumab groups. From initiation through Week 52 of the trials, suicidal ideation or behavior occurred in 7 of 4019 subjects (0.2 per 100 subject-years) treated with SILIQ and in 2 of 613 subjects (0.4 per 100 subject-years) treated with ustekinumab.

During the course of the clinical trials for plaque psoriasis, suicidal ideation or behavior occurred in 34 of 4464 subjects treated with SILIQ (0.37 per 100 subject-years). Eight of the 10 subjects who attempted or completed suicide had a history of depression and/or suicidal ideation or behavior *[see Warnings and Precautions (5.1, 5.2)]*.

Infections
During the 12-week randomized treatment period, infections occurred in 25.4% of the SILIQ group compared to 23.4% of the placebo group. The majority of infections consisted of nasopharyngitis, upper respiratory tract infection, pharyngitis, urinary tract infections, bronchitis, and influenza, and did not necessitate treatment discontinuation. The SILIQ group had a higher rate of fungal infections compared to the placebo group (1.8% vs 0.9%). The fungal infections were primarily non-serious skin and mucosal candida infections *[see Warnings and Precautions (5.3)]*.

Neutropenia
During the 12-week randomized treatment period, neutropenia occurred in 0.7% of subjects in the SILIQ group. Most adverse reactions of neutropenia were transient. In subjects with normal absolute neutrophil count (ANC) at baseline, a reduction in ANC occurred in 6.8% of subjects in the SILIQ group, compared to 3.3% in the ustekinumab group, and 3.6% in the placebo group. Neutropenia ≥ Grade 3 (< 1000/mm^3) occurred in 0.5% of subjects in the SILIQ group compared to 0.2% of subjects in the ustekinumab group and none in the placebo group. From Week 0 to end of trial, the exposure-adjusted rate of treatment-emergent neutropenia was 0.4 per 100 subject-years (0.1 per 100 subject-years were ≥ Grade 3). No serious infections were associated with cases of neutropenia.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity with SILIQ. Approximately 3% of subjects treated with SILIQ developed antibodies to brodalumab through the 52-week treatment period. Of the subjects who developed antibodies to brodalumab, none had antibodies that were classified as neutralizing. However, the assay to test for neutralizing antibodies had limitations detecting neutralizing antibodies in the presence of brodalumab; therefore, the incidence of neutralizing antibody development could be underestimated.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SILIQ with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Live Vaccinations

Avoid use of live vaccines in patients treated with SILIQ *[see Warnings and Precautions (5.6)]*.

7.2 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Treatment with SILIQ may modulate serum levels of some cytokines.

Therefore, upon initiation or discontinuation of SILIQ in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug

concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data on SILIQ use in pregnant women to inform a drug associated risk. Human IgG antibodies are known to cross the placental barrier; therefore, SILIQ may be transmitted from the mother to the developing fetus. In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of brodalumab during organogenesis through parturition at doses up to 26 times the maximum recommended human dose (MRHD)*[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

A combined embryofetal development and pre- and post-natal development study was conducted in cynomolgus monkeys administered brodalumab. No brodalumab-related effects on embryofetal toxicity or malformations, or on morphological, functional or immunological development were observed in infants from pregnant monkeys administered weekly subcutaneous doses of brodalumab up to 26 times the MRHD from the beginning of organogenesis to parturition (on a mg/kg basis of 90 mg/kg/week).

8.2 Lactation

Risk Summary

There are no data on the presence of brodalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Brodalumab was detected in the milk of lactating cynomolgus monkeys. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SILIQ and any potential adverse effects on the breastfed infant from SILIQ or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of SILIQ have not been evaluated in pediatric patients.

8.5 Geriatric Use

Of the 3066 plaque psoriasis subjects initially randomized to SILIQ in clinical trials, 192 (6%) were ≥ 65 years old and no subjects were ≥ 75 years old. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 years and older was not sufficient to determine whether they responded differently from younger subjects *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Brodalumab is a human monoclonal IgG2κ antibody directed against human interleukin-17 receptor A (IL-17RA). It is expressed in a Chinese Hamster Ovary (CHO) cell line. Brodalumab is comprised of 1312 amino acids and has an estimated molecular mass of 144,000 Daltons.

SILIQ (brodalumab) Injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution, delivered via subcutaneous injection. A few translucent to white, amorphous particles may be present. SILIQ is supplied in a single-dose 2.25 mL syringe made from type 1 glass with stainless steel 27G x ½" needle. Each SILIQ

single-dose prefilled syringe delivers 1.5 mL of solution containing 210 mg of brodalumab formulated in glutamate (6.5 mg), polysorbate 20 (0.15 mg), proline (36 mg), and Water for Injection, USP at pH 4.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Brodalumab is a human monoclonal IgG2 antibody that selectively binds to human IL-17RA and inhibits its interactions with cytokines IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer and IL-25. IL-17RA is a protein expressed on the cell surface and is a required component of receptor complexes utilized by multiple IL-17 family cytokines. Blocking IL-17RA inhibits IL-17 cytokine-induced responses including the release of pro-inflammatory cytokines and chemokines.

12.2 Pharmacodynamics

Elevated levels of IL-17A, IL-17C and IL-17F are found in psoriatic plaques. Serum IL-17A levels, measured at Weeks 12, 24, and 48 of SILIQ 210 mg every 2 weeks of treatment, were higher than the baseline levels in subjects with moderate to severe plaque psoriasis. The relationship between the pharmacodynamic activity and the mechanism(s) by which brodalumab exerts its clinical effects is unknown.

12.3 Pharmacokinetics

Absorption

Following a single subcutaneous dose of 210 mg in subjects with plaque psoriasis, brodalumab reached peak mean (±SD) serum concentration (C_{max}) of 13.4±7.3 mcg/mL by approximately 3 days post dose. The mean (±SD) area-under-the-concentration-time curve (AUC) of brodalumab was 111±64 mcg•day/mL.

Following multiple subcutaneous doses of 210 mg every 2 weeks, steady-state was achieved by Week 4. The mean (±SD) C_{max} was 20.6±14.6 mcg/mL and the mean (±SD) AUC over the two week dosing interval was 227±167 mcg•day/mL.

Following subcutaneous administration, brodalumab bioavailability was approximately 55%.

Distribution

Following a single subcutaneous administration of brodalumab 210 mg in subjects with plaque psoriasis, the mean (±SD) apparent volume of distribution (Vz/F) of brodalumab was 8.9±9.4 L.

Elimination

The metabolic pathway of brodalumab has not been characterized. As a human monoclonal IgG2 antibody, brodalumab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

Following a single subcutaneous administration of brodalumab 210 mg in subjects with plaque psoriasis, the mean (±SD) apparent total clearance (CL/F) was 3.0±3.5 L/day. The clearance of brodalumab increased with decreasing doses due to nonlinear elimination.

Dose Linearity

Brodalumab exhibited non-linear pharmacokinetics with exposures that increased greater than dose-proportionally over a dose range from 140 mg (approximately 0.67 times the recommended dose) to 350 mg (approximately 1.67 times the recommended dose) following subcutaneous administrations in subjects with plaque psoriasis.

Weight

Brodalumab trough concentrations were lower in subjects with higher body weight.

Specific Populations

Hepatic or Renal Impairment

No trials were conducted to assess the effect of hepatic or renal impairment on the pharmacokinetics of brodalumab.

Age: Geriatric Population

Population pharmacokinetic analysis indicated that age did not significantly influence the clearance of brodalumab in subjects with plaque psoriasis. Subjects who were 65 years or older had a similar brodalumab clearance as compared to subjects less than 65 years old.

Drug Interaction Studies

In subjects with plaque psoriasis, one week following a single subcutaneous administration of 210 mg brodalumab, the exposure of midazolam (CYP3A4 substrate) was increased by 24% *[see Drug Interactions (7.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of SILIQ. The published literature is mixed on the potential effects on malignancy risk due to the inhibition of the IL-17RA, the pharmacological action of SILIQ. Some published literature suggests that IL-17A directly promotes cancer cell invasion, which suggests a potential beneficial effect of SILIQ. However, other reports indicate IL-17A promotes T-cell mediated tumor rejection, which suggests a potential adverse effect by SILIQ. However, inhibition of the IL-17RA with SILIQ has not been studied in these models. Therefore, the relevance of experimental findings in these models for malignancy risk in humans is unknown.

In cynomolgus monkeys, there were no effects on fertility parameters such as changes in reproductive organs or sperm analysis following subcutaneous administration of brodalumab at dose levels up to 90 mg/kg/week for six months (26 times the MRHD on a mg/kg basis). The monkeys were not mated in this study to evaluate effects on fertility.

14 CLINICAL STUDIES

Three multicenter, randomized, double-blind, controlled trials (Trials 1, 2, and 3) enrolled a total of 4373 subjects 18 years of age and older with at least a 6-month history of moderate to severe plaque psoriasis, defined as having a minimum affected body surface area (BSA) of 10%, a Psoriasis Area and Severity Index (PASI) score $\geq$ 12, a static Physician's Global Assessment (sPGA) score $\geq$3 in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 5, and who were candidates for systemic therapy or phototherapy. In all three trials, subjects were randomized to subcutaneous treatment with placebo or SILIQ 210 mg at Weeks 0, 1, and 2, followed by treatments every 2 weeks [Q2W] through Week 12. In the two active comparator trials (Trials 2 and 3), subjects randomized to ustekinumab received a 45 mg dose if their weight was less than or equal to 100 kg and a 90 mg dose if their weight was greater than 100 kg at Weeks 0, 4, and 16, followed by the same dose every 12 weeks.

All three trials assessed the change from baseline to Week 12 compared to placebo in the two co-primary endpoints: 1) PASI 75, the proportion of subjects who achieved at least a 75% reduction in the PASI composite score that takes into consideration both the percentage of body surface area affected and the nature and severity of psoriatic changes (induration, erythema, and scaling) within the affected region, and 2) the proportion of subjects with an sPGA of 0 (clear) or 1 (almost clear), and at least a 2-point improvement from baseline. In Trials 2 and 3, comparisons were also made to ustekinumab for the primary endpoint of the proportion of subjects who achieved a reduction in PASI score of 100% (PASI 100) from baseline at Week 12.

Other evaluated outcomes included the proportion of subjects who achieved an sPGA of 0 (clear) at Week 12, and the proportion of subjects who achieved a Psoriasis Symptom Inventory (PSI) score of 0 (not at all) or 1 (mild) on every item (itch, redness, scaling, burning, stinging, cracking, flaking, and pain) at Week 12. Baseline demographics and disease characteristics were generally consistent across all treatment groups in all three trials. Subjects were predominantly men (69%) and white (91%), with a mean age of 45 years. The mean baseline body weight was 90.5 kg and 28% of subjects had body weight greater than 100 kg. The baseline PASI score ranged from 9.4 to 72 (median: 17.4) and the baseline affected BSA ranged from 10 to 97% (median: 21%). Baseline sPGA scores ranged from "3 (moderate)" (58%) to "5 (very severe)" (5%).

Approximately 21% of subjects had a history of psoriatic arthritis. Approximately 30% of subjects had previously received a biologic therapy and 12% of subjects had failed previous biologic therapy.

Clinical Response at Week 12

The results of Trials 1, 2, and 3 are presented in Table 2.

Table 2: Efficacy Results at Week 12 in Adults with Plaque Psoriasis in Trials 1, 2, and 3 (NRI[a])

Endpoint	Trial 1		Trial 2			Trial 3		
	SILIQ 210 mg Q2W (N=222) n (%)	Placebo (N=220) n (%)	SILIQ 210 mg Q2W (N=612) n (%)	Ustekinumab (N=300) n (%)	Placebo (N=309) n (%)	SILIQ 210 mg Q2W (N=624) n (%)	Ustekinumab (N=313) n (%)	Placebo (N=315) n (%)
PASI 75[b] response	185 (83)	6 (3)	528 (86)	210 (70)	25 (8)	531 (85)	217 (69)	19 (6)
PASI 100 response	93 (42)	1 (<1)	272 (44)[b]	65 (22)	2 (1)	229 (37)[b]	58 (19)	1 (<1)
sPGA success clear (0) or almost clear (1)[b]	168 (76)	3 (1)	481 (79)	183 (61)	12 (4)	497 (80)	179 (57)	13 (4)
sPGA of clear (0)	93 (42)	1 (<1)	274 (45)	65 (21)	2 (1)	229 (37)	58 (19)	1 (<1)

[a]NRI = non-responder imputation

[b]Co-primary endpoints

Examination of age, gender, race, use of prior systemic or phototherapy, and use of prior biologics did not identify differences in response to SILIQ among these subgroups.

At Week 12, compared to subjects in the placebo group, a greater proportion of subjects in SILIQ 210 mg Q2W group achieved a Psoriasis Symptom Inventory (PSI) score of 0 (not at all) or 1 (mild) on every item (itch, redness, scaling, burning, stinging, cracking, flaking, pain).

Maintenance of Effect

In Trial 1, subjects randomized to receive SILIQ and who were responders at Week 12 (i.e., sPGA of 0 or 1) were re-randomized to receive either placebo or SILIQ. Among responders at Week 12, 83% (69/83) of subjects re-randomized to continued treatment with SILIQ 210 mg Q2W maintained this response (sPGA of 0 or 1) at Week 52 compared to none (0/84) who were re-randomized to placebo and withdrawn from SILIQ. In addition, 87% (72/83) of subjects re-randomized to continued treatment with SILIQ 210 mg Q2W achieved PASI 75 response at Week 52 compared to none (0/84) who were re-randomized to placebo and withdrawn from SILIQ.

Trials 2 and 3 included a re-randomized phase during which subjects originally randomized to receive SILIQ during the first 12 weeks were re-randomized to one of four SILIQ regimens at the Week 12 visit and placebo subjects were crossed

over to receive SILIQ 210 mg Q2W. Subjects receiving ustekinumab continued the same treatment until crossed over at Week 52 to SILIQ 210 mg Q2W. For sPGA 0 or 1 responders at Week 12, the percentage of subjects who maintained this response at Week 52 was 79% for subjects treated with SILIQ 210 mg Q2W. For PASI 100 responders at Week 12, 72% of the subjects who continued on SILIQ 210 mg Q2W maintained the response at Week 52.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SILIQ (brodalumab) Injection is available in a single-dose prefilled syringe containing a sterile, preservative-free clear to slightly opalescent, colorless to slightly yellow solution that may contain a few translucent to white, amorphous particles.

- NDC 0187-0004-02: Carton of two 210 mg/1.5 mL single-dose prefilled syringes

16.2 Storage and Handling

- Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light and physical damage during storage.
- When necessary, prefilled syringes can be stored at room temperature up to a maximum of 77°F (25°C) in the original carton for a maximum single period of 14 days with protection from light and sources of heat. Once the prefilled syringe has reached room temperature, do not place back into the refrigerator. Discard after 14 days at room temperature.
- Do not freeze.
- Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use)* before the patient starts using SILIQ, and each time the prescription is renewed, as there may be new information they need to know.

Suicidal Thoughts and Behavior

Instruct patients and their caregivers to monitor for the emergence of suicidal thoughts and behavior and promptly seek medical attention if the patient experiences suicidal thoughts, new or worsening depression, anxiety, or other mood changes *[see Warnings and Precautions (5.1)]*.

Instruct patients to carry the wallet card provided and to call the National Suicide Prevention Lifeline at 1-800-273-8255 if they experience suicidal thoughts.

SILIQ REMS Program

Because of the observed suicidal thoughts and behavior in subjects treated with SILIQ, SILIQ is available only through a restricted program called the SILIQ REMS Program *[see Warnings and Precautions (5.2)]*. Inform the patient of the following:

- Patients must enroll in the program *[see Warnings and Precautions (5.1, 5.2)]*.
- Patients will be given a SILIQ Patient Wallet Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation. Advise the patient to show the SILIQ Patient Wallet Card to other treating healthcare providers.

SILIQ is available only from certified pharmacies participating in the program. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

Infections

Inform patients that SILIQ may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to their healthcare providers and to contact their healthcare providers if they develop any signs or symptoms of infection *[see Warnings and Precautions (5.3)]*.

Crohn's Disease

Instruct patients to seek medical advice if they develop signs and symptoms of Crohn's disease *[see Warnings and Precautions (5.5)]*.

Instructions for Injection

Instruct the patient to perform the first self-injection under the guidance and supervision of a qualified healthcare professional for proper training in subcutaneous injection technique.

Instruct patients who are self-administering to inject the full dose of SILIQ *[see Dosage and Administration (2.1) and Instructions for Use]*.

Instruct patients or caregivers in the technique of proper syringe and needle disposal *[see Instructions for Use]*.

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SILIQ™ (SIL-EEK)
(brodalumab)
injection, for subcutaneous use

What is the most important information I should know about SILIQ?

SILIQ may cause serious side effects, including:

- **Suicidal thoughts or behavior have happened in** some people treated with SILIQ. Some people have ended their own lives. Your risk of suicidal thoughts and behavior may be increased if you have a history of suicidal thoughts or depression. It is not known if SILIQ causes suicidal thoughts or behavior. Get medical help right away if you or your caregiver notice any of the following symptoms:
  - o new or worsening depression or anxiety
  - o thoughts of suicide, dying, or hurting yourself
  - o changes in behavior or mood
  - o acting on dangerous impulses
  - o attempt to commit suicide

Your healthcare provider will give you a SILIQ Patient Wallet Card about symptoms you should get medical help for right away. Carry the card with you at all times during treatment with SILIQ and show it to all of your healthcare providers.

- **Serious infections.** SILIQ may lower the ability of your immune system to fight infections and may increase your risk of infections. Your healthcare provider will check you for tuberculosis (TB) before starting treatment with SILIQ and may treat you for TB before you begin treatment with SILIQ if you have a history of TB or have active TB. Your healthcare provider should watch you closely for signs and symptoms of infection and TB during and after treatment with SILIQ.
  Tell your healthcare provider right away if you have an infection or have symptoms of an infection, including:
  - o fever, sweats, or chills
  - o muscle aches
  - o cough
  - o shortness of breath
  - o sore throat or difficulty swallowing
  - o warm, red, or painful skin or sores on your body
  - o diarrhea or stomach pain
  - o burning when you urinate or urinate more often than normal

See **"What are the possible side effects of SILIQ?"** for more information about side effects.

What is SILIQ?

SILIQ is a prescription medicine used to treat adults with moderate to severe plaque psoriasis:

- who may benefit from taking injections or pills (systemic therapy) or phototherapy (ultraviolet light treatment), **and**
- who have not responded or lost response to other systemic therapy

It is not known if SILIQ is safe and effective in children.

Do not use SILIQ if you have Crohn's disease.

Before you use SILIQ, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of mental problems, including suicidal thoughts, depression, anxiety, or mood problems.
- have an infection that does not go away or that keeps coming back.
- have TB or have been in close contact with someone with TB.
- have recently received or are scheduled to receive an immunization (vaccine). You should avoid receiving live vaccines during treatment with SILIQ.
- are pregnant or plan to become pregnant. It is not known if SILIQ can harm your unborn baby. If you are pregnant or plan on becoming pregnant, consult with your healthcare provider.
- are breastfeeding or plan to breastfeed. It is not known if SILIQ passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use SILIQ?

- **See the detailed "Instructions for Use" that comes with SILIQ for information on how to inject a dose of SILIQ and how to properly store and throw away (dispose of) used SILIQ prefilled syringes.**
- Use SILIQ exactly as your healthcare provider tells you to use it.
- Your healthcare provider may stop SILIQ if your plaque psoriasis does not improve within 12 to 16 weeks of treatment.

What are the possible side effects of SILIQ?

SILIQ may cause serious side effects. See "What is the most important information I should know about SILIQ?"

- **Crohn's disease.** Tell your healthcare provider if you develop diarrhea, painful diarrhea, bloody stools, stomach pain or cramping, sudden or uncontrollable bowel movements, loss of appetite, constipation, weight loss, fever, or tiredness.

The most common side effects of SILIQ include: joint pain, headache, tiredness, diarrhea, mouth or throat pain, nausea, muscle pain, injection site reactions, flu (influenza), low white blood count (neutropenia), and fungal infections of the skin.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about safe and effective use of SILIQ

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SILIQ for a condition for which it was not prescribed. Do not give SILIQ to other people even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about SILIQ that is written for health professionals.

Manufactured for: Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 USA
Manufactured by: Valeant Pharmaceuticals Luxembourg S.à.r.l., Grand Duchy of Luxembourg, L-1931, Luxembourg
U.S. License Number 2053, Part number *XXXX*
For more information, go to www.SILIQ.com or call Valeant Pharmaceuticals at 1-800-321-4576.
U.S. Patents 7,939,070; 7,786,284; 7,833,527; 7,767,206; 8,790,648; 8,545,842; 8,435,518; 9,073,999; 9,096,673
Siliq is a trademark of Valeant Pharmaceuticals International, Inc. or its affiliates. ©Valeant Pharmaceuticals North America LLC
This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: February/2017
Reference ID: 4056898

Instructions for Use

SILIQ is supplied as a single-dose prefilled syringe. Each prefilled syringe contains one 210 mg dose of SILIQ. **Each SILIQ prefilled syringe can only be used one time.**

Your healthcare provider has prescribed SILIQ and will tell you how often it should be injected. If your healthcare provider decides that you or a caregiver may be able to give your injections of SILIQ at home, you should receive training on the right way to prepare and inject SILIQ. Do not try to inject yourself until you have been shown the right way to give the injections by your healthcare provider.

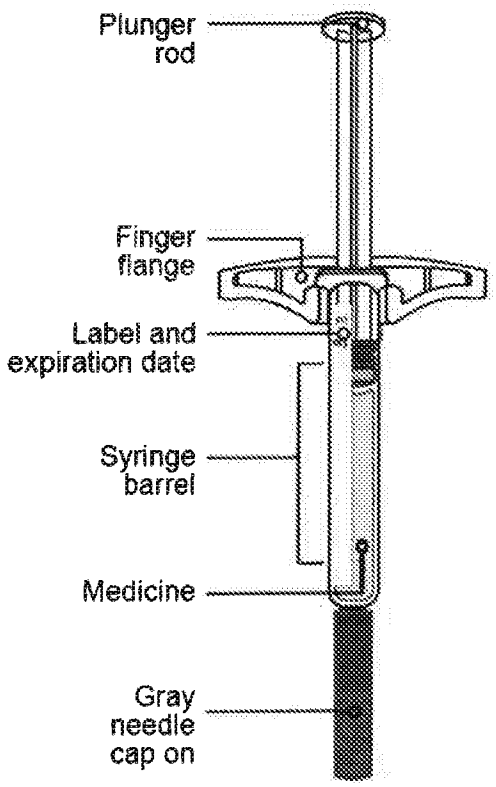
Read all of the instructions before using the SILIQ prefilled syringe. Call your healthcare provider if you or your caregiver have any questions about the right way to inject SILIQ.

Instructions for Use
SILIQ™ (SIL-EEK)
(brodalumab)
injection, for subcutaneous use

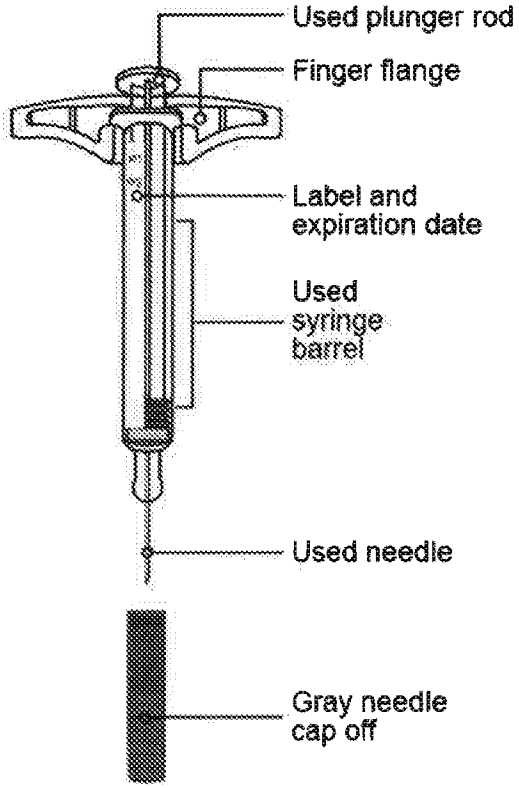
Single-Dose Prefilled Syringe

Guide to parts

Before use



After use



Important: Needle is inside the gray needle cap.

Important

Storing your SILIQ prefilled syringe

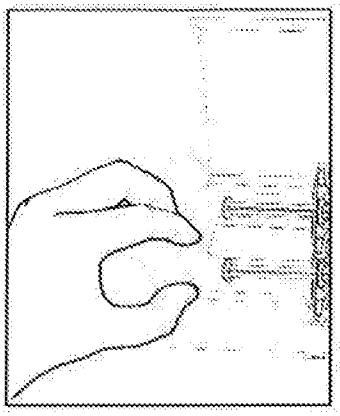
- Store SILIQ prefilled syringe in the refrigerator at 36°F to 46°F (2°C to 8°C).
- If needed, SILIQ prefilled syringe may be stored at room temperature up to 77°F (25°C) for up to 14 days. **Do not** place SILIQ prefilled syringe stored at room temperature back into the refrigerator.
- Throw away SILIQ prefilled syringe that has been stored at room temperature after 14 days.
- Protect SILIQ prefilled syringe from heat.
- **Do not** freeze.
- Keep SILIQ prefilled syringe in the original carton to protect from light and physical damage.
- Keep SILIQ prefilled syringe and all medicines out of reach of children.

Using your SILIQ prefilled syringe

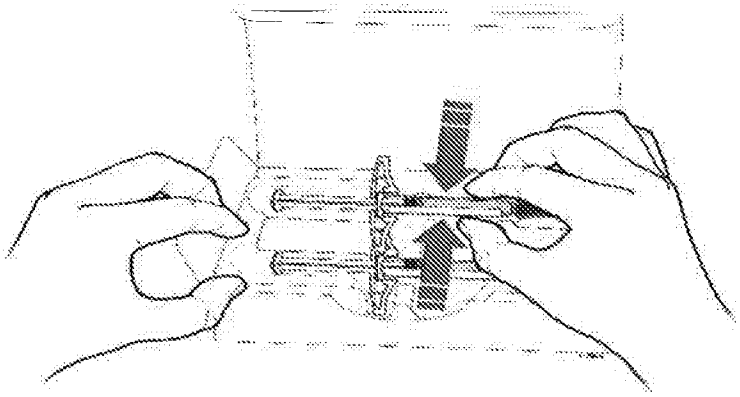
- It is important that you do not try to give the injection unless you or your caregiver has received training from your healthcare provider.
- **Do not** use a SILIQ prefilled syringe after the expiration date on the label.
- **Do not** shake the SILIQ prefilled syringe.
- **Do not** remove the gray needle cap from the SILIQ prefilled syringe until you are ready to inject.
- **Do not** use a SILIQ prefilled syringe if it has been dropped on a hard surface. Part of the SILIQ prefilled syringe may be broken even if you cannot see the break. Use a new SILIQ prefilled syringe, and call 1-800-321-4576.

Step 1: Prepare

A Remove one SILIQ prefilled syringe from the package.
Grab the syringe by the barrel to remove the prefilled syringe from the tray.



Place your finger or thumb on the edge of the tray to hold it while you remove the prefilled syringe.



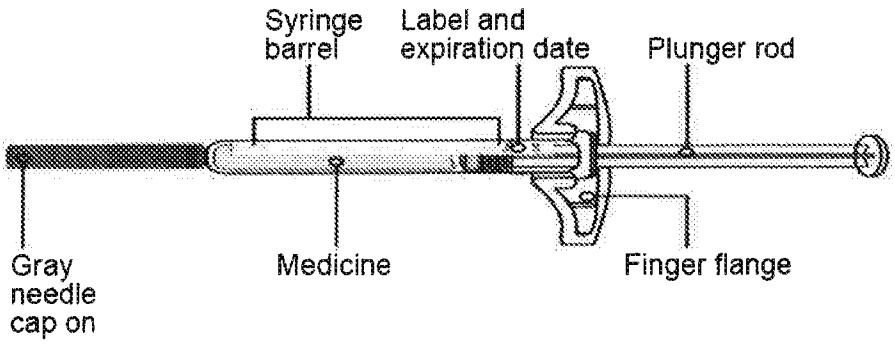
Put the original package with any unused prefilled syringes back in the refrigerator.

For safety reasons:
- **Do not** grab the plunger rod.
- **Do not** grab the gray needle cap.
- **Do not** remove the gray needle cap until you are ready to inject.

Wait about 30 minutes to let the prefilled syringe warm to room temperature before you use it.
- **Do not** put the prefilled syringe back in the refrigerator after it has reached room temperature.
- **Do not** try to warm the prefilled syringe by using a heat source such as hot water or microwave.
- **Do not** leave the prefilled syringe in direct sunlight.
- **Do not** shake the prefilled syringe.

Important: Always hold the prefilled syringe by the syringe barrel.

B Inspect the SILIQ prefilled syringe.



Make sure the medicine in the prefilled syringe is clear and colorless to slightly yellow.

- **Do not** use the syringe if:
  - The medicine is cloudy or discolored or contains flakes or particles.
  - Any part appears cracked or broken.
  - The gray needle cap is missing or not securely attached.
  - The expiration date printed on the label has passed.

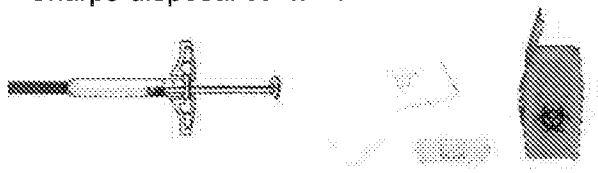
In all cases, use a new prefilled syringe, and call 1-800-321-4576.

C Gather all materials needed for your injection.

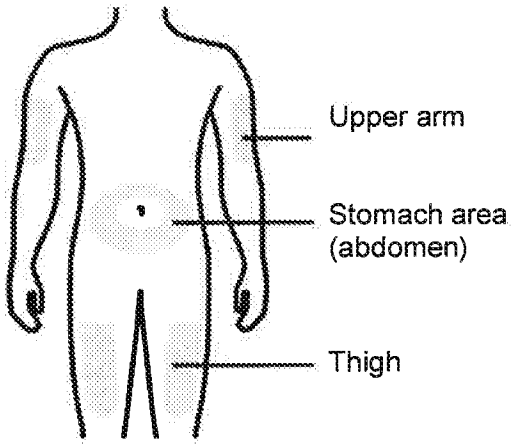
Wash your hands thoroughly with soap and water.

On a clean, well-lit work surface, place the:

- Prefilled syringe
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container



D Prepare and clean your injection site.



You can use:

- Your thigh
- Stomach area (abdomen), except for a 2-inch area right around your navel (belly button)
- Outer area of upper arm (only if someone else is giving you the injection)

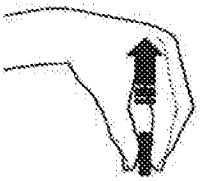
Clean your injection site with an alcohol wipe. Let your skin dry.

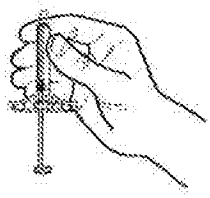
- **Do not** touch this area again before injecting.
- Choose a different site each time you give yourself an injection. If you want to use the same injection site, make sure it is not the same spot on the injection site that you used for a previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

- Avoid injecting directly into raised, thick, red, or scaly skin patch or lesion.

Step 2: Get ready

E Pull the gray needle cap straight off and away from your body when you are ready to inject.

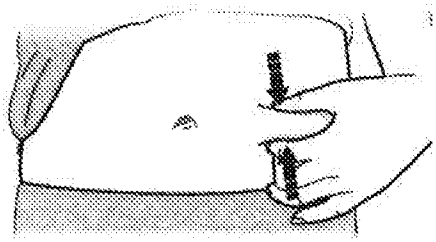




It is normal to see a drop of liquid at the end of the needle.
- **Do not** twist or bend the gray needle cap.
- **Do not** put the gray needle cap back onto the prefilled syringe.
- **Do not** remove the gray needle cap from the prefilled syringe until you are ready to inject.

Important: Throw the needle cap into the sharps disposal container provided.

F Pinch your injection site to create a firm surface.

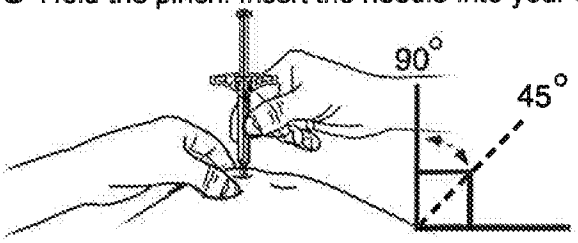


Pinch skin firmly between your thumb and fingers, creating an area about **2** inches wide.

Important: Keep skin pinched while injecting.

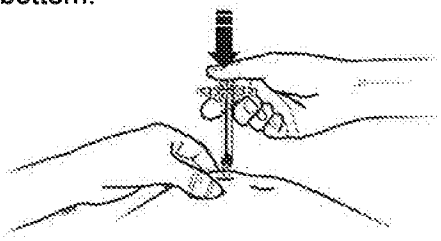
Step 3: Inject

G Hold the pinch. Insert the needle into your skin at 45 to 90 degrees.

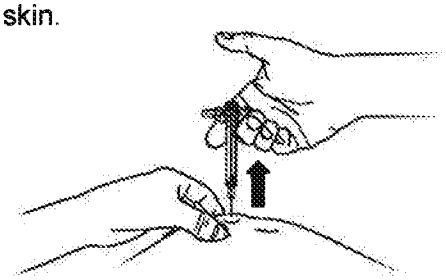


Do not place your finger on the plunger rod while inserting the needle.

H Using slow and constant pressure, push the plunger rod all the way down until it reaches the bottom.



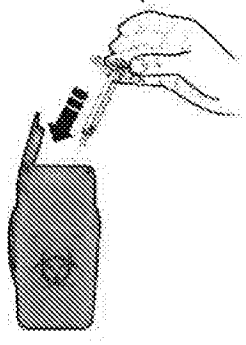
I When done, release your thumb, and gently lift the syringe and pull the needle out of your skin.



J Inspect the syringe. If there is still medicine in the syringe barrel, this means you have not received a full dose. Call your healthcare provider right away.

Step 4: Finish

K Discard (throw away) the used syringe.



- Put the used SILIQ syringe in an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the syringe in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** reuse the syringe.
- **Do not** recycle the syringe or sharps disposal container or throw them into household trash.

Important: Always keep the sharps disposal container out of the reach of children.

L Examine the injection site.
If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

Manufactured for:
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Bridgewater, NJ 08807 USA

Manufactured by:
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Grand Duchy of Luxembourg, L-1931, Luxembourg
U.S. License Number 2053

For more information, go to www.SILIQ.com or call Valeant Pharmaceuticals at 1-800-321-4576.

U.S. Patents 7,939,070; 7,786,284; 7,833,527; 7,767,206; 8,790,648; 8,545,842; 8,435,518; 9,073,999; 9,096,673

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Part number *XXXX*
Issued: February/2017

Exhibit C

(12) **United States Patent**
Tocker et al.

(10) **Patent No.: US 7,767,206 B2**
(45) **Date of Patent: *Aug. 3, 2010**

(54) **NEUTRALIZING DETERMINANTS OF IL-17 RECEPTOR A AND ANTIBODIES THAT BIND THERETO**

(75) Inventors: **Joel Tocker**, Issaquah, WA (US); **Christopher Mehlin**, Seattle, WA (US); **Ai Ching Lim**, Mercer Island, WA (US)

(73) Assignee: **Amgen Inc.**, Thousand Oaks, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 82 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/906,079**

(22) Filed: **Sep. 27, 2007**

(65) **Prior Publication Data**

US 2008/0221307 A1 Sep. 11, 2008

Related U.S. Application Data

(60) Provisional application No. 60/969,895, filed on Sep. 4, 2007, provisional application No. 60/873,072, filed on Dec. 5, 2006, provisional application No. 60/827,882, filed on Oct. 2, 2006.

(51) **Int. Cl.**
C07K 16/24 (2006.01)

(52) **U.S. Cl.** **424/133.1**; 530/387.3; 530/387.9; 530/388.22

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(Continued)

Primary Examiner—Lynn Bristol
(74) *Attorney, Agent, or Firm*—James E. Klaniecki

(57) **ABSTRACT**

The present invention relates to the identification of neutralizing determinants on IL-17 Receptor A (IL-17RA or IL-17R) and the antigen binding proteins, such as antibodies, that bind thereto and inhibit IL-17 ligand family members from binding to and activating IL-17 Receptor A or a receptor complex comprising IL-17 Receptor A.

8 Claims, 18 Drawing Sheets

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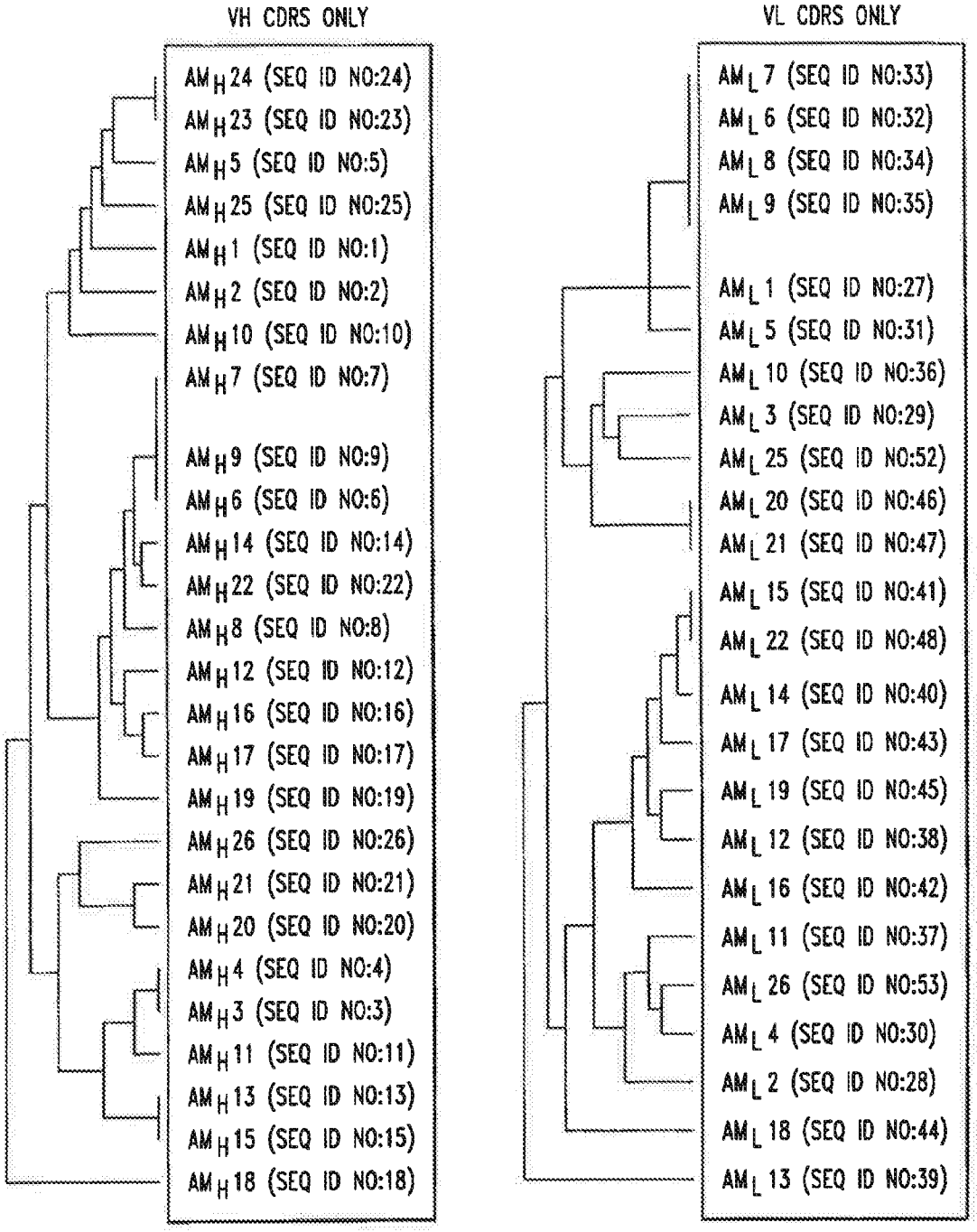

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AM L 26 (SEQ ID NO:53)
AM L 4 (SEQ ID NO:30)
AM L 2 (SEQ ID NO:28)
AM L 18 (SEQ ID NO:44)
AM L 13 (SEQ ID NO:39)

Fig. 1

V_H DOMAINS	CDR1	SYNTHETIC LINKER	CDR2	SYNTHETIC LINKER	CDR3
SEQ ID NO:24	--SYYWS	GGGAAAGGGAAA	RIY...PSG.RTN...YNPSLKS	GGGAAAGGGAAA	...E.A..Y.ELQLG...LYYYYGMDV
SEQ ID NO:23	--SYYWS	GGGAAAGGGAAA	RIY...PSG.RTN...YNPSLKS	GGGAAAGGGAAA	...E.A..Y.ELQLG...LYYYYGMDV
SEQ ID NO:5	--SYYWS	GGGAAAGGGAAA	RIY...PSG.NTI...YNPSLKS	GGGAAAGGGAAA	...E.N..YSE.SSG...LYYYYGMDV
SEQ ID NO:1	--NYYWN	GGGAAAGGGAAA	DIY...YSG.STN...YNPSLKS	GGGAAAGGGAAA	D.GELANYY...GSGSYQFYYYYGMDV
SEQ ID NO:2	--GYYWS	GGGAAAGGGAAA	EIN...HSG.RTN...YNPSLKS	GGGAAAGGGAAA	..GP...YYFD.SSG.Y.LYYYYGLDV
SEQ ID NO:25	SGGYYWS	GGGAAAGGGAAA	YIY...YSG.NTY...YNPSLRS	GGGAAAGGGAAA	EAGGNSAYY.....Y..GMDV
SEQ ID NO:10	SGGYYWS	GGGAAAGGGAAA	YIY...FSG.SAY...YNPSLKS	GGGAAAGGGAAA	E.....YY.D.SSG.....YPDAFDI
SEQ ID NO:7	--RYGIS	GGGAAAGGGAAA	..WISAYNG.NTN...YAQKLQG	GGGAAAGGGAAA	R.....DYDILT.G.....YYNGFDP
SEQ ID NO:9	--RYGIS	GGGAAAGGGAAA	..WISAYNG.NTN...YAQKLQG	GGGAAAGGGAAA	R.....DYDILT.G.....YYNGFDP
SEQ ID NO:6	--RYGIS	GGGAAAGGGAAA	..WISAYNG.NTN...YAQKLQG	GGGAAAGGGAAA	R.....DYDILT.G.....YYNGFDP
SEQ ID NO:8	--RYGIS	GGGAAAGGGAAA	..WISAYNG.NTN...YAQNLQG	GGGAAAGGGAAA	R.....DYDILT.G.....YYNGFDP
SEQ ID NO:14	--RYGIS	GGGAAAGGGAAA	..WISTYSG.NTN...YAQKLQG	GGGAAAGGGAAA	R..QLYFDY----------
SEQ ID NO:22	--RYGIS	GGGAAAGGGAAA	..WISAYSG.NTN...YAQKLQG	GGGAAAGGGAAA	R..QLYFDY----------
SEQ ID NO:16	--SYGIS	GGGAAAGGGAAA	..WISAYNG.NTK...YAQKLQG	GGGAAAGGGAAA	K..QLVFDY----------
SEQ ID NO:17	--SYGIS	GGGAAAGGGAAA	..WISAYSG.NTK...YAQKLQG	GGGAAAGGGAAA	K..QLVFDY----------
SEQ ID NO:12	--SYGIS	GGGAAAGGGAAA	..WISTYKG.NTN...YAQKLQG	GGGAAAGGGAAA	K..QLVFDY----------
SEQ ID NO:19	--SYGIS	GGGAAAGGGAAA	..WISAYSG.NTK...YAQKFQG	GGGAAAGGGAAA	R..QLALDY----------
SEQ ID NO:13	--SYGMQ	GGGAAAGGGAAA	VIW...YDG.NKK..YYADSVKG	GGGAAAGGGAAA	.....GRVR.D.....YYYGMDV
SEQ ID NO:15	--SYGMQ	GGGAAAGGGAAA	VIW...YDG.NKK..YYADSVKG	GGGAAAGGGAAA	.....GRVR.D.....YYYGMDV
SEQ ID NO:4	--SYGMH	GGGAAAGGGAAA	VIW...YDGSN.K..HYADSVKG	GGGAAAGGGAAA	...D.T...G.V.....Y------
SEQ ID NO:3	--SYGMH	GGGAAAGGGAAA	VIW...YDGSN.K..HYADSVKG	GGGAAAGGGAAA	...D.T...G.V.....Y------
SEQ ID NO:11	--SYGMH	GGGAAAGGGAAA	VIW...YDGSN.K..YYADSVKG	GGGAAAGGGAAA	...D.T...K.D.....Y------
SEQ ID NO:21	--SYSMN	GGGAAAGGGAAA	II.....SSRS.SIIHYADSVKG	GGGAAAGGGAAA	...PKV...G..G.....GMDV
SEQ ID NO:20	--SYSMN	GGGAAAGGGAAA	FI.....SARS.STIYYADSVKG	GGGAAAGGGAAA	...PKV...G..G.....GMDV
SEQ ID NO:26	--DYYMS	GGGAAAGGGAAA	YI.....SS.SGSTIYYADSVKG	GGGAAAGGGAAA	...DRTYYFGS.G.S.....Y.EGMDV
SEQ ID NO:18	--DYYMH	GGGAAAGGGAAA	..WMHPNSGG.TDL...AQRFQG	GGGAAAGGGAAA	.CG.....Y..CST.LSCSFYFY.FDL

Fig. 2

V_L DOMAINS	CDR1	SYNTHETIC LINKER	CDR2	SYNTHETIC LINKER	CDR3
SEQ ID NO:33	RASQGIR.N....D.LG	GGGAAAGGGAAA	AASSLQS	GGGAAAGGGAAA	LQH.KSY...PL.T
SEQ ID NO:32	RASQGIR.N....D.LG	GGGAAAGGGAAA	AASSLQS	GGGAAAGGGAAA	LQH.KSY...PL.T
SEQ ID NO:34	RASQGIR.N....D.LG	GGGAAAGGGAAA	AASSLQS	GGGAAAGGGAAA	LQH.KSY...PL.T
SEQ ID NO:35	RASQGIR.N....D.LG	GGGAAAGGGAAA	AASSLQS	GGGAAAGGGAAA	LQH.KSY...PL.T
SEQ ID NO:31	RASQGIR.N....D.LG	GGGAAAGGGAAA	AASSFQS	GGGAAAGGGAAA	LQH.NSY...PP.T
SEQ ID NO:27	RASQGIR.N....D.LG	GGGAAAGGGAAA	AASSLQS	GGGAAAGGGAAA	LQH.NSN...PF.T
SEQ ID NO:49	RASQGII.N....D.LG	GGGAAAGGGAAA	AASSLQS	GGGAAAGGGAAA	LQH.NSY...PP.T
SEQ ID NO:36	RASQGIR.S.....WLA	GGGAAAGGGAAA	AASSLQS	GGGAAAGGGAAA	.Q..Q.ANNFPR.T
SEQ ID NO:52	RASQAI..S....IYLA	GGGAAAGGGAAA	AASSLQS	GGGAAAGGGAAA	.Q..Q.YSSYPR.T
SEQ ID NO:46	RASQGI..S....NYLA	GGGAAAGGGAAA	AASTLQS	GGGAAAGGGAAA	.Q..K.YNRAPF.T
SEQ ID NO:47	RASQGI..S....NYLA	GGGAAAGGGAAA	AASTLQS	GGGAAAGGGAAA	.Q..K.YNRAPF.T
SEQ ID NO:29	RASQSI..S....SYLN	GGGAAAGGGAAA	AASSLQS	GGGAAAGGGAAA	.Q..QSYS.TPF.T
SEQ ID NO:53	RASQSV.YS....N.LA	GGGAAAGGGAAA	GASTRAT	GGGAAAGGGAAA	.Q..Q.YYNWP.WT
SEQ ID NO:30	RASQSV..SR...N.LA	GGGAAAGGGAAA	GASTRAT	GGGAAAGGGAAA	.Q..Q.YNNWPTWT
SEQ ID NO:37	RASQSV..SS...N.LA	GGGAAAGGGAAA	GASTRAA	GGGAAAGGGAAA	.Q..H.YINWPKWT
SEQ ID NO:41	RASQSV..SS...N.LA	GGGAAAGGGAAA	DASTRAA	GGGAAAGGGAAA	.Q..Q.YDNWPL.T
SEQ ID NO:48	RASQSV..SS...N.LA	GGGAAAGGGAAA	DASTRAA	GGGAAAGGGAAA	.Q..Q.YDNWPL.T
SEQ ID NO:40	RASQSV..SS...N.LA	GGGAAAGGGAAA	DASTRAT	GGGAAAGGGAAA	.Q..Q.YDNWPL.T
SEQ ID NO:43	RASQSV..SS...N.LA	GGGAAAGGGAAA	GASTRAT	GGGAAAGGGAAA	.Q..Q.YDNWPL.T
SEQ ID NO:38	RASQSI..SS...S.LA	GGGAAAGGGAAA	GASTRAT	GGGAAAGGGAAA	.Q..Q.YDNWPL.T
SEQ ID NO:45	RASQSI..SS...N.LA	GGGAAAGGGAAA	GASTRAT	GGGAAAGGGAAA	.Q..Q.YDTWPL.T
SEQ ID NO:42	RASQSI..ST...S.LA	GGGAAAGGGAAA	GTSTRAT	GGGAAAGGGAAA	.Q..Q.YDIWPL.T
SEQ ID NO:28	RASQSV..SR...N.LV	GGGAAAGGGAAA	GASTRAN	GGGAAAGGGAAA	.Q..Q.YKSW..RT
SEQ ID NO:44	KTSQSVLYSSKNKNFLA	GGGAAAGGGAAA	WASTRES	GGGAAAGGGAAA	.Q..Q.YYSTP.FT
SEQ ID NO:39	KSSQSLLHS.DGKTYLY	GGGAAAGGGAAA	EVSTRFS	GGGAAAGGGAAA	MQSIQL....PL.T
SEQ ID NO:50	RSSQSLVYS.DGHTCLN	GGGAAAGGGAAA	KVSNWDS	GGGAAAGGGAAA	MQ....GTHWPLCS
SEQ ID NO:51	RSSQSLVYS.DGHTCLN	GGGAAAGGGAAA	KVSNWDS	GGGAAAGGGAAA	MQ....GTHWPLCS

Fig. 3

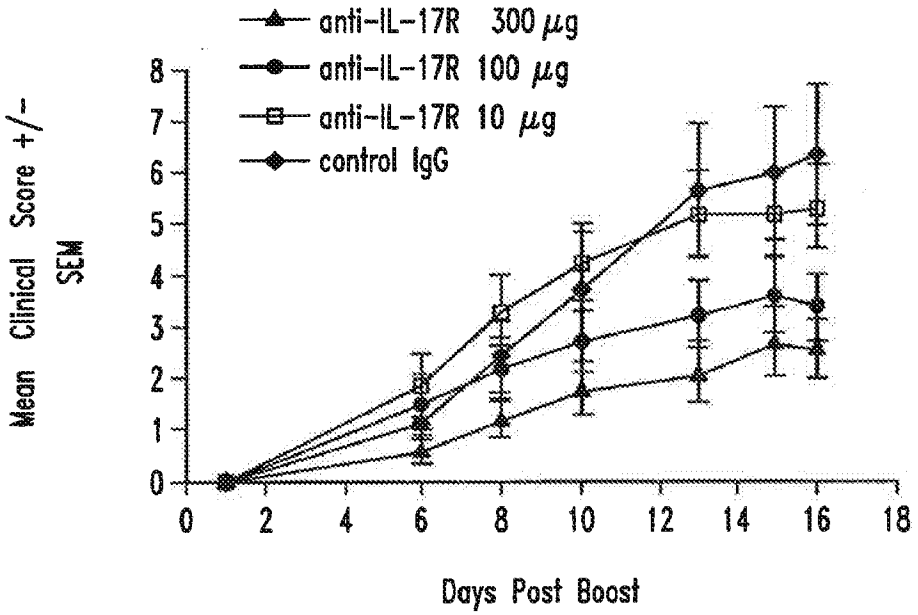

anti-IL-17R 300 μg
anti-IL-17R 100 μg
anti-IL-17R 10 μg
control IgG
Mean Clinical Score +/- SEM
0
1
2
3
4
5
6
7
8
0
2
4
6
8
10
12
14
16
18
Days Post Boost

Fig. 4

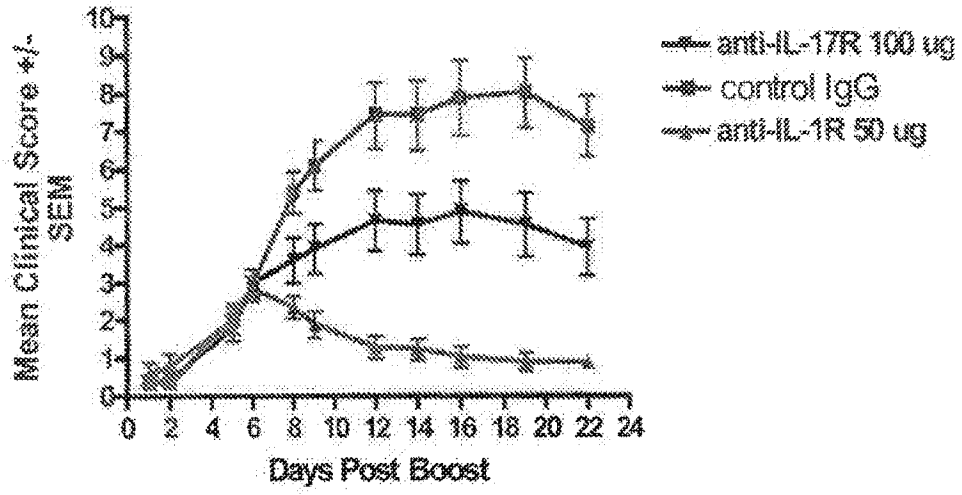

Mean Clinical Score +/- SEM
0
1
2
3
4
5
6
7
8
9
10
0 2 4 6 8 10 12 14 16 18 20 22 24
Days Post Boost
anti-IL-17R 100 ug
control IgG
anti-IL-1R 50 ug

FIG. 5

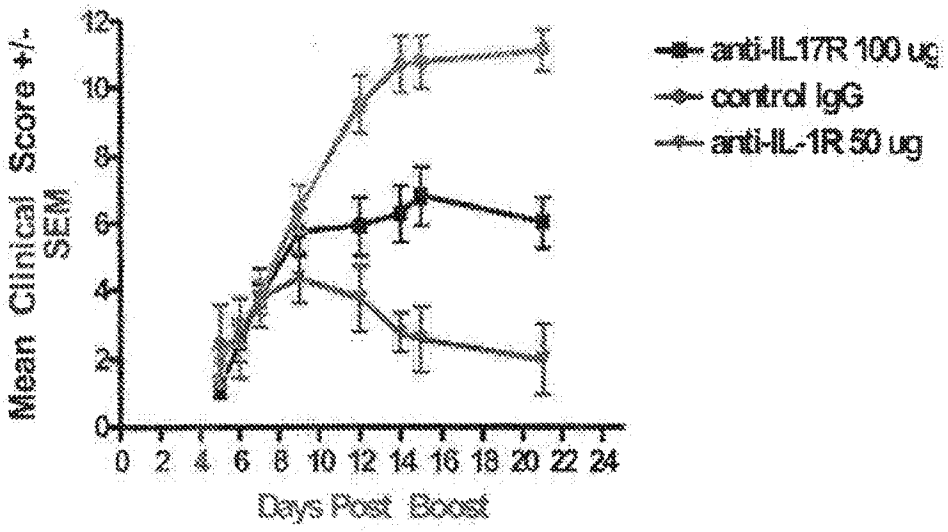

Mean Clinical Score +/- SEM
0
2
4
6
8
10
12
0 2 4 6 8 10 12 14 16 18 20 22 24
Days Post Boost
anti-IL17R 100 ug
control IgG
anti-IL-1R 50 ug

FIG. 6

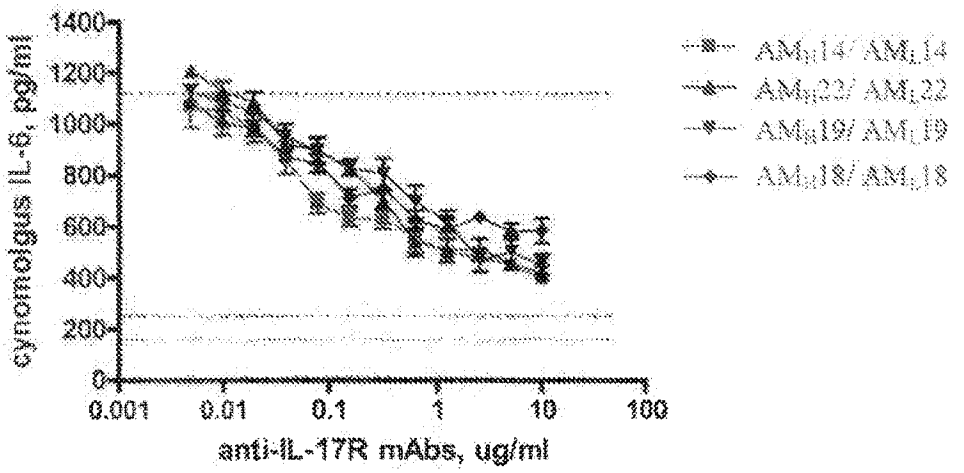

1400
1200
1000
800
600
400
200
0
cynomolgus IL-6, pg/ml
0.001
0.01
0.1
1
10
100
anti-IL-17R mAbs, ug/ml
AM0.14/ AM1.14
AM0.22/ AM1.22
AM0.19/ AM1.19
AM0.18/ AM1.18

FIG. 7

	Bead Region	33	34	35	36	37	38	42	43	72
BIN	mAb	A	B	P	C	D	E	H	F	huIgG
1	A	-220	1199	6592	330	337	300	8643	345	84
1	B	-326	453	5020	150	213	182	6786	173	37
1	C	-178	816	5963	260	264	163	2948	239	54
1	D	-233	684	5645	217	207	192	3181	269	123
1	E	-70.5	447	3527	173	168	130	2536	152	26
1	F	114	545	1716	253	179	175	3971	187	140
1	G	-162	1305	4487	354	344	260	3995	304	-5
2	H	7507	1643	3421	2495	790	573	-140	2805	74
3	I	3482	853	2627	4910	1636	1360	211	2133	22
3	J	1812	420	2258	2775	875	807	-109	1810	35
3	K	3125	834	2605	4553	1622	1412	216	2124	100
3	L	2356	571	2093	3517	1084	890	64	1589	34
3	M	1936	455	1897	3040	888	765	73	1410	32
3	N	2473	597	2468	3975	1202	999	68	1917	56
3	O	2998	630	2536	4511	1368	1256	120	2223	95
4	P	12079	3005	474	10707	3369	3424	6069	2543	73
5	Q	9527	1897	2157	4766	1383	1174	10203	2201	28
6	R	6796	1065	1411	2994	783	666	8296	1242	50
	huIgG	-194	-6	216	118	46	45	-34	25.5	65

Fig. 8A

	Bead Region	45	46	47	51	52	53	55	56	61	62	72
BIN	mAb	R	I	J	K	Q	L	G	M	N	O	huIgG
1	A	7064	5302	2323	7206	9649	3017	454	1859	2646	3800	84
1	B	5885	3710	1395	4970	8280	1980	235	1303	1948	2638	37
1	C	3954	6723	3591	8223	5497	3540	346	2882	3632	5517	54
1	D	3552	6652	3644	8684	4686	4257	318	2975	3843	5545	123
1	E	1655	4333	2420	5605	2394	2661	334	1766	2409	3313	26
1	F	1120	3107	2123	4107	1650	1724	342	1021	1511	2626	140
1	G	5109	6887	2901	8972	7846	3591	480	2377	3231	5377	-5
2	H	7525	-5	-51	-111	9606	-41	3208	-75	24	5.5	74
3	I	48	33	2	-182	57	-26	4909	13	56	16	22
3	J	53.5	-5	72	-100	86	-11	1915	10	38	75	35
3	K	114	1	-3	-196	90	-76	4492	85	66	28	100
3	L	52	63	61	-25	105	39	3714	44	41	72	34
3	M	40	26	31	-5	60	18	3275	20	11	49	32
3	N	76	18	8	-44	98	-1	4258	40	43	55	56
3	O	76	10	59	-111	135	18	4492	73	83	139	95
4	P	2553	5003	4475	6271	3718	2521	6001	1645	2359	3788	73
5	Q	34	2.5	23	-181	100	-58	6276	44.5	39	175	28
6	R	25	58	26	-29	60	15	4016	24	24	140	50
	huIgG	31	-72	42	-235	64	-36	216	27	3	20	65

Fig. 8B

MAIRRCWPRVVPGPALGWLLLLLNVLAPGRASPRLLDFPAPVCAQEGLSCR
VK Domain A

NSTCLDDSWIHPKNLTPSSPKNIYINLSVSSTQHGELVPVLHVEWTLQTDASI
LY Domain B

LEGAELSVLQLNTNERLCVKFQFLSMLQHHRKRWRFSFSHFVVDPGQEYE
Domain C

VTVHHLPKPIPDGDPNHKSKIIFVPDCEDSKMKMTTSCVSSGSLWDPNITV
Domain D

ETLDTQHLRVDFTLWNESTPYQVLLESFSDSENHSCFDVVKQIFAPRQEEF
HQ Domain E Domain F

RANVTFTLSKFHWCCHHHVQVQPFFSSCLNDCLRHAVTVPCPVISNTTVP
KPVADYIPLW

SEQ ID NO:432

Fig. 9

FIG. 10A

```
                          101                                                 150
Construct A  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
Construct B  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
Construct C  (101)  QTDASILYLEGAELSVLQLNTNERLCVKFQFLSMLQNHRRKWRFSFSHFV
Construct D  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
Construct E  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
construct F  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
Construct G  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
Construct H  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
Construct I  (101)  QTDASILYLEGAELSVLQLNTNERLCVKFQFLSMLQNHRRKWRFSFSHFV
Construct J  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
construct M  (101)  QTDASILYLEGAELSVLQLNTNERLCVKFQFLSMLQNHRRKWRFSFSHFV
Construct N  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
Construct K  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
construct L  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
 huIL17RFpH  (101)  QTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRNHHRRWRFTFSHFV
   muIL-17R  (101)  QTDASILYLEGAELSVLQLNTNERLCVKFQFLSMLQNHRRKWRFSFSHFV
                          151                                                 200
Construct A  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
Construct B  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
Construct C  (151)  VDPGQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
Construct D  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHKSKIIFVPDCEDSKMKVTTSCVSSG
Construct E  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
construct F  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
Construct G  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
Construct H  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
Construct I  (151)  VDPGQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
Construct J  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHKSKIIFVPDCEDSKMKVTTSCVSSG
construct M  (151)  VDPGQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
Construct N  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHKSKIIFVPDCEDSKMKVTTSCVSSG
Construct K  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
construct L  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
 huIL17RFpH  (151)  VDPDQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSG
   muIL-17R  (151)  VDPGQEYEVTVHHLPKPIPDGDPNHKSKIIFVPDCEDSKMKVTTSCVSSG
```

FIG. 10B

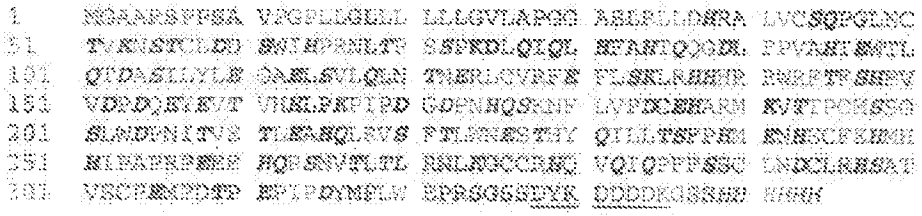
FIG. 10C

```
                    301                                                 349
Construct A  (301) VSCPEMPDT--PEPIPDYMPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
Construct B  (301) VSCPEMPDT--PEPIPDYMPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
Construct C  (301) VSCPEMPDT--PEPIPDYMPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
Construct D  (301) VSCPEMPDT--PEPIPDYMPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
Construct E  (301) VSCPEMPDT--PEPIPDYMPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
construct F  (301) VPCPVISNTTVPEPVADYIPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
Construct G  (301) VSCPEMPDT--PEPIPDYMPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
Construct H  (301) VSCPEMPDT--PEPIPDYMPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
Construct I  (301) VSCPEMPDT--PEPIPDYMPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
Construct J  (301) VSCPEMPDT--PEPIPDYMPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
construct K  (301) VPCPVISNTTVPEPVADYIPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
Construct M  (301) VPCPVISNTTVPEPVADYIPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
Construct K  (301) VPCPVISNTTVPEPVADYIPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
construct L  (301) VPCPVISNTTVPEPVADYIPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
huIL17RFpM   (301) VSCPEMPDT--PEPIPDYMPLWEPRSGSSDYKDDDDKGSSHHHHHH~~~~
  muIL-17R   (301) VPCPVISNTTVPEPVADYIPLW~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

FIG. 10D

		Zal 38-51 chimera A	75-96	128-134	176-197	213-220	225-319	A+E	B+E	C+E	D+E	A+F	B+F	C+F	D+F
			B	C	D	E	F	G	H	I	J	K	L	M	N
BIN 1	AM_{19}/AM_{19}	0.063	0.063	0.052	0.068	0.067	3108.0	0.052	0.069	0.059	0.084	21.310	0.092	1.551	n.d.
BIN 2	AM_{19}/AM_{1}	0.238	0.00	0.049	0.00	0.172	0.158	0.210	0.0358	0.034	139.30	0.235	277.200	0.078	n.d.
BIN 3	AM_{19}/AM_{22}	0.042	0.064	0.160	0.00	0.057	0.041	0.038	0.043	0.0358	150.50	0.033	0.056	0.135	n.d.
	AM_{19}/AM_{14}	0.022	0.038	0.081	14.600	0.048	0.021	0.023	0.060	0.027	1.681	0.017	0.045	0.047	n.d.
	AM_{19}/AM_{19}	0.060	0.112	0.032	31.020	0.078	0.068	0.076	0.130	0.131	149.40	0.043	0.100	0.092	n.d.
	AM_{19}/AM_{23}	0.072	0.2884	3.959	2.169	0.076	0.046	0.083	2.269	2.680	218.50	0.061	0.169	0.769	n.d.
BIN 4	AM_{19}/AM_{26}	0.265	0.201	0.156	0.145	0.323	0.80	0.283	0.419	0.289	0.284	0.00	0.0006	0.80	n.d.
BIN 5	AM_{19}/AM_{21}	0.018	0.017	0.038	0.134	0.026	0.026	0.025	0.025	0.032	0.008	0.017	0.025	0.035	0.378
BIN 6	AM_{19}/AM_{20}	0.023	0.020	0.046	2.675	0.022	0.029	0.027	0.033	0.042	0.887	0.022	0.037	0.049	182.400

FIG. 11



SEQ ID NO:431

FIG. 12

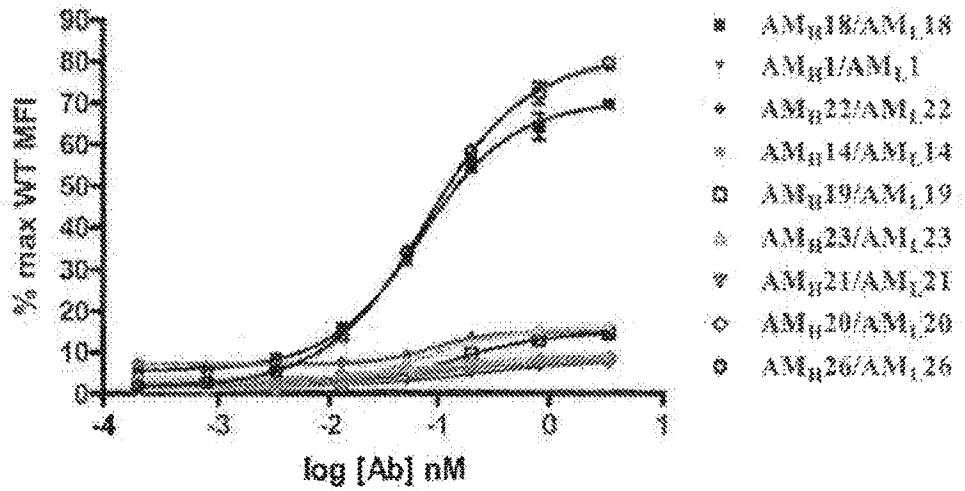

% max WT MFI
90
80
70
60
50
40
30
20
10
0
-4
-3
-2
-1
0
1
log [Ab] nM
AMH18/AML18
AMH1/AML1
AMH22/AML22
AMH14/AML14
AMH19/AML19
AMH23/AML23
AMH21/AML21
AMH20/AML20
AMH26/AML26

FIG. 13

		chimera	arginine mutants
BIN 1	$AM_{0.18}/AM_{.18}$	F: 229-319	S220R, E226R, T228R, S236R, L270R, Q284R
BIN 2	$AM_{0.1}/AM_{.1}$	B: 76-96 D: 176-197	D152R
BIN 3	$AM_{0.22}/AM_{.22}$	C: 128-154 D: 176-197	D152R, D154R, E156R, D184R, E186R, S198R
	$AM_{0.14}/AM_{.14}$	D: 176-197	D152R, D154R, E156R, D184R, E186R, H297R
	$AM_{0.19}/AM_{.19}$	D: 176-197	D152R, D154R, E156R, D184R, E186R
	$AM_{0.23}/AM_{.23}$	B: 75-96 C: 128-154 D: 176-197	E97R, D152R, D154R, E156R, Q176R, D184R, E186R, S198R, T235R, H297R
BIN 4	$AM_{0.26}/AM_{.26}$	F: 229-319	H138R, K166R, H216R, S220R, E226R, T228R, S236R, E241R, H243R, L270R
BIN 5	$AM_{0.21}/AM_{.21}$	D: 176-197	E113R, S116R, D152R, D154R, E156R, S177R, S198R
BIN 6	$AM_{0.20}/AM_{.20}$	D: 176-197	D152R, D154R, E156R, S177R, L270R

FIG. 14

NEUTRALIZING DETERMINANTS OF IL-17 RECEPTOR A AND ANTIBODIES THAT BIND THERETO

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119 of U.S. Provisional Application Ser. No. 60/969,895, filed Sep. 4, 2007, U.S. Provisional Application Ser. No. 60/873,072, filed Dec. 5, 2006 and U.S. Provisional Application Ser. No. 60/827,882, filed Oct. 2, 2006, which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to the identification of neutralizing determinants on IL-17 Receptor A (IL-17RA or IL-17R) and antibodies that bind thereto. Aspects of the invention also include antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein.

BACKGROUND

IL-17A and IL-17F bind and activate IL-17RA. IL-17RA has been shown to be important in regulating immune responses. Activation of the IL-17RA leads to production of cytokines, chemokines, growth factors, and other proteins that contribute to the symptoms and/or pathology of numerous diseases. IL-17A is an inflammatory cytokine that induces the production of cytokines and other mediators leading to diseases and physiological effects such as inflammation, cartilage degradation, and bone resorption. IL-17A also plays a role in a number of inflammatory conditions including arthritis (rheumatoid arthritis), psoriasis, inflammatory bowel disease, multiple sclerosis, and asthma. (Li et al., 2004, *Huazhong Univ. Sci. Technolog. Med. Sci.* 24:294-296; Fujino et al., 2003, *Gut.* 52:65-70; Kauffman et al., 2004, *J. Invest. Dermatol.* 123:1037-1044; Mannon et al., 2004, *N. Engl. J Med.* 351:2069-2079; Matusevicius et al., 1999, *Mult Scler* 5, 101-104; Linden et al., *Eur Respir J.* 2000 May; 15(5):973-7; Molet et al., 2001, *J. Allergy Clin. Immunol.* 108:430-438). Recent studies have suggested that IL-17F plays a role in the induction of inflammatory responses (Oda et al., 2006, *American J. Resp. Crit. Care Medicine*, Jan. 15, 2006; Numasaki et al., 2004, *Immunol Lett.* 95:97-104).

Aspects of the invention provide for the identification of neutralizing determinants on IL-17RA that neutralizing antibodies bind and thereby inhibit IL-17 ligand family members from binding to and activating IL-17 Receptor A or a receptor complex comprising IL-17 Receptor A. Aspects of the invention also include antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a phylogenetic dentogram analysis of the CDRs (complementarity determining regions) of the variable heavy (V_H) and variable light (V_L) domains of various IL-17R antigen binding proteins (antibodies).

FIG. **2** depicts an alignment of the amino acid sequences of the CDRs of the variable heavy (V_H) domains of various IL-17R antigen binding proteins (antibodies). The CDR1, CDR2, and CDR3 regions are highlighted.

FIG. **3** depicts an alignment of the amino acid sequences of the CDRs of the variable light (V_L) domains of various IL-17R antigen binding proteins (antibodies). The CDR1, CDR2, and CDR3 regions are highlighted.

FIG. **4** shows dose-dependent inhibition by an IL-17RA mAb in a wild-type (WT) collagen-induced arthritis (CIA) model. A $P<0.05$ was seen when comparing IL-17RA mAb at 100 μg and 300 μg treatment groups versus control treatment group (days 13, 15 and 16).

FIG. **5** shows the results of therapeutic treatment with IL-17RA mAb. The data shows stabilized mean clinical scores in wild-type mice in a standard CIA model of arthritis. These data demonstrate that IL-17RA inhibition by an IL-17RA antigen binding protein may be therapeutically useful in treating rheumatoid arthritis (RA), especially in the preservation of joint bone and cartilage.

FIG. **6** shows that therapeutic treatment with IL-17RA mAb stabilized mean clinical scores in TNFR p55/p75 knockout mice in a standard CIA model of arthritis. These data show that IL-17RA inhibition by an IL-17RA antigen binding protein may be therapeutically useful in treating RA, especially in the preservation of joint bone and cartilage. Notably, IL-17RA inhibition was able to stabilize disease in a model independent of TNF signaling.

FIG. **7** shows exemplary IL-17RA human mAbs (AM_H14/AM_L14, AM_H22/AM_L22, AM_H19/AM_L19, and AM_H18/AM_L18) were able to inhibit cynomolgus IL-17-induced IL-6 production from JTC-12 cells (cynomolgus kidney cell line). The (----) line depicts the positive control value of cynomolgus IL-17 in combination with TNF-alpha. The (-.-.-) line depicts the positive control value of cynomolgus TNF-alpha. The (...) line depicts the media control value.

FIGS. **8**A and **8**B show the results of multiplexed binning of IL-17RA antibodies. Shaded values indicate antibody pairs that can bind to IL-17RA simultaneously, suggesting that these antibodies bind to different neutralizing determinants. Boxed values indicate antibodies paired against themselves.

FIG. **9** shows mouse IL-17RA (SEQ ID NO:432) and the 5 domains, A, B, C, D, E, and F that replaced the counterpart domains in the human IL-17RA sequence.

FIGS. **10**A-**10**D shows the amino acid sequences for human and mouse IL-17RA and human/mouse chimeric IL-17RA proteins.

FIG. **11** is a table summarizing the IL-17RA mAbs capacity to bind the various chimeric proteins. Shaded values denote where the IL-17RA mAbs lost binding to that particular chimera (n.d. means not determined).

FIG. **12** depicts the amino acid residues that were replaced with an arginine residue in SEQ ID NO:431.

FIG. **13** illustrates titration curves of various IL-17RA mAbs binding to the D152R IL-17RA mutant.

FIG. **14** is a summary of the arginine scan, binning, and chimera data for various IL-17RA mAbs.

DETAILED DESCRIPTION OF THE INVENTION

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, tissue culture and transformation, protein purification etc. Enzymatic reactions and purification techniques may be performed according to the manufacturer's specifications or as commonly accomplished in the art or as described herein. The following procedures and techniques may be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the specification. See, e.g., Sambrook et al., 2001,

Molecular Cloning. A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., which is incorporated herein by reference for any purpose. Unless specific definitions are provided, the nomenclature used in connection with, and the laboratory procedures and techniques of, analytical chemistry, organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical synthesis, chemical analyses, pharmaceutical preparation, formulation, and delivery and treatment of patients.

Aspects of the invention include, but are not limited to: Embodiment one: An isolated monoclonal antibody, or IL-17RA-binding fragment thereof, that specifically binds to IL-17RA and competes for binding with an antibody selected from the group consisting of:

A. an isolated antibody, or IL-17RA-binding fragment thereof, comprising
   a. a light chain variable domain sequence that is at least 80% identical to a light chain variable domain sequence of AM_L2, 3, 5, 9, 10, 12, 14-17, and 19-25 (SEQ ID NOs:28, 29, 31, 35, 36, 38, 40-43, and 45-53, respectively);
   b. a heavy chain variable domain sequence that is at least 80% identical to a heavy chain variable domain sequence of AM_H2, 3, 5, 9, 10, 12, 14-17, and 19-25 (SEQ ID NOs:2, 3, 5, 9, 10, 12, 14-17, and 19-25, respectively);
   c. the light chain variable domain of (a) and the heavy chain variable domain of (b); wherein said antibody specifically binds to human IL-17RA;

B. an isolated antibody, or IL-17RA-binding fragment thereof, comprising
   a. a light chain CDR1 (SEQ ID NO:188), CDR2 (SEQ ID NO:189), CDR3 (SEQ ID NO:190) and a heavy chain CDR1 (SEQ ID NO:110), CDR2 (SEQ ID NO:111), CDR3 (SEQ ID NO:112) of antibody AM-2;
   b. a light chain CDR1 (SEQ ID NO:191), CDR2 (SEQ ID NO:192), CDR3 (SEQ ID NO:193) and a heavy chain CDR1 (SEQ ID NO:113), CDR2 (SEQ ID NO:114), CDR3 (SEQ ID NO:115) of antibody AM-3;
   c. a light chain CDR1 (SEQ ID NO:197), CDR2 (SEQ ID NO:198), CDR3 (SEQ ID NO:199) and a heavy chain CDR1 (SEQ ID NO:119), CDR2 (SEQ ID NO:120), CDR3 (SEQ ID NO:121) of antibody AM-5;
   d. a light chain CDR1 (SEQ ID NO:209), CDR2 (SEQ ID NO:210), CDR3 (SEQ ID NO:211) and a heavy chain CDR1 (SEQ ID NO:131), CDR2 (SEQ ID NO:132), CDR3 (SEQ ID NO:133) of antibody AM-9;
   e. a light chain CDR1 (SEQ ID NO:212), CDR2 (SEQ ID NO:213), CDR3 (SEQ ID NO:214) and a heavy chain CDR1 (SEQ ID NO:134), CDR2 (SEQ ID NO:135), CDR3 (SEQ ID NO:136) of antibody AM-10;
   f. a light chain CDR1 (SEQ ID NO:218), CDR2 (SEQ ID NO:219), CDR3 (SEQ ID NO:220) and a heavy chain CDR1 (SEQ ID NO:140), CDR2 (SEQ ID NO:141), CDR3 (SEQ ID NO:142) of antibody AM-12;
   g. a light chain CDR1 (SEQ ID NO:224), CDR2 (SEQ ID NO:225), CDR3 (SEQ ID NO:226) and a heavy chain CDR1 (SEQ ID NO:146), CDR2 (SEQ ID NO:147), CDR3 (SEQ ID NO:148) of antibody AM-14;
   h. a light chain CDR1 (SEQ ID NO:227), CDR2 (SEQ ID NO:228), CDR3 (SEQ ID NO:229) and a heavy chain CDR1 (SEQ ID NO:149), CDR2 (SEQ ID NO:150), CDR3 (SEQ ID NO:151) of antibody AM-15;
   i. a light chain CDR1 (SEQ ID NO:230), CDR2 (SEQ ID NO:231), CDR3 (SEQ ID NO:232) and a heavy chain CDR1 (SEQ ID NO:152), CDR2 (SEQ ID NO:153), CDR3 (SEQ ID NO:154) of antibody AM-16;
   j. a light chain CDR1 (SEQ ID NO:233), CDR2 (SEQ ID NO:234), CDR3 (SEQ ID NO:235) and a heavy chain CDR1 (SEQ ID NO:155), CDR2 (SEQ ID NO:156), CDR3 (SEQ ID NO:157) of antibody AM-17;
   k. a light chain CDR1 (SEQ ID NO:239), CDR2 (SEQ ID NO:240), CDR3 (SEQ ID NO:241) and a heavy chain CDR1 (SEQ ID NO:161), CDR2 (SEQ ID NO:162), CDR3 (SEQ ID NO:163) of antibody AM-19;
   l. a light chain CDR1 (SEQ ID NO:242), CDR2 (SEQ ID NO:243), CDR3 (SEQ ID NO:244) and a heavy chain CDR1 (SEQ ID NO:164), CDR2 (SEQ ID NO:165), CDR3 (SEQ ID NO:166) of antibody AM-20;
   m. a light chain CDR1 (SEQ ID NO:245), CDR2 (SEQ ID NO:246), CDR3 (SEQ ID NO:247) and a heavy chain CDR1 (SEQ ID NO:167), CDR2 (SEQ ID NO:168), CDR3 (SEQ ID NO: 169) of antibody AM-21;
   n. a light chain CDR1 (SEQ ID NO:248), CDR2 (SEQ ID NO:249), CDR3 (SEQ ID NO:250) and a heavy chain CDR1 (SEQ ID NO:170), CDR2 (SEQ ID NO:171), CDR3 (SEQ ID NO:172) of antibody AM-22;
   o. a light chain CDR1 (SEQ ID NO:251), CDR2 (SEQ ID NO:252), CDR3 (SEQ ID NO:253) and a heavy chain CDR1 (SEQ ID NO:173), CDR2 (SEQ ID NO:174), CDR3 (SEQ ID NO:175) of antibody AM-23;
   p. a light chain CDR1 (SEQ ID NO:254), CDR2 (SEQ ID NO:255), CDR3 (SEQ ID NO:256) and a heavy chain CDR1 (SEQ ID NO:173), CDR2 (SEQ ID NO:174), CDR3 (SEQ ID NO:175) of antibody AM-23;
   q. a light chain CDR1 (SEQ ID NO:257), CDR2 (SEQ ID NO:258), CDR3 (SEQ ID NO:259) and a heavy chain CDR1 (SEQ ID NO:176), CDR2 (SEQ ID NO:177), CDR3 (SEQ ID NO:178) of antibody AM-24;
   r. a light chain CDR1 (SEQ ID NO:260), CDR2 (SEQ ID NO:261), CDR3 (SEQ ID NO:262) and a heavy chain CDR1 (SEQ ID NO:179), CDR2 (SEQ ID NO:180), CDR3 (SEQ ID NO:181) of antibody AM-25;

   wherein said antibody specifically binds to human IL-17RA; and

C. an isolated antibody, or IL-17RA-binding fragment thereof, comprising
   a. a light chain variable domain and a heavy chain variable domain of AM_L2/AM_H2 (SEQ ID NO:28/SEQ ID NO:2);
   b. a light chain variable domain and a heavy chain variable domain of AM_L3/AM_H3 (SEQ ID NO:29/SEQ ID NO:3);
   c. a light chain variable domain and a heavy chain variable domain of AM_L5/AM_H5 (SEQ ID NO:31/SEQ ID NO:5);
   d. a light chain variable domain and a heavy chain variable domain of AM_L9/AM_H9 (SEQ ID NO:35/SEQ ID NO:9);

e. a light chain variable domain and a heavy chain variable domain of AM_L10/AM_H10 (SEQ ID NO:36/SEQ ID NO:10);

f. a light chain variable domain and a heavy chain variable domain of AM_L12/AM_H12 (SEQ ID NO:38/SEQ ID NO:12);

g. a light chain variable domain and a heavy chain variable domain of AM_L14/AM_H14 (SEQ ID NO:40/SEQ ID NO:14);

h. a light chain variable domain and a heavy chain variable domain of AM_L15/AM_H15 (SEQ ID NO:41/SEQ ID NO:15);

i. a light chain variable domain and a heavy chain variable domain of AM_L16/AM_H16 (SEQ ID NO:42/SEQ ID NO:16);

j. a light chain variable domain and a heavy chain variable domain of AM_L17/AM_H17 (SEQ ID NO:43/SEQ ID NO:17);

k. a light chain variable domain and a heavy chain variable domain of AM_L19/AM_H19 (SEQ ID NO:45/SEQ ID NO:19);

l. a light chain variable domain and a heavy chain variable domain of AM_L20/AM_H20 (SEQ ID NO:46/SEQ ID NO:20);

m. a light chain variable domain and a heavy chain variable domain of AM_L21/AM_H21 (SEQ ID NO:47/SEQ ID NO:21);

n. a light chain variable domain and a heavy chain variable domain of AM_L22/AM_H22 (SEQ ID NO:48/SEQ ID NO:22);

o. a light chain variable domain and a heavy chain variable domain of AM_L23/AM_H23 (SEQ ID NO:49 or SEQ ID NO:50/SEQ ID NO:23);

p. a light chain variable domain and a heavy chain variable domain of AM_L24/AM_H24 (SEQ ID NO:51/SEQ ID NO:24);

q. a light chain variable domain and a heavy chain variable domain of AM_L25/AM_H25 (SEQ ID NO:52/SEQ ID NO:25);

wherein said antibody specifically binds to human IL-17RA.

Embodiment two: the antibody of embodiment 1, wherein said antibody is selected from the group consisting of:

A. an isolated antibody, or IL-17RA-binding fragment thereof, comprising

a. a light chain variable domain sequence that is at least 80% identical to a light chain variable domain sequence of AM_L9, 14, 16, 17, 19-23v2, and 26 (SEQ ID NOs:35, 40, 42, 43, 45-50, and 53, respectively);

b. a heavy chain variable domain sequence that is at least 80% identical to a heavy chain variable domain sequence of AM_H9, 14, 16, 17, 19-23, and 26 (SEQ ID NOs:9, 14, 16, 17, 19-23, and 26, respectively);

c. the light chain variable domain of (a) and the heavy chain variable domain of (b); wherein said antibody specifically binds to human IL-17RA;

B. an isolated antibody, or IL-17RA-binding fragment thereof, comprising

a. a light chain CDR1 (SEQ ID NO:209), CDR2 (SEQ ID NO:210), CDR3 (SEQ ID NO:211) and a heavy chain CDR1 (SEQ ID NO:131), CDR2 (SEQ ID NO:132), CDR3 (SEQ ID NO:133) of antibody AM-9;

b. a light chain CDR1 (SEQ ID NO:224), CDR2 (SEQ ID NO:225), CDR3 (SEQ ID NO:226) and a heavy chain CDR1 (SEQ ID NO:146), CDR2 (SEQ ID NO:147), CDR3 (SEQ ID NO:148) of antibody AM-14;

c. a light chain CDR1 (SEQ ID NO:230), CDR2 (SEQ ID NO:231), CDR3 (SEQ ID NO:232) and a heavy chain CDR1 (SEQ ID NO:152), CDR2 (SEQ ID NO:153), CDR3 (SEQ ID NO:154) of antibody AM-16;

d. a light chain CDR1 (SEQ ID NO:233), CDR2 (SEQ ID NO:234), CDR3 (SEQ ID NO:235) and a heavy chain CDR1 (SEQ ID NO:155), CDR2 (SEQ ID NO:156), CDR3 (SEQ ID NO:157) of antibody AM-17;

e. a light chain CDR1 (SEQ ID NO:239), CDR2 (SEQ ID NO:240), CDR3 (SEQ ID NO:241) and a heavy chain CDR1 (SEQ ID NO:161), CDR2 (SEQ ID NO:162), CDR3 (SEQ ID NO:163) of antibody AM-19;

f. a light chain CDR1 (SEQ ID NO:242), CDR2 (SEQ ID NO:243), CDR3 (SEQ ID NO:244) and a heavy chain CDR1 (SEQ ID NO:164), CDR2 (SEQ ID NO:165), CDR3 (SEQ ID NO:166) of antibody AM-20;

g. a light chain CDR1 (SEQ ID NO:245), CDR2 (SEQ ID NO:246), CDR3 (SEQ ID NO:247) and a heavy chain CDR1 (SEQ ID NO:167), CDR2 (SEQ ID NO:168), CDR3 (SEQ ID NO:169) of antibody AM-21;

h. a light chain CDR1 (SEQ ID NO:248), CDR2 (SEQ ID NO:249), CDR3 (SEQ ID NO:250) and a heavy chain CDR1 (SEQ ID NO:170), CDR2 (SEQ ID NO:171), CDR3 (SEQ ID NO:172) of antibody AM-22;

i. a light chain CDR1 (SEQ ID NO:251), CDR2 (SEQ ID NO:252), CDR3 (SEQ ID NO:253) and a heavy chain CDR1 (SEQ ID NO:173), CDR2 (SEQ ID NO:174), CDR3 (SEQ ID NO:175) of antibody AM-23;

j. a light chain CDR1 (SEQ ID NO:254), CDR2 (SEQ ID NO:255), CDR3 (SEQ ID NO:256) and a heavy chain CDR1 (SEQ ID NO:173), CDR2 (SEQ ID NO:174), CDR3 (SEQ ID NO:175) of antibody AM-23;

k. a light chain variable domain and a heavy chain variable domain of AM_L26/AM_H26 (SEQ ID NO:53/SEQ ID NO:26);

wherein said antibody specifically binds to human IL-17RA; and

C. an isolated antibody, or IL-17RA-binding fragment thereof, comprising

a. a light chain variable domain and a heavy chain variable domain of AM_L9/AM_H9 (SEQ ID NO:35/SEQ ID NO:9);

b. a light chain variable domain and a heavy chain variable domain of AM_L14/AM_H14 (SEQ ID NO:40/SEQ ID NO:14);

c. a light chain variable domain and a heavy chain variable domain of AM_L16/AM_H16 (SEQ ID NO:42/SEQ ID NO:16);

d. a light chain variable domain and a heavy chain variable domain of AM_L17/AM_H17 (SEQ ID NO:43/SEQ ID NO:17);

e. a light chain variable domain and a heavy chain variable domain of AM_L19/AM_H19 (SEQ ID NO:45/SEQ ID NO:19);

f. a light chain variable domain and a heavy chain variable domain of AM_L20/AM_H20 (SEQ ID NO:46/SEQ ID NO:20);

g. a light chain variable domain and a heavy chain variable domain of AM_L21/AM_H21 (SEQ ID NO:47/SEQ ID NO:21);

h. a light chain variable domain and a heavy chain variable domain of AM_L22/AM_H22 (SEQ ID NO:48/SEQ ID NO:22);

i. a light chain variable domain and a heavy chain variable domain of AM_L23/AM_H23 (SEQ ID NO:49 or SEQ ID NO:50/SEQ ID NO:23);

j. a light chain variable domain and a heavy chain variable domain of AM_L26/AM_H26 (SEQ ID NO:53/SEQ ID NO:26);

wherein said antibody specifically binds to human IL-17RA.

Embodiment three: the antibody of embodiment one, wherein said antibody selected from the group consisting of:

A. an isolated antibody, or IL-17RA-binding fragment thereof, comprising

a. a light chain variable domain sequence that is at least 80% identical to a light chain variable domain sequence of AM_L12, 14, 16, 17, 19, and 22 (SEQ ID NOs:38, 40, 42, 43, 45, and 48 respectively);

b. a heavy chain variable domain sequence that is at least 80% identical to a heavy chain variable domain sequence of AM_H12, 14, 16, 17, 19, and 22 (SEQ ID NOs:12, 14, 16, 17, 19, and 22, respectively);

c. the light chain variable domain of (a) and the heavy chain variable domain of (b); wherein said antibody specifically binds to human IL-17RA;

B. an isolated antibody, or IL-17RA-binding fragment thereof, comprising

a. a light chain CDR1 (SEQ ID NO:218), CDR2 (SEQ ID NO:219), CDR3 (SEQ ID NO:220) and a heavy chain CDR1 (SEQ ID NO:140), CDR2 (SEQ ID NO:141), CDR3 (SEQ ID NO:142) of antibody AM-12;

b. a light chain CDR1 (SEQ ID NO:224), CDR2 (SEQ ID NO:225), CDR3 (SEQ ID NO:226) and a heavy chain CDR1 (SEQ ID NO:146), CDR2 (SEQ ID NO:147), CDR3 (SEQ ID NO:148) of antibody AM-14;

c. a light chain CDR1 (SEQ ID NO:230), CDR2 (SEQ ID NO:231), CDR3 (SEQ ID NO:232) and a heavy chain CDR1 (SEQ ID NO:152), CDR2 (SEQ ID NO:153), CDR3 (SEQ ID NO:154) of antibody AM-16;

d. a light chain CDR1 (SEQ ID NO:233), CDR2 (SEQ ID NO:234), CDR3 (SEQ ID NO:235) and a heavy chain CDR1 (SEQ ID NO:155), CDR2 (SEQ ID NO:156), CDR3 (SEQ ID NO:157) of antibody AM-17;

e. a light chain CDR1 (SEQ ID NO:239), CDR2 (SEQ ID NO:240), CDR3 (SEQ ID NO:241) and a heavy chain CDR1 (SEQ ID NO:161), CDR2 (SEQ ID NO:162), CDR3 (SEQ ID NO:163) of antibody AM-19;

f. a light chain CDR1 (SEQ ID NO:248), CDR2 (SEQ ID NO:249), CDR3 (SEQ ID NO:250) and a heavy chain CDR1 (SEQ ID NO:170), CDR2 (SEQ ID NO:171), CDR3 (SEQ ID NO:172) of antibody AM-22;

wherein said antibody specifically binds to human IL-17RA; and

C. an isolated antibody, or IL-17RA-binding fragment thereof, comprising

a. a light chain variable domain and a heavy chain variable domain of AM_L12/AM_H12 (SEQ ID NO:38/SEQ ID NO:12);

b. a light chain variable domain and a heavy chain variable domain of AM_L14/AM_H14 (SEQ ID NO:40/SEQ ID NO:14);

c. a light chain variable domain and a heavy chain variable domain of AM_L16/AM_H16 (SEQ ID NO:42/SEQ ID NO:16);

d. a light chain variable domain and a heavy chain variable domain of AM_L17/AM_H17 (SEQ ID NO:43/SEQ ID NO:17);

e. a light chain variable domain and a heavy chain variable domain of AM_L19/AM_H19 (SEQ ID NO:45/SEQ ID NO:19);

c. a light chain variable domain and a heavy chain variable domain of AM_L22/AM_H22 (SEQ ID NO:48/SEQ ID NO:22);

wherein said antibody specifically binds to human IL-17RA.

Embodiment four: the antibody of embodiment one, wherein said antibody is selected from the group consisting of:

A. an isolated antibody, or IL-17RA-binding fragment thereof, comprising

a. a light chain variable domain sequence that is at least 80% identical to a light chain variable domain sequence SEQ ID NO: 40;

b. a heavy chain variable domain sequence that is at least 80% identical to a heavy chain variable domain sequence of SEQ ID NO:14;

c. the light chain variable domain of (a) and the heavy chain variable domain of (b); wherein said antibody specifically binds to human IL-17RA;

B. an isolated antibody, or IL-17RA-binding fragment thereof, comprising a light chain CDR1 (SEQ ID NO:224), CDR2 (SEQ ID NO:225), CDR3 (SEQ ID NO:226) and a heavy chain CDR1 (SEQ ID NO:146), CDR2 (SEQ ID NO:147), CDR3 (SEQ ID NO:148); wherein said antibody specifically binds to human IL-17RA; and

C. an isolated antibody, or IL-17RA-binding fragment thereof, comprising a light chain variable domain of SEQ ID NO:40 and a heavy chain variable domain SEQ ID NO:14; wherein said antibody specifically binds to human IL-17RA.

Embodiment five: the antibody of embodiment one, wherein said antibody is selected from the group consisting of:

a. a human antibody;

b. a humanized antibody;

c. a chimeric antibody;

d. a monoclonal antibody;

e. an antigen-binding antibody fragment;

f. a single chain antibody;

g. a diabody;

h. a triabody;

i. a tetrabody;

i. a Fab fragment;

k. a F(ab')2 fragment;

l. an IgD antibody;

m. an IgE antibody;

n. an IgM antibody;

o. an IgG1 antibody;

p. an IgG2 antibody;

q. an IgG3 antibody; and

r. an IgG4 antibody.

Embodiment six: the antibody of embodiment five, wherein said antibody inhibits human IL-17A from binding to human IL-17RA. Embodiment seven: the antibody of

embodiment six, wherein said antibody inhibits human IL-17A and IL-17F from binding to human IL-17RA. Embodiment eight: the antibody of embodiment six, wherein said antibody inhibits human IL-17A or IL-17F from binding to human IL-17RA.

Embodiment nine: an isolated monoclonal antibody, or IL-17RA-binding fragment thereof, selected from the group consisting of:

a) a monoclonal antibody that specifically binds human IL-17RA of SEQ ID NO:431 but does not specifically bind to a chimeric polypeptide consisting of SEQ ID NO:434;

b) a monoclonal antibody that specifically binds human IL-17RA of SEQ ID NO:431 but does not specifically bind to a chimeric polypeptide consisting of SEQ ID NO:435; and

c) a monoclonal antibody that specifically binds human IL-17RA of SEQ ID NO:431 but does not specifically bind to a chimeric polypeptide consisting of SEQ ID NO:436.

Embodiment ten: An isolated monoclonal antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant selected from the group consisting of:

a) a polypeptide comprising amino acids 75-96 of SEQ ID NO:431 of human IL-17RA;

b) a polypeptide comprising amino acids 128-154 of SEQ ID NO:431 of human IL-17RA;

c) a polypeptide comprising amino acids 176-197 of SEQ ID NO:431 of human IL-17RA;

d) a polypeptide comprising amino acids 152-297 of SEQ ID NO:431 of human IL-17RA;

e) a polypeptide comprising amino acids 220-284 of SEQ ID NO:431 of human IL-17RA;

f) a polypeptide comprising amino acids 152-198 of SEQ ID NO:431 of human IL-17RA;

g) a polypeptide comprising amino acids 152-186 of SEQ ID NO:431 of human IL-17RA;

h) a polypeptide comprising amino acids 97-297 of SEQ ID NO:431 of human IL-17RA;

i) a polypeptide comprising amino acids 138-270 of SEQ ID NO:431 of human IL-17RA;

j) a polypeptide comprising amino acids 113-198 of SEQ ID NO:431 of human IL-17RA; and

k) a polypeptide comprising amino acids 152-270 of SEQ ID NO:431 of human IL-17RA.

Embodiment eleven: an isolated monoclonal antibody, or IL-17RA-binding fragment thereof, that specifically binds human IL-17RA of SEQ ID NO:431, but does not specifically bind said IL-17RA having any one of the following amino acid substitutions E97R, E113R, S115R, H138R, D152R, D154R, E156R, K166R, Q176R, S177R, D184R, E186R, S198R, H215R, S220R, T228R, T235R, E241R, H243R, L270R, Q284R, or H297R of SEQ ID NO:431. Embodiment twelve: the antibody of embodiment eleven, wherein said antibody specifically binds human IL-17RA of SEQ ID NO:431, but does not specifically bind said IL-17RA having any one of the following amino acid substitutions D152R, D154R, E156R, D184R, E186R, or H297R of SEQ ID NO:431. Embodiment thirteen: the antibody of embodiment eleven, wherein said antibody specifically binds human IL-17RA of SEQ ID NO:431, but does not specifically bind said IL-17RA having the aspartic acid residue at position 152 of SEQ ID NO:431 substituted with an arginine. Embodiment fourteen: the antibody of embodiment eleven, wherein said antibody specifically binds an epitope defined by any one of amino acids D152, D154, E156, D184, E186, or H297 of SEQ ID NO:431.

Embodiment fifteen: the antibody of embodiment fourteen, wherein said antibody specifically binds an epitope defined by at least two of the following amino acids D152, D154, E156, D184, E186, or H297 of SEQ ID NO:431. Embodiment sixteen: the antibody of embodiment fourteen, wherein said antibody specifically binds an epitope defined by at least three of the following amino acids D152, D154, E156, D184, E186, or H297 of SEQ ID NO:431. Embodiment seventeen: the antibody of embodiment fourteen, wherein said antibody specifically binds an epitope defined by at least four of the following amino acids D152, D154, E156, D184, E186, or H297 of SEQ ID NO:431. Embodiment eighteen: the antibody of embodiment fourteen, wherein said antibody specifically binds an epitope defined by at least five of the following amino acids D152, D154, E156, D184, E186, or H297 of SEQ ID NO:431. Embodiment nineteen: the antibody of embodiment fourteen, wherein said antibody specifically binds an epitope defined by amino acids D152, D154, E156, D184, E186, H297 of SEQ ID NO:431.

Embodiment twenty: an isolated monoclonal antibody, or IL-17RA-binding fragment thereof, that specifically binds to IL-17RA and competes for binding with an antibody comprising:

a. a heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of:
   i. X_1YGIS, wherein X_1 is selected from the group consisting of R, S and G;
b. a heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of:
   i. WISX$_1$YX$_2$GNTX$_3$YAQX$_4$X$_5$QG, wherein X_1 is selected from the group consisting of A, X_2 is selected from the group consisting of N, S and K, X_3 is selected from the group consisting of N and K, X_4 is selected from the group consisting of K and N, and X_5 is selected from the group consisting of L and F;
c. a heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of:
   i. X$_1$QLX$_2$X$_3$DY, wherein X_1 is selected from the group consisting of R and K, X_2 is selected from the group consisting of Y, V, and A, and X_3 is selected from the group consisting of F and L;
   ii. X$_1$QLX$_2$FDY, wherein X_1 is selected from the group consisting of R and K, and X_2 is selected from the group consisting of Y and V;
d. a light chain CDR1 comprising an amino acid sequence selected from the group consisting of:
   i. RASQSX$_1$X$_2$X$_3$X$_4$LA, wherein X_1 is selected from the group consisting of V and I, X_2 is selected from the group consisting of I and S, X_3 is selected from the group consisting of S and T, X_4 is selected from the group consisting of N and S, and X_5 is selected from the group consisting of A and N;
   ii. RASQSX$_1$SSNLA, wherein X_1 is selected from the group consisting of V and I;
e. a light chain CDR2 comprising an amino acid sequence selected from the group consisting of:
   i. X$_1$X$_2$STRAX$_3$, wherein X_1 is selected from the group consisting of G and D, X_2 is selected from the group consisting of A and T, and X_3 is selected from the group consisting of T and A;
   ii. X$_1$ASTRAX$_2$, wherein X_1 is selected from the group consisting of G and D, and X_2 is selected from the group consisting of A and T; and
f. a light chain CDR3 comprising an amino acid sequence selected from the group consisting of:
   i. QQYDX$_1$WPLT, wherein X_1 is selected from the group consisting of N, T, and I.

Embodiment twenty one: the antibody of embodiment twenty, wherein said antibody comprises:

a. a heavy chain CDR1 amino acid sequence comprising X_1YGIS, wherein X_1 is selected from the group consisting of R, S and G;

b. a heavy chain CDR2 amino acid sequence comprising $WISX_1YX_2GNTX_3YAQX_4X_5QG$, wherein X_1 is selected from the group consisting of A, X_2 is selected from the group consisting of N, S and K, X_3 is selected from the group consisting of N and K, X_4 is selected from the group consisting of K and N, and X_5 is selected from the group consisting of L and F;

c. a heavy chain CDR3 amino acid sequence comprising X_1QLX_2FDY, wherein X_1 is selected from the group consisting of R and K, and X_2 is selected from the group consisting of Y and V;

d. a light chain CDR1 amino acid sequence comprising $RASQSX_1SSNLA$, wherein X_1 is selected from the group consisting of V and I;

e. a light chain CDR2 amino acid sequence comprising $X_1ASTRAX_2$, wherein X_1 is selected from the group consisting of G and D, and X_2 is selected from the group consisting of A and T; and

f. a light chain CDR3 amino acid sequence comprising $QQYDX_1WPLT$, wherein X_1 is selected from the group consisting of N, T, and I.

Embodiment twenty two: the antibody of embodiment 20, wherein said antibody is selected from the group consisting of:

a. a human antibody;
b. a humanized antibody;
c. a chimeric antibody;
d. a monoclonal antibody;
e. an antigen-binding antibody fragment;
f. a single chain antibody;
g. a diabody;
h. a triabody;
i. a tetrabody;
j. a Fab fragment;
k. a F(ab')2 fragment;
l. an IgD antibody;
m. an IgE antibody;
n. an IgM antibody;
o. an IgG1 antibody;
p. an IgG2 antibody;
q. an IgG3 antibody; and
r. an IgG4 antibody.

Embodiment twenty three: the antibody of embodiment twenty two, wherein said antibody inhibits human IL-17A from binding to human IL-17RA. Embodiment twenty four: the antibody of embodiment twenty two, wherein said antibody inhibits human IL-17A and IL-17F from binding to human IL-17RA. Embodiment twenty five: the antibody of embodiment twenty two, wherein said antibody inhibits human IL-17A or IL-17F from binding to human IL-17RA.

IL-17A, IL-17F, and IL-17RA

"IL-17 receptor A" or "IL-17RA" (interchangeably used herein, as well as IL-17 receptor and IL-17R to refer to the same receptor) as used herein is meant the cell surface receptor and receptor complexes (such as but not limited to IL-17RA-IL-17RC complex), that bind IL-17A and IL-17F and as a result initiates a signal transduction pathway within the cell. IL-17RA proteins may also include variants. IL-17RA proteins may also include fragments, such as the extracellular domain that don't have all or part of the transmembrane and/or the intracellular domain, as well as fragments of the extracellular domain. The cloning, characterization, and preparation of IL-17RA are described, for example, in U.S. Pat. No. 6,072,033, which is incorporated herein by reference in its entirety. The amino acid sequence of the human IL-17RA is shown in SEQ ID NO:430. Soluble forms of huIL-17RA useful in the methods of the present invention include the extracellular domain or the mature form lacking the signal peptide or a fragment of the extracellular domain that retains the capacity to bind IL-17A and/or IL-17F, or a heteromeric version of IL-17A and/or IL-17F. Other forms of IL-17RA include muteins and variants that are at least between 70% and 99% homologous to the native IL-17RA of SEQ ID NO:430 and as described in U.S. Pat. No. 6,072,033, so long as the IL-17RA retains the capacity to bind IL-17A and/or IL-17F, or a heteromeric version of IL-17A and/or IL-17F. The term "IL-17RA" also includes post-translational modifications of the IL-17RA amino acid sequence. Post-translational modifications include, but is not limited to, N- and O-linked glycosylation.

IL-17RA Neutralizing Antibodies

Antibodies that specifically bind to human IL-17RA and inhibit IL-17A and/or IL-17F from binding and activating IL-17RA, or a heteromeric complex of IL-17RA and IL-17RC, are disclosed herein. Said antibodies specifically bind to human IL-17RA and may inhibit an IL-17A/IL-17F heteromer from binding and activating IL-17RA, or a heteromeric complex of IL-17RA and IL-17RC. Throughout the specification, when reference is made to inhibiting IL-17A and/or IL-17F, it is understood that this also includes inhibiting heteromers of IL-17A and IL-17F. Said antibodies that specifically bind to human IL-17RA may partially or fully inhibit IL-17RA from forming either a homomeric or heteromeric functional receptor complex, such as, but not limited to, an IL-17RA-IL-17RC complex. Said antibodies may partially or fully inhibit IL-17RA from forming either a homomeric or heteromeric functional receptor complex, such as, but not limited to IL-17RA/IL-17RC complex and do not necessarily inhibit IL-17A and/or IL-17F or an IL-17A/IL-17F heteromer from binding to IL-17RA or a IL-17RA heteromeric receptor complex.

Aspects of the invention include antibodies that compete for binding to human IL-17RA with the aforementioned IL-17RA antibodies. Aspects of the invention include antibodies that bind to the neutralizing determinants described herein. The antibodies that compete for binding to human IL-17RA with the IL-17RA antibodies described herein and the antibodies that bind to the neutralizing determinants described herein will also the same or similar functional attributes described in the previous paragraph. To be clear, antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein, or antibodies that bind to the neutralizing determinants described herein are particular embodiments of the present invention.

The antibodies described herein specifically bind to IL-17RA. "Specifically binds" as used herein means that the antigen binding protein preferentially binds IL-17RA over other proteins. In some embodiments "specifically binds" means that the IL-17RA antigen binding proteins have a higher affinity for IL-17RA than for other proteins. For example, the equilibrium dissociation constant is $<10^{-7}$ to 10^{-11} M, or $<10^{-8}$ to $<10^{-10}$ M, or $<10^{-9}$ to $<10^{-10}$ M.

It is understood that when reference is made to the various embodiments of the IL-17RA antibodies, as well as antibodies that compete for binding to human IL-17RA with the IL-17RA neutralizing antibodies described herein, or antibodies that bind to the neutralizing determinants described

herein, that it also encompasses IL-17RA-binding fragments thereof. An IL-17RA-binding fragment comprises any of the antibody fragments or domains described herein that retains the ability to specifically bind to IL-17RA. Said IL-17RA-binding fragments may be in any of the scaffolds described herein. Said IL-17RA-binding fragments also have the capacity to inhibit activation of the IL-17RA, as described throughout the specification.

One characteristic of the IL-17RA antibodies described herein, or antibodies that compete for binding with the IL-17RA antibodies described herein, or antibodies that bind to the neutralizing determinants described herein, is that they can inhibit binding of IL-17A and/or IL-17F to IL-17RA and one or more biological activities of, or mediated by, IL-17RA. Such antibodies are considered neutralizing antibodies because of their capacity to inhibit IL-17A and/or IL-17F from binding and causing IL-17RA signaling and/or biological activity. In this case, an IL-17RA neutralizing antibody or antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein, or antibodies that bind to the neutralizing determinants described herein specifically binds IL-17RA and inhibits binding of IL-17A and/or IL-17F to IL-17RA from anywhere between 10 to 100%, such as by at least about 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99% or more (for example by measuring binding in an in vitro competitive binding assay as described herein). An antibody that competes for binding, as described in the examples, is an antibody that inhibits the binding of another antibody to a specific target, which in this case is IL-17RA. Inhibition, in the antibody competition for binding, may be from anywhere between 10 to 100%, such as by at least about 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99% or more (for example by measuring binding in an in vitro competitive binding assay as described herein). For example, IL-17RA antibodies or antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein, or antibodies that bind to the neutralizing determinants described herein may be tested for neutralizing ability by testing them for the production of IL-6 in human foreskin fibroblast (HFF) assay (see for example Examples 4 and 5), or any suitable assay known in the art. Of course, this is just one example of an assay and any suitable assay known in the art may be employed to determine antibodies that fall within the scope of the claims. Further examples, for illustrative purposes only, of additional biological activity of IL-17RA (e.g., assay readouts) to test for inhibition of IL-17RA signaling and/or biological activity include in vitro and/or in vivo measurement of one or more of IL-8, CXCL1, CXCL2, GM-CSF, G-CSF, M-CSF, RANK-L, LIF, PGE2, IL-12, MMPs (such as but not limited to MMP3 and MMP9), GROα, NO, and/or C-telopeptide and the like.

Embodiments of antibodies that compete for binding to human IL-17RA with the IL-17RA neutralizing antibodies described herein, or antibodies that bind to the neutralizing determinants described herein comprise a scaffold structure, as variously define herein, with one or more complementarity determining regions (CDRs). Embodiments of antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein comprise a scaffold structure with one or more variable domains, either heavy or light.

Aspects of the invention include antibodies that compete for binding with the IL-17RA neutralizing antibodies, or antibodies that bind to the neutralizing determinants described herein, wherein said IL-17RA neutralizing antibodies comprise a light chain variable region selected from the group consisting of AM_L1 through AM_L26 (SEQ ID NO:27-53, respectively, with AM_L23 having two versions—SEQ ID NOs:49 and 50) and/or a heavy chain variable region selected from the group consisting of AM_H1 through AM_H26 (SEQ ID NO:1-26, respectively), as well as human IL-17R-binding fragments, derivatives, muteins, and variants thereof.

Aspects of the invention include antibodies that compete for binding with the IL-17RA neutralizing antibodies, or antibodies that bind to the neutralizing determinants described herein, wherein said IL-17RA neutralizing antibodies comprise variable light and variable heavy domains of: AM_L1/AM_H1 (SEQ ID NO:27/SEQ ID NO:1), AM_L2/AM_H2 (SEQ ID NO:28/SEQ ID NO:2), AM_L3/AM_H3 (SEQ ID NO:29/SEQ ID NO:3), AM_L4/AM_H4 (SEQ ID NO:30/SEQ ID NO:4), AM_L5/AM_H5 (SEQ ID NO:31/SEQ ID NO:5), AM_L6/AM_H6 (SEQ ID NO:32/SEQ ID NO:6), AM_L7/AM_H7 (SEQ ID NO:33/SEQ ID NO:7), AM_L8/AM_H8 (SEQ ID NO:34/SEQ ID NO:8), AM_L9/AM_H9 (SEQ ID NO:35/SEQ ID NO:9), AM_L10/AM_H10 (SEQ ID NO:36/SEQ ID NO:10), AM_L11/AM_H11 (SEQ ID NO:37/SEQ ID NO:11), AM_L12/AM_H12 (SEQ ID NO:38/SEQ ID NO:12), AM_L13/AM_H13 (SEQ ID NO:39/SEQ ID NO:13), AM_L14/AM_H14 (SEQ ID NO:40/SEQ ID NO:14), AM_L15/AM_H15 (SEQ ID NO:41/SEQ ID NO:15), AM_L16/AM_H16 (SEQ ID NO:42/SEQ ID NO:16), AM_L17/AM_H17 (SEQ ID NO:43/SEQ ID NO:17), AM_L18/AM_H18 (SEQ ID NO:44/SEQ ID NO:18), AM_L19/AM_H19 (SEQ ID NO:45/SEQ ID NO:19), AM_L20/AM_H20 (SEQ ID NO:46/SEQ ID NO:20), AM_L21/AM_H21 (SEQ ID NO:47/SEQ ID NO:21), AM_L22/AM_H22 (SEQ ID NO:48/SEQ ID NO:22), AM_L23/AM_H23 (SEQ ID NO:49 or SEQ ID NO:50/SEQ ID NO:23), AM_L24/AM_H24 (SEQ ID NO:51/SEQ ID NO:24), AM_L25/AM_H25 (SEQ ID NO:52/SEQ ID NO:25), AM_L26/AM_H26 (SEQ ID NO:53/SEQ ID NO:26), as well as IL-17RA-binding fragments thereof and combinations thereof.

Aspects of the invention include antibodies that compete for binding with the IL-17RA neutralizing antibodies, or antibodies that bind to the neutralizing determinants described herein, wherein said IL-17RA neutralizing antibodies comprise, wherein said antibodies specifically bind to human IL-17RA and inhibit IL-17A and/or IL-17F from binding and activating IL-17RA, or a heteromeric complex of IL-17RA and IL-17RC. Further embodiments include antibodies that specifically bind to human IL-17RA and inhibit an IL-17A/IL-17F heteromer from binding and activating IL-17RA, or a heteromeric complex of IL-17RA and IL-17RC. Further embodiments include antibodies that specifically bind to human IL-17RA and partially or fully inhibit IL-17RA from forming either a homomeric or heteromeric functional receptor complex, such as, but not limited to IL-17RA-IL-17RC complex. Further embodiments include antibodies that specifically bind to human IL-17RA and partially or fully inhibit IL-17RA from forming either a homomeric or heteromeric functional receptor complex, such as, but not limited to IL-17RA/IL-17RC complex and do not necessarily inhibit IL-17A and/or IL-17F or an IL-17A/IL-17F heteromer from binding to IL-17RA or a IL-17RA heteromeric receptor complex.

Aspects of the invention include antibodies that compete for binding with the IL-17RA neutralizing antibodies, or antibodies that bind to the neutralizing determinants described herein, wherein said IL-17RA neutralizing antibodies comprise at least one CDR from antibodies comprising AM_L1/AM_H1 (SEQ ID NO:27/SEQ ID NO:1), AM_L2/AM_H2 (SEQ ID NO:28/SEQ ID NO:2), AM_L3/AM_H3 (SEQ ID NO:29/SEQ ID NO:3), AM_L4/AM_H4 (SEQ ID NO:30/SEQ ID NO:4), AM_L5/AM_H5 (SEQ ID NO:31/SEQ ID NO:5), AM_L6/AM_H6 (SEQ ID NO:32/SEQ ID NO:6), AM_L7/AM_H7 (SEQ ID NO:33/SEQ ID NO:7), AM_L8/AM_H8 (SEQ ID NO:34/SEQ ID NO:8), AM_L9/AM_H9 (SEQ ID NO:35/SEQ ID NO:9), AM_L10/AM_H10 (SEQ ID NO:36/SEQ ID NO:10), AM_L11/AM_H11 (SEQ ID NO:37/SEQ ID NO:11), AM_L12/AM_H12 (SEQ ID NO:38/SEQ ID NO:12), AM_L13/AM_H13 (SEQ ID NO:39/SEQ ID NO:13), AM_L14/AM_H14 (SEQ ID NO:40/SEQ ID NO:14), AM_L15/AM_H15 (SEQ ID NO:41/SEQ ID NO:15), AM_L16/AM_H16 (SEQ ID NO:42/SEQ ID NO:16), AM_L17/AM_H17 (SEQ ID NO:43/SEQ ID NO:17), AM_L18/AM_H18 (SEQ ID NO:44/SEQ ID NO:18), AM_L19/AM_H19 (SEQ ID NO:45/SEQ ID NO:19), AM_L20/AM_H20 (SEQ ID NO:46/SEQ ID NO:20), AM_L21/AM_H21 (SEQ ID NO:47/SEQ ID NO:21), AM_L22/AM_H22 (SEQ ID NO:48/SEQ ID NO:22), AM_L23/AM_H23 (SEQ ID NO:49 or SEQ ID NO:50/SEQ ID NO:23), AM_L24/AM_H24 (SEQ ID NO:51/SEQ ID NO:24), AM_L25/AM_H25 (SEQ ID NO:52/SEQ ID NO:25), AM_L26/AM_H26 (SEQ ID NO:53/SEQ ID NO:26), as well as IL-17RA-binding fragments thereof and combinations thereof. See Table 1.

Aspects of the invention include antibodies that compete for binding with the IL-17RA neutralizing antibodies, or antibodies that bind to the neutralizing determinants described herein, wherein said IL-17RA neutralizing antibodies comprise at least one, two, or three H-CDR regions of any of SEQ ID NOs:107-184 and at least one, two, or three L-CDR region of any of SEQ ID NOs:185-265. See Table 1.

Examples 8-11 describe various studies elucidating domains on human IL-17RA that neutralizing IL-17RA mAbs bound. These domains are referred to as neutralizing determinants. A neutralizing determinant is a contiguous stretch of IL-17RA, that when mutated, negatively affects the binding of at least one of the neutralizing antibodies disclosed herein. A neutralizing determinant comprises at least one epitope. A neutralizing determinant may have primary, secondary, tertiary, and/or quarternary structural characteristics. A neutralizing antibody is any of the antibodies described herein that specifically binds human IL-17RA and inhibits binding of IL-17A and/or IL-17F and thereby inhibits IL-17RA signaling and/or biological activity. In addition, a neutralizing antibody encompasses antibodies that compete for binding to human IL-17RA with the IL-17RA antibodies described herein, as well as antibodies that bind to the neutralizing determinants described herein.

FIGS. **8**A and **8**B show that antibodies A: AM_H11/AM_L11, B: AM_H4/AM_L4, C: AM_H8/AM_L8, D: AM_H7/AM_L7, E: AM_H6/AM_L6, F: AM_H10/AM_L10, and G: AM_H18/AM_L18 competed with one another for binding to human IL-17RA and fell into a defined group (Bin 1). In general, antibodies I: AM_H22/AM_L22, J: AM_H23/AM_L23, K: AM_H14/AM_L14, L: AM_H19/AM_L19, M: AM_H12/AM_L12, N: AM_H17/AM_L17, O: AM_H16/AM_L16 competed with one another for binding to human IL-17RA and as a consequence fell into a different group (Bin 3). Generally speaking, the antibodies of Bin 1 did not compete with the antibodies of Bin 3. Antibody AM_H1/AM_L1 was unique in its competition pattern and formed Bin 2, but is most similar to Bin 3. Antibody P: AM_H26/AM_L26 formed Bin 4 and showed little cross-competition with any of the other antibodies, suggesting a neutralizing determinant unique to this antibody. Antibodies Q: AM_H21/AM_L21 and R: AM_H20/AM_L20 showed individually unique competition patterns, but with considerable similarities to Bin 3 antibodies, and formed Bins 5 and 6, respectively. This method identified groups of antibodies binding to different neutralizing determinants and provides evidence of several species within a subgenus of cross-competing antibodies.

Example 10 describes the use of human/mouse IL-17RA chimeric proteins to determine neutralizing determinants on human IL-17RA. FIG. **11** show that at least three neutralizing determinants were identified based on those regions affecting the binding of neutralizing IL-17RA antibodies, namely neutralizing determinant B spanning amino acids 75-96 of human IL-17RA (SEQ ID NO:431), neutralizing determinant C spanning amino acids 128-154 of human IL-17RA (SEQ ID NO:431), and neutralizing determinant D spanning amino acids 176-197 of human IL-17RA (SEQ ID NO:431). Neutralizing determinant B spanning amino acids 75-96 of human IL-17RA (SEQ ID NO:431) negatively affected the binding of neutralizing antibodies AM_H1/AM_L1 and AM_H23/AM_L23. Neutralizing determinant C spanning amino acids 128-154 of human IL-17RA (SEQ ID NO:431) negatively affected the binding of neutralizing antibodies AM_H22/AM_L22 and AM_H23/AM_L23. Neutralizing determinant D spanning amino acids 176-197 of human IL-17RA (SEQ ID NO:431) negatively affected the binding of neutralizing antibodies AM_H1/AM_L1, AM_H22/AM_L22, AM_H14/AM_L14, AM_H19/AM_L19, AM_H23/AM_L23, AM_H21/AM_L21, and AM_H20/AM_L20. Thus, neutralizing determinants B, C, and D are all considered neutralizing determinants.

Example 11 describes the use of arginine scan techniques to further elucidate the domains on human IL-17R that the IL-17RA neutralizing antibodies bound. A summary of the arginine scan, binning, and chimera data is presented in FIG. **11**. The arginine scan methodology identified several neutralizing determinants: AM_H18/AM_L18 bound a domain spanning amino acids 220-284 of human IL-17RA (SEQ ID NO:431); AM_H1/AM_L1 bound a domain focused on amino acid residue 152 of human IL-17RA (SEQ ID NO:431); AM_H22/AM_L22 bound a domain spanning amino acids 152-198 of human IL-17RA (SEQ ID NO:431); AM_H14/AM_L14 bound a domain spanning amino acids 152-297 of human IL-17RA (SEQ ID NO:431); AM_H19/AM_L19 bound a domain spanning amino acids 152-186 of human IL-17RA (SEQ ID NO:431); AM_H23/AM_L23 bound a domain spanning amino acids 97-297 of human IL-17RA (SEQ ID NO:431); AM_H26/AM_L26 bound a domain spanning amino acids 138-270 of human IL-17RA (SEQ ID NO:431); AM_H21/AM_L21 bound a domain spanning amino acids 113-198 of human IL-17RA (SEQ ID NO:431); and AM_H20/AM_L20 bound a domain spanning amino acids 152-270 of human IL-17RA (SEQ ID NO:431). All of the residues shown in FIG. **14** have been shown to significantly reduce or essentially eliminate binding of a neutralizing human monoclonal antibody that specifically binds to human IL-17RA.

Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds to IL-17RA and competes for binding with any one of antibodies AM_H3/AM_L3, AM_H20/AM_L20, AM_H22/AM_L22, AM_H23/AM_L23, AM_H14/AM_L14, AM_H21/AM_L21, AM_H19/AM_L19, AM_H12/AM_L12, AM_H17/AM_L17, or AM_H16/AM_L16, or any subset therein.

Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds to IL-17R and competes for binding with any one of antibodies AM_H22/AM_L22,

AM_H23/AM_L23, AM_H14/AM_L14, AM_H19/AM_L19, AM_H12/AM_L12, AM_H17/AM_L17, or AM_H16/AM_L16, or any subset therein.

Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds human IL-17RA of SEQ ID NO:431 but does not specifically bind to a chimeric polypeptide consisting of SEQ ID NO:434. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds human IL-17RA of SEQ ID NO:431 but does not specifically bind to a chimeric polypeptide consisting of SEQ ID NO:435. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds human IL-17RA of SEQ ID NO:431 but does not specifically bind to a chimeric polypeptide consisting of SEQ ID NO:436.

Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant comprising amino acids 75-96 of SEQ ID NO:431 of human IL-17RA. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant comprising amino acids 128-154 of SEQ ID NO:431 of human IL-17RA. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant comprising amino acids 176-197 of SEQ ID NO:431 of human IL-17RA. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant comprising amino acids 152-297 of SEQ ID NO:431 of human IL-17RA. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant comprising amino acids 220-284 of SEQ ID NO:431 of human IL-17RA. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant comprising amino acids 152-198 of SEQ ID NO:431 of human IL-17RA. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant comprising amino acids 152-186 of SEQ ID NO:431 of human IL-17RA. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant comprising amino acids 97-297 of SEQ ID NO:431 of human IL-17RA. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant comprising amino acids 138-270 of SEQ ID NO:431 of human IL-17RA. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant comprising amino acids 113-198 of SEQ ID NO:431 of human IL-17RA. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds a neutralizing determinant comprising amino acids 152-270 of SEQ ID NO:431 of human IL-17RA.

Further embodiments include an antibody, or IL-17RA-binding fragment thereof, that binds human IL-17RA of SEQ ID NO:431, but does not bind said IL-17RA having an amino acid substituted with arginine at any one of E97R, E113R, S115R, H138R, D152R, D154R, E156R, K166R, Q176R, S177R, D184R, E186R, S198R, H215R, S220R, T228R, T235R, E241R, H243R, L270R, Q284R, H297R of SEQ ID NO:431. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that binds human IL-17RA of SEQ ID NO:431, but does not bind said IL-17RA having an amino acid substituted with arginine at any one of D152R, D154R, E156R, D184R, E186R, H297R of SEQ ID NO:431. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that binds human IL-17RA of SEQ ID NO:431, but does not bind said IL-17RA having an amino acid substituted with arginine at D152R of SEQ ID NO:431.

Further embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds an epitope defined by any one of amino acids D152, D154, E156, D184, E186, H297 of SEQ ID NO:431. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds an epitope defined by at least two amino acids selected from the group consisting of: D152, D154, E156, D184, E186, H297 of SEQ ID NO:431. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds an epitope defined by at least three amino acids selected from the group consisting of: D152, D154, E156, D184, E186, H297 of SEQ ID NO:431. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds an epitope defined by at least four amino acids selected from the group consisting of: D152, D154, E156, D184, E186, H297 of SEQ ID NO:431. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds an epitope defined by at least five amino acids selected from the group consisting of: D152, D154, E156, D184, E186, H297 of SEQ ID NO:431. Embodiments include an antibody, or IL-17RA-binding fragment thereof, that specifically binds an epitope defined by amino acids D152, D154, E156, D184, E186, H297 of SEQ ID NO:431.

The antibodies of the invention include scaffold regions and one or more CDRs: between one and six CDRs (as typically do naturally occurring antibodies), for example, one heavy chain CDR1 ("H-CDR1"), and/or one heavy chain CDR2 ("H-CDR2"), and/or one heavy chain CDR3 ("H-CDR3"), and/or one light chain CDR1 ("L-CDR1"), and/or one light chain CDR2 ("L-CDR2"), and/or one light chain CDR3 ("L-CDR3").

The term "naturally occurring" as used throughout the specification in connection with biological materials such as peptides, polypeptides, nucleic acids, host cells, and the like, refers to materials which are found in nature. In naturally occurring antibodies, a H-CDR1 typically comprises about five (5) to about seven (7) amino acids, H-CDR2 typically comprises about sixteen (16) to about nineteen (19) amino acids, and H-CDR3 typically comprises about three (3) to about twenty five (25) amino acids. L-CDR1 typically comprises about ten (10) to about seventeen (17) amino acids, L-CDR2 typically comprises about seven (7) amino acids, and L-CDR3 typically comprises about seven (7) to about ten (10) amino acids. Specific CDRs of the IL-17RA neutralizing antibodies are provided in TABLE 1 and the Sequence Listing.

TABLE 1

	Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 1 of AM_H1 Vh SEQ ID NO:107 NYYWN	SEQ ID NO:266
Amino acid sequence of CDR 2 of AM_H1 Vh SEQ ID NO:108 DIYYSGSTNYNPSLKS	SEQ ID NO:267
Amino acid sequence of CDR 3 of AM_H1 Vh SEQ ID NO:109 DGELANYYGSGSYQFYYYYGMDV	SEQ ID NO:268

TABLE 1-continued

	Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 1 of $AM_{H}2$ Vh	SEQ ID NO:269
Amino acid sequence of CDR 2 of $AM_{H}2$ Vh	SEQ ID NO:270
Amino acid sequence of CDR 3 of $AM_{H}2$ Vh	SEQ ID NO:271
Amino acid sequence of CDR 1 of $AM_{H}3$ Vh	SEQ ID NO:272
Amino acid sequence of CDR 2 of $AM_{H}3$ Vh	SEQ ID NO:273
Amino acid sequence of CDR 3 of $AM_{H}3$ Vh	SEQ ID NO:274
Amino acid sequence of CDR 1 of $AM_{H}4$ Vh	SEQ ID NO:275
Amino acid sequence of CDR 2 of $AM_{H}4$ Vh	SEQ ID NO:276
Amino acid sequence of CDR 3 of $AM_{H}4$ Vh	SEQ ID NO:277
Amino acid sequence of CDR 1 of $AM_{H}5$ Vh	SEQ ID NO:278
Amino acid sequence of CDR 2 of $AM_{H}5$ Vh	SEQ ID NO:279
Amino acid sequence of CDR 3 of $AM_{H}5$ Vh	SEQ ID NO:280
Amino acid sequence of CDR 1 of $AM_{H}6$ Vh	SEQ ID NO:281
Amino acid sequence of CDR 2 of $AM_{H}6$ Vh	SEQ ID NO:282
Amino acid sequence of CDR 3 of $AM_{H}6$ Vh	SEQ ID NO:283

TABLE 1-continued

	Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 1 of $AM_{H}7$ Vh	SEQ ID NO:284
Amino acid sequence of CDR 2 of $AM_{H}7$ Vh	SEQ ID NO:285
Amino acid sequence of CDR 3 of $AM_{H}7$ Vh	SEQ ID NO:286
Amino acid sequence of CDR 1 of $AM_{H}8$ Vh	SEQ ID NO:287
Amino acid sequence of CDR 2 of $AM_{H}8$ Vh	SEQ ID NO:288
Amino acid sequence of CDR 3 of $AM_{H}8$ Vh	SEQ ID NO:289
Amino acid sequence of CDR 1 of $AM_{H}9$ Vh	SEQ ID NO:290
Amino acid sequence of CDR 2 of $AM_{H}9$ Vh	SEQ ID NO:291
Amino acid sequence of CDR 3 of $AM_{H}9$ Vh	SEQ ID NO:292
Amino acid sequence of CDR 1 of $AM_{H}10$ Vh	SEQ ID NO:293
Amino acid sequence of CDR 2 of $AM_{H}10$ Vh	SEQ ID NO:294
Amino acid sequence of CDR 3 of $AM_{H}10$ Vh	SEQ ID NO:295
Amino acid sequence of CDR 1 of $AM_{H}11$ Vh	SEQ ID NO:296
Amino acid sequence of CDR 2 of $AM_{H}11$ Vh	SEQ ID NO:297
Amino acid sequence of CDR 3 of $AM_{H}11$ Vh	SEQ ID NO:298

TABLE 1-continued

	Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 1 of $AM_{\gamma}12$ Vh SEQ ID NO:140 SYGIS	SEQ ID NO:299
Amino acid sequence of CDR 2 of $AM_{\gamma}12$ Vh SEQ ID NO:141 WISTYKGNTNYA QKLQG	SEQ ID NO:300
Amino acid sequence of CDR 3 of $AM_{\kappa}12$ Vh SEQ ID NO:142 KQLVFDY	SEQ ID NO:301
Amino acid sequence of CDR 1 of $AM_{\kappa}13$ Vh SEQ ID NO:143 SYGMQ	SEQ ID NO:302
Amino acid sequence of CDR 2 of $AM_{\kappa}13$ Vh SEQ ID NO:144 VIWYDGNKKYYA DSVKG	SEQ ID NO:303
Amino acid sequence of CDR 3 of $AM_{\kappa}13$ Vh SEQ ID NO:145 GRVRDYYYGMD V	SEQ ID NO:304
Amino acid sequence of CDR 1 of $AM_{\gamma}14$ Vh SEQ ID NO:146 RYGIS	SEQ ID NO:305
Amino acid sequence of CDR 2 of $AM_{\gamma}14$ Vh SEQ ID NO:147 WISTYSGNTNYA QKLQG	SEQ ID NO:306
Amino acid sequence of CDR 3 of $AM_{\gamma}14$ Vh SEQ ID NO:148 KQLYFDY	SEQ ID NO:307
Amino acid sequence of CDR 1 of $AM_{\gamma}15$ Vh SEQ ID NO:149 SYGMQ	SEQ ID NO:308
Amino acid sequence of CDR 2 of $AM_{\gamma}15$ Vh SEQ ID NO:150 VIWYDGNKKYYA DSVKG	SEQ ID NO:309
Amino acid sequence of CDR 3 of $AM_{\kappa}15$ Vh SEQ ID NO:151 GRVRDYYYGMD V	SEQ ID NO:310
Amino acid sequence of CDR 1 of $AM_{\gamma}16$ Vh SEQ ID NO:152 SYGIS	SEQ ID NO:311
Amino acid sequence of CDR 2 of $AM_{\gamma}16$ Vh SEQ ID NO:153 WISAYNGNTKYA QKLQG	SEQ ID NO:312
Amino acid sequence of CDR 3 of $AM_{\gamma}16$ Vh SEQ ID NO:154 KQLVFDY	SEQ ID NO:313

TABLE 1-continued

	Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 1 of $AM_{\gamma}17$ Vh SEQ ID NO:155 SYGIS	SEQ ID NO:314
Amino acid sequence of CDR 2 of $AM_{\gamma}17$ Vh SEQ ID NO:156 WISAYSGNTKYA QKLQG	SEQ ID NO:315
Amino acid sequence of CDR 3 of $AM_{\gamma}17$ Vh SEQ ID NO:157 KQLVFDY	SEQ ID NO:316
Amino acid sequence of CDR 1 of $AM_{\gamma}18$ Vh SEQ ID NO:158 DYYMH	SEQ ID NO:317
Amino acid sequence of CDR 2 of $AM_{\gamma}18$ Vh SEQ ID NO:159 QRPQG	SEQ ID NO:318
Amino acid sequence of CDR 3 of $AM_{\gamma}18$ Vh SEQ ID NO:160 YFDL	SEQ ID NO:319
Amino acid sequence of CDR 1 of $AM_{\kappa}19$ Vh SEQ ID NO:161 SYGIS	SEQ ID NO:320
Amino acid sequence of CDR 2 of $AM_{\kappa}19$ Vh SEQ ID NO:162 WISAYSGNTKYA QKFQG	SEQ ID NO:321
Amino acid sequence of CDR 3 of $AM_{\kappa}19$ Vh SEQ ID NO:163 RQLALDY	SEQ ID NO:322
Amino acid sequence of CDR 1 of $AM_{\gamma}20$ Vh SEQ ID NO:164 SYSMN	SEQ ID NO:323
Amino acid sequence of CDR 2 of $AM_{\gamma}20$ Vh SEQ ID NO:165 FISARSSTIYYADS VKG	SEQ ID NO:324
Amino acid sequence of CDR 3 of $AM_{\gamma}20$ Vh SEQ ID NO:166 PKVGGGMDV	SEQ ID NO:325
Amino acid sequence of CDR 1 of $AM_{\gamma}21$ Vh SEQ ID NO:167 SYSMN	SEQ ID NO:326
Amino acid sequence of CDR 2 of $AM_{\gamma}21$ Vh SEQ ID NO:168 YISSRSSIIHYADSV KG	SEQ ID NO:327
Amino acid sequence of CDR 3 of $AM_{\gamma}21$ Vh SEQ ID NO:169 PKVGGGMDV	SEQ ID NO:328

TABLE 1-continued

	Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 1 of AM_H22 Vh SEQ ID NO:170 RYGIS	SEQ ID NO:329
Amino acid sequence of CDR 2 of AM_H22 Vh SEQ ID NO:171 WISAYSGNTNYA QELQG	SEQ ID NO:330
Amino acid sequence of CDR 3 of AM_H22 Vh SEQ ID NO:172 RQLYPDY	SEQ ID NO:331
Amino acid sequence of CDR 1 of AM_H23 Vh SEQ ID NO:173 SYYWS	SEQ ID NO:332
Amino acid sequence of CDR 2 of AM_H23 Vh SEQ ID NO:174 RIYPSGRTNYNPS LKS	SEQ ID NO:333
Amino acid sequence of CDR 3 of AM_H23 Vh SEQ ID NO:175 EAYELQLGLYYY YGMDV	SEQ ID NO:334
Amino acid sequence of CDR 1 of AM_H24 Vh SEQ ID NO:176 SYYWS	SEQ ID NO:335
Amino acid sequence of CDR 2 of AM_H24 Vh SEQ ID NO:177 RIYPSGRTNYNPS LKS	SEQ ID NO:336
Amino acid sequence of CDR 3 of AM_H24 Vh SEQ ID NO:178 EAYELQLGLYYY YGMDV	SEQ ID NO:337
Amino acid sequence of CDR 1 of AM_H25 Vh SEQ ID NO:179 SGGYYWS	SEQ ID NO:338
Amino acid sequence of CDR 2 of AM_H25 Vh SEQ ID NO:180 YSGNTYYNPSLRS	SEQ ID NO:339
Amino acid sequence of CDR 3 of AM_H25 Vh SEQ ID NO:181 EAGGNSAYYYGM DV	SEQ ID NO:340
Amino acid sequence of CDR 1 of AM_H26 Vh SEQ ID NO:182 DYYMS	SEQ ID NO:341
Amino acid sequence of CDR 2 of AM_H26 Vh SEQ ID NO:183 YISSSGSTIYYADS VKG	SEQ ID NO:342
Amino acid sequence of CDR 3 of AM_H26 Vh SEQ ID NO:184 DRTYYFGSGSYEG MDV	SEQ ID NO:343

TABLE 1-continued

	Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 1 of AM_L1 Vl SEQ ID NO:185 RASQGIRNDLG	SEQ ID NO:345
Amino acid sequence of CDR 2 of AM_L1 Vl SEQ ID NO:186 AASSLQS	SEQ ID NO:346
Amino acid sequence of CDR 3 of AM_L1 Vl SEQ ID NO:187 LQHNSNPPT	SEQ ID NO:347
Amino acid sequence of CDR 1 of AM_L2 Vl SEQ ID NO:188 RASQSVSRNLV	SEQ ID NO:348
Amino acid sequence of CDR 2 of AM_L2 Vl SEQ ID NO:189 GASTRAN	SEQ ID NO:349
Amino acid sequence of CDR 3 of AM_L2 Vl SEQ ID NO:190 QQYKSWRT	SEQ ID NO:350
Amino acid sequence of CDR 1 of AM_L3 Vl SEQ ID NO:191 RASQSISSYLN	SEQ ID NO:351
Amino acid sequence of CDR 2 of AM_L3 Vl SEQ ID NO:192 AASSLQS	SEQ ID NO:352
Amino acid sequence of CDR 3 of AM_L3 Vl SEQ ID NO:193 QQSYSTPPT	SEQ ID NO:353
Amino acid sequence of CDR 1 of AM_L4 Vl SEQ ID NO:194 RASQSVSRNLA	SEQ ID NO:354
Amino acid sequence of CDR 2 of AM_L4 Vl SEQ ID NO:195 GASTRAT	SEQ ID NO:355
Amino acid sequence of CDR 3 of AM_L4 Vl SEQ ID NO:196 QQYNNWPTWT	SEQ ID NO:356
Amino acid sequence of CDR 1 of AM_L5 Vl SEQ ID NO:197 RASQGIRNDLG	SEQ ID NO:357
Amino acid sequence of CDR 2 of AM_L5 Vl SEQ ID NO:198 AASSFQS	SEQ ID NO:358
Amino acid sequence of CDR 3 of AM_L5 Vl SEQ ID NO:199 LQHNSYPPT	SEQ ID NO:359

TABLE 1-continued

	Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 1 of AM_L6 V1 SEQ ID NO:200 RASQGIRNDLG	SEQ ID NO:360
Amino acid sequence of CDR 2 of AM_L6 V1 SEQ ID NO:201 AASSLQS	SEQ ID NO:361
Amino acid sequence of CDR 3 of AM_L6 V1 SEQ ID NO:202 LQHKSYPLT	SEQ ID NO:362
Amino acid sequence of CDR 1 of AM_L7 V1 SEQ ID NO:203 RASQGIRNDLG	SEQ ID NO:363
Amino acid sequence of CDR 2 of AM_L7 V1 SEQ ID NO:204 AASSLQS	SEQ ID NO:364
Amino acid sequence of CDR 3 of AM_L7 V1 SEQ ID NO:205 LQHKSYPLT	SEQ ID NO:365
Amino acid sequence of CDR 1 of AM_L8 V1 SEQ ID NO:206 RASQGIRNDLG	SEQ ID NO:366
Amino acid sequence of CDR 2 of AM_L8 V1 SEQ ID NO:207 AASSLQS	SEQ ID NO:367
Amino acid sequence of CDR 3 of AM_L8 V1 SEQ ID NO:208 LQHKSYPLT	SEQ ID NO:368
Amino acid sequence of CDR 1 of AM_L9 V1 SEQ ID NO:209 RASQGIRNDLG	SEQ ID NO:369
Amino acid sequence of CDR 2 of AM_L9 V1 SEQ ID NO:210 AASSLQS	SEQ ID NO:370
Amino acid sequence of CDR 3 of AM_L9 V1 SEQ ID NO:211 LQHKSYPLT	SEQ ID NO:371
Amino acid sequence of CDR 1 of AM_L10 V1 SEQ ID NO:212 RASQGIRSWLA	SEQ ID NO:372
Amino acid sequence of CDR 2 of AM_L10 V1 SEQ ID NO:213 AASSLQS	SEQ ID NO:373
Amino acid sequence of CDR 3 of AM_L10 V1 SEQ ID NO:214 QQANNFPRT	SEQ ID NO:374

TABLE 1-continued

	Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 1 of AM_L11 V1 SEQ ID NO:215 RASQSVSSNLA	SEQ ID NO:375
Amino acid sequence of CDR 2 of AM_L11 V1 SEQ ID NO:216 GASTRAA	SEQ ID NO:376
Amino acid sequence of CDR 3 of AM_L11 V1 SEQ ID NO:217 QHYINWPKWT	SEQ ID NO:377
Amino acid sequence of CDR 1 of AM_L12 V1 SEQ ID NO:218 RASQSISSSLA	SEQ ID NO:378
Amino acid sequence of CDR 2 of AM_L12 V1 SEQ ID NO:219 GASTRAT	SEQ ID NO:379
Amino acid sequence of CDR 3 of AM_L12 V1 SEQ ID NO:220 QQYDNWPLT	SEQ ID NO:380
Amino acid sequence of CDR 1 of AM_L13 V1 SEQ ID NO:221 YLY KSSQSLLHSDGKT	SEQ ID NO:381
Amino acid sequence of CDR 2 of AM_L13 V1 SEQ ID NO:222 EVSTRFS	SEQ ID NO:382
Amino acid sequence of CDR 3 of AM_L13 V1 SEQ ID NO:223 MQSIQLPLT	SEQ ID NO:383
Amino acid sequence of CDR 1 of AM_L14 V1 SEQ ID NO:224 RASQSVSSNLA	SEQ ID NO:384
Amino acid sequence of CDR 2 of AM_L14 V1 SEQ ID NO:225 DASTRAT	SEQ ID NO:385
Amino acid sequence of CDR 3 of AM_L14 V1 SEQ ID NO:226 QQYDNWPLT	SEQ ID NO:386
Amino acid sequence of CDR 1 of AM_L15 V1 SEQ ID NO:227 RASQSVSSNLA	SEQ ID NO:387
Amino acid sequence of CDR 2 of AM_L15 V1 SEQ ID NO:228 DASTRAA	SEQ ID NO:388
Amino acid sequence of CDR 3 of AM_L15 V1 SEQ ID NO:229 QQYDDWPLT	SEQ ID NO:389

TABLE 1-continued

	Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 1 of AM_L16 V1	SEQ ID NO:390
Amino acid sequence of CDR 2 of AM_L16 V1	SEQ ID NO:391
Amino acid sequence of CDR 3 of AM_L16 V1	SEQ ID NO:392
Amino acid sequence of CDR 1 of AM_L17 V1	SEQ ID NO:393
Amino acid sequence of CDR 2 of AM_L17 V1	SEQ ID NO:394
Amino acid sequence of CDR 3 of AM_L17 V1	SEQ ID NO:395
Amino acid sequence of CDR 1 of AM_L18 V1	SEQ ID NO:396
Amino acid sequence of CDR 2 of AM_L18 V1	SEQ ID NO:397
Amino acid sequence of CDR 3 of AM_L18 V1	SEQ ID NO:398
Amino acid sequence of CDR 1 of AM_L19 V1	SEQ ID NO:399
Amino acid sequence of CDR 2 of AM_L19 V1	SEQ ID NO:400
Amino acid sequence of CDR 3 of AM_L19 V1	SEQ ID NO:401
Amino acid sequence of CDR 1 of AM_L20 V1	SEQ ID NO:402
Amino acid sequence of CDR 2 of AM_L20 V1	SEQ ID NO:403
Amino acid sequence of CDR 3 of AM_L20 V1	SEQ ID NO:404

TABLE 1-continued

	Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 1 of AM_L21 V1	SEQ ID NO:405
Amino acid sequence of CDR 2 of AM_L21 V1	SEQ ID NO:406
Amino acid sequence of CDR 3 of AM_L21 V1	SEQ ID NO:407
Amino acid sequence of CDR 1 of AM_L22 V1	SEQ ID NO:408
Amino acid sequence of CDR 2 of AM_L22 V1	SEQ ID NO:409
Amino acid sequence of CDR 3 of AM_L22 V1	SEQ ID NO:410
Amino acid sequence of CDR 1 of AM_L23 V1 version 1	SEQ ID NO:411
Amino acid sequence of CDR 2 of AM_L23 V1 version 1	SEQ ID NO:412
Amino acid sequence of CDR 3 of AM_L23 V1 version 1	SEQ ID NO:413
Amino acid sequence of CDR 1 of AM_L23 V1 version 2	SEQ ID NO:414
Amino acid sequence of CDR 2 of AM_L23 V1 version 2	SEQ ID NO:415
Amino acid sequence of CDR 3 of AM_L23 V1 version 2	SEQ ID NO:416
Amino acid sequence of CDR 1 of AM_L24 V1	SEQ ID NO:417
Amino acid sequence of CDR 2 of AM_L24 V1	SEQ ID NO:418

TABLE 1-continued

		Corresponding Polynucleotide Sequence
Amino acid sequence of CDR 3 of AM_L24 VL	SEQ ID NO:259 MQGTHWPLCS	SEQ ID NO:419
Amino acid sequence of CDR 1 of AM_L25 VL	SEQ ID NO:260 RASQAISIYLA	SEQ ID NO:420
Amino acid sequence of CDR 2 of AM_L25 VL	SEQ ID NO:261 AASSLQS	SEQ ID NO:421
Amino acid sequence of CDR 3 of AM_L25 VL	SEQ ID NO:262 QQYSSYPPRT	SEQ ID NO:422
Amino acid sequence of CDR 1 of AM_L26 VL	SEQ ID NO:263 RASQSVYSNLA	SEQ ID NO:423
Amino acid sequence of CDR 2 of AM_L26 VL	SEQ ID NO:264 GASTRAT	SEQ ID NO:424
Amino acid sequence of CDR 3 of AM_L26 VL	SEQ ID NO:265 QQYYNWPWT	SEQ ID NO:425

As used herein, the term "antibody" refers to the various forms of monomeric or multimeric proteins comprising one or more polypeptide chains that specifically binds to an antigen, as variously described herein. In certain embodiments, antibodies are produced by recombinant DNA techniques. In additional embodiments, antibodies are produced by enzymatic or chemical cleavage of naturally occurring antibodies. In another aspect, the antibody is selected from the group consisting of: a) a human antibody; b) a humanized antibody; c) a chimeric antibody; d) a monoclonal antibody; e) a polyclonal antibody; f) a recombinant antibody; g) an antigen-binding antibody fragment; h) a single chain antibody; i) a diabody; j) a triabody; k) a tetrabody; l) a Fab fragment; m) a $F(ab')_2$ fragment; n) an IgD antibody; o) an IgE antibody; p) an IgM antibody; q) an IgA antibody; r) an IgG1 antibody; s) an IgG2 antibody; t) an IgG3 antibody; and u) an IgG4 antibody.

Traditional antibody structural units typically comprise a tetramer. Each tetramer is typically composed of two identical pairs of polypeptide chains, each pair having one "light" (typically having a molecular weight of about 25 kDa) and one "heavy" chain (typically having a molecular weight of about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subclasses, including, but not limited to IgG1, IgG2, IgG3, and IgG4. IgM has subclasses, including, but not limited to, IgM1 and IgM2. Embodiments of the invention include all such classes of antibodies that incorporate the variable domains or the CDRs of the antigen binding proteins, as described herein.

The general structure and properties of CDRs within naturally occurring antibodies have been described in the art. Briefly, in a traditional antibody scaffold, the CDRs are embedded within a framework in the heavy and light chain variable region where they constitute the regions largely responsible for antigen binding and recognition. A variable region comprises at least three heavy or light chain CDRs (Kabat et al., 1991, *Sequences of Proteins of Immunological Interest*, Public Health Service N.I.H., Bethesda, Md.; see also Chothia and Lesk, 1987, *J. Mol. Biol.* 196:901-917; Chothia et al., 1989, *Nature* 342: 877-883), within a framework region (designated framework regions 1-4, FR1, FR2, FR3, and FR4, by Kabat et al., 1991; see also Chothia and Lesk, 1987, supra). The CDRs provided by the present invention, however, may not only be used to define the antigen binding domain of a traditional antibody structure, but may be embedded in a variety of other scaffold structures, as described herein.

Antibodies of the invention can comprise any constant region known in the art. The light chain constant region can be, for example, a kappa- or lambda-type light chain constant region, e.g., a human kappa- or lambda-type light chain constant region. The heavy chain constant region can be, for example, an alpha-, delta-, epsilon-, gamma-, or mu-type heavy chain constant regions, e.g., a human alpha-, delta-, epsilon-, gamma-, or mu-type heavy chain constant region. In one embodiment, the light or heavy chain constant region is a fragment, derivative, variant, or mutein of a naturally occurring constant region.

The CDRs of the invention also include consensus sequences derived from groups of related monoclonal antibodies. The antibodies may be related by both sequence homology and function, as shown in the Examples. As described herein, a "consensus sequence" refers to amino acid sequences having conserved amino acids common among a number of sequences and variable amino acids that vary within given amino acid sequences. The CDR consensus sequences of the invention include CDRs corresponding to each of H-CDR1, H-CDR2, H-CDR3, L-CDR1, L-CDR2 and L-CDR3.

Consensus sequences were determined using standard phylogenic analyses of the CDRs corresponding to the VH (i.e., Variable Heavy, etc.) & VL of anti-IL-17RA antibodies. Two different approaches were employed. In a first approach, the consensus sequences were determined by keeping the CDRs contiguous within the same sequence corresponding to a VH or VL. In a second approach, the consensus sequences were determined by aligning the various types of CDRs, i.e., H-CDR1, H-CDR2, H-CDR3, L-CDR1, L-CDR2 and L-CDR3 sequences of the IL-17RA antigen binding proteins disclosed herein independently.

In the first approach, briefly, amino acid sequences corresponding to the entire variable domains of either VH or VL were converted to FASTA formatting for ease in processing comparative alignments and inferring phylogenies. Next, framework regions of these sequences were replaced with an artificial linker sequence (GGGAAAGGGAAA, SEQ ID NO:448) so that examination of the CDRs alone could be performed without introducing any amino acid position weighting bias due to coincident events (e.g., such as unrelated antibodies that serendipitously share a common germline framework heritage) whilst still keeping CDRs contigu-

ous within the same sequence corresponding to a VH or VL. VH or VL sequences of this format were then subjected to sequence similarity alignment interrogation using a program that employs a standard ClutalW-like algorithm (see, Thompson et al., 1994, *Nucleic Acids Res.* 22:4673-4680). A gap creation penalty of 8.0 was employed along with a gap extension penalty of 2.0. This program likewise generated phylograms (phylogenic tree illustrations) based on sequence similarity alignments using either UPGMA (unweighted pair group method using arithmetic averages) or Neighbor-Joining methods (see, Saitou and Nei, 1987, *Molecular Biology and Evolution* 4:406-425) to construct & illustrate similarity and distinction of sequence groups via branch length comparison and grouping. Both methods produced similar results but UPGMA-derived trees were ultimately used as the method employs a simpler and more conservative set of assumptions. UPGMA-derived trees are shown in FIG. **1** where similar groups of sequences were defined as having fewer than 15 substitutions per 100 residues (see legend in tree illustrations for scale) amongst individual sequences within the group and were used to define consensus sequence collections. The original sequence alignments generated were employed to empirically examine and document the occurrence of amino acids tolerated at each position with a consensus group and are shown in FIGS. **2** and **3**. Consensus sequences for the groups of similar sequences within each CDR were then prepared. Amino acids that varied within each group were noted with the notation X_n within each consensus sequence.

The H-CDR1 consensus sequences include amino acid sequences selected from the group consisting of: a) X_1YGIS (SEQ ID NO:453), wherein X_1 is selected from the group consisting of R, S and G; b) $X_1YX_2MX_3$ (SEQ ID NO:454), wherein X_1 is selected from the group consisting of D and S; X_2 is selected from the group consisting of Y and S; and X_3 is selected from the group consisting of S and N; and c) SYGMX_1 (SEQ ID NO:455), wherein X_1 is selected from the group consisting of H and Q;

The H-CDR2 consensus sequences include amino acid sequence selected from the group consisting of: a) $WISX_1YX_2GNTX_3YAQX_4X_5QG$ (SEQ ID NO:456), wherein X_1 is selected from the group consisting of A and T; X_2 is selected from the group consisting of N, S and K; X_3 is selected from the group consisting of N and K; X_4 is selected from the group consisting of K and N; and X_5 is selected from the group consisting of L and F; b) $X_1X_2SX_3X_4X_5SX_6IX_7YADSVKG$ (SEQ ID NO:457), wherein X_1 is selected from the group consisting of Y, I and F; X_2 is selected from the group consisting of I and S; X_3 is selected from the group consisting of S and A; X_4 is selected from the group consisting of S and R; and X_5 is selected from the group consisting of G, S and no amino acid; X_6 is selected from the group consisting of T and I; and X_7 is selected from the group consisting of Y and H; and c) $VIWYDGX_1X_2KX_3YADSVKG$ (SEQ ID NO:458), wherein X_1 is selected from the group consisting of S and N; X_2 is selected from the group consisting of N and K; and X_3 is selected from the group consisting of H and Y.

The H-CDR3 consensus sequences include amino acid sequence selected from the group consisting of: a) $X_1QLX_2X_3DY$ (SEQ ID NO:459), wherein X_1 is selected from the group consisting of R and K, X_2 is selected from the group consisting of Y, V, and A, and X_3 is selected from the group consisting of F and L and b) X_1QLX_2PDY (SEQ ID NO:460), wherein X_1 is selected from the group consisting of R and K, and X_2 is selected from the group consisting of Y and V.

The L-CDR1 consensus sequence includes an amino acid sequence selected from the group consisting of: a) $RASQX_1IX_2X_3X_4LX_5$ (SEQ ID NO:461), wherein X_1 is selected from the group consisting of G, S, and A; X_2 is selected from the group consisting of R and S; X_3 is selected from the group consisting of S, I and N; X_4 is selected from the group consisting of W and Y, and X_5 is selected from the group consisting of A and N; b) $RASQSX_1X_2X_3X_4LA$ (SEQ ID NO:462), wherein X_1 is selected from the group consisting of V and I; X_2 is selected from the group consisting of I and S; X_3 is selected from the group consisting of S and T; X_4 is selected from the group consisting of N and S; and X_5 is selected from the group consisting of A and N; and c) $RASQSVX_1X_2NLX_3$ (SEQ ID NO:463), wherein X_1 is selected from the group consisting of Y and S; X_2 is selected from the group consisting of S and R; and X_3 is selected from the group consisting of A and V.

The L-CDR2 consensus sequence includes an amino acid sequence selected from the group consisting of: a) $AASSX_1QS$ (SEQ ID NO:464), wherein X_1 is selected from the group consisting of L and F; b) $AASX_1LQS$ (SEQ ID NO:465), wherein X_1 is selected from the group consisting of S and T; c) $X_1X_2STRAX_3$, wherein X_1 is selected from the group consisting of G and D; X_2 is selected from the group consisting of A and T; and X_3 is selected from the group consisting of T and A; and d) $GASTRAX_1$ (SEQ ID NO:466), wherein X_1 is selected from the group consisting of A, T and N.

The L-CDR3 consensus sequences include amino acid sequences selected from the group consisting of: a) $LQHX_1SYX_2X_3T$ (SEQ ID NO:467), wherein X_1 is selected from the group consisting of K and N; X_2 is selected from the group consisting of P and N; and X_3 is selected from the group consisting of L, F and P; b) $QX_1X_2X_3X_4X_5PX_6T$ (SEQ ID NO:468), wherein X_1 is selected from the group consisting of Q and K; X_2 is selected from the group consisting of A, S and Y; X_3 is selected from the group consisting of N, Y and S; X_4 is selected from the group consisting of N, S and R; X_5 is selected from the group consisting of F, T, Y and A; and X_6 is selected from the group consisting of R and F; c) $QQYDX_1WPLT$ (SEQ ID NO:469), wherein X_1 is selected from the group consisting of N, T and I; and d) $QX_1YX_2X_3WX_4X_5X_6T$ (SEQ ID NO:470), wherein X_1 is selected from the group consisting of H and Q; X_2 is selected from the group consisting of I, Y, N and K; X_3 is selected from the group consisting of N and S; X_4 is selected from the group consisting of P and R; X_5 is selected from the group consisting of K, no amino acid, and T; and X_6 is selected from the group consisting of W and no amino acid.

FIGS. **1**, **2**, **3**, **8A**, **8B**, **11**, and **14** show that a clear pattern in the data exists between sequence homology in the CDR domains and the antibodies function, as determined by cross-competition binning and the determination of where the antibodies bound to IL-17RA. Thus, a structure/function relation for classes of antibodies has been established for the IL-17RA antibodies provided herein.

In a second approach CDR consensus sequences were determined for each separate CDR, independently of their contiguous context within the same sequence corresponding to a VH or VL. In this approach the consensus sequences were determined by aligning each H-CDR1, H-CDR2, H-CDR3, L-CDR1, L-CDR2, and L-CDR3 in groups, i.e., by aligning the individual H-CDR1 sequences of the IL-17RA antigen binding proteins disclosed herein to determine a H-CDR1 consensus sequence, by aligning the individual H-CDR2 sequences of the IL-17RA antigen binding proteins disclosed herein to determine a H-CDR2 consensus sequence, by align-

ing the individual H-CDR3 sequences of the IL-17RA antigen binding proteins disclosed herein to determine a H-CDR3 consensus sequence, by aligning the individual L-CDR1 sequences of the IL-17RA antigen binding proteins disclosed herein to determine a L-CDR1 consensus sequence, by aligning the individual L-CDR2 sequences of the IL-17RA antigen binding proteins disclosed herein to determine a L-CDR2 consensus sequence, and by aligning the individual L-CDR3 sequences of the IL-17RA antigen binding proteins disclosed herein to determine a L-CDR3 consensus sequence. Similarities between sequences within each individual CDR sequences were identified. Consensus sequences for the groups of similar sequences within each CDR were then prepared. Amino acids that varied within each group were noted with the notation X_n within each consensus sequence.

Within light and heavy chains, the variable and constant regions are joined by a "J" region of about twelve (12) or more amino acids, with the heavy chain also including a "D" region of about ten (10) more amino acids. See, generally, Paul, W., ed., 1989, Fundamental Immunology Ch. 7, 2nd ed. Raven Press, N.Y. The variable regions of each light/heavy chain pair form the antibody binding site. Scaffolds of the invention include such regions.

Some naturally occurring antibodies, for example found in camels and llamas, are dimers consisting of two heavy chain and include no light chains. Muldermans et al., 2001, *J. Biotechnol.* 74:277-302; Desmyter et al., 2001, *J. Biol. Chem.* 276:26285-26290. Crystallographic studies of a camel antibody have revealed that the CDR3 regions form a surface that interacts with the antigen and thus is critical for antigen binding like in the more typical tetrameric antibodies. The invention encompasses dimeric antibodies consisting of two heavy chains, or fragments thereof, that can bind to and/or inhibit the biological activity of IL-17RA.

The variable regions of the heavy and light chains typically exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, i.e., the complementarity determining regions or CDRs. The CDRs are the hypervariable regions of an antibody (or antigen binding protein, as outlined herein), that are responsible for antigen recognition and binding. The CDRs from the two chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat Sequences of Proteins of Immunological Interest. Chothia et al., 1987, *J. Mol. Biol.* 196:901-917; Chothia et al., 1989, *Nature* 342:878-883. Scaffolds of the invention include such regions.

CDRs constitute the major surface contact points for antigen binding. See, e.g., Chothia and Lesk, 1987, *J. Mol. Biol.* 196:901-917. Further, CDR3 of the light chain and, especially, CDR3 of the heavy chain may constitute the most important determinants in antigen binding within the light and heavy chain variable regions. See, e.g., Chothia and Lesk, 1987, supra; Desiderio et al., 2001, *J. Mol. Biol.* 310:603-615; Xu and Davis, 2000, *Immunity* 13:37-45; Desmyter et al., 2001, *J. Biol. Chem.* 276:26285-26290; and Muyldermans, 2001, *J. Biotechnol.* 74:277-302. In some antibodies, the heavy chain CDR3 appears to constitute the major area of contact between the antigen and the antibody. Desmyter et al., 2001, supra. In vitro selection schemes in which CDR3 alone is varied can be used to vary the binding properties of an antibody. Muyldermans, 2001, supra; Desiderio et al. 2001, supra.

Naturally occurring antibodies typically include a signal sequence, which directs the antibody into the cellular pathway for protein secretion and which is not present in the mature antibody. A polynucleotide encoding an antibody of the invention may encode a naturally occurring signal sequence or a heterologous signal sequence as described below.

In some embodiments, however, the scaffold components can be a mixture from different species. As such, if the antigen binding protein is an antibody, such antibody may be a chimeric antibody and/or a humanized antibody. In general, both "chimeric antibodies" and "humanized antibodies" refer to antibodies that combine regions from more than one species. For example, "chimeric antibodies" traditionally comprise variable region(s) from a mouse (or rat, in some cases) and the constant region(s) from a human.

"Humanized antibodies" generally refer to non-human antibodies that have had the variable-domain framework regions swapped for sequences found in human antibodies. Generally, in a humanized antibody, the entire antibody, except the CDRs, is encoded by a polynucleotide of human origin or is identical to such an antibody except within its CDRs. The CDRs, some or all of which are encoded by nucleic acids originating in a non-human organism, are grafted into the beta-sheet framework of a human antibody variable region to create an antibody, the specificity of which is determined by the engrafted CDRs. The creation of such antibodies is described in, e.g., WO 92/11018, Jones, 1986, *Nature* 321:522-525, Verhoeyen et al., 1988, *Science* 239:1534-1536. Humanized antibodies can also be generated using mice with a genetically engineered immune system. Roque et al., 2004, *Biotechnol. Prog.* 20:639-654. In the present invention, the identified CDRs are human, and thus both humanized and chimeric antibodies in this context include some non-human CDRs; for example, humanized antibodies may be generated that comprise the CDRH3 and CDRL3 regions, with one or more of the other CDR regions being of a different special origin.

In one embodiment, the antibodies of the invention are a multispecific antibody, and notably a bispecific antibody, also sometimes referred to as "diabodies". These are antibodies that bind to two (or more) different antigens. Diabodies can be manufactured in a variety of ways known in the art (Holliger and Winter, 1993, *Current Opinion Biotechnol.* 4:446-449), e.g., prepared chemically or from hybrid hybridomas.

In one embodiment, the antibody of the invention is a minibody. Minibodies are minimized antibody-like proteins comprising a scFv joined to a CH3 domain. Hu et al., 1996, *Cancer Res.* 56:3055-3061. In one embodiment, the antibody of the invention is a domain antibody; see, for example U.S. Pat. No. 6,248,516. Domain antibodies (dAbs) are functional binding domains of antibodies, corresponding to the variable regions of either the heavy (VH) or light (VL) chains of human antibodies dABs have a molecular weight of approximately 13 kDa, or less than one-tenth the size of a full antibody. dABs are well expressed in a variety of hosts including bacterial, yeast, and mammalian cell systems. In addition, dAbs are highly stable and retain activity even after being subjected to harsh conditions, such as freeze-drying or heat denaturation. See, for example, U.S. Pat. Nos. 6,291,158; 6,582,915; 6,593,081; 6,172,197; US Serial No. 2004/0110941; European Patent 0368684; U.S. Pat. No. 6,696,245, WO04/058821, WO04/003019 and WO03/002609.

In one embodiment, the antibody of the invention is an antibody fragment that retains binding specificity to IL-17RA. In various embodiments, the antibody fragments comprise, but are not limited to, a F(ab), F(ab'), F(ab')2, Fv, or

a single chain Fv fragments. At a minimum, an antibody, as meant herein, comprises a polypeptide that can bind specifically to IL-17RA comprising all or part of a light or heavy chain variable region, such as one or more CDRs.

Further examples of IL-17RA-binding antibody fragments (to be clear, IL-17RA-binding antibody fragments that either compete for binding to human IL-17RA with at least one of the IL-17RA neutralizing antibodies described herein, or bind to one or more of the neutralizing determinants on IL-17RA described herein) include, but are not limited to, (i) the Fab fragment consisting of VL, VH, CL and CH1 domains, (ii) the Fd fragment consisting of the VH and CH1 domains, (iii) the Fv fragment consisting of the VL and VH domains of a single antibody; (iv) the dAb fragment (Ward et al., 1989, *Nature* 341:544-546) which consists of a single variable, (v) isolated CDR regions, (vi) $F(ab')_2$ fragments, a bivalent fragment comprising two linked Fab fragments (vii) single chain Fv molecules (scFv), wherein a VH domain and a VL domain are linked by a peptide linker which allows the two domains to associate to form an antigen binding site (Bird et al., 1988, *Science* 242:423-426, Huston et al., 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:5879-5883), (viii) bispecific single chain Fv dimers (PCT/US92/09965) and (ix) "diabodies" or "triabodies", multivalent or multispecific fragments constructed by gene fusion (Tomlinson et. al., 2000, *Methods Enzymol.* 326:461-479; WO94/13804; Holliger et al., 1993, *Proc. Natl. Acad. Sci. U.S.A.* 90:6444-6448). The antibody fragments may be modified. For example, the molecules may be stabilized by the incorporation of disulphide bridges linking the VH and VL domains (Reiter et al., 1996, *Nature Biotech.* 14:1239-1245). Aspects of the invention include embodiments wherein the non-CDR components of these fragments are human sequences.

In one embodiment, the antibody of the invention is a fully human antibody. In this embodiment, as outlined above, specific structures comprise complete heavy and light chains depicted comprising the CDR regions. Additional embodiments utilize one or more of the CDRs of the invention, with the other CDRs, framework regions, J and D regions, constant regions, etc., coming from other human antibodies. For example, the CDRs of the invention can replace the CDRs of any number of human antibodies, particularly commercially relevant antibodies

Single chain antibodies may be formed by linking heavy and light chain variable domain (Fv region) fragments via an amino acid bridge (short peptide linker), resulting in a single polypeptide chain. Such single-chain Fvs (scFvs) have been prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable domain polypeptides (V_L and V_H). The resulting polypeptides can fold back on themselves to form antigen-binding monomers, or they can form multimers (e.g., dimers, trimers, or tetramers), depending on the length of a flexible linker between the two variable domains (Kortt et al., 1997, Prot. Eng. 10:423; Kortt et al., 2001, Biomol. Eng. 18:95-108). By combining different V_L and V_H-comprising polypeptides, one can form multimeric scFvs that bind to different epitopes (Kriangkum et al., 2001, Biomol. Eng. 18:31-40). Techniques developed for the production of single chain antibodies include those described in U.S. Pat. No. 4,946,778; Bird, 1988, Science 242:423; Huston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879; Ward et al., 1989, Nature 334:544, de Graaf et al., 2002, Methods Mol Biol. 178:379-87.

In one embodiment, the antibodies that compete for binding to human IL-17RA with the IL-17RA neutralizing antibodies described herein, or antibodies that bind to the neutralizing determinants described herein may be an antibody fusion protein (sometimes referred to herein as an "antibody conjugate"). The conjugate partner can be proteinaceous or non-proteinaceous; the latter generally being generated using functional groups on the antigen binding protein (see the discussion on covalent modifications of the antigen binding proteins) and on the conjugate partner. For example linkers are known in the art; for example, homo- or hetero-bifunctional linkers as are well known (see, 1994 Pierce Chemical Company catalog, technical section on cross-linkers, pages 155-200, incorporated herein by reference).

In one embodiment, the antibodies that compete for binding to human IL-17RA with the IL-17RA neutralizing antibodies described herein, or antibodies that bind to the neutralizing determinants described herein may be an antibody analog, sometimes referred to as "synthetic antibodies." For example, a variety of recent work utilizes either alternative protein scaffolds or artificial scaffolds with grafted CDRs. Such scaffolds include, but are not limited to, mutations introduced to stabilize the three-dimensional structure of the binding protein as well as wholly synthetic scaffolds consisting for example of biocompatible polymers. See, for example, Korndorfer et al., 2003, *Proteins: Structure, Function, and Bioinformatics*, Volume 53, Issue 1:121-129. Roque et al., 2004, *Biotechnol. Prog.* 20:639-654. In addition, peptide antibody mimetics ("PAMs") can be used, as well as work based on antibody mimetics utilizing fibronectin components as a scaffold. As it is known in the art, a number of different programs can be used to identify the degree of sequence identity or similarity a protein or nucleic acid has to a known sequence.

By "protein," as used herein, is meant at least two covalently attached amino acids, which includes proteins, polypeptides, oligopeptides and peptides. In some embodiments, the two or more covalently attached amino acids are attached by a peptide bond. The protein may be made up of naturally occurring amino acids and peptide bonds, for example when the protein is made recombinantly using expression systems and host cells, as outlined below. Alternatively, the protein may include synthetic amino acids (e.g., homophenylalanine, citrulline, ornithine, and norleucine), or peptidomimetic structures, i.e., "peptide or protein analogs", such as peptoids (see, Simon et al., 1992, *Proc. Natl. Acad. Sci. U.S.A.* 89:9367, incorporated by reference herein), which can be resistant to proteases or other physiological and/or storage conditions. Such synthetic amino acids may be incorporated in particular when the antigen binding protein is synthesized in vitro by conventional methods well known in the art. In addition, any combination of peptidomimetic, synthetic and naturally occurring residues/structures can be used. "Amino acid" also includes imino acid residues such as proline and hydroxyproline. The amino acid "R group" or "side chain" may be in either the (L)- or the (S)-configuration. In a specific embodiment, the amino acids are in the (L)- or (S)-configuration.

In some embodiments, the antigen binding proteins of the invention are isolated proteins or substantially pure proteins. An "isolated" protein is unaccompanied by at least some of the material with which it is normally associated in its natural state, for example constituting at least about 5%, or at least about 50% by weight of the total protein in a given sample. It is understood that the isolated protein may constitute from 5 to 99.9% by weight of the total protein content depending on the circumstances. For example, the protein may be made at a significantly higher concentration through the use of an inducible promoter or high expression promoter, such that the protein is made at increased concentration levels. The defini-

tion includes the production of an antigen binding protein in a wide variety of organisms and/or host cells that are known in the art.

For amino acid sequences, sequence identity and/or similarity is determined by using standard techniques known in the art, including, but not limited to, the local sequence identity algorithm of Smith and Waterman, 1981, *Adv. Appl. Math.* 2:482, the sequence identity alignment algorithm of Needleman and Wunsch, 1970, *J. Mol. Biol.* 48:443, the search for similarity method of Pearson and Lipman, 1988, *Proc. Nat. Acad. Sci. U.S.A.* 85:2444, computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.), the Best Fit sequence program described by Devereux et al., 1984, *Nucl. Acid Res.* 12:387-395, preferably using the default settings, or by inspection. Preferably, percent identity is calculated by FastDB based upon the following parameters: mismatch penalty of 1; gap penalty of 1; gap size penalty of 0.33; and joining penalty of 30, "Current Methods in Sequence Comparison and Analysis," Macromolecule Sequencing and Synthesis, Selected Methods and Applications, pp 127-149 (1988), Alan R. Liss, inc. An example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments. It can also plot a tree showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng & Doolittle, 1987, *J. Mol. Evol.* 35:351-360; the method is similar to that described by Higgins and Sharp, 1989, *CABIOS* 5:151-153. Useful PILEUP parameters including a default gap weight of 3.00, a default gap length weight of 0.10, and weighted end gaps.

Another example of a useful algorithm is the BLAST algorithm, described in: Altschul et al., 1990, *J. Mol. Biol.* 215: 403-410; Altschul et al., 1997, *Nucleic Acids Res.* 25:3389-3402; and Karin et al., 1993, *Proc. Natl. Acad. Sci. U.S.A.* 90:5873-5787. A particularly useful BLAST program is the WU-BLAST-2 program which was obtained from Altschul et al., 1996, *Methods in Enzymology* 266:460-480. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span=1, overlap fraction=0.125, word threshold (T)=11. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity.

An additional useful algorithm is gapped BLAST as reported by Altschul et al., 1993, *Nucl. Acids Res.* 25:3389-3402. Gapped BLAST uses BLOSUM-62 substitution scores; threshold T parameter set to 9; the two-hit method to trigger ungapped extensions, charges gap lengths of k a cost of 10+k; X_u set to 16, and X_g set to 40 for database search stage and to 67 for the output stage of the algorithms. Gapped alignments are triggered by a score corresponding to about 22 bits.

Amino acid substitutions are typically of single residues; insertions usually will be on the order of from about one (1) to about twenty (20) amino acid residues, although considerably larger insertions may be tolerated. Deletions range from about one (1) to about twenty (20) amino acid residues, although in some cases deletions may be much larger.

Substitutions, deletions, insertions or any combination thereof may be used to arrive at a final derivative or variant. Generally these changes are done on a few amino acids to minimize the alteration of the molecule, particularly the immunogenicity and specificity of the antigen binding protein. However, larger changes may be tolerated in certain circumstances. Conservative substitutions are generally made in accordance with the following chart depicted as TABLE 2.

TABLE 2

Original Residue	Exemplary Substitutions
Ala	Ser
Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Pro
His	Asn, Gln
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile
Phe	Met, Leu, Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp, Phe
Val	Ile, Leu

Substantial changes in function or immunological identity are made by selecting substitutions that are less conservative than those shown in TABLE 2. For example, substitutions may be made which more significantly affect: the structure of the polypeptide backbone in the area of the alteration, for example the alpha-helical or beta-sheet structure; the charge or hydrophobicity of the molecule at the target site; or the bulk of the side chain. The substitutions which in general are expected to produce the greatest changes in the polypeptide's properties are those in which (a) a hydrophilic residue, e.g., seryl or threonyl, is substituted for (or by) a hydrophobic residue, e.g., leucyl, isoleucyl, phenylalanyl, valyl or alanyl; (b) a cysteine or proline is substituted for (or by) any other residue; (c) a residue having an electropositive side chain, e.g., lysyl, arginyl, or histidyl, is substituted for (or by) an electronegative residue, e.g., glutamyl or aspartyl; or (d) a residue having a bulky side chain, e.g., phenylalanine, is substituted for (or by) one not having a side chain, e.g., glycine.

The variants typically exhibit the same qualitative biological activity and will elicit the same immune response as the naturally-occurring analogue, although variants also are selected to modify the characteristics of the antigen binding protein proteins as needed. Alternatively, the variant may be designed such that the biological activity of the antigen binding protein is altered. For example, glycosylation sites may be altered or removed as discussed herein.

Antibodies that compete for binding to human IL-17RA with the IL-17RA neutralizing antibodies described herein, or antibodies that bind to the neutralizing determinants described herein may comprise oligomers that contain one or more antibody polypeptides. Oligomers may be in the form of covalently-linked or non-covalently-linked dimers, trimers, or higher oligomers. Oligomers comprising two or more IL-17RA antibody polypeptides are contemplated for use, with one example being a homodimer. Other oligomers include heterodimers, homotrimers, heterotrimers, homotetramers, heterotetramers, etc. Such oligomers may be joined via covalent or non-covalent interactions between peptide moieties fused to the IL-17RA antibody polypeptides. Such

peptides may be peptide linkers (spacers), or peptides that have the property of promoting oligomerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote oligomerization of IL-17RA antibody polypeptides attached thereto, as described in more detail below.

In one embodiment, an oligomer is prepared using polypeptides derived from immunoglobulins. Preparation of fusion proteins comprising certain heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described, e.g., by Ashkenazi et al., 1991, PNAS USA 88:10535; Byrn et al., 1990, Nature 344:677; and Hollenbaugh et al., 1992 "Construction of Immunoglobulin Fusion Proteins", in *Current Protocols in Immunology*, Suppl. 4, pages 10.19.1-10.19.11.

One embodiment is directed to a dimer comprising two fusion proteins created by fusing an IL-17RA binding fragment of an IL-17RA antibody to the Fc region of an antibody. The dimer can be made by, for example, inserting a gene fusion encoding the fusion protein into an appropriate expression vector, expressing the gene fusion in host cells transformed with the recombinant expression vector, and allowing the expressed fusion protein to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc moieties to yield the dimer.

The term "Fc polypeptide" as used herein includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising Fc moieties (and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

One suitable Fc polypeptide, described in PCT application WO 93/10151 (hereby incorporated by reference), is a single chain polypeptide extending from the N-terminal hinge region to the native C-terminus of the Fc region of a human IgG antibody. Another useful Fc polypeptide is the Fc mutein described in U.S. Pat. No. 5,457,035 and in Baum et al., 1994, *EMBO J.* 13:3992-4001. The amino acid sequence of this mutein is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. The mutein exhibits reduced affinity for Fc receptors.

Use of Antibodies that Compete for Binding with the IL-17RA Antibodies, or Antibodies that Bind IL-17RA Neutralizing Determinants for Diagnostic and Therapeutic Purposes

Antibodies that compete for binding to human IL-17RA with the IL-17RA neutralizing antibodies described herein, or antibodies that bind to the neutralizing determinants described herein can be used in diagnostic assays, e.g., binding assays to detect and/or quantify IL-17RA expressed in a tissue or cell. Said antibodies may be used in research to further investigate the role of IL-17RA in disease. Said antibodies may be used to further investigate the role of IL-17RA in forming homomeric and/or heteromeric receptor complexes and the role of said complexes in disease. Said antibodies may be used to further investigate the role of IL-17RA activation to homomeric and/or heteromeric IL-17 ligand complexes. Said antibodies may be used to further investigate the role of IL-17RA activation to homomeric mid/or heteromeric IL-17 ligand complexes and how said homomeric and/or heteromeric IL-17 ligand complexes relate to disease.

The IL-17RA neutralizing antibodies and antibodies that compete for binding to human IL-17RA with the IL-17RA neutralizing antibodies described herein, or antibodies that bind to the neutralizing determinants described herein can be used for the prevention or treatment of diseases or conditions associated with the IL-17A and/or IL-17F activity. A disease or condition associated with IL-17A and/or IL-17F means any disease, condition, or pathology whose onset in a patient is caused or exacerbated by the interaction of IL-17A and/or IL-17F with IL-17RA. The severity of the disease, condition, or pathology can also be increased or decreased by the modulating the interaction of IL-17A and/or IL-17F with IL-17RA or a heterologous complex comprising IL-17RA and IL-17RC.

Antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein may be used to reduce IL-17RA activity. Antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein may be used to inhibit binding and/or signaling of IL-17A and/or IL-17F to IL-17RA. In certain embodiments, the antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein inhibits binding and/or signaling of IL-17A and IL-17F to IL-17RA. In additional embodiments, the antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein inhibits binding and/or signaling of IL-17A but not IL-17F to IL-17RA. In other embodiments, the antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein inhibits binding and/or signaling of IL-17F and not IL-17A to IL-17RA. The antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein may be used in treating the consequences, symptoms, and/or the pathology associated with IL-17RA activity. The antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein may be used to inhibit the production of one or more of an inflammatory cytokine, chemokine, matrix metalloproteinase, or other molecule associated with IL-17RA activation. The antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein may be used in methods of inhibiting production of molecules such as but is not limited to: IL-6, IL-8, CXCL1, CXCL2, GM-CSF, G-CSF, M-CSF, IL-1β, TNFα, RANK-L, LIF, PGE2, IL-12, MMPs (such as but not limited to MMP3 and MMP9), GROα, NO, and/or C-telopeptide and the like, comprising administering an antigen binding protein. The antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein inhibit proinflammatory and proautoimmune immune responses and may be used to treat diseases associated with activity of the IL-17A and/or IL-17F/IL-17RA pathway.

Aspects of the invention include antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein that specifically bind to human IL-17RA and partially or fully inhibit IL-17RA from forming either a homomeric or heteromeric functional receptor complex, such as, but not limited to IL-17RA/IL-17RC complex and do not necessarily inhibit IL-17A and/or IL-17F or an

IL-17A/IL-17F heteromer from binding to IL-17RA or a IL-17RA heteromeric receptor complex. Thus, disease states associated with IL-17RC are also associated with IL-17RA due to the fact that IL-17RC cannot signal without IL-17RA. For example, see You, Z., et al., *Cancer Res.*, 2006 Jan. 1; 66(1):175-83 and You, Z., et al., *Neoplasia*, 2007 June; 9(6): 464-70.

Antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein can be used for diagnostic purposes to detect, diagnose, or monitor diseases and/or conditions associated with IL-17A or IL-17RA. The invention provides for the detection of the presence of IL-17RA in a sample using classical immunohistological methods known to those of skill in the art (e.g., Tijssen, 1993, *Practice and Theory of Enzyme Immunoassays*, vol 15 (Eds R. H. Burdon and P. H. van Knippenberg, Elsevier, Amsterdam); Zola, 1987, *Monoclonal Antibodies: A Manual of Techniques*, pp. 147-158 (CRC Press, Inc.); Jalkanen et al., 1985, *J. Cell. Biol.* 101:976-985; Jalkanen et al., 1987, *J. Cell Biol.* 105:3087-3096). The detection of IL-17RA can be performed in vivo or in vitro.

Diagnostic applications provided herein include use of the antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein to detect expression of IL-17RA and binding of the ligands to IL-17RA. Examples of methods useful in the detection of the presence of IL-17RA include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA).

One aspect of the invention provides for identifying a cell or cells that express IL-17RA. In a specific embodiment, the antibodies that compete for binding with the IL-17RA neutralizing antibodies described herein or antibodies that bind to the neutralizing determinants described herein is labeled with a labeling group and the binding of the labeled antigen binding protein to IL-17RA is detected.

All references cited within the body of the instant specification are hereby expressly incorporated by reference in their entirety.

EXAMPLES

The following examples, including the experiments conducted and the results achieved, are provided for illustrative purposes only and are not to be construed as limiting the invention.

Example 1

IL-17RA neutralizing antibodies were shown to reduce incidence of arthritis in a CIA (Collagen-Induced Arthritis) mouse model when administered prophylactically and therapeutically. The IL-17RA inhibition reduced clinical arthritis in both a prophylactic and therapeutic manner for several models if CIA.

The surrogate neutralizing mouse IL-17RA mAb administered prophylactically reduced mean clinical scores in wild-type CIA model in a dose-dependent manner. FIG. **4** shows the dose-dependent inhibition by IL-17RA mAb in wild-type CIA model. Mice were treated with either IL-17RA mAb or control Ig on a Monday, Wednesday and Friday schedule for 2.5 weeks post boost. Administration of 100 μg and 300 μg of IL-17RA antibodies resulted in a lower clinical score for 18 days post-boost than compared to isotype control Ig.

A reduction in bone loss and cartilage erosion in the joint was associated with the reduction of mean clinical scores at the 300 μg dose of the IL-17RA mAb. Histopathologic analysis and radiographic images analysis were compared to the IgG control. By both means of analysis, the ankle joint of the near paw of CBA/1 male mouse treated with an IL-18R mAb (isotype control) showed marked inflammation: subchondrial bone erosion of the talus, marked joint architecture disruption of tarsal-metatarsal joints (subchondrial bone and articular cartilage erosion), and reactive periosteal bone formation (osteophytosis). In stark contrast, the ankle joint of the rear paw of a DBA/1 mouse treated with 300 μg anti-IL-17RA mAb showed well-defined joint spaces, lack of edema and lack of periosteal reactive bone or lytic lesions indicated reduced bone loss and cartilage erosion.

Example 2

IL-17RA inhibition was also shown to be effective in a CIA model when dosing was initiated after the onset of clinical signs (i.e, therapeutic dosing protocol) in a wild-type and TNFR p55/p75 KO model. Treatment was initiated approximately 6-7 days post collagen introduction in both models. FIG. **5** shows that therapeutic treatment with IL-17RA mAb stabilized mean clinical scores in both wild-type mice. FIG. **6** shows that therapeutic treatment with IL-17RA mAb stabilized mean clinical scores in TNFR p55/p75 KO models. Mice were treated with either an IL-17RA mAb, IL-1R mAb, or control Ig on a Monday, Wednesday and Friday schedule for 2 weeks post randomization into therapeutic treatment groups. These data are representative of 2 independent experiments performed in both WT and TNFR p55/p75 KO CIA models. Administering IL-17RA mAbs showed a reduced clinical score as compared to control IgG in CIA induced wild-type mice. Surprisingly, the similar efficacy of IL-17RA mAbs in the TNF p55/p75 KO model stabilized CIA independently of TNF signaling. This data suggests IL-17RA neutralizing antibodies therapy may pick up non-responders to anti-TNF therapies. Combination therapy of an IL-17RA antigen binding protein with anti-TNF therapies may be more beneficial than either alone.

Example 3

The development of fully human monoclonal antibodies directed against human IL-17RA was carried out using Abgenix (now Amgen Fremont Inc.) XenoMouse® technology (U.S. Pat. Nos. 6,114,598; 6,162,963; 6,833,268; 7,049,426; 7,064,244, which are incorporated herein by reference in their entirety; Green et al, 1994, *Nature Genetics* 7:13-21; Mendez et al., 1997, *Nature Genetics* 15:146-156; Green and Jakobovitis, 1998, *J. Ex. Med.* 188:483-495)). TABLE 4 shows the portions of the IL-17RA protein used as an immunogen and cell lines used to generate and screen anti-IL-17RA antibodies.

TABLE 4

Reagent	Description
IL-17RA.Fc	Human IL-17RA extracellular domain with a C-terminal human Fc domain. Expressed in a stable CHO cell line.
IL-17RA-FLAG-polyHis (SEQ ID NO: 431)	Human IL-17RA extracellular domain with a C-terminal FLAG-polyHis tag. Expressed by transient transfection in COS PKB cells.

TABLE 4-continued

Reagent	Description
IL-17RA CHO cells	Human IL-17RA full-length expressed on the surface of CHO cells.

IgG2 XenoMouse® mice were immunized/boosted with IL-17RA-Fc (group 1) and IL-17RA-FLAG-polyHis (group 2). Serum titers were monitored by ELISA and mice with the best titers were fused to generate hybridomas. The resulting polyclonal supernatants were screened for binding to IL-17RA by ELISA, and the positive supernatants were screened for binding to IL-17RA CHO cells by FMAT. Positive supernatants were subjected to additional screening. IgG2 XenoMouse® mice were immunized with the following immunogens: IL-17RA-Fc (group 3) and IL-17RA-FLAG-pHis (group 4) and were tested following additional immunizations.

Example 4

The IL-17RA antibodies were characterized. Non-clonal hybridoma supernatants were prepared in volumes of 1-2 mls (the Ig concentrations were not determined for these supernatants). The anti-IL-17RA non-clonal hybridoma supernatants were initially screened by FACS for their ability to inhibit biotinylated human IL-17A binding to CHO cells over-expressing human IL-17RA and another CHO cell line over-expressing cynomolgus IL-17RA. Nonclonal supernatants that were able to completely or nearly completely inhibit binding of human IL-17A to CHO-huIL-17RA and CHO-cynoIL-17RA were subsequently screened at several dilutions in an IL-17A-induced cytokine/chemokine secretion assay using a human foreskin fibroblast (HFF) cell line. Anti-IL-17RA non-clonal supernatants were incubated with HFF cells (5000 cells/well in 96 well plate) for 30 minutes at 36° C. and then stimulated overnight with either IL-17A (5 ng/ml) alone or IL-17F (20 ng/ml) and TNF-alpha (5 ng/ml). Fibroblast culture supernatants were then analyzed by ELISA for the presence of either IL-6 or GRO-alpha. Anti-IL-17RA non-clonal hybridomas were selected for sub-cloning based on their performance in the CHO-IL-17RA FACS assay and HFF bioassay. An example of the selection is shown in TABLES 5, 6, and 7.

TABLE 5

				HFF Bioassay		Repeat assays		
	% positive	% positive	MFI	1:4 dil.	1:32	1:4	1:32	1:128
				% inhibition of IL-6 production				
Neg. Cntl.	1.09	1.57	10					
IL-17 biot. (500 ng/ml)	8.85	10.22	77					
Supernatant I.D.								
1	1.34	1.78	9	56	14			
2 (incl. AM_H15/AM_L15)	0.60	3.77	6	80	72	98	91	81
3	1.04	1.60	8	46	−5			
4 (incl. AM_H14/AM_L14)	1.72	0.79	10	90	82	99	92	84
5	1.59	1.43	11	76	52			
6	1.45	1.93	14	82	79			
7	1.00	1.28	8	71	58			
8	1.43	1.60	14	69	31			
9	1.34	2.28	18	59	20			
10	0.79	1.96	11	58	−2			
11	1.93	1.69	11	72	21			
12	2.23	1.69	8	69	7			
13 (incl. AM_H21/AM_L21)	1.49	0.49	6	82	53			
14	1.01	1.25	8	63	23			
15	1.31	1.45	9	74	45			
16	1.39	0.72	8	58	4			
17	0.91	0.94	7	73	38			
18	1.37	2.85	13	49	6			
19	1.47	1.15	8	74	61			
20	1.60	1.20	7	72	46			
21	1.30	1.65	8	47	4			
22	0.93	1.02	8	54	16			
23	1.08	1.12	7	72	59			

In TABLE 5, anti-IL-17RA non-clonal hybridoma supernatants were screened for binding to IL-17RA. The first half of TABLE 5 shows the % positive and mean fluorescent intensity (MFI) in results from flow cytometry (i.e, FACS). The % positive shows inhibition of biotin-huIL-17A binding to huIL-17RA$^+$ CHO cells by the non-clonal hybridoma supernatants. The MFI column shows inhibition of biotinylated huIL-17A binding to cyno IL-17RA$^+$ CHO cells by the non-clonal hybridoma supernatants. The second half of TABLE 5 shows the HFF binding intensity for the non-clonal and mAbs as measured by the % intensity of IL-6 production. The first 2 columns show an IL-17A/HFF bioassay with non-clonal hybridoma supernatants and the last 4 columns are repeat IL-17A/HFF bioassay results with non-clonal hybridoma supernatants.

TABLE 6

	FACS results on 293-Cyno IL-17RA-expressing Cells			HFF bioassay		repeat			
	% positive	% positive	MFI	1:4 dilution	1:32	1:4	1:32	1:128	1:512
				% inhibition of IL-6 production					
Neg. Cntl	1.09	1.57	1.0						
IL-17 biot. (500 ng/ml) Supernatant I.D.	8.85	10.22	77						
1 (incl. AM_H1/AM_L1)	1.32	1.4	9						
2	0.87	2.92	9						
3	1.0	4.47	16						
4	1.03	5.01	17						
5	0.6	6.53	18						
6 (incl. AM_H5/AM_L5)	0.73	4.55	9						
7	0.59	5.18	8						
8	0.45	7.25	7						
9	2.34	2.36	6	61	36				
10	6.76	8.35	64	37	12				
11	0.78	1.16	6	61	24				
12	0.61	1.64	6	74	56	71	67	45	35
13	2.98	5.48	22	−2	−13				
14	5.34	10.64	49	22	2	3	39	31	34
15	0.5	3.24	11	51	−7				
16 (incl. AM_H22/AM_L22)	0.54	2.93	18	92	72	91	73	73	29
17	1.25	2.2	17	−8	−76				
18	0.61	0.99	7	73	28				
19 (incl. AM_H23)	0.69	1.72	10	79	72	86	76	67	50
20	1.53	1.94	31	5	−31				
21	6.66	9.63	66	−15	4				
22	6.33	10.32	71	1	14				
23	0.3	2.55	7	50	35				
24	0.24	4.11	6	34	15				
25	0.81	0.99	8	−49	11				
26	0.43	1.31	7	67	48				
27	0.7	1.23	11	50	26				
28	0.58	1.32	9	56	47				
29 (incl. AM_H1/AM_L1)	0.8	1.85	11	77	76	90	87	79	66
30	0.69	1.55	11	40	16				
31	0.56	1.96	12	12	−11				
32	0.21	1.11	8	46	7				
33	1.24	1.15	13	68	43				
34	0.74	0.81	11	36	8				
35	0.71	1.37	9	65	21				
36	0.57	1.21	7	78	32				
37	0.59	1.0	8	71	3				
38	0.65	1.43	8	63	−38				
39	0.28	1.23	7	43	−21				
40	0.35	2.48	9	50	−39				
41	0.64	1.61	8	49	−19				
42	0.12	1.04	8	87	68	96	92	80	66
43	0.21	1.12	11	79	34				
44	0.32	1.33	8	68	−3				
45	0.74	1.68	10	40	−16				
46	0.58	1.74	10	64	7				

TABLE 6 shows IL-17RA non-clonal hybridoma supernatant screening data. The % positive and MFI columns show results from flow cytometry (FACS). The % positive columns show inhibition of biotin-huIL-17A binding to huIL-17RA$^+$ CHO cells by the non-clonal hybridoma supernatants. The MFI column shows inhibition of biotinylated huIL-17A binding to cyno IL-17RA$^+$ CHO cells by the non-clonal hybridoma supernatants. The first 2 HFF bioassay columns are IL-17A/HFF bioassay with non-clonal hybridoma supernatants and the last 4 bioassay columns are repeat IL-17A/HFF

bioassay results with selected non-clonal hybridoma supernatants. A number of supernatants were selected for subcloning.

TABLE 7

				HFF bioassay		
	% positive		MFI	1:4 % inhibition of IL-6 Production	1:32	1:128
Neg. Ctrl	1.09	1.57	10			
IL-17 biot. (500 ng/ml)	8.85	10.22	77			
Supernatant I.D.						
1	1.85	1.33	10	29	9	21
2	1.08	1.46	16	90	61	50
3	1.29	1.39	22	33	10	4
4	1.55	1.33	18	53	66	58
5	1.69	0.7	8	76	46	30
6 (incl. AM_H13/AM_L13)	1.52	0.89	6	73	78	75
7	1.54	0.98	7	79	71	45
8	1.78	3.44	34	73	63	30
9	6.34	8.45	53	57	48	34
10	1.23	1.58	10	82	71	31
11	1.62	2.1	28	-10	-6	-10
12	1.15	1.04	16	71	63	37
13	2.43	1.67	12	58	23	-4
14	1.43	1.03	13	42	17	18
15	1.62	1.59	18	67	59	31
16	1.79	2.2	25	61	57	45
17	0.91	1.85	10	49	54	23
18 (incl. AM_H12/AM_L12)	1	1.36	6	75	82	61
19 (incl. AM_H17/AM_L17)	1.75	1.23	8	90	81	73
20	2.31	0.49	9	35	20	38
21 (incl. AM_H16/AM_L16)	1.84	0.76	6	86	90	71

TABLE 7 shows anti-IL-17RA non-clonal hybridoma supernatant screening data. The first two columns are flow cytometry data (FACS). The % positive columns show inhibition of biotin-huIL-17A binding to huIL-17RA$^+$ CHO cells by the non-clonal hybridoma supernatants. The MFI column shows inhibition of biotinylated huIL-17A binding to cynomolgus IL-17RA$^-$ CHO cells by the non-clonal hybridoma supernatants. The final three columns show IL-17A/HFF bioassay results with non-clonal hybridoma supernatants. Supernatants 6, 18, 19 and 21 were selected for subcloning.

TABLE 8

Sub-clone ID	IL-17A/HFF bioassay IC_{50} (nM)	Low resolution BIAcore K_D(nM)
1. Subclone of (AM_H14/AM_L14)	0.12	0.69
2. Subclone of (AM_H14/AM_L14)2	0.20	ND
3. Subclone of (AM_H14/AM_L14)3	0.075	ND
4. Subclone of (AM_H21/AM_L21)	2.3	ND
5. Subclone of (AM_H21/AM_L21)	3.1	ND
6. Subclone of (AM_H21/AM_L21)	3.3	16.7
7. Subclone of (AM_H20/AM_L20)	8.1	ND
8. Subclone of (AM_H20/AM_L20)	6.6	ND
9. Subclone of (AM_H20/AM_L20)	6.7	11.6
10. Subclone of (AM_H19/AM_L19)	0.22	3.1
11. Subclone of (AM_H19/AM_L19)	1.1	ND
12. Subclone of (AM_H19/AM_L19)	0.50	ND
13. Subclone of (AM_H13/AM_L13)	>10	7.6
14. Subclone of (AM_H18/AM_L18)	0.44	ND
15. Subclone of (AM_H18/AM_L18)	0.40	ND
16. Subclone of (AM_H18/AM_L18)	0.17	14.9
17. Subclone of (AM_H12/AM_L12)	3.5	ND
18. Subclone of (AM_H12/AM_L12)	3.7	8.2
20. Subclone of (AM_H12/AM_L12)	5.5	ND
21. Subclone of (AM_H17/AM_L17)	2.5	8.2
22. Subclone of (AM_H17/AM_L17)	5.3	ND

TABLE 8-continued

Sub-clone ID	IL-17A/HFF bioassay IC_{50} (nM)	Low resolution BIAcore K_D(nM)
23. Subclone of (AM_H17/AM_L17)	0.57	ND
24. Subclone of (AM_H16/AM_L16)	1.6	ND
25. Subclone of (AM_H16/AM_L16)	2.3	6.2
26. Subclone of (AM_H16/AM_L16)	1.4	ND
27. Subclone of (AM_H22/AM_L22)	0.046	1.5
28. Subclone of (AM_H22/AM_L22)	0.09	ND
29. Subclone of (AM_H22/AM_L22)	0.07	ND

ND = not determined

TABLE 8 shows IL-17A/HFF bioassay IC50 values and low resolution BIAcore® K_D values for subcloned hybridomas. Lower IC50 and K_D values in the IL-17A/HFF IL-17RA binding assays showed that the IL-17RA mAbs inhibited binding of IL-17A to IL-17 receptor A. Antibodies were selected for further characterization based on low K_D values for inhibiting IL-17A binding to human IL-17RA.

Example 5

IL-17RA human mAb clones having the heavy and light chain sequences (AM_H22/AM_L22), (AM_H19/AM_L19), (AM_H18/AM_L18) and (AM_H14/AM_L14) were selected for further bioassay characterization. TABLE 9 below shows IC50 values for the selected Abs in the HFF bioassay and a primary lung fibroblast bioassay against both IL-17A and IL-17F.

TABLE 9

IL-17RA mAb	IL-17A/HFF IC50 (nM)	IL-17F/HFF IC50(nM)	IL-17A/lung fibroblast IC50(nM)
(AM_H14/AM_L14)	0.13	0.067	0.04
(AM_H22/AM_L22)	0.10	0.033	0.14
(AM_H19/AM_L19)	0.20	0.087	0.22
(AM_H18/AM_L18)	0.33	0.073	0.081

The selected human mAbs inhibited IL-17A binding to IL-17RA. In addition to the lower IC50 values observed for IL-17A binding to IL-17RA, the selected human mAbs exhibited reduced IC50 values inhibiting the binding of IL-17F to IL-17RA (second column). Therefore, the selected human mAbs inhibit both IL-17A-IL-17RA binding and IL-17F-IL-17RA binding.

Example 6

Exemplary IL-17RA human mAbs were tested in a cynomolgus bioassay utilizing the cynomolgus-derived kidney epithelial cell line JTC-12 stimulated with cynomolgus IL-17A. FIG. 4 shows IL-17RA mAbs having the heavy and light chain sequences (AM_H22/AM_L22), (AM_H19/AM_L19), (AM_H18/AM_L18) and (AM_H14/AM_L14) in the inhibition of cynomolgus IL-17A-induced IL-6 production from JTC-12 cells. The (----) line depicts the positive control value of cynomolgus IL-17 in combination with TNF-alpha. The (-.-.-) line depicts the positive control value of cynomolgus TNF-alpha. The (....) line depicts the media control value. JTC-12 cells were preincubated for 30 mins with anti-IL-17RA mAbs and then stimulated overnight with cynomolgus IL-17A (5 ng/ml) and human TNF-alpha (5 ng/ml). FIG. 7 shows that each antibody was able to inhibit cynomolgus

IL-17A from binding IL-17RA and inhibit IL-17RA activation, as determined by IL-6 production from JTC-12 cells. The IL-17RA antibody (AM_H14/AM_L14) was able to antagonize cynomolgus IL-17A-induced IL-6 production from JTC-12 cells with an IC50 of approximately 1.2 nM.

Example 7

In vitro binding of IL-17RA mAbs was assayed. The binding affinities of IL-17RA antibodies were measured by surface plasmon resonance using a Biacore 3000® instrument by standard methods known in the art. Antibody candidates were captured on CM4 chips derivatized with goat anti-human IgG (H+L) antibody (Jackson Immuno Research, Bar Harbor, Me.). A CM4 chip coated with goat anti-human IgG (H+L) antibody but without captured antibody was used as a reference. Soluble huIL-17RA-FLAG-polyHis (SEQ ID NO:431) at a concentration range of 0.46-1000 nM was flowed over the chips for 2 minutes (association phase) followed by a 15-30 minute disassociation phase. FLAG peptide, Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys (DYKDDDDK) (SEQ ID NO:447) as described in Hopp et al., *Bio/Technology* 6:1204, 1988, and U.S. Pat. No. 5,011,912 enables rapid assay and facile purification of expressed recombinant protein. Reagents useful for preparing fusion proteins in which the FLAG peptide is fused to a given polypeptide are commercially available (Sigma, St. Louis, Mo.).

Experiments were conducted at 25° C. using a 50 uL/min flow rate. Data was fit to a 1:1 Model+Local Rmax using BIAeval Software® (v4.1).

TABLE 10

Human Antibody	k_a (1/Ms)	K_D (1/s)	K_A (1/M)	K_D (M)
(AM_H14/AM_L14)	2.60×10^5	6.22×10^{-5}	4.18×10^9	2.39×10^{-10}
(AM_H22/AM_L22)	2.35×10^5	1.17×10^{-4}	2.01×10^9	4.98×10^{-10}
(AM_H19/AM_L19)	1.42×10^5	1.14×10^{-4}	1.25×10^9	8.02×10^{-10}
(AM_H18/AM_L18)	1.02×10^5	1.01×10^{-3}	1.01×10^8	9.88×10^{-9}

TABLE 10 shows the K_D of the human mAb clones was on the order of 10^{-10} to 10^{-9}, with the clone having the heavy and light chain sequences (AM_H14/AM_L14) having the highest affinity. Each of the human monoclonal antibodies' kinetic data was consistent with the equilibrium data. The antibody with the heavy and light chain variable sequences (AM_H14/AM_L14; SEQ ID NO:14 and SEQ ID NO:40, respectively) had the highest affinity for IL-17RA, as well as the slowest off-rate.

Example 8

Studies were conducted to determine where the various IL-17RA neutralizing antibodies bound on human IL-17RA. The ForteBio™ Octet System is one of several systems and techniques available for measuring antibody binding. The methods used for screening antibody binding essentially followed the manufacturer's recommendations. For more information see www.fortebio.com. In brief, streptavidin sensors (ForteBio™) were presoaked for 10 minutes in PBSAT (1% BSA/PBS+0.05% Tween20® (polyoxyethylene sorbitan monolaurate). Biotinylated AM_H14/AM_L14 at 10 ug/mL in PBSAT was loaded onto the sensors for 900 seconds. A new baseline was run for 600 seconds in PBSAT. Wild-type IL-17RA-FLAG-polyHis (SEC ID NO:431) at 10 ug/mL in PBSAT was then bound to the sensors for 900 seconds. A new baseline was established for 600 seconds in PBSAT. 200 nM of the following mAbs AM_H22/AM_L22, AM_H19/AM_L19, and AM_H18/AM_L18 were associated for 900 seconds, followed by dissociation for 900 seconds in PBSAT. The data showed that AM_H18/AM_L18 did not compete with AM_H14/AM_L14 for binding, showing that AM_H14/AM_L14 and AM_H18/AM_L18 bind to different neutralizing determinants. AM_H22/AM_L22 and AM_H19/AM_L19 did not bind in the presence of AM_H14/AM_L14, suggesting that all three of these antibodies bind to the same or to a similar neutralizing determinant and therefore are considered to bin together.

Example 9

Cross-competition studies were performed to determine IL-17RA binding characteristics of exemplary IL-17RA neutralizing antibodies. A modification of the multiplexed binning method described by Jia, et al. was used (see Jia, et al., *J. Immun. Meth.*, 2004, 288:91-98). The method employed the Bio-Plex Workstation and software (BioRad, Hercules, Calif.), as well as reagents from Luminex® Corp. (Austin, Tex.). The manufacturers' basic protocols were followed except where noted below (see www.bio-rad.com and www.luminexcorp.com for details). Each bead code of streptavidin-coated Luminex® beads (Luminex®, #L100-LIXX-01, where "XX" specifies the bead code) were incubated in 150 ul of 50 ug/ml biotinylated monovalent mouse-anti-human IgG capture antibody (BD Pharmingen, Becton Dickinson, Franklin Lakes, N.J., product #555785) for 1 hour at room temperature in the dark and then washed 3 times with PBSAT. The mouse-anti-human IgG coating was evaluated and the beads quantified by FACS. Each bead code was separately incubated with 10 ul of anti-IL-17RA antibody for 1 hour at room temperature and then washed. The beads were pooled and then dispensed to a 96-well filter plate (Millipore, Billerica, Mass., product #MSBVN1250). 80 ul of 2 ug/ml IL-17RA (SEQ ID NO:431) was added to half the wells and buffer to the other half and incubated at room temperature for 1 hour then washed with PBSAT. 10 ul of an anti-IL-17RA antibody was added to one well with IL-17RA (SEQ ID NO:431) and one well without IL-17RA and incubated at room temperature for 1 hour then washed with PBSAT. An irrelevant human-IgG (Jackson Labs., Bar Harbor, Me., product #009-000-003) was included as a negative control. 50 ul PE-conjugated monovalent mouse-anti-human IgG (BD Pharmingen, Becton Dickinson, Franklin Lakes, N.J., #555787) was added to each well and incubated at room temperature for 1 hour and then washed with PBSAT. The PE-tagged monovalent antibody will detect the presence of the second mAb added to the well, but not the first mAb captured by the monovalent mouse-anti-human IgG antibody. Beads were resuspended in 120 ul PBSAT and at least 100 events/bead code were collected on the Bio-Plex workstation as per the manufacturer's recommended protocol.

Median Fluorescent Intensity (MFI) of the antibody pair without IL-17RA was subtracted from the MFI signal of the corresponding reaction containing IL-17RA to normalize for background noise. The criteria for determining if two antibodies cross-competed with each other and therefore "binned" together was a matter of determining the degree to which the second antibody was detectable. If the normalized MFI was higher than the highest of any of the following three values, then the anti-IL-17RA antibodies were considered to be simultaneously bound to IL-17RA and were considered to be in different bins (i.e., the antibodies did not cross-compete): the normalized MFI is greater than 3 times the MFI value of the antibody paired with itself, or 3 times the MFI value of the antibody paired with a huIgG control, or a MFI of 300. Generally speaking, antibodies assigned to different bins

bind different parts of IL-17RA and antibodies assigned to the same bin(s) bind similar parts of IL-17RA.

FIGS. **8**A and **8**B show the results of multiplexed binning of anti-IL-17RA antibodies. Shaded values indicate antibody pairs that bind to IL-17RA simultaneously, suggesting that these antibodies bind to different neutralizing determinants. Boxed values indicate antibodies paired against themselves and cross-compete. The following monoclonal human antibodies containing the ascribed heavy and light variable domains were tested: A: AM_H11/AM_L11, B: AM_H4/AM_L4, C: AM_H8/AM_L8, D: AM_H7/AM_L7, E: AM_H6/AM_L6, F: AM_H10/AM_L10, G: AM_H18/AM_L18, H: AM_H1/AM_L1, I: AM_H22/AM_L22, J: AM_H23/AM_L23, K: AM_H14/AM_L14, L: AM_H19/AM_L19, M: AM_H12/AM_L12, N: AM_H17/AM_L17, O: AM_H16/AM_L16, P: AM_H26/AM_L26, Q: AM_H21/AM_L21, and R: AM_H20/AM_L20.

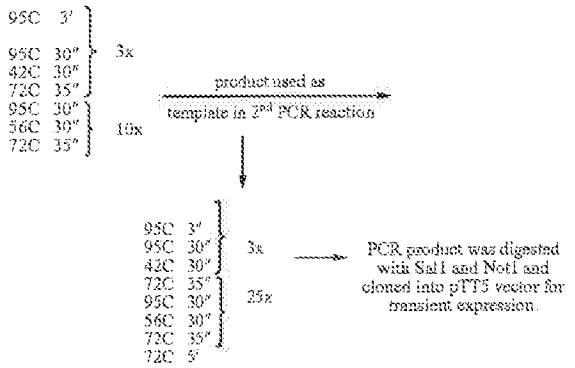
FIGS. **8**A and **8**B also show that antibodies A: AM_H11/AM_L11, B: AM_H4/AM_L4, C: AM_H8/AM_L8, D: AM_H7/AM_L7, E: AM_H6/AM_L6, F: AM_H10/AM_L10, and G: AM_H18/AM_L18 competed with one another for binding to human IL-17RA and as a consequence fell into a defined group (Bin 1). In general, antibodies I: AM_H22/AM_L22, J: AM_H23/AM_L23, K: AM_H14/AM_L14, L: AM_H19/AM_L19, M: AM_H12/AM_L12, N: AM_H17/AM_L17, O: AM_H16/AM_L16 competed with one another for binding to human IL-17RA and as a consequence fell into a defined group (Bin 3). Generally speaking, the antibodies of Bin 1 did not compete with the antibodies of Bin 3.

Antibody H: AM_H1/AM_L1 was unique in its competition pattern and formed Bin 2, but is most similar to Bin 3. Antibody P: AM_H26/AM_L26 formed Bin 4 and showed little cross-competition with any of the other antibodies, suggesting a neutralizing determinant unique to this antibody. Antibodies Q: AM_H21/AM_L21 and R: AM_H20/AM_L20, showed individually unique competition patterns, but with considerable similarities to Bin 3 antibodies, and formed Bins 5 and 6, respectively. This data provides evidence of several species within a subgenus of cross-competing antibodies.

Example 10

As described above, antibodies that bind human IL-17RA and inhibit, or neutralize, the binding of IL-17A and/or IL-17F were created and characterized. To determine the neutralizing determinants on human IL-17RA that these various IL-17RA antibodies bound, a number of chimeric human/mouse IL-17RA proteins were constructed. This method takes advantage of the non-cross reactivity of the various IL-17RA antibodies with mouse IL-17RA. For each chimera, one or two regions of human IL-17RA extracellular domain (SEQ ID NO:431) was/were replaced with the corresponding region(s) of mouse IL-17RA (SEQ ID NO:432). FIG. **9** shows mouse IL-17RA (SEQ ID NO:432) and the 5 domains, A, B, C, D, E, and F that replaced the counterpart domains in the human IL-17RA sequence. Such techniques are known in the art, see for example Stemmer, W. P. C. et al., 1995 *Gene* 164:49-53.

Six single-region and 8 double-region chimeras were constructed in pTT5 vectors. Chimeric constructs A through F (single region chimeras) were made synthetically by PCR annealing of 65-mer sense and antisense oligonucleotides which span the protein from a Sal1 site 5' of the initiation codon to a Not1 site 3' of the termination codon. The template used in the first round of PCR was a mix of oligos (sense and antisense) spanning the region from the Sal1 site to the Not1 site. PCR was done in 2 steps as follows:



Double chimeric constructs were made by digestion of single chimeras A through D with Sal1 and Sac1 restriction enzymes and a 3-way ligation with Sac1 and Not1 digested chimeras E and F using pTT5 as the expression vector. The chimeras, huIL-17RA-FLAG-polyHis (SEQ ID NO:431), and muIL-17RA-FLAG-polyHis (SEQ ID NO:432) were expressed transiently using 2936-E cells (available from the National Research Council of Canada (NRCC); see NRCC document L-11565 for further information) as host cells in roller bottles. Such transient expression techniques are well known in the art, see for example Durocher, Y. et al., 2002 *Nucleic Acids Res. Janurary* 15; 30(2):E9. The supernatants were purified using a HisTrap™ HP column as per the manufacturer's general guidelines (GE Healthcare, Piscataway N.J.) and eluted using a standard imidazole gradient (see manufacturer's recommended protocols). Purified protein was desalted into PBS, pH 7.2.

The chimeras were aligned using standard analysis tools, such as ClustalW (EMBL-EBI). The resulting chimeric proteins are shown in FIGS. **10**A-**10**D. With reference to FIGS. **9** and **10**A-**10**D, Chimera A (SEQ ID NO:433) is human IL-17RA extracellular domain with mouse Domain A; Chimera B (SEQ ID NO:434) is human IL-17RA extracellular domain with mouse Domain B; Chimera C (SEQ ID NO:435) is human IL-17RA extracellular domain with mouse Domain C; Chimera D (SEQ ID NO:436) is human IL-17RA extracellular domain with mouse Domain D; Chimera E (SEQ ID NO:437) is human IL-17RA extracellular domain with mouse Domain E; Chimera F (SEQ ID NO:438) is human IL-17RA extracellular domain with mouse Domain F; Chimera G (SEQ ID NO:439) is human IL-17RA extracellular domain with mouse Domains A and E; Chimera H (SEQ ID NO:440) is human IL-17RA extracellular domain with mouse Domains B and E; Chimera I (SEQ ID NO:441) is human IL-17RA extracellular domain with mouse Domains C and E; Chimera J (SEQ ID NO:442) is human IL-17RA extracellular domain with mouse Domains D and E; Chimera K (SEQ ID NO:443) is human IL-17RA extracellular domain with mouse Domains A and F; Chimera L (SEQ ID NO:444) is human IL-17RA extracellular domain with mouse Domains B and F; Chimera M (SEQ ID NO:445) is human IL-17RA extracellular domain with mouse Domains C and F; and Chimera N (SEQ ID NO:446) is human IL-17RA extracellular domain with mouse Domains D and F.

Using methods similar to those described in Example 9, multiplex analysis using the Bio-Plex Workstation and software (BioRad, Hercules, Calif.) was performed to determine neutralizing determinants on human IL-17RA by analyzing exemplary human IL-17RA mAbs differential binding to chi-

meric versus wild-type IL-17RA proteins. Twelve bead codes of pentaHis-coated beads (Qiagen, Valencia, Calif.; see www1.qiagen.com) were used to capture histidine-tagged protein. The 12 bead codes allowed the multiplexing of 11 chimeric and the wild type human IL-17RA.

To prepare the beads, 100 ul of wild-type IL-17RA supernatant from transient expression culture and 100 ul of 2.5 ug/ml chimeric protein were bound to penta-His-coated beads overnight at 4° C. or 2 hours at room temperature with vigorous shaking. The beads were washed as per the manufacturer's protocol and the 12 bead set was pooled and aliquoted into 2 or 3 columns of a 96-well filter plate (Millipore, Billerica, Mass., product #MSBVN1250) for duplicate or triplicate assay points, respectively. 100 ul anti-IL-17RA antibodies in 4-fold dilutions were added to the wells, incubated for 1 hour at room temperature, and washed. 100 ul of a 1:100 dilution of PE-conjugated anti-human IgG Fc (Jackson Labs., Bar Harbor, Me., product #109-116-170) was added to each well, incubated for 1 hour at room temperature and washed. Beads were resuspended in 1% BSA, shaken for 3 minutes, and read on the Bio-Plex workstation. Antibody binding to IL-17RA chimeric protein was compared to antibody binding to the human IL-17RA wild-type from the same pool. A titration of antibody over approximately a 5 log scale was performed. Median Fluorescence Intensity (MFI) of chimeric proteins was graphed as a percent of maximum wild-type human IL-17RA signal. Mutations (i.e., mouse domains) that increase the EC50 (expressed in nM) for the IL-17RA mAb by 3-fold or greater (as calculated by GraphPad Prism®) were considered to have negatively affected IL-17RA mAb binding. Through these methods, neutralizing determinants for various IL-17RA antibodies were elucidated.

FIG. **11** is a table summarizing the IL-17RA mAbs capacity to bind the various chimeric proteins. Shaded values denote where the IL-17RA mAb did not meet the criteria for binding to that particular chimeric protein ("n.d.," i.e., "not determined" means that the chimera was not assayed). As described above, EC50 values are provided. A zero value indicates that antibody binding was ablated. The underlined value was assigned an EC50 value by the GraphPad Prism® even though the titration curve was essentially flat. TABLE 11 shows the control values in nM for the assay.

TABLE 11

mAb	mu WT	huWT ctrl	3 x wt ctrl	2 x wt ctrl
AM_H18/AM_L18	0.000	0.061	0.182	0.121
AM_H1/AM_L1	1.879	0.134	0.403	0.269
AM_H22/AM_L22	0.000	0.043	0.128	0.085
AM_H14/AM_L14	3416.000	0.027	0.082	0.055
AM_H19/AM_L19	770.100	0.062	0.187	0.125
AM_H23/AM_L23	0.000	0.053	0.158	0.106
AM_H26/AM_L26	0.000	0.281	0.843	0.562
AM_H21/AM_L21	0.196	0.018	0.055	0.037
AM_H20/AM_L20	1.333	0.022	0.066	0.044

As can be seen in FIG. **11**, at least three neutralizing determinants were identified based on those regions affecting the binding of neutralizing IL-17RA antibodies, namely Domain B spanning amino acids 75-96 of human IL-17RA (SEQ ID NO:431), Domain C spanning amino acids 128-154 of human IL-17RA (SEQ ID NO:431), and Domain D spanning amino acids 176-197 of human IL-17RA (SEQ ID NO:431). Domain B spanning amino acids 75-96 of human IL-17RA (SEQ ID NO:431) negatively affected the binding of neutralizing antibodies AM_H1/AM_L1 and AM_H23/AM_L23. Domain C spanning amino acids 128-154 of human IL-17RA (SEQ ID NO:431) negatively affected the binding of neutralizing antibodies AM_H22/AM_L22 and AM_H23/AM_L23. Domain D spanning amino acids 176-197 of human IL-17RA (SEQ ID NO:431) negatively affected the binding of neutralizing antibodies AM_H1/AM_L1, AM_H22/AM_L22, AM_H14/AM_L14, AM_H19/AM_L19, AM_H23/AM_L23, AM_H21/AM_L21, and AM_H20/AM_L20. The binding characteristics of the IL-17RA antibodies in relation to where the antibodies bound on human IL-17RA was confirmed by the double chimeras. Thus, Domain B, C, and D are considered neutralizing determinants.

Example 11

As described above, antibodies that bind human IL-17RA and inhibit, or neutralize, the binding of IL-17A and/or IL-17F were created and characterized. To determine the neutralizing determinants on human IL-17RA that these various IL-17RA antibodies bound, a number of mutant IL-17RA proteins were constructed having arginine substitutions at select amino acid residues of human IL-17RA. Arginine scanning is an art-recognized method of evaluating where antibodies, or other proteins, bind to another protein, see for example Nanevicz, T., et al., 1995, J. Biol. Chem., 270:37, 21619-21625 and Zupnick, A., et al., 2006, J. Biol. Chem., 281:29, 20464-20473. In general, the arginine sidechain is positively charged and relatively bulky as compared to other amino acids, which may disrupt antibody binding to a region of the antigen where the mutation is introduced. Arginine scanning is a method that determines if a residue is part of a neutralizing determinant and/or an epitope.

95 amino acids distributed throughout the human IL-17RA extracellular domain were selected for mutation to arginine. The selection was biased towards charged or polar amino acids to maximize the possibility of the residue being on the surface and reduce the likelihood of the mutation resulting in misfolded protein. FIG. **12** depicts the amino acid residues that were replaced with an arginine residue in SEQ ID NO:431. Using standard techniques known in the art, sense and anti-sense oligonucleotides containing the mutated residues were designed based on criteria provided by Stratagene Quickchange® II protocol kit (Stratagene/Agilent, Santa Clara, Calif.). Mutagenesis of the wild-type (WT) HuIL-17RA-Flag-pHis was performed using a Quickchange® II kit (Stratagene). All chimeric constructs were constructed to encode a FLAG-histidine tag (six histidines) on the carboxy terminus of the extracellular domain to facilitate purification via the poly-His tag.

Multiplex analysis using the Bio-Plex Workstation and software (BioRad, Hercules, Calif.) was performed to determine neutralizing determinants on human IL-17RA by analyzing exemplary human IL-17RA mAbs differential binding to arginine mutants versus wild-type IL-17RA proteins. Twelve bead codes of pentaHis-coated beads (Qiagen, Valencia, Calif.; see www1.qiagen.com) were used to capture histidine-tagged protein. The 12 bead codes allowed the multiplexing of 11 IL-17RA arginine mutants and wild-type human IL-17RA (SEQ ID NO:431).

To prepare the beads, 100 ul of wild-type IL-17RA and IL-17RA arginine mutant supernatants from transient expression culture were bound to penta-His-coated beads overnight at 4° C. or 2 hours at room temperature with vigorous shaking. The beads were washed as per the manufacturer's protocol and the 12 bead set was pooled and aliquoted into 2 or 3 columns of a 96-well filter plate (Millipore, Bellerica, Mass., product #MSBVN1250) for duplicate or triplicate assay

points, respectively. 100 ul anti-IL-17RA antibodies in 4-fold dilutions were added to the wells, incubated for 1 hour at room temperature, and washed. 100 ul of a 1:100 dilution of PE-conjugated anti-human IgG Fc (Jackson Labs., Bar Harbor, Me., product #109-116-170) was added to each well, incubated for 1 hour at room temperature and washed. Beads were resuspended in 1% BSA, shaken for 3 minutes, and read on the Bio-Plex workstation. Antibody binding to IL-17RA arginine mutant protein was compared to antibody binding to the human IL-17RA wild-type from the same pool. A titration of antibody over approximately a 5 log scale was performed. Median Fluorescence Intensity (MWI) of IL-17RA arginine mutant proteins was graphed as a percent of maximum wild-type human IL-17RA signal. Those mutants for which signal from all the antibodies are below 30% of wild-type IL-17RA were deemed to be either of too low a protein concentration on the head due to poor expression in the transient culture or possibly misfolded and were excluded from analysis: these were T51R, K53R, S55R, H64R, D75R, E110R, Q118R, T121, E123R, S147R, H148R, E158R, T160R, H163R, K191R, T193R, E213R, H251R, T269R, H279R, and D293R of SEQ ID NO:431. Mutations (i.e., arginine substitutions) that increase the EC50 for the IL-17RA mAb by 3-fold or greater (as calculated by GraphPad Prism®) were considered to have negatively affected IL-17RA mAb binding. Through these methods, neutralizing determinants and epitopes for various IL-17RA antibodies were elucidated.

FIG. **13** illustrates titration curves of various IL-17RA mAbs binding to the D152R IL-17RA mutant (i.e., the aspartic acid at position 152 of SEQ ID NO:431 was mutagenized to be an arginine). Antibodies AM_H1/AM_L1, AM_H22/AM_L22, AM_H14/AM_L14, AM_H19/AM_L19, AM_H23/AM_L23, AM_H21/AM_L21, and AM_H20/AM_L20 lost the capacity to bind the D152R IL-17RA mutant. Antibodies AM_H18/AM_L18 and AM_H26/AM_L26 were only marginally affected but did not meet the cutoff criteria.

A summary of the arginine scan, binning, and chimera data is presented in FIG. **14**. The arginine scan methodology identified several neutralizing determinants: AM_H18/AM_L18 bound a domain spanning amino acids 220-284 of human IL-17RA (SEQ ID NO:431); AM_H1/AM_L1 bound a domain focused on amino acid residue 152 of human IL-17RA (SEQ ID NO:431); AM_H22/AM_L22 bound a domain spanning amino acids 152-198 of human IL-17RA (SEQ ID NO:431); AM_H14/AM_L14 bound a domain spanning amino acids 152-297 of human IL-17RA (SEQ ID NO:431); AM_H19/AM_L19 bound a domain spanning amino acids 152-186 of human IL-17RA (SEQ ID NO:431); AM_H23/AM_L23 bound a domain spanning amino acids 97-297 of human IL-17RA (SEQ ID NO:431); AM_H26/AM_L26 bound a domain spanning amino acids 138-270 of human IL-17RA (SEQ ID NO:431); AM_H21/AM_L21 bound a domain spanning amino acids 113-198 of human IL-17RA (SEQ ID NO:431); and AM_H20/AM_L20 bound a domain spanning amino acids 152-270 of human IL-17RA (SEQ ID NO:431).

All of the residues shown in FIG. **14** have been shown to reduce binding of a neutralizing human monoclonal antibody that specifically binds to human IL-17RA.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 470

<210> SEQ ID NO 1
<211> LENGTH: 131
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                  10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Asn Tyr
            20                  25                  30

Tyr Trp Asn Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Asp Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Thr Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Asp Gly Glu Leu Ala Asn Tyr Tyr Gly Ser Gly Ser Tyr Gln Phe
            100                 105                 110

Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
        115                 120                 125

Val Ser Ser
    130
```

<210> SEQ ID NO 2
<211> LENGTH: 127

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Phe Ser Gly Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn His Ser Gly Arg Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Gly Pro Tyr Tyr Phe Asp Ser Ser Gly Tyr Leu Tyr Tyr Tyr Tyr
100 105 110

Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 3
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Asn Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Gly Val Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> SEQ ID NO 4
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Asn Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val
50 55 60

-continued

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Gly Val Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> SEQ ID NO 5
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Pro Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Ser Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Tyr Arg Ser Gly Asn Thr Ile Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Met Ser Ile Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Thr Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Glu Asn Tyr Ser Glu Ser Ser Gly Leu Tyr Tyr Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 6
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu Thr Arg Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Gly Phe Asp
100 105 110

Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 7
<211> LENGTH: 124

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<213> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu Thr Arg Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Gly Phe Asp
100 105 110

Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 8
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Asn Thr Phe Thr Gly Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Asn Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Gly Phe Asp
100 105 110

Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 9
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Gln Val Gln Leu Val Gln Ser Gly Val Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu Thr Arg Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu

-continued

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    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Gly Phe Asp
            100                 105                 110

Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 10
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
            20                  25                  30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35                  40                  45

Trp Ile Gly Tyr Ile Tyr Phe Ser Gly Ser Ala Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Val Ala Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Glu Tyr Tyr Asp Ser Ser Gly Tyr Pro Asp Ala Phe Asp
            100                 105                 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 11
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Ile Thr Phe Ser Ser Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Thr Lys Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110

Ser Ser

<210> SEQ ID NO 12
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<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Thr Tyr Lys Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Lys Gln Leu Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 13
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Asn Lys Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Arg Val Arg Asp Tyr Tyr Tyr Gly Met Asp Val Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 14
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

-continued

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Gly Trp Ile Ser Thr Tyr Ser Gly Asn Thr Asn Tyr Ala Gln Lys Leu
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Gln Leu Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser
        115


<210> SEQ ID NO 15
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Gly Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Val Ile Trp Tyr Asp Gly Asn Lys Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Arg Val Arg Asp Tyr Tyr Tyr Gly Met Asp Val Trp Gly
            100                 105                 110

Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 16
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Lys Tyr Ala Gln Lys Leu
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Lys Gln Leu Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser
        115
```

-continued

<210> SEQ ID NO 17
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ala Val Lys Val Ser Cys Lys Ala Thr Gly Tyr Thr Leu Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Ser Gly Asn Thr Lys Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Lys Gln Leu Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 18
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met His Pro Asn Ser Gly Gly Thr Asp Leu Ala Gln Arg Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Tyr Cys Ser Thr Leu Ser Cys Ser Phe Tyr Trp Tyr
100 105 110

Phe Asp Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 19
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

-continued

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        35                  40                  45

Gly Trp Ile Ser Ala Tyr Ser Gly Asn Thr Lys Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Gln Leu Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser
        115


<210> SEQ ID NO 20
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Phe Ile Ser Ala Arg Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Pro Lys Val Gly Gly Gly Met Asp Val Trp Gly Gln Gly Thr
            100                 105                 110

Thr Val Thr Val Ser Ser
        115


<210> SEQ ID NO 21
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ile Ile Ser Ser Ser Arg Ser Ser Ile Ile His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Pro Lys Val Gly Gly Gly Met Asp Val Trp Gly Gln Gly Thr
            100                 105                 110

Thr Val Thr Val Ser Ser
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115

<210> SEQ ID NO 22
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Ser Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Gln Leu Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 23
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Arg Leu Glu Trp Ile
35 40 45

Gly Arg Ile Tyr Pro Ser Gly Arg Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Glu Ala Tyr Glu Leu Gln Leu Gly Leu Tyr Tyr Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 24
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

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Tyr Trp Ser Trp Ile Arg Gln Ala Ala Gly Lys Arg Leu Glu Trp Ile
        35                  40                  45

Gly Arg Ile Tyr Pro Ser Gly Arg Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Glu Ala Tyr Glu Leu Gln Leu Gly Leu Tyr Tyr Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser
        115                 120                 125


<210> SEQ ID NO 25
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
            20                  25                  30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35                  40                  45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Arg Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Glu Ala Gly Gly Asn Ser Ala Tyr Tyr Tyr Gly Met Asp
            100                 105                 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 26
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Thr Tyr Tyr Phe Gly Ser Gly Ser Tyr Glu Gly Met
            100                 105                 110
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Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125


<210> SEQ ID NO 27
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

Asp Ile Leu Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Asn Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 28
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Arg Asn
            20                  25                  30

Leu Val Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Thr Arg Ala Asn Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Lys Ser Trp Arg Thr
                85                  90                  95

Phe Gly Gln Gly Ser Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 29
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45
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Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
     50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                   70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Lys Ser Tyr Pro Leu
                 85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 30
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1                5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Arg Asn
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                   70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Thr
                 85                  90                  95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 31
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1                5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Phe Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Gly Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                   70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Pro
                 85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 32
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Lys Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 33
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Lys Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 34
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Lys Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> SEQ ID NO 35
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Lys Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 36
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Phe Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Asn Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 37
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Ala Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Gly Gly Ser Gly Thr Ala Phe Thr Leu Thr Ile Ser Asn Leu Gln Ser
65 70 75 80

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```
Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Ile Asn Trp Pro Lys
                85                  90                  95

Trp Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 38
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ser
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asn Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Asn Trp Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 39
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
1               5                   10                  15

Gln Pro Ala Ser Ile Ala Cys Lys Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Pro
        35                  40                  45

Pro Gln Leu Leu Ile Tyr Glu Val Ser Thr Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Phe Tyr Cys Met Gln Ser
                85                  90                  95

Ile Gln Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 40
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20                  25                  30
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```
Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Pro Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Thr Arg Ala Thr Gly Val Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Asn Trp Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 41
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15

Glu Arg Val Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20                  25                  30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Pro Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Thr Arg Ala Ala Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Asn Trp Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 42
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Thr Ser
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Gly Thr Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Tyr Asp Ile Trp Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 43
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 43

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Ser Cys Gln Gln Tyr Asp Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 44
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Thr Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Lys Asn Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Leu Asn Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
100 105 110

Lys

<210> SEQ ID NO 45
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Asp
50 55 60

Asn Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Tyr Asp Thr Trp Pro Leu
85 90 95

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```
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 46
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Phe Pro Glu Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Arg Ala Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 47
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Phe Pro Glu Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Arg Ala Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 48
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                  10                  15

Glu Arg Val Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20                  25                  30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Pro Leu Ile
        35                  40                  45
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```
Tyr Asp Ala Ser Thr Arg Ala Ala Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Asn Trp Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 49
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Gly Ile Ile Asn Asp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 50
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1               5                   10                  15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
            20                  25                  30

Asp Gly His Thr Cys Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
        35                  40                  45

Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Trp Asp Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Asp Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85                  90                  95

Thr His Trp Pro Leu Cys Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile
            100                 105                 110

Lys


<210> SEQ ID NO 51
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51
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```
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1               5                  10                  15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
            20                  25                  30

Asp Gly His Thr Cys Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
        35                  40                  45

Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Trp Asp Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Asp Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85                  90                  95

Thr His Trp Pro Leu Cys Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile
            100                 105                 110

Lys


<210> SEQ ID NO 52
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ala Ile Ser Ile Tyr
            20                  25                  30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
    50                  55                  60

Ser Val Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro Arg
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 53
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

Glu Ile Leu Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Tyr Ser Asn
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Ser Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Trp Pro Trp
                85                  90                  95
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Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 54
<211> LENGTH: 393
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctcaggtgg ctccatcagt aattactact ggagctggat ccggcagtcc 120

ccagggaagg gactggagtg gattggggat atctattaca gtgggagcac caactacaac 180

ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag agatggggaa 300

ctcgccaatt actatggttc ggggagttat cagttctact actactacgg tatggacgtc 360

tggggccaag ggaccacggt caccgtctcc tca 393

<210> SEQ ID NO 55
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctctggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggaatg gattggggaa atcaatcata gtggacgcac caattacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtttatt actgtgcgag aggccttat 300

tactttgata gtagtggtta ctttactac tactacggtt tggacgtctg gggccaaggg 360

accacggtca ccgtctcctc a 381

<210> SEQ ID NO 56
<211> LENGTH: 342
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggaat caacttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaacactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatact 300

ggggtctact ggggccaggg aaccctggtc accgtctcct ca 342

<210> SEQ ID NO 57
<211> LENGTH: 342
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggaat caacttcagt agctatggca tgcactgggt ccgccaggct 120

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ccaggcaagg ggctggagtg ggtggcagtt atatggcatg atggaagtaa taaacactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatact 300

ggggtctact ggggccaggg aaccctggtc accgtctcct ca 342

<210> SEQ ID NO 58
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgccctc 60

acctgcactg tctctggtgg ctccatcaga agttactact ggagctggat ccggcagccc 120

gccgggaagg gactggagtg gattgggcgt atctatcgca gtgggaacac catctacaac 180

ccctccctca agagtcgagt caccatgtca atagacacgt ccaagaacca gttctccctg 240

aagctgagtt ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag agagaattac 300

tctgagagta gtggttctta ctactactac ggtatggacg tctgggggca agggaccacg 360

gtcaccgtct cctca 375

<210> SEQ ID NO 59
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta caccttaacc agatatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggttgg atcagcgctt acaatggtaa cacaaactat 180

gcacagaagc tccagggcag agtcaccatg accacagaca cgtccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaagggat 300

tacgatattt tgactggtta ttataacggg ttcgaccact ggggccaggg aaccctggtc 360

accgtctcct ca 372

<210> SEQ ID NO 60
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta caccttaacc agatatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggttgg atcagcgctt acaatggtaa cacaaactat 180

gcacagaagc tccagggcag agtcaccatg accacagaca cgtccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaagggat 300

tacgatattt tgactggtta ttataacggg ttcgaccact ggggccaggg aaccctggtc 360

accgtctcct ca 372

<210> SEQ ID NO 61
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 61

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtaa cacctttacc ggctatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacaaactat 180

gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaagggat 300

tacgatattt tgactggtta ttataacggg ttcgacccct ggggccaggg aaccctggtc 360

accgtctcct ca 372

<210> SEQ ID NO 62
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

caggttcagc tggtgcagtc tggagttgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacttaacc agatatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggttgg atcagcgctt acaatggtaa cacaaactat 180

gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaagggat 300

tacgatattt tgactggtta ttataacggg ttcgacccct ggggccaggg aaccctggtc 360

accgtctcct ca 372

<210> SEQ ID NO 63
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatct atttcagtgg gagcgcctac 180

tacaacccgt ccctcaagag tcgagtcgcc atatcagtgg acacgtctaa gaaccagttc 240

tccctgaagc tgagctctgt gactgccgcg gacacggccg tatattactg tgcgagagaa 300

tactatgata gtagtggtta ccccgatgct tttgatatct ggggccaagg gacaatggtc 360

accgtctcct ca 372

<210> SEQ ID NO 64
<211> LENGTH: 342
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

caggtgcaac tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcaa cgtccggaat caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatattat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatacg 300

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aaggactact ggggccaggg aaccctggtc accgtctcct ca 342

<210> SEQ ID NO 65
<211> LENGTH: 348
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctgggcctc agtgaaggtc 60

tcctgcaagg cttctggtta caccctcacc agctatggta tcagctgggt gcgacaggcc 120

cctggacaag gacttgagtg gatgggatgg atcagcactt acaaaggtaa cacaaactat 180

gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaaagcag 300

ctcgtctttg actactgggg tcagggaacc ctggtcaccg tctcctca 348

<210> SEQ ID NO 66
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt agctatggca tgcagtgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaaataa gaaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaggacgt 300

gttagggact actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360

tca 363

<210> SEQ ID NO 67
<211> LENGTH: 350
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctgggcctc agtgaaggtc 60

tcctgcaagg cttctggtta caccttacc agatatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcactt acagtggtaa cacaaactat 180

gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagacggcag 300

ctttactttg actactgggg ccagggaacc ctggtcaccg tctcctcagc 350

<210> SEQ ID NO 68
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtccggatt caccttcagt agctatggca tgcagtgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaaataa gaaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

-continued

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaggacgt 300

gttagggact actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360

tca 363

<210> SEQ ID NO 69
<211> LENGTH: 348
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta caccttacc agctatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacaaagtat 180

gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagtctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaaagcag 300

ctcgtctttg actactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> SEQ ID NO 70
<211> LENGTH: 348
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg ctactggtta caccttgacc agctatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acagtggtaa tacaaagtat 180

gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaaagcag 300

ctcgtctttg actactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> SEQ ID NO 71
<211> LENGTH: 378
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata ctccttcacc gactactaca tgcactgggt gcgacaggcc 120

cctggacaag gacttgagtg gatgggatgg atgcaccctа acagtggtgg cacagacttа 180

gcacagaggt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagggaga 300

tattgtagta ctttgagctg ctccttctac tggtacttcg atctctgggg ccgtggcacc 360

ctggtcactg tctcctca 378

<210> SEQ ID NO 72
<211> LENGTH: 348
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

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tcctgraagg cttctggtta caccttgacc agctatggaa tcagttgggt gcgacaggcc 120

ccnggacaag ggcttgagtg gatgggatgg atcagcgctt acagtggtaa cacaaagtat 180

gcacagaagt tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaaggcag 300

ctcgcgttgg actactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> SEQ ID NO 73
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagc agctatagca tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtttcattc attagtgcta gaagtagtac catatactac 180

gcagactctg tgaagggccg attcaccatc tccagagaca atgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agacgaggac acggctgtgt attactgtgc gagacctaaa 300

gtgggggggc gtatggacgt ctggggccaa gggaccacgg tcaccgtctc ctca 354

<210> SEQ ID NO 74
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

gaggtgcagt tggtggagtc tgggggaggc tcggtacagc ctggggggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt agctatagca tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtttcaatc attagtagta gaagtagtat catacactac 180

gcagactctg tgaagggccg attcaccatc tccagagaca atgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agacgaggac acggctgtgt attactgtgc gagacctaaa 300

gtgggggggc gtatggacgt ctggggccaa gggaccacgg tcaccgtctc ctca 354

<210> SEQ ID NO 75
<211> LENGTH: 348
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta caccttttacc agatatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acagtggtaa cacaaactat 180

gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagacggcag 300

ctttacttttg actactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> SEQ ID NO 76
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

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acctgcactg tcactggtgg ctccatcagg agttactact ggagctggat ccggcagccc 120

gccgggaaga gactggagtg gattgggcgt atctatccca gtgggagaac caactacaac 180

cctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gtttctcctg 240

aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag agaggcatat 300

gagctgcaac tgggcctcta ctactactac ggtatggacg tctgggccca agggaccccg 360

gtcaccgtct cctca 375

<210> SEQ ID NO 77
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tcactggtgg ctccatcagg agttactact ggagctggat ccggcaggcc 120

gccgggaaga gactggagtg gattgggcgt atctatccca gtgggagaac caactacaac 180

cctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gtttctcctg 240

aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag agaggcatat 300

gagctgcaac tgggcctcta ctactactac ggtatggacg tctgggccca agggaccccg 360

gtcaccgtct cctca 375

<210> SEQ ID NO 78
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gaacacctac 180

tacaacccgt ccctcaggag tcgagttacc atatcagttg acacgtctaa gaaccagttc 240

tccctgaagc tgaactctgt gactgccgcg gacacggccg tgtattactg tgcgagagag 300

gccggtggta actccgccta ctactacggt atggacgtct gggccaagg gaccacggtc 360

accgtctcct ca 372

<210> SEQ ID NO 79
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct 120

ccagggaagg ggctggagtg ggtttcatac attagtagta gtggtagtac catatactac 180

gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagatcgc 300

acgtattact ttggttcggg gagttatgaa gggatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

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<210> SEQ ID NO 80
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

gacatcctga tgacccagtc tccatcctcc ctgtctgcat ctgtcggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatcc 180

aggttcagcg gcagtggctc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacag cataatagta acccattcac tttcggccct 300

gggaccaaag tggatatcaa a 321

<210> SEQ ID NO 81
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agaaacttag tctggtacca gcagagacct 120

ggccaggctc ccaggctcct catctatggg gcatccacta gggccaatgg tatcccagcc 180

aggttcagtg gcagtgggtc agggacagaa ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tataaaagct ggcggacgtt cggccaaggg 300

tccaaggtgg aaatcaaa 318

<210> SEQ ID NO 82
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta ccccattcac tttcggccct 300

gggaccaaag tggatatcaa a 321

<210> SEQ ID NO 83
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagt aggaatttag cctggtacca gcagaaacct 120

ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tataataact ggccccacgtg gacgttcggc 300

caagggacca aggtggaaat caaa 324

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<210> SEQ ID NO 84
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaaacgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagga ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacag cataatagtt acccctcgac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 85
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacag cataaaagtt acccgctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 86
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacag cataaaagtt acccgctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 87
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacag cataagagtt acccgctcac tttcggcgga 300

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gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 88
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctacgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacag cataaaagtt acccgctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 89
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagg agctggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctttgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttacta ttgtcaacag gctaacaatt tccctcggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 90
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120

ggccaggctc ccaggctcct catctatggt gcatccacca gggccgctgg tatcccagcc 180

aggttcagtg gcggtgggtc tgggacagcg ttcactctca ccatcagcaa cctacagtct 240

gaagattttg cagtttatta ctgtcagcac tatataaact ggcctaagtg gacgttcggc 300

caagggacca aggtggacat caaa 324

<210> SEQ ID NO 91
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

gaaatagtaa tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtattagc agcagcttag cctggtacca gcagaaacct 120

ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaaaattttg cagtttatta ctgtcagcaa tatgataact ggcccgctcac tttcggcgga 300

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gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 92
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

gatattgtga tgacccagac tccactctct ctgtccgtca cccctggaca gccggcctcc 60

atctcctgca agtctagtca gagcctcctg catagtgatg gaaagaccta tttgtattgg 120

tacctgcaga agccaggcca gcctccacag ctcctgatct atgaagtttc caaccggttc 180

tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 240

agccgggtgg aggctgagga tgttggggtt ttttactgca tgcaaagtat acagcttccg 300

ctcactttcg gcggagggac caaggtggag atcaaa 336

<210> SEQ ID NO 93
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctcctgggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtttca gcagaaacct 120

ggccaggctc ccaggctccc catctatgat gcatccacca gggccactgg tgtcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tatgataact ggcccgctac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 94
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccaggggа aagagtcacc 60

ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtttca gcagaaacct 120

ggccaggctc ccaggctccc catctatgat gcatccacca gggccgctgg tatcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tatgataact ggcccgctac tttcggcgga 300

ggaaccaagg tggagatcaa a 321

<210> SEQ ID NO 95
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccaggggа aagagccacc 60

ctctcctgca gggccagtca gagtattagc accagcttag cctggtacca gcagaaacct 120

ggccaggctc ccaggctcct catctatggt acatccacca gggccactgg tatcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

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gaagatttg cagtttattt ctgtcaacag tatgatatct ggccgctcac tttcggcgga 300

gggaccaagg tggagatcaa acga 324

<210> SEQ ID NO 96
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120

ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaagatttg cagtttattc ctgtcagcag tatgataact ggccgctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 97
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60

atcaactgca agaccagcca gagtgttta tacagctcca aaaacaagaa cttcttagct 120

tggtatcagc agaaaccagg acagcctctt aacctgctca tttactgggc atctaccggg 180

gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240

atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttatagtact 300

ccattcactt tcggccctgg gaccaaagtg gatatcaaa 339

<210> SEQ ID NO 98
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtattagc agcaacttag cctggtacca gcagaaacct 120

ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180

aggttcagtg acaatgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttattt ctgtcagcag tatgatacct ggcctctcac tttcggcggc 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 99
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcgagtca gggcattagc aattatttag cctggnatca gcagaaacca 120

gggaaatttc ctgagctcct gatctatgct gcatccactt tacaatcagg ggtccccatct 180

cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

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gaagatgttg caacttatta ctgtcaaaag tataaccgtg ccccattcac tttcggccct 300

gggaccaaag tggatatcaa a 321

<210> SEQ ID NO 100
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcgagtca gggcattagc aattatttag cctggtatca gcagaaacca 120

gggaaatttc ctgagctcct gatctatgct gcatccactt tgcaatcagg ggtccccatct 180

cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagatgttg caacttatta ctgtcaaaag tataaccgtg ccccattcac tttcggccct 300

gggaccaaag tggatatcaa a 321

<210> SEQ ID NO 101
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagtcagc 60

ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtttca gcagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccacca gggccgctgg tatcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tatgataact ggcctcgtcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 102
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgttggaga cagagtcacc 60

atcttttgcc gggcaagtca gggcattata aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactttca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacag cataatagtt acccctcgac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 103
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccttggaca gccggcctcc 60

atctcctgca ggtctagtca aagcctcgta tatagtgatg gacacacctg cttgaattgg 120

tttcagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taactgggac 180

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tctggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240

agcagggtgg aggctgacga tgttggggtt tattactgca tgcaaggtac acactggcct 300

ctgtgcagtt ttggccaggg gaccaagctg gagatcaaa 339

<210> SEQ ID NO 104
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccttggaca gccggcctcc 60

atctcctgca ggtctagtca aagcctcgta tatagtgatg gacacaccctg cttgaattgg 120

tttcagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taactgggac 180

tctggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240

agcagggtgg aggctgacga tgttggggtt tattactgca tgcaaggtac acactggcct 300

ctgtgcagtt ttggccaggg gaccaagctg gagatcaaa 339

<210> SEQ ID NO 105
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca ggccattagc atttatttag cctggtttca gcagaaacca 120

gggaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aagttcagcg gcagtgtatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgccaacag tatagtagtt acccctcggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 106
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

gaaatattga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgtttac agcaacttag cctggtacca gcagaaacct 120

ggccaggctc ccagactcct catctctggt gcttccacca gggccactgg tatcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tattataact ggcctctggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 107
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

Asn Tyr Tyr Trp Asn
1 5

<210> SEQ ID NO 108

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<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

Asp Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 109
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

Asp Gly Glu Leu Ala Asn Tyr Tyr Gly Ser Gly Ser Tyr Gln Phe Tyr
1 5 10 15

Tyr Tyr Tyr Gly Met Asp Val
20

<210> SEQ ID NO 110
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

Gly Tyr Tyr Trp Ser
1 5

<210> SEQ ID NO 111
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

Glu Ile Asn His Ser Gly Arg Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 112
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

Gly Pro Tyr Tyr Phe Asp Ser Ser Gly Tyr Leu Tyr Tyr Tyr Tyr Gly
1 5 10 15

Leu Asp Val

<210> SEQ ID NO 113
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 114
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val Lys
1 5 10 15

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Gly

<210> SEQ ID NO 115
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

Asp Thr Gly Val Tyr
1 5

<210> SEQ ID NO 116
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 117
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 118
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

Asp Thr Gly Val Tyr
1 5

<210> SEQ ID NO 119
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

Ser Tyr Tyr Trp Ser
1 5

<210> SEQ ID NO 120
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

Arg Ile Tyr Arg Ser Gly Asn Thr Ile Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 121
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

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Glu Asn Tyr Ser Glu Ser Ser Gly Leu Tyr Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 122
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

Arg Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 123
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> SEQ ID NO 124
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

Arg Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Gly Phe Asp Pro
1 5 10 15

<210> SEQ ID NO 125
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

Arg Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 126
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> SEQ ID NO 127
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

Arg Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Gly Phe Asp Pro
1 5 10 15

<210> SEQ ID NO 128
<211> LENGTH: 5
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

Gly Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 129
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Asn Leu Gln
1 5 10 15

Gly

<210> SEQ ID NO 130
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

Arg Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Gly Phe Asp Pro
1 5 10 15

<210> SEQ ID NO 131
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

Arg Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 132
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> SEQ ID NO 133
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

Arg Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Gly Phe Asp Pro
1 5 10 15

<210> SEQ ID NO 134
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

Ser Gly Gly Tyr Tyr Trp Ser
1 5

<210> SEQ ID NO 135

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<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

Tyr Ile Tyr Phe Ser Gly Ser Ala Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 136
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

Glu Tyr Tyr Asp Ser Ser Gly Tyr Pro Asp Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 137
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 138
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 139
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

Asp Thr Lys Asp Tyr
1 5

<210> SEQ ID NO 140
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

Ser Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 141
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

Trp Ile Ser Thr Tyr Lys Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

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<210> SEQ ID NO 142
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

Lys Gln Leu Val Phe Asp Tyr
1 5

<210> SEQ ID NO 143
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

Ser Tyr Gly Met Gln
1 5

<210> SEQ ID NO 144
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 144

Val Ile Trp Tyr Asp Gly Asn Lys Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 145
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

Gly Arg Val Arg Asp Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 146
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

Arg Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 147
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

Trp Ile Ser Thr Tyr Ser Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> SEQ ID NO 148
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 148

Arg Gln Leu Tyr Phe Asp Tyr

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1 5

<210> SEQ ID NO 149
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

Ser Tyr Gly Met Gln
1 5

<210> SEQ ID NO 150
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

Val Ile Trp Tyr Asp Gly Asn Lys Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 151
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

Gly Arg Val Arg Asp Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 152
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

Ser Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 153
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

Trp Ile Ser Ala Tyr Asn Gly Asn Thr Lys Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> SEQ ID NO 154
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

Lys Gln Leu Val Phe Asp Tyr
1 5

<210> SEQ ID NO 155
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

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Ser Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 156
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

Trp Ile Ser Ala Tyr Ser Gly Asn Thr Lys Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> SEQ ID NO 157
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

Lys Gln Leu Val Phe Asp Tyr
1 5

<210> SEQ ID NO 158
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158

Asp Tyr Tyr Met His
1 5

<210> SEQ ID NO 159
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

Trp Met His Pro Asn Ser Gly Gly Thr Asp Leu Ala Gln Arg Phe Gln
1 5 10 15

Gly

<210> SEQ ID NO 160
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 160

Gly Gly Tyr Cys Ser Thr Leu Ser Cys Ser Phe Tyr Trp Tyr Phe Asp
1 5 10 15

Leu

<210> SEQ ID NO 161
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

Ser Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 162
<211> LENGTH: 17

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

Trp Ile Ser Ala Tyr Ser Gly Asn Thr Lys Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> SEQ ID NO 163
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

Arg Gln Leu Ala Leu Asp Tyr
1 5

<210> SEQ ID NO 164
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 164

Ser Tyr Ser Met Asn
1 5

<210> SEQ ID NO 165
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 165

Phe Ile Ser Ala Arg Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 166
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

Pro Lys Val Gly Gly Gly Met Asp Val
1 5

<210> SEQ ID NO 167
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

Ser Tyr Ser Met Asn
1 5

<210> SEQ ID NO 168
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 168

Ile Ile Ser Ser Arg Ser Ser Ile Ile His Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

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<210> SEQ ID NO 169
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

Pro Lys Val Gly Gly Gly Met Asp Val
1 5

<210> SEQ ID NO 170
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

Arg Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 171
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

Trp Ile Ser Ala Tyr Ser Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> SEQ ID NO 172
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

Arg Gln Leu Tyr Phe Asp Tyr
1 5

<210> SEQ ID NO 173
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

Ser Tyr Tyr Trp Ser
1 5

<210> SEQ ID NO 174
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

Arg Ile Tyr Pro Ser Gly Arg Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 175
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

Glu Ala Tyr Glu Leu Gln Leu Gly Leu Tyr Tyr Tyr Tyr Gly Met Asp
1 5 10 15

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Val

<210> SEQ ID NO 176
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

Ser Tyr Tyr Trp Ser
1 5

<210> SEQ ID NO 177
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

Arg Ile Tyr Pro Ser Gly Arg Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 178
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

Glu Ala Tyr Glu Leu Gln Leu Gly Leu Tyr Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 179
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

Ser Gly Gly Tyr Tyr Trp Ser
1 5

<210> SEQ ID NO 180
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Arg Ser
1 5 10

<210> SEQ ID NO 181
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

Glu Ala Gly Gly Asn Ser Ala Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 182
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

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Asp Tyr Tyr Met Ser
1 5

<210> SEQ ID NO 183
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 184
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

Asp Arg Thr Tyr Tyr Phe Gly Ser Gly Ser Tyr Glu Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 185
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> SEQ ID NO 186
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 187
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

Leu Gln His Asn Ser Asn Pro Phe Thr
1 5

<210> SEQ ID NO 188
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188

Arg Ala Ser Gln Ser Val Ser Arg Asn Leu Val
1 5 10

<210> SEQ ID NO 189
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

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Gly Ala Ser Thr Arg Ala Asn
1 5

<210> SEQ ID NO 190
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

Gln Gln Tyr Lys Ser Trp Arg Thr
1 5

<210> SEQ ID NO 191
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> SEQ ID NO 192
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 193
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193

Gln Gln Ser Tyr Ser Thr Pro Phe Thr
1 5

<210> SEQ ID NO 194
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194

Arg Ala Ser Gln Ser Val Ser Arg Asn Leu Ala
1 5 10

<210> SEQ ID NO 195
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

Gly Ala Ser Thr Arg Ala Thr
1 5

<210> SEQ ID NO 196
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

Gln Gln Tyr Asn Asn Trp Pro Thr Trp Thr
1 5 10

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<210> SEQ ID NO 197
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> SEQ ID NO 198
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

Ala Ala Ser Ser Phe Gln Ser
1 5

<210> SEQ ID NO 199
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199

Leu Gln His Asn Ser Tyr Pro Pro Thr
1 5

<210> SEQ ID NO 200
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> SEQ ID NO 201
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 202
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 202

Leu Gln His Lys Ser Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 203
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

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<210> SEQ ID NO 204
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 204

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 205
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 205

Leu Gln His Lys Ser Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 206
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 206

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> SEQ ID NO 207
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 207

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 208
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 208

Leu Gln His Lys Ser Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 209
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 209

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> SEQ ID NO 210
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 210

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 211
<211> LENGTH: 9

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<213> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 211

Leu Gln His Lys Ser Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 212
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 212

Arg Ala Ser Gln Gly Ile Arg Ser Trp Leu Ala
1 5 10

<210> SEQ ID NO 213
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 213

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 214
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214

Gln Gln Ala Asn Asn Phe Pro Arg Thr
1 5

<210> SEQ ID NO 215
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 215

Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala
1 5 10

<210> SEQ ID NO 216
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 216

Gly Ala Ser Thr Arg Ala Ala
1 5

<210> SEQ ID NO 217
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 217

Gln His Tyr Ile Asn Trp Pro Lys Trp Thr
1 5 10

<210> SEQ ID NO 218
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 218

Arg Ala Ser Gln Ser Ile Ser Ser Ser Leu Ala
1 5 10

<210> SEQ ID NO 219
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 219

Gly Ala Ser Thr Arg Ala Thr
1 5

<210> SEQ ID NO 220
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 220

Gln Gln Tyr Asp Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 221
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 221

Lys Ser Ser Gln Ser Leu Leu His Ser Asp Gly Lys Thr Tyr Leu Tyr
1 5 10 15

<210> SEQ ID NO 222
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 222

Glu Val Ser Thr Arg Phe Ser
1 5

<210> SEQ ID NO 223
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 223

Met Gln Ser Ile Gln Leu Pro Leu Thr
1 5

<210> SEQ ID NO 224
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 224

Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala
1 5 10

<210> SEQ ID NO 225
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 225

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Asp Ala Ser Thr Arg Ala Thr
1 5

<210> SEQ ID NO 226
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 226

Gln Gln Tyr Asp Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 227
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 227

Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala
1 5 10

<210> SEQ ID NO 228
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 228

Asp Ala Ser Thr Arg Ala Ala
1 5

<210> SEQ ID NO 229
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 229

Gln Gln Tyr Asp Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 230
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 230

Arg Ala Ser Gln Ser Ile Ser Thr Ser Leu Ala
1 5 10

<210> SEQ ID NO 231
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 231

Gly Thr Ser Thr Arg Ala Thr
1 5

<210> SEQ ID NO 232
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 232

Gln Gln Tyr Asp Ile Trp Pro Leu Thr

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1 5

<210> SEQ ID NO 233
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 233

Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala
1 5 10

<210> SEQ ID NO 234
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 234

Gly Ala Ser Thr Arg Ala Thr
1 5

<210> SEQ ID NO 235
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 235

Gln Gln Tyr Asp Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 236
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 236

Lys Thr Ser Gln Ser Val Leu Tyr Ser Ser Lys Asn Lys Asn Phe Leu
1 5 10 15

Ala

<210> SEQ ID NO 237
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 237

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> SEQ ID NO 238
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 238

Gln Gln Tyr Tyr Ser Thr Pro Phe Thr
1 5

<210> SEQ ID NO 239
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 239

Arg Ala Ser Gln Ser Ile Ser Ser Asn Leu Ala

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1 5 10

<210> SEQ ID NO 240
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 240

Gly Ala Ser Thr Arg Ala Thr
1 5

<210> SEQ ID NO 241
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 241

Gln Gln Tyr Asp Thr Trp Pro Leu Thr
1 5

<210> SEQ ID NO 242
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 242

Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
1 5 10

<210> SEQ ID NO 243
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 243

Ala Ala Ser Thr Leu Gln Ser
1 5

<210> SEQ ID NO 244
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 244

Gln Lys Tyr Asn Arg Ala Pro Phe Thr
1 5

<210> SEQ ID NO 245
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 245

Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
1 5 10

<210> SEQ ID NO 246
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 246

Ala Ala Ser Thr Leu Gln Ser
1 5

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<210> SEQ ID NO 247
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 247

Gln Lys Tyr Asn Arg Ala Pro Phe Thr
1 5

<210> SEQ ID NO 248
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 248

Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala
1 5 10

<210> SEQ ID NO 249
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 249

Asp Ala Ser Thr Arg Ala Ala
1 5

<210> SEQ ID NO 250
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 250

Gln Gln Tyr Asp Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 251
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 251

Arg Ala Ser Gln Gly Ile Ile Asn Asp Leu Gly
1 5 10

<210> SEQ ID NO 252
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 252

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 253
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 253

Leu Gln His Asn Ser Tyr Pro Pro Thr
1 5

<210> SEQ ID NO 254

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<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 254

Arg Ser Ser Gln Ser Leu Val Tyr Ser Asp Gly His Thr Cys Leu Asn
1 5 10 15

<210> SEQ ID NO 255
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 255

Lys Val Ser Asn Trp Asp Ser
1 5

<210> SEQ ID NO 256
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 256

Met Gln Gly Thr His Trp Pro Leu Cys Ser
1 5 10

<210> SEQ ID NO 257
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 257

Arg Ser Ser Gln Ser Leu Val Tyr Ser Asp Gly His Thr Cys Leu Asn
1 5 10 15

<210> SEQ ID NO 258
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 258

Lys Val Ser Asn Trp Asp Ser
1 5

<210> SEQ ID NO 259
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 259

Met Gln Gly Thr His Trp Pro Leu Cys Ser
1 5 10

<210> SEQ ID NO 260
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 260

Arg Ala Ser Gln Ala Ile Ser Ile Tyr Leu Ala
1 5 10

<210> SEQ ID NO 261
<211> LENGTH: 7
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 261

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 262
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 262

Gln Gln Tyr Ser Ser Tyr Pro Arg Thr
1 5

<210> SEQ ID NO 263
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 263

Arg Ala Ser Gln Ser Val Tyr Ser Asn Leu Ala
1 5 10

<210> SEQ ID NO 264
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 264

Gly Ala Ser Thr Arg Ala Thr
1 5

<210> SEQ ID NO 265
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 265

Gln Gln Tyr Tyr Asn Trp Pro Trp Thr
1 5

<210> SEQ ID NO 266
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 266

aattactact ggaac 15

<210> SEQ ID NO 267
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 267

ccagggaagg gactggagtg gattggggat atctattaca gtgggagcac caactacaac 60

cctccctca agagt 75

<210> SEQ ID NO 268
<211> LENGTH: 69
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 268

gatggggaac tgccaattа ctatggttcg gggagttatc agttctacta ctactacggt 60

atggacgtc 69

<210> SEQ ID NO 269
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 269

ggttactact ggagc 15

<210> SEQ ID NO 270
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 270

gaaatcaatc atagtggacg caccaattac aacccgtccc tcaagagt 48

<210> SEQ ID NO 271
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 271

ggcccttatt actttgatag tagtggttac ctttactact actacggttt ggacgtc 57

<210> SEQ ID NO 272
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 272

agctatggca tgcac 15

<210> SEQ ID NO 273
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 273

gttatatggt atgatggaag taataaacac tatgcagact ccgtgaaggg c 51

<210> SEQ ID NO 274
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 274

gatactgggg tctac 15

<210> SEQ ID NO 275
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 275

agctatggca tgcac 15

<210> SEQ ID NO 276
<211> LENGTH: 51

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 276

gttatatggt atgatggaag taataaacac tatgcagact ccgtgaaggg c 51

<210> SEQ ID NO 277
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 277

gatactgggg tctac 15

<210> SEQ ID NO 278
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 278

agttactact ggagc 15

<210> SEQ ID NO 279
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 279

cgtatctatc gcagtgggaa caccatctac aaccccteee tcaagagt 48

<210> SEQ ID NO 280
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 280

gagaattact ctgagagtag tggtctctac tactactacg gtatggacgt c 51

<210> SEQ ID NO 281
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 281

agatatggta tcagc 15

<210> SEQ ID NO 282
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 282

tggatcagcg cttacaatgg taacacaaac tatgcacaga agctccaggg c 51

<210> SEQ ID NO 283
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 283

agggattacg atattttgac tggttattat aacgggttcg accca 45

<210> SEQ ID NO 284

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<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 284

agatatggta tcagc 15

<210> SEQ ID NO 285
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 285

tggatcagcg cttacaatgg taacacaaac tatgcacaga agctccaggg c 51

<210> SEQ ID NO 286
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 286

agggattacg atattttgac tggttattat aacgggttcg acccc 45

<210> SEQ ID NO 287
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 287

ggctatggta tcagc 15

<210> SEQ ID NO 288
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 288

tggatcagcg cttacaatgg taacacaaac tatgcacaga acctccaggg c 51

<210> SEQ ID NO 289
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 289

agggattacg atattttgac tggttattat aacgggttcg acccc 45

<210> SEQ ID NO 290
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 290

agatatggta tcagc 15

<210> SEQ ID NO 291
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 291

tggatcagcg cttacaatgg taacacaaac tatgcacaga agctccaggg 50

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<210> SEQ ID NO 292
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 292

agggattacg atattttgac tggttattat aacgggttcg acccc 45

<210> SEQ ID NO 293
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 293

agtggtggtt actactggag c 21

<210> SEQ ID NO 294
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 294

tacatctatt tcagtgggag cgcctactac aacccgtccc tcaagagt 48

<210> SEQ ID NO 295
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 295

gaatactatg atagtagtgg ttaccccgat gattttgata tc 42

<210> SEQ ID NO 296
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 296

agctatggca tgcac 15

<210> SEQ ID NO 297
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 297

gttatatggt atgatggaag taataaatat tatgcagact ccgtgaaggg c 51

<210> SEQ ID NO 298
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 298

gatacgaagg actac 15

<210> SEQ ID NO 299
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 299

agctatggta tcagc 15

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<210> SEQ ID NO 300
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 300

tggatcagca cttacaaagg taacacaaac tatgcacaga agctccaggg c 51

<210> SEQ ID NO 301
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 301

aagcagctcg tctttgacta c 21

<210> SEQ ID NO 302
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 302

agctatggca tgcag 15

<210> SEQ ID NO 303
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 303

gttatatggt atgatggaaa taagaaatac tatgcagact ccgtgaaggg c 51

<210> SEQ ID NO 304
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 304

ggacgtggtta gggactacta ctacggtatg gacgtc 36

<210> SEQ ID NO 305
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 305

agatatggta tcagc 15

<210> SEQ ID NO 306
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 306

tggatcagca cttacagtgg taacacaaac tatgcacaga agctccaggg c 51

<210> SEQ ID NO 307
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 307

cggcagcttt actttgacta c 21

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<210> SEQ ID NO 308
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 308

agctatggca tgcag 15

<210> SEQ ID NO 309
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 309

gttatatggt atgatggaaa taagaaatac tatgcagact ccgtgaaggg c 51

<210> SEQ ID NO 310
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 310

ggacgtgtta gggactacta ctacggtatg gacgtc 36

<210> SEQ ID NO 311
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 311

agctatggta tcagc 15

<210> SEQ ID NO 312
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 312

tggatcagcg cttacaatgg taacacaaag tatgcacaga agctccaggg c 51

<210> SEQ ID NO 313
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 313

aagcagctcg tcttgactta c 21

<210> SEQ ID NO 314
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 314

agctatggta tcagc 15

<210> SEQ ID NO 315
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 315

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tggatcagcg cttacagtgg taatacaaag tatgcacaga agttccaggg c 51

<210> SEQ ID NO 316
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 316

aagcagctcg tcatttgacta c 21

<210> SEQ ID NO 317
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 317

gactactacg tgcac 15

<210> SEQ ID NO 318
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 318

tggatgcacc ctaacagtgg tggcacagac ttagcacaga ggtttcaggg c 51

<210> SEQ ID NO 319
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 319

gggggatatt gtagtacttt gagctgctcc ttctactggt acttcgatct c 51

<210> SEQ ID NO 320
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 320

agctatggaa tcagt 15

<210> SEQ ID NO 321
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 321

tggatcaggg cttacagtgg taacacaaag tatgcacaga agttccaggg c 51

<210> SEQ ID NO 322
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 322

aggcagctcg cgttggacta c 21

<210> SEQ ID NO 323
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 323

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agctatagca tgaac 15

<210> SEQ ID NO 324
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 324

ttcattagtg ctagaagtag taccatatac tacgcagact ctgtgaaggg c 51

<210> SEQ ID NO 325
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 325

cctaaagtgg ggggcggtat ggacgtc 27

<210> SEQ ID NO 326
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 326

agctatagca tgaac 15

<210> SEQ ID NO 327
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 327

atcattagta gtagaagtag tatcatacac tacgcagact ctgtgaaggg c 51

<210> SEQ ID NO 328
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 328

cctaaagtgg ggggcggtat ggacgtc 27

<210> SEQ ID NO 329
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 329

agatatggta tcagc 15

<210> SEQ ID NO 330
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 330

tggatcagcg cttacagtgg taacacaaac tatgcacaga agctccaggg c 51

<210> SEQ ID NO 331
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<212> TYPE: DNA
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<400> SEQUENCE: 331

cggcagcttt actttgacta c 21

<210> SEQ ID NO 332
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 332

agttactact ggagc 15

<210> SEQ ID NO 333
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 333

cgtatctatc ccagtgggag aaccaactac aacccctccc tcaagagt 48

<210> SEQ ID NO 334
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 334

gaggcatatg agctgcaact gggcctctac tactactacg gtatggacgt c 51

<210> SEQ ID NO 335
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 335

agttactact ggagc 15

<210> SEQ ID NO 336
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 336

cgtatctatc ccagtgggag aaccaactac aacccctccc tcaagagt 48

<210> SEQ ID NO 337
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 337

gaggcatatg agctgcaact gggcctctac tactactacg gtatggacgt c 51

<210> SEQ ID NO 338
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 338

agtggtggtt actactggag c 21

<210> SEQ ID NO 339
<211> LENGTH: 39
<212> TYPE: DNA
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<400> SEQUENCE: 339

tacagtggga acacctacta caacccgtcc ctcaggagt 39

<210> SEQ ID NO 340
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 340

gaggccgggtg gtaactccgc ctactactac ggtatggacg tc 42

<210> SEQ ID NO 341
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 341

gactactaca tgagc 15

<210> SEQ ID NO 342
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 342

tacattagta gtagtcgtag taccatatac tacgcagact ctgtgaaggg c 51

<210> SEQ ID NO 343
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 343

gatcgcacgt attactttgg ttcggggagt tatgaaggga tggacgtc 48

<210> SEQ ID NO 344
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 344

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Pro Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Arg Ala Thr Gly Val Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys
85

<210> SEQ ID NO 345
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 345

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cgggcaagtc agggcattag aaatgattta ggc 33

<210> SEQ ID NO 346
<211> LENGTH: 21
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 346

gctgcatcca gtttgcaaag t 21

<210> SEQ ID NO 347
<211> LENGTH: 27
<212> TYPE: DNA
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<400> SEQUENCE: 347

ctacagcata atagtaacac attcact 27

<210> SEQ ID NO 348
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 348

agggccagtc agagtgttag cagaaactta gtc 33

<210> SEQ ID NO 349
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 349

ggggcatcca ctagggccaa t 21

<210> SEQ ID NO 350
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 350

cagcagtata aaagctggcg gacg 24

<210> SEQ ID NO 351
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 351

cgggcaagtc agagcattag cagctattta aat 33

<210> SEQ ID NO 352
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 352

gctgcatcca gtttgcaaag t 21

<210> SEQ ID NO 353
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 353

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caacagagtt acagtaccca attcact 27

<210> SEQ ID NO 354
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 354

agggccagtc agagtgttag taggaattta gcc 33

<210> SEQ ID NO 355
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 355

ggtgcatcca ccagggccac t 21

<210> SEQ ID NO 356
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 356

cagcagtata ataactggcc cacgtggacg 30

<210> SEQ ID NO 357
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 357

cgggcaagtc agggcattag aaatgattta ggc 33

<210> SEQ ID NO 358
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 358

gctgcatcca gtttccaaag t 21

<210> SEQ ID NO 359
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 359

ctacagcata atagttaccc tccgacg 27

<210> SEQ ID NO 360
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 360

cgggcaagtc agggcattag aaatgattta ggc 33

<210> SEQ ID NO 361
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 361

gctgcatcca gtttgcaaag t 21

<210> SEQ ID NO 362
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 362

ctacagcata aaagttaccc gctcact 27

<210> SEQ ID NO 363
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 363

cgggcaagtc agggcattag aaatgattta ggc 33

<210> SEQ ID NO 364
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 364

gctgcatcca gtttgcaaag t 21

<210> SEQ ID NO 365
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 365

ctacagcata aaagttaccc gctcact 27

<210> SEQ ID NO 366
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 366

cgggcaagtc agggcattag aaatgattta ggc 33

<210> SEQ ID NO 367
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 367

gctgcatcca gtttgcaaag t 21

<210> SEQ ID NO 368
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 368

ctacagcata agagttaccc gctcact 27

<210> SEQ ID NO 369
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 369

cgggcaagtc agggcattag aaatgattta 30

<210> SEQ ID NO 370
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 370

gctgcatcca gtttgcaaag t 21

<210> SEQ ID NO 371
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 371

ctacagcata aaagttaccc gctcact 27

<210> SEQ ID NO 372
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 372

cgggcgagtc agggtattag gagctggtta gcc 33

<210> SEQ ID NO 373
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 373

gctgcatcca gtttgcaaag t 21

<210> SEQ ID NO 374
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 374

caacaggcta acaattttcc tcggacg 27

<210> SEQ ID NO 375
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 375

agggccagtc agagtgttag cagcaactta gcc 33

<210> SEQ ID NO 376
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 376

ggtgcatcca gcagggcagc t 21

<210> SEQ ID NO 377
<211> LENGTH: 30
<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 377

cagcactata taaactggcc taagtggacg 30

<210> SEQ ID NO 378
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 378

agggccagtc agagtattag cagcagctta gcc 33

<210> SEQ ID NO 379
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 379

ggtgcatcca ccagggccac t 21

<210> SEQ ID NO 380
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 380

cagcaatatg ataactggcc gctcact 27

<210> SEQ ID NO 381
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 381

aagtctagtc agagcctcct gcatagtgat ggaaagacct atttgtat 48

<210> SEQ ID NO 382
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 382

gaagtttcca ccaggttctc t 21

<210> SEQ ID NO 383
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 383

atgcaaagta tacagcttcc gctcact 27

<210> SEQ ID NO 384
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 384

agggccagtc agagcgttag cagcaactta gcc 33

<210> SEQ ID NO 385
<211> LENGTH: 21

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 385

gatgcatcca ccagggccac t 21

<210> SEQ ID NO 386
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 386

cagcagtatg ataactggcc gctcact 27

<210> SEQ ID NO 387
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 387

agggccagtc agagtgttag cagcaactta gcc 33

<210> SEQ ID NO 388
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 388

gatgcatcca ccagggccgc t 21

<210> SEQ ID NO 389
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 389

cagcagtatg ataactggcc gctcact 27

<210> SEQ ID NO 390
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 390

agggccagtc agagtattag caccagctta gcc 33

<210> SEQ ID NO 391
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 391

ggtacatcca ccagggccac t 21

<210> SEQ ID NO 392
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 392

caacagtatg atatctggcc gctcact 27

<210> SEQ ID NO 393

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<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 393

agggccagtc agagtgttag cagcaactta gcc 33

<210> SEQ ID NO 394
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 394

ggtgcatcca ccagggccac t 21

<210> SEQ ID NO 395
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 395

cagcagtatg ataactggcc gctcact 27

<210> SEQ ID NO 396
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 396

aagaccagcc agagtgtttt atacagctcc aaaaacaaga acttcttagc t 51

<210> SEQ ID NO 397
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 397

tgggcatcta ccctggaatc c 21

<210> SEQ ID NO 398
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 398

cagcaatatt atagtactcc attcact 27

<210> SEQ ID NO 399
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 399

agggccagtc agagtattag cagcaactta gcc 33

<210> SEQ ID NO 400
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 400

ggtgcatcca ccagggccac t 21

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<210> SEQ ID NO 401
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 401

cagcagtatg ataccatggcc totcact 27

<210> SEQ ID NO 402
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 402

cgggcgagtc agggcattag caatttattta gcc 33

<210> SEQ ID NO 403
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 403

gctgcatcca ctttacaatc a 21

<210> SEQ ID NO 404
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 404

caaaagtata accgtgcccc attcact 27

<210> SEQ ID NO 405
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 405

cgggcgagtc agggcattag caatttattta gcc 33

<210> SEQ ID NO 406
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 406

gctgcatcca ctttgcaatc a 21

<210> SEQ ID NO 407
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 407

caaaagtata accgtgcccc attcact 27

<210> SEQ ID NO 408
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 408

agggccagtc agagtgttag cagcaactta gcc 33

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<210> SEQ ID NO 409
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 409

gatgcatcca ccagggccgc t 21

<210> SEQ ID NO 410
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 410

cagcagtatg ataactggcc gctcact 27

<210> SEQ ID NO 411
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 411

cgggcaagtc agggcattat aaatgattta ggc 33

<210> SEQ ID NO 412
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 412

gctgcatcca gcttgcaaag t 21

<210> SEQ ID NO 413
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 413

ctacagcata atagttaccc tccgacg 27

<210> SEQ ID NO 414
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 414

aggtctagtc aaagcctcgt atatagtgat ggacacacct gcttgaat 48

<210> SEQ ID NO 415
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 415

aaggtttcta actgggactc t 21

<210> SEQ ID NO 416
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 416

atgcaaggta cacactggcc tctgtgcagt 30

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<210> SEQ ID NO 417
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 417

aggtctagtc aaagcctcgt atatagtgat ggacacacct gcttgaat 48

<210> SEQ ID NO 418
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 418

aaggtttcta actgggactc t 21

<210> SEQ ID NO 419
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 419

atgcaaggta cacactggcc tctgtgcagt 30

<210> SEQ ID NO 420
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 420

cgggcgagtc aggccattag catttattta gcc 33

<210> SEQ ID NO 421
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 421

gctgcatcca gtttgcaaag t 21

<210> SEQ ID NO 422
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 422

caacagtata gtagttaccc tcggacg 27

<210> SEQ ID NO 423
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 423

agggccagtc agagtgttta cagcaactta gcc 33

<210> SEQ ID NO 424
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 424

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ggtgcttcca ccagggccac t                                                21


<210> SEQ ID NO 425
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 425

cagcagtact ataactggcc gtggacg                                          27


<210> SEQ ID NO 426
<211> LENGTH: 1409
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (16)..(1398)

<400> SEQUENCE: 426

gtcgacgccg ccacc atg gag tgg acc tgg agg gtc ctt ttc ttg gtg gca       51
                Met Glu Trp Thr Trp Arg Val Leu Phe Leu Val Ala
                1               5                   10

gca gca aca ggt gcc cac tcc cag gtt cag ctg gtg cag tct gga gct        99
Ala Ala Thr Gly Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala
        15                  20                  25

gag gtg aag aag cct ggg gcc tca gtg aag gtc tcc tgc aag gct tct       147
Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser
    30                  35                  40

ggt tac acc ttt acc aga tat ggt atc agc tgg gtg cga cag gcc cct       195
Gly Tyr Thr Phe Thr Arg Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro
45                  50                  55                  60

gga caa ggg ctt gag tgg atg gga tgg atc agc act tac agt ggt aac       243
Gly Gln Gly Leu Glu Trp Met Gly Trp Ile Ser Thr Tyr Ser Gly Asn
                65                  70                  75

aca aac tat gca cag aag ctc cag ggc aga gtc acc atg acc aca gac       291
Thr Asn Tyr Ala Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp
            80                  85                  90

aca tcc acg agc aca gcc tac atg gag ctg agg agc ctg aga tct gac       339
Thr Ser Thr Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp
        95                  100                 105

gac acg gcc gtg tat tac tgt gcg aga cgg cag ctt tac ttt gac tac       387
Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Gln Leu Tyr Phe Asp Tyr
    110                 115                 120

tgg ggc cag gga acc ctg gtc acc gtc tcc tca gct agc acc aag ggc       435
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
125                 130                 135                 140

cca tcg gtc ttc ccc ctg gcg ccc tgc tcc agg agc acc tcc gag agc       483
Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
                145                 150                 155

aca gcg gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccg gtg       531
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
            160                 165                 170

acg gtg tcg tgg aac tca ggc gct ctg acc agc ggc gtg cac acc ttc       579
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
        175                 180                 185

cca gct gtc cta cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg       627
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
    190                 195                 200

acc gtg ccc tcc agc aac ttc ggc acc cag acc tac acc tgc aac gta       675
Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
205                 210                 215                 220
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```
gat cac aag ccc agc aac acc aag gtg gac aag aca gtt gag cgc aaa      723
Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
                225                 230                 235

tgt tgt gtc gag tgc cca ccg tgc cca gca cca cct gtg gca gga ccg      771
Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
            240                 245                 250

tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc tcc      819
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        255                 260                 265

cgg acc cct gag gtc acg tgc gtg gtg gtg gac gtg agc cac gaa gac      867
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    270                 275                 280

ccc gag gtc cag ttc aac tgg tac gtg gac ggc gtg gag gtg cat aat      915
Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
285                 290                 295                 300

gcc aag aca aag cca cgg gag gag cag ttc aac agc acg ttc cgt gtg      963
Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
                305                 310                 315

gtc agc gtc ctc acc gtt gtg cac cag gac tgg ctg aac ggc aag gag     1011
Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
            320                 325                 330

tac aag tgc aag gtc tcc aac aaa ggc ctc cca gcc ccc atc gag aaa     1059
Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
        335                 340                 345

acc atc tcc aaa acc aaa ggg cag ccc cga gaa cca cag gtg tac acc     1107
Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    350                 355                 360

ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc ctg acc     1155
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
365                 370                 375                 380

tgc ctg gtc aaa ggc ttc tac ccc agc gac atc gcc gtg gag tgg gag     1203
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                385                 390                 395

agc aat ggg cag ccg gag aac aac tac aag acc aca cct ccc atg ctg     1251
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
            400                 405                 410

gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg gac aag     1299
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        415                 420                 425

agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg atg cat gag     1347
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    430                 435                 440

gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg tct ccg ggt     1395
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
445                 450                 455                 460

aaa tgagcggccg c                                                   1409
Lys
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<210> SEQ ID NO 427
<211> LENGTH: 461
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 427

```
Met Glu Trp Thr Trp Arg Val Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45
```

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```
Thr Arg Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
     50                  55                  60

Glu Trp Met Gly Trp Ile Ser Thr Tyr Ser Gly Asn Thr Asn Tyr Ala
 65                  70                  75                  80

Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                 85                  90                  95

Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Arg Gln Leu Tyr Phe Asp Tyr Trp Gly Gln Gly
        115                 120                 125

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
    130                 135                 140

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
145                 150                 155                 160

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
                165                 170                 175

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
            180                 185                 190

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
        195                 200                 205

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
    210                 215                 220

Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
225                 230                 235                 240

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
                245                 250                 255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            260                 265                 270

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
        275                 280                 285

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    290                 295                 300

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
305                 310                 315                 320

Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                325                 330                 335

Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            340                 345                 350

Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
        355                 360                 365

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    370                 375                 380

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
385                 390                 395                 400

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
                405                 410                 415

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            420                 425                 430

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        435                 440                 445

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460
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<210> SEQ ID NO 428
<211> LENGTH: 741
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (24)..(725)

<400> SEQUENCE: 428

gtcgacgttt aaacgcggcc acc atg gaa gcg ccg gcg cag ctt ctc ttc ctc 53
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu
1 5 10

ctg cta ctc tgg ctc cca gat acc act gga gaa ata gtg atg acg cag 101
Leu Leu Leu Trp Leu Pro Asp Thr Thr Gly Glu Ile Val Met Thr Gln
15 20 25

tct cca gcc acc ctg tct gtg tct cct ggg gaa aga gcc acc ctc tcc 149
Ser Pro Ala Thr Leu Ser Val Ser Pro Gly Glu Arg Ala Thr Leu Ser
30 35 40

tgc agg gcc agt cag agt gtt agc agc aac tta gcc tgg ttc cag cag 197
Cys Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala Trp Phe Gln Gln
45 50 55

aaa cct ggc cag gct ccc agg ccc ctc atc tat gat gca tcc acc agg 245
Lys Pro Gly Gln Ala Pro Arg Pro Leu Ile Tyr Asp Ala Ser Thr Arg
60 65 70

gcc act ggt gtc cca gcc agg ttc agt ggc agt ggg tct ggg aca gac 293
Ala Thr Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
75 80 85 90

ttc act ctc acc atc agc agc ctg cag tct gaa gat ttt gca gtt tat 341
Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr
95 100 105

tac tgt cag cag tat gat aac tgg ccg ctc act ttc ggc gga ggg acc 389
Tyr Cys Gln Gln Tyr Asp Asn Trp Pro Leu Thr Phe Gly Gly Gly Thr
110 115 120

aag gtg gag atc aaa cgt acg gtg gct gca cca tct gtc ttc atc ttc 437
Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
125 130 135

ccg cca tct gat gag cag ttg aaa tct gga act gcc tct gtt gtg tgc 485
Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
140 145 150

ctg ctg aat aac ttc tat ccc aga gag gcc aaa gta cag tgg aag gtg 533
Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
155 160 165 170

gat aac gcc ctc caa tcg ggt aac tcc cag gag agt gtc aca gag cag 581
Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
175 180 185

gac agc aag gac agc acc tac agc ctc agc agc acc ctg acg ctg agc 629
Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
190 195 200

aaa gca gac tac gag aaa cac aaa gtc tac gcc tgc gaa gtc acc cat 677
Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
205 210 215

cag ggc ctg agc tcg ccc gtc aca aag agc ttc aac agg gga gag tgt 725
Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
220 225 230

taggatccgc ggccgc 741

<210> SEQ ID NO 429
<211> LENGTH: 234
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 429

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30

Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45

Val Ser Ser Asn Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60

Arg Pro Leu Ile Tyr Asp Ala Ser Thr Arg Ala Thr Gly Val Pro Ala
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95

Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp
100 105 110

Asn Trp Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
115 120 125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
130 135 140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145 150 155 160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
165 170 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
180 185 190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
195 200 205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
210 215 220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230

<210> SEQ ID NO 430
<211> LENGTH: 866
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 430

Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1 5 10 15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
20 25 30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
35 40 45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
50 55 60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65 70 75 80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
85 90 95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
100 105 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
115 120 125

-continued

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
130 135 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145 150 155 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
165 170 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
180 185 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
195 200 205

Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
210 215 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225 230 235 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
245 250 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
260 265 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
275 280 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
290 295 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305 310 315 320

Val Tyr Trp Phe Ile Thr Gly Ile Ser Ile Leu Leu Val Gly Ser Val
325 330 335

Ile Leu Leu Ile Val Cys Met Thr Trp Arg Leu Ala Gly Pro Gly Ser
340 345 350

Glu Lys Tyr Ser Asp Asp Thr Lys Tyr Thr Asp Gly Leu Pro Ala Ala
355 360 365

Asp Leu Ile Pro Pro Pro Leu Lys Pro Arg Lys Val Trp Ile Ile Tyr
370 375 380

Ser Ala Asp His Pro Leu Tyr Val Asp Val Val Leu Lys Phe Ala Gln
385 390 395 400

Phe Leu Leu Thr Ala Cys Gly Thr Glu Val Ala Leu Asp Leu Leu Glu
405 410 415

Glu Gln Ala Ile Ser Glu Ala Gly Val Met Thr Trp Val Gly Arg Gln
420 425 430

Lys Gln Glu Met Val Glu Ser Asn Ser Lys Ile Ile Val Leu Cys Ser
435 440 445

Arg Gly Thr Arg Ala Lys Trp Gln Ala Leu Leu Gly Arg Gly Ala Pro
450 455 460

Val Arg Leu Arg Cys Asp His Gly Lys Pro Val Gly Asp Leu Phe Thr
465 470 475 480

Ala Ala Met Asn Met Ile Leu Pro Asp Phe Lys Arg Pro Ala Cys Phe
485 490 495

Gly Thr Tyr Val Val Cys Tyr Phe Ser Glu Val Ser Cys Asp Gly Asp
500 505 510

Val Pro Asp Leu Phe Gly Ala Ala Pro Arg Tyr Pro Leu Met Asp Arg
515 520 525

Phe Glu Glu Val Tyr Phe Arg Ile Gln Asp Leu Glu Met Phe Gln Pro
530 535 540

Gly Arg Met His Arg Val Gly Glu Leu Ser Gly Asp Asn Tyr Leu Arg

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545                 550                 555                 560

Ser Pro Gly Gly Arg Gln Leu Arg Ala Ala Leu Asp Arg Phe Arg Asp
                565                 570                 575

Trp Gln Val Arg Cys Pro Asp Trp Phe Glu Cys Glu Asn Leu Tyr Ser
            580                 585                 590

Ala Asp Asp Gln Asp Ala Pro Ser Leu Asp Glu Glu Val Phe Glu Glu
        595                 600                 605

Pro Leu Leu Pro Pro Gly Thr Gly Ile Val Lys Arg Ala Pro Leu Val
    610                 615                 620

Arg Glu Pro Gly Ser Gln Ala Cys Leu Ala Ile Asp Pro Leu Val Gly
625                 630                 635                 640

Glu Glu Gly Gly Ala Ala Val Ala Lys Leu Glu Pro His Leu Gln Pro
                645                 650                 655

Arg Gly Gln Pro Ala Pro Gln Pro Leu His Thr Leu Val Leu Ala Ala
            660                 665                 670

Glu Glu Gly Ala Leu Val Ala Ala Val Glu Pro Gly Pro Leu Ala Asp
        675                 680                 685

Gly Ala Ala Val Arg Leu Ala Leu Ala Gly Glu Gly Glu Ala Cys Pro
    690                 695                 700

Leu Leu Gly Ser Pro Gly Ala Gly Arg Asn Ser Val Leu Phe Leu Pro
705                 710                 715                 720

Val Asp Pro Glu Asp Ser Pro Leu Gly Ser Ser Thr Pro Met Ala Ser
                725                 730                 735

Pro Asp Leu Leu Pro Glu Asp Val Arg Glu His Leu Glu Gly Leu Met
            740                 745                 750

Leu Ser Leu Phe Glu Gln Ser Leu Ser Cys Gln Ala Gln Gly Gly Cys
        755                 760                 765

Ser Arg Pro Ala Met Val Leu Thr Asp Pro His Thr Pro Tyr Glu Glu
    770                 775                 780

Glu Gln Arg Gln Ser Val Gln Ser Asp Gln Gly Tyr Ile Ser Arg Ser
785                 790                 795                 800

Ser Pro Gln Pro Pro Glu Gly Leu Thr Glu Met Glu Glu Glu Glu Glu
                805                 810                 815

Glu Glu Gln Asp Pro Gly Lys Pro Ala Leu Pro Leu Ser Pro Glu Asp
            820                 825                 830

Leu Glu Ser Leu Arg Ser Leu Gln Arg Gln Leu Leu Phe Arg Gln Leu
        835                 840                 845

Gln Lys Asn Ser Gly Trp Asp Thr Met Gly Ser Glu Ser Glu Gly Pro
    850                 855                 860

Ser Ala
865
```

<210> SEQ ID NO 431
<211> LENGTH: 344
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 431

```
Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30
```

-continued

```
Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225                 230                 235                 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
                245                 250                 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
            260                 265                 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
    290                 295                 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305                 310                 315                 320

Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys Gly
                325                 330                 335

Ser Ser His His His His His His
            340
```

<210> SEQ ID NO 432
<211> LENGTH: 322
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 432

```
Met Ala Ile Arg Arg Cys Trp Pro Arg Val Val Pro Gly Pro Ala Leu
1               5                   10                  15

Gly Trp Leu Leu Leu Leu Leu Asn Val Leu Ala Pro Gly Arg Ala Ser
            20                  25                  30

Pro Arg Leu Leu Asp Phe Pro Ala Pro Val Cys Ala Gln Glu Gly Leu
        35                  40                  45

Ser Cys Arg Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60
```

-continued

```
Pro Lys Asn Leu Thr Pro Ser Ser Pro Lys Asn Ile Tyr Ile Asn Leu
65                  70                  75                  80

Ser Val Ser Ser Thr Gln His Gly Glu Leu Val Pro Val Leu His Val
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Lys
        115                 120                 125

Phe Gln Phe Leu Ser Met Leu Gln His His Arg Lys Arg Trp Arg Phe
    130                 135                 140

Ser Phe Ser His Phe Val Val Asp Pro Gly Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Lys
                165                 170                 175

Ser Lys Ile Ile Phe Val Pro Asp Cys Glu Asp Ser Lys Met Lys Met
            180                 185                 190

Thr Thr Ser Cys Val Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Asp Thr Gln His Leu Arg Val Asp Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr Pro Tyr Gln Val Leu Leu Glu Ser Phe Ser Asp Ser
225                 230                 235                 240

Glu Asn His Ser Cys Phe Asp Val Val Lys Gln Ile Phe Ala Pro Arg
                245                 250                 255

Gln Glu Glu Phe His Gln Arg Ala Asn Val Thr Phe Thr Leu Ser Lys
            260                 265                 270

Phe His Trp Cys Cys His His His Val Gln Val Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ala Val Thr Val Pro Cys Pro
    290                 295                 300

Val Ile Ser Asn Thr Thr Val Pro Lys Pro Val Ala Asp Tyr Ile Pro
305                 310                 315                 320

Leu Trp


<210> SEQ ID NO 433
<211> LENGTH: 344
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      construct

<400> SEQUENCE: 433

Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp Phe Pro Ala Pro Val Cys Ala Gln Glu Gly Leu
        35                  40                  45

Ser Cys Arg Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95
```

-continued

```
Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225                 230                 235                 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
                245                 250                 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
            260                 265                 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
    290                 295                 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305                 310                 315                 320

Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys Gly
                325                 330                 335

Ser Ser His His His His His His
            340
```

<210> SEQ ID NO 434
<211> LENGTH: 344
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 434

```
Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asn Ile Tyr Ile Asn Leu
65                  70                  75                  80

Ser Val Ser Ser Thr Gln His Gly Glu Leu Val Pro Val Leu His Val
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
```

-continued

```
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225                 230                 235                 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
                245                 250                 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
            260                 265                 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
    290                 295                 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305                 310                 315                 320

Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys Gly
                325                 330                 335

Ser Ser His His His His His His
            340


<210> SEQ ID NO 435
<211> LENGTH: 344
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      construct

<400> SEQUENCE: 435

Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110
```

-continued

```
Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Lys
        115                 120                 125

Phe Gln Phe Leu Ser Met Leu Gln His His Arg Lys Arg Trp Arg Phe
    130                 135                 140

Ser Phe Ser His Phe Val Val Asp Pro Gly Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225                 230                 235                 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
                245                 250                 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
            260                 265                 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
    290                 295                 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305                 310                 315                 320

Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys Gly
                325                 330                 335

Ser Ser His His His His His His
            340
```

<210> SEQ ID NO 436
<211> LENGTH: 344
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 436

```
Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125
```

-continued

```
Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Lys
                165                 170                 175

Ser Lys Ile Ile Phe Val Pro Asp Cys Glu Asp Ser Lys Met Lys Met
            180                 185                 190

Thr Thr Ser Cys Val Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225                 230                 235                 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
                245                 250                 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
            260                 265                 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
    290                 295                 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305                 310                 315                 320

Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys Gly
                325                 330                 335

Ser Ser His His His His His His
            340
```

<210> SEQ ID NO 437
<211> LENGTH: 344
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 437

```
Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
```

-continued

```
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Asp Thr Gln His Leu Arg Val Asp Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225                 230                 235                 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
                245                 250                 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
            260                 265                 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
    290                 295                 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305                 310                 315                 320

Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys Gly
                325                 330                 335

Ser Ser His His His His His His
            340
```

<210> SEQ ID NO 438
<211> LENGTH: 346
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 438

```
Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
    130                 135                 140
```

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```
Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr Pro Tyr Gln Val Leu Leu Glu Ser Phe Ser Asp Ser
225                 230                 235                 240

Glu Asn His Ser Cys Phe Asp Val Val Lys Gln Ile Phe Ala Pro Arg
                245                 250                 255

Gln Glu Glu Phe His Gln Arg Ala Asn Val Thr Phe Thr Leu Ser Lys
            260                 265                 270

Phe His Trp Cys Cys His His His Val Gln Val Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ala Val Thr Val Pro Cys Pro
    290                 295                 300

Val Ile Ser Asn Thr Thr Val Pro Lys Pro Val Ala Asp Tyr Ile Pro
305                 310                 315                 320

Leu Trp Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp
                325                 330                 335

Lys Gly Ser Ser His His His His His His
            340                 345
```

<210> SEQ ID NO 439
<211> LENGTH: 344
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 439

```
Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp Phe Pro Ala Pro Val Cys Ala Gln Glu Gly Leu
        35                  40                  45

Ser Cys Arg Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160
```

-continued

```
Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Asp Thr Gln His Leu Arg Val Asp Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225                 230                 235                 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
                245                 250                 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
            260                 265                 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
    290                 295                 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305                 310                 315                 320

Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys Gly
                325                 330                 335

Ser Ser His His His His His His
            340
```

<210> SEQ ID NO 440
<211> LENGTH: 344
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 440

```
Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asn Ile Tyr Ile Asn Leu
65                  70                  75                  80

Ser Val Ser Ser Thr Gln His Gly Glu Leu Val Pro Val Leu His Val
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His His Arg Arg Trp Arg Phe
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
```

-continued

```
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Asp Thr Gln His Leu Arg Val Asp Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225                 230                 235                 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
                245                 250                 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
            260                 265                 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
    290                 295                 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305                 310                 315                 320

Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys Gly
                325                 330                 335

Ser Ser His His His His His His
            340
```

<210> SEQ ID NO 441
<211> LENGTH: 344
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 441

```
Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Lys
        115                 120                 125

Phe Gln Phe Leu Ser Met Leu Gln His His Arg Lys Arg Trp Arg Phe
    130                 135                 140

Ser Phe Ser His Phe Val Val Asp Pro Gly Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175
```

-continued

```
Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Asp Thr Gln His Leu Arg Val Asp Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225                 230                 235                 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
                245                 250                 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
            260                 265                 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
    290                 295                 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305                 310                 315                 320

Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys Gly
                325                 330                 335

Ser Ser His His His His His His
            340
```

<210> SEQ ID NO 442
<211> LENGTH: 344
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 442

```
Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Lys
                165                 170                 175

Ser Lys Ile Ile Phe Val Pro Asp Cys Glu Asp Ser Lys Met Lys Met
            180                 185                 190
```

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```
Thr Thr Ser Cys Val Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Asp Thr Gln His Leu Arg Val Asp Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225                 230                 235                 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
                245                 250                 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
            260                 265                 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
    290                 295                 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305                 310                 315                 320

Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys Gly
                325                 330                 335

Ser Ser His His His His His His
            340


<210> SEQ ID NO 443
<211> LENGTH: 346
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      construct

<400> SEQUENCE: 443

Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp Phe Pro Ala Pro Val Cys Ala Gln Glu Gly Leu
        35                  40                  45

Ser Cys Arg Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
```

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```
        195                 200                 205

Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr Pro Tyr Gln Val Leu Leu Glu Ser Phe Ser Asp Ser
225                 230                 235                 240

Glu Asn His Ser Cys Phe Asp Val Val Lys Gln Ile Phe Ala Pro Arg
                245                 250                 255

Gln Glu Glu Phe His Gln Arg Ala Asn Val Thr Phe Thr Leu Ser Lys
            260                 265                 270

Phe His Trp Cys Cys His His His Val Gln Val Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ala Val Thr Val Pro Cys Pro
    290                 295                 300

Val Ile Ser Asn Thr Thr Val Pro Lys Pro Val Ala Asp Tyr Ile Pro
305                 310                 315                 320

Leu Trp Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp
                325                 330                 335

Lys Gly Ser Ser His His His His His His
            340                 345


<210> SEQ ID NO 444
<211> LENGTH: 346
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      construct

<400> SEQUENCE: 444

Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asn Ile Tyr Ile Asn Leu
65                  70                  75                  80

Ser Val Ser Ser Thr Gln His Gly Glu Leu Val Pro Val Leu His Val
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205
```

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```
Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr Pro Tyr Gln Val Leu Leu Glu Ser Phe Ser Asp Ser
225                 230                 235                 240

Glu Asn His Ser Cys Phe Asp Val Val Lys Gln Ile Phe Ala Pro Arg
                245                 250                 255

Gln Glu Glu Phe His Gln Arg Ala Asn Val Thr Phe Thr Leu Ser Lys
            260                 265                 270

Phe His Trp Cys Cys His His His Val Gln Val Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ala Val Thr Val Pro Cys Pro
    290                 295                 300

Val Ile Ser Asn Thr Thr Val Pro Lys Pro Val Ala Asp Tyr Ile Pro
305                 310                 315                 320

Leu Trp Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp
                325                 330                 335

Lys Gly Ser Ser His His His His His His
            340                 345


<210> SEQ ID NO 445
<211> LENGTH: 346
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      construct

<400> SEQUENCE: 445

Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Lys
        115                 120                 125

Phe Gln Phe Leu Ser Met Leu Gln His His Arg Lys Arg Trp Arg Phe
    130                 135                 140

Ser Phe Ser His Phe Val Val Asp Pro Gly Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
    210                 215                 220
```

-continued

```
Asn Glu Ser Thr Pro Tyr Gln Val Leu Leu Glu Ser Phe Ser Asp Ser
225                 230                 235                 240

Glu Asn His Ser Cys Phe Asp Val Val Lys Gln Ile Phe Ala Pro Arg
                245                 250                 255

Gln Glu Glu Phe His Gln Arg Ala Asn Val Thr Phe Thr Leu Ser Lys
            260                 265                 270

Phe His Trp Cys Cys His His His Val Gln Val Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ala Val Thr Val Pro Cys Pro
    290                 295                 300

Val Ile Ser Asn Thr Thr Val Pro Lys Pro Val Ala Asp Tyr Ile Pro
305                 310                 315                 320

Leu Trp Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp
                325                 330                 335

Lys Gly Ser Ser His His His His His His
            340                 345


<210> SEQ ID NO 446
<211> LENGTH: 346
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      construct

<400> SEQUENCE: 446

Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
1               5                   10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80

His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Lys
                165                 170                 175

Ser Lys Ile Ile Phe Val Pro Asp Cys Glu Asp Ser Lys Met Lys Met
            180                 185                 190

Thr Thr Ser Cys Val Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr Pro Tyr Gln Val Leu Leu Glu Ser Phe Ser Asp Ser
```

-continued

```
225                 230                 235                 240

Glu Asn His Ser Cys Phe Asp Val Val Lys Gln Ile Phe Ala Pro Arg
                245                 250                 255

Gln Glu Glu Phe His Gln Arg Ala Asn Val Thr Phe Thr Leu Ser Lys
            260                 265                 270

Phe His Trp Cys Cys His His His Val Gln Val Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ala Val Thr Val Pro Cys Pro
    290                 295                 300

Val Ile Ser Asn Thr Thr Val Pro Lys Pro Val Ala Asp Tyr Ile Pro
305                 310                 315                 320

Leu Trp Glu Pro Arg Ser Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp
                325                 330                 335

Lys Gly Ser Ser His His His His His His
            340                 345


<210> SEQ ID NO 447
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 447

Asp Tyr Lys Asp Asp Asp Asp Lys
1               5


<210> SEQ ID NO 448
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 448

Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala
1               5                   10


<210> SEQ ID NO 449
<211> LENGTH: 88
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      construct

<400> SEQUENCE: 449

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys
                85
```

-continued

<210> SEQ ID NO 450
<211> LENGTH: 88
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 450

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys
85

<210> SEQ ID NO 451
<211> LENGTH: 88
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 451

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys
85

<210> SEQ ID NO 452
<211> LENGTH: 88
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 452

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

-continued

```
Tyr Asp Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Pro Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys
                85


<210> SEQ ID NO 453
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 453

Xaa Tyr Gly Ile Ser
1               5


<210> SEQ ID NO 454
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
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Gly

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Gly

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Leu Gln His Xaa Ser Tyr Xaa Xaa Thr
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Gln Xaa Xaa Xaa Xaa Xaa Pro Xaa Thr
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<400> SEQUENCE: 469

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<400> SEQUENCE: 470

Gln Xaa Tyr Xaa Xaa Trp Xaa Xaa Xaa Thr
1               5                   10
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What is claimed is:

1. An isolated monoclonal antibody, comprising a first isolated monoclonal antibody, or IL-17RA-binding fragment thereof, that specifically binds to IL-17RA and competes for binding with a second isolated monoclonal antibody, wherein said second isolated monoclonal antibody, or IL-17RA-binding fragment thereof, comprises a light chain CDR1 (SEQ ID NO:224), CDR2 (SEQ ID NO:225), CDR3 (SEQ ID NO:226) and a heavy chain CDR1 (SEQ ID NO:146), CDR2 (SEQ ID NO:147), CDR3 (SEQ ID NO:148).

2. The first isolated monoclonal antibody of claim 1, wherein said first isolated monoclonal antibody is selected from the group consisting of:

a. a human antibody;
b. a humanized antibody;
c. a chimeric antibody;
d. a single chain antibody;
e. a diabody;
f. a triabody;
g. a tetrabody;
h. a Fab fragment;
i. a F(ab')2 fragment;
j. an IgD antibody;
k. an IgE antibody;
l. an IgM antibody;
m. an IgG1 antibody;
n. an IgG2 antibody;
o. an IgG3 antibody; and
p. an IgG4 antibody.

3. The first isolated monoclonal antibody of claim 2, wherein said antibody inhibits human IL-17A from binding to human IL-17RA.

4. The first isolated monoclonal antibody of claim 3, wherein said antibody inhibits human IL-17A and human IL-17F from binding to human IL-17RA.

5. The first isolated monoclonal antibody of claim 2, wherein said antibody inhibits human IL-17A or human IL-17F from binding to human IL-17RA.

6. An isolated monoclonal antibody, comprising a first isolated monoclonal antibody, or IL-17RA-binding fragment thereof, that specifically binds to IL-17RA and competes for binding with a second isolated monoclonal antibody, wherein said second isolated monoclonal antibody, or IL-17RA-binding fragment thereof, comprises a light chain variable domain sequence comprising SEQ ID NO:40 and a heavy chain variable domain sequence comprising SEQ ID NO:14.

7. An isolated monoclonal antibody, comprising a first isolated monoclonal antibody, or IL-17RA-binding fragment thereof, that specifically binds to IL-17RA and competes for binding with a second isolated monoclonal antibody, wherein said second isolated monoclonal antibody, or IL-17RA-binding fragment thereof, comprises a light chain sequence comprising SEQ ID NO:429 and a heavy chain sequence comprising SEQ ID NO:427.

8. An isolated monoclonal antibody, comprising a first isolated monoclonal antibody, or IL-17RA-binding fragment thereof, that specifically binds to IL-17RA and competes for binding with a second isolated monoclonal antibody, wherein said second isolated monoclonal antibody, or IL-17RA-binding fragment thereof, comprises at least two light chain sequences comprising SEQ ID NO:429 and at least two heavy chain sequences comprising SEQ ID NO:427.

* * * * *

Exhibit D

United States Patent and Trademark Office

Office of the Commissioner for Patents

Maintenance Fee Statement

CURRENT CORRESPONDENCE ADDRESS	CUSTOMER #	ENTITY STATUS	STATEMENT GENERATED
AMGEN INC. LAW - PATENT OPERATIONS, M/S 28-2-C ONE AMGEN CENTER DRIVE THOUSAND OAKS, US 91320-1799	37500	UNDISCOUNTED	04/09/2017 11:55:29

Invention

NEUTRALIZING DETERMINANTS OF IL-17 RECEPTOR A AND ANTIBODIES THAT BIND THERETO

PATENT #	APPLICATION #	FILING DATE	ISSUE DATE
7767206	11906079	09/27/2007	08/03/2010

Payment Details

PAYMENT DATE	DATE POSTED	TRANSACTION ID	ATTORNEY DOCKET #	TOTAL PAYMENT
01/08/2014	01/09/2014	010914RAMBULKS00006759504623	KIRIN-AMGEN, INC.	$1,600.00

Fee Code	Description	Sub ID	Fee Amount
1551	MAINTENANCE FEE DUE AT 3.5 YEARS	010914RAMBULKS00006759	$1,600.00

According to the records of the United States Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed above. The payment above may be subject to actual collection. If the payment is refused or charged back by a financial institution the payment will be void, and the maintenance fee and any necessary surcharge unpaid.

Exhibit E

Product Report

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Query: Drug Name = brodalumab

Entry Number	474135
Record Creation Date	Mar 28, 2008
Last Updated Date	Mar 01, 2017
CAS Registry No.	
Molecular Formula	
Molecular Weight	
Highest Phase	Launched-2016
Under Active Development	Yes
Link to Integrity	

Chemical Structure

Brodalumab

Sequence

Heavy chain:

QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYGISWVRQAPGQGL

EWMGWISTYSGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDD

TAVYYCARRQLYFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTS

ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS

LSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPC

PAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQF

NWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYK

CKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSL

TCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKL

TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Light chain:

EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWFQQKPGQAPR

PLIYDASTRATGVPARFSGSGSGTDFTLTISSLQSEDFAVYYCQQ

YDNWPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL

LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT

LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Chemical Name/Description

Immunoglobulin G, anti - (human interleukin 17 receptor A) (human monoclonal heavy chain), disulfide with human monoclonal light chain, dimer

Immunoglobulin G2, anti - (human interleukin - 17 receptor A (IL - 17RA, CDw217, CD217)); human monoclonal AMG827 gamma2 heavy chain (130 - 214') - disulfide with human monoclonal AMG827 kappa light chain dimer (218 - 218":219 - 219":222 - 222":225 - 225") - tetrakisdisulfide

Code Name	**Generic Name**	**Brand Name**
AMG-827 KHK-4827 MEDI-6365	Brodalumab (Prop INN; USAN)	Lumicef Siliq

Product Category	**Prescription/ Indication Type**	**Natural Source**
Human Monoclonal Antibodies		

Molecular Mechanism	**Cellular Mechanism**
Signal Transduction Modulators	

Anti-IL-17 Receptor (IL-17R, IL-17RA)		
Organization Leo AstraZeneca Kyowa Hakko Kirin Amgen (Originator) Valeant	**Therapeutic Group** Treatment of Musculoskeletal & Connective Tissue Diseases (Miscellaneous) Asthma Therapy Inflammatory Bowel Disease, Agents for Rheumatoid Arthritis, Treatment of Psoriatic Arthritis, Treatment of Antipsoriatics Dermatologic Drugs	**Condition** Dermatological Disorders Psoriasis, plaque Asthma Arthritis, psoriatic Spondyloarthritis Pustular psoriasis (generalized) Rheumatoid arthritis Crohn's disease

Product Summary
Brodalumab, a fully human monoclonal antibody that binds to and blocks signaling via the IL-17 receptor, was originated at Amgen. In 2016 the product was first launched in Japan by Kyowa Hakko Kirin for the treatment of pustular psoriasis (generalized), psoriatic erythroderma, plaque psoriasis and psoriatic arthritis in patients who respond inadequately to existing therapies. Brodalumab was approved in 2017 by the FDA for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. The product is awaiting registration in the E.U. for this indication. The antibody is in phase III clinical studies at AstraZeneca for the treatment of psoriatic arthritis. Clinical evaluation of the compound for the treatment of rheumatoid arthritis was discontinued in 2012. In 2011, the compound was licensed to Kyowa Hakko Kirin by Amgen in Japan, China and other Asian countries. In 2012, the compound was licensed to AstraZeneca by Amgen for global joint development and commercialization, except territories previously partnered with Kyowa Hakko Kirin. In 2015, Amgen terminated its participation in the co-development and commercialization of brodalumab with AstraZeneca. Amgen transitions the program to AstraZeneca, which gained rights for the clinical development and submission of marketing applications for all territories, except for certain Asian territories where Kyowa Hakko Kirin has rights. The same year, AstraZeneca licensed to Valeant the exclusive rights to develop and commercialize the product, except in Japan and certain other Asian. In 2016, this agreement with Valeant was terminated in Europe, and AstraZeneca licensed to Leo Pharma exclusive European development and commercialization rights to brodalumab.

Development Status Summary

Phase	Organization	Condition
Launched - 2016	Kyowa Hakko Kirin	Arthritis, psoriatic
Launched - 2016	Kyowa Hakko Kirin	Psoriasis, plaque
Launched - 2016	Kyowa Hakko Kirin	Pustular psoriasis (generalized)

Development Status - Launched, Registered or Under Active Development

Country/ Area	Phase	Organization	Brand Name	Condition	Notes
European Union	Pre-Registered	AstraZeneca		Psoriasis, plaque	Treatment of moderate to severe plaque psoriasis subcutaneous Injections, 210 mg
Japan	Launched - 2016	Kyowa Hakko Kirin	Lumicef	Arthritis, psoriatic	In patients who respond inadequately to existing therapies subcutaneous Injections, 210mg
Japan	Launched -	Kyowa Hakko	Lumicef	Psoriasis,	Treatment of psoriasis

	2016	Kirin		plaque	vulgaris in patients who respond inadequately to existing therapies subcutaneous Injections, 210mg
Japan	Launched - 2016	Kyowa Hakko Kirin	Lumicef	Pustular psoriasis (generalized)	Treatment of pustular psoriasis and psoriatic erythroderma in patients who respond inadequately to existing therapies subcutaneous Injections, 210mg
United States	Registered - 2017	Valeant	Siliq	Psoriasis, plaque	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies subcutaneous Injections, 210 mg/1.5 ml
	Phase III	AstraZeneca		Arthritis, psoriatic	subcutaneous

Development Status - No Development Reported

Country/ Area	Phase	Organization	Brand Name	Condition	Notes
	Discontinued	Amgen		Rheumatoid arthritis	In patients with rheumatoid arthritis and an inadequate response to methotrexate
	Discontinued	AstraZeneca		Asthma	
	Phase II	Amgen		Asthma	Treatment of patients with inadequately controlled asthma
	Phase II	Amgen		Crohn's disease	In patients with moderate to severe Crohn's disease
	Phase III	Amgen		Arthritis, psoriatic	subcutaneous
	Phase III	Amgen		Psoriasis, plaque	Treatment of moderate to severe plaque psoriasis subcutaneous

Update History (40 most recent)

Change Date	Change Type	Change Value
Mar 01, 2017	New Related Reference	Am J Gastroenterol 2016, 111(11): 1599
Feb 17, 2017	New Product Name	Siliq (Brand Name)
Feb 17, 2017	New Related Reference	Thomson Reuters Drug News (formerly DailyDrugNews.com) February 16, 2017

Feb 17, 2017	New Related Reference	Drugs@FDA Web Site 2017, February 15
Feb 17, 2017	New Milestone	Registered (BLA Approved) in US by Valeant for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies; Injections, 210 mg/1.5 ml; Subcutaneous
Feb 16, 2017	New Related Reference	Br J Dermatol 2016, 175(5): 1065
Feb 16, 2017	New Related Reference	J Eur Acad Dermatol Venereol 2016, 30(11): 1957
Feb 02, 2017	New Related Reference	Kyowa Hakko Kirin Press Release 2017, January 31
Feb 01, 2017	New Milestone	Phase III initiated by Kyowa Hakko Kirin in KR for the treatment of moderate to severe plaque psoriasis; Injections; Subcutaneous
Feb 01, 2017	New Related Reference	Kyowa Hakko Kirin Web Site 2017, January 31
Dec 14, 2016	New Milestone	Phase III scheduled by Kyowa Hakko Kirin in KR for the treatment of moderate to severe plaque psoriasis; Injections; Subcutaneous
Dec 14, 2016	New Related Reference	Arch Pharmacal Res 2016, 39(11): 1537
Dec 10, 2016	New Related Reference	ClinicalTrials.gov Web Site 2016, December 08
Dec 08, 2016	New Related Reference	ClinicalTrials.gov Web Site 2016, December 06
Oct 31, 2016	New Related Reference	Kyowa Hakko Kirin Press Release 2016, October 28
Sep 30, 2016	Updated Highest Phase Field	Launched-2016
Sep 30, 2016	New Milestone	Launched by Kyowa Hakko Kirin in JP for the ttreatment of psoriasis vulgaris in patients who respond inadequately to existing therapies; Injections, 210mg; Subcutaneous
Sep 30, 2016	New Milestone	Launched by Kyowa Hakko Kirin in JP for the treatment of pustular psoriasis and psoriatic erythroderma in patients who respond inadequately to existing therapies; Injections, 210mg; Subcutaneous
Sep 30, 2016	New Milestone	Launched by Kyowa Hakko Kirin in JP for the treatment of psoriatic arthritis in patients who respond inadequately to existing therapies; Injections, 210mg; Subcutaneous
Jul 29, 2016	New Related Reference	Kyowa Hakko Kirin Press Release 2016, July 29
Jul 20, 2016	New Milestone	Recommended Approval received in US by Valeant for the treatment of moderate to severe plaque psoriasis; Injections, 210 mg; Subcutaneous
Jul 20, 2016	New Related Reference	Thomson Reuters Drug News (formerly DailyDrugNews.com) July 20, 2016
Jul 04, 2016	Updated Highest Phase Field	Registered-2016
Jul 04, 2016	New Related Reference	Thomson Reuters Drug News (formerly DailyDrugNews.com) July 4, 2016
Jul 04, 2016	New Related Reference	J Rheumatol 2016, 43(2): 343
Jul 04, 2016	New Milestone	Registered in JP by Kyowa Hakko Kirin for the treatment of pustular psoriasis and psoriatic erythroderma in patients who respond inadequately to existing therapies; Injections, 210mg; Subcutaneous
Jul 04, 2016	New Milestone	Registered in JP by Kyowa Hakko Kirin for the treatment of psoriatic arthritis in patients who respond inadequately to existing therapies; Injections, 210mg; Subcutaneous
Jul 04, 2016	New Milestone	Registered in JP by Kyowa Hakko Kirin for the treatment of psoriasis vulgaris in patients who respond inadequately to existing therapies; Injections, 210mg; Subcutaneous

Jul 04, 2016	New Product Name	MEDI-6365 (Code Name)
Jul 04, 2016	New Product Name	Lumicef (Brand Name)
Jul 03, 2016	New Therapeutic Group	Dermatologic Drugs
Jul 03, 2016	New Related Reference	Thomson Reuters Drug News (formerly DailyDrugNews.com) July 1, 2016
Jul 03, 2016	New Milestone	Licensed to Leo from AstraZeneca exclusive development and commercialization rights in Europe for the treatment of dermatological disorders
Jul 03, 2016	New Milestone	License agreement terminated by AstraZeneca and Valeant in Europe; Valeant retained development and commercialisation rights in the US and all other markets included in the original agreement
Jul 03, 2016	New Milestone	Registered (MAA Approval) in EU scheduled by AstraZeneca and Leo for the treatment of moderate to severe plaque psoriasis; Injections, 210 mg; Subcutaneous
Jul 03, 2016	New Organization	Leo
Jul 03, 2016	New Condition	Dermatological Disorders
Jun 16, 2016	New Related Reference	J Derm Treat 2016, 27(4): 311
Jun 16, 2016	New Related Reference	Valeant Pharmaceuticals Press Release 2016, June 09
Mar 31, 2016	New Related Reference	74th Annu Meet Am Acad Dermatol (AAD) (March 4-8, Washington DC) 2016, Abst 3172

Related Information - Records in other Knowledge Areas

Drugs & Biologics	0	Companies & Research Institutions	5
Literature	180	Targets & Pathways	2
Patents	2	Experimental Pharmacology	0
Disease Briefings	2	Pharmcokinetics/ Metabolism	126
Clinical Studies	79	Biomarkers	17
Organic Synthesis	0	Experimental Models	1
Genomics	0		

Exhibit F

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names: List 67

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [*Off. Rec. Wld Health Org.*, 1955, **60**, 3 (Resolution EB15.R7); 1969, **173**, 10 (Resolution EB43.R9); Resolution EB115.R4 (EB115/2005/REC/1)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.
Lists of Proposed (1–105) and Recommended (1–66) International Nonproprietary Names can be found in *Cumulative List No. 14, 2011* (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES: Liste 67

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, **60**, 3 (résolution EB15.R7); 1969, **173**, 10 (résolution EB43.R9); résolution EB115.R4 (EB115/2005/REC/1)] les dénominations ci-dessous sont choisies par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.
On trouvera d'autres listes de Dénominations communes internationales proposées (1–105) et recommandées (1–66) dans la *Liste récapitulative No. 14, 2011* (disponible sur CD-ROM seulement).

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS: Lista 67

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [*Act. Of. Mund. Salud*, 1955, **60**, 3 (Resolución EB15.R7); 1969, **173**, 10 (Resolución EB43.R9); Résolution EB115.R4 (EB115/2005/REC/1) EB115.R4 (EB115/2005/REC/1)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.
Las listas de Denominaciones Comunes Internacionales Propuestas (1–105) y Recomendadas (1–66) se encuentran reunidas en *Cumulative List No. 14, 2011* (disponible sólo en CD-ROM).

Latin, English, French, Spanish: *Recommended INN*	*Chemical name or description; Molecular formula; Graphic formula*
DCI Recommandée	*Nom chimique ou description; Formule brute; Formule développée*
DCI Recomendada	*Nombre químico o descripción; Fórmula molecular; Fórmula desarrollada*

abexinostatum
abexinostat

3-[(dimethylamino)methyl]-*N*-{2-[4-(hydroxycarbamoyl)phenoxy]ethyl}-1-benzofuran-2-carboxamide

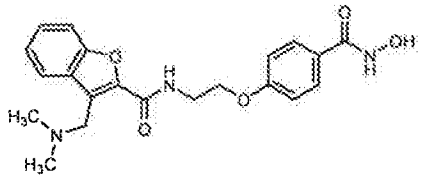
abexinostat

3-[(diméthylamino)méthyl]-*N*-{2-[4-(hydroxycarbamoyl)phénoxy]éthyl}-1-benzofurane-2-carboxamide

abexinostat

3-[(dimetilamino)metil]-*N*-{2-[4-(hidroxicarbamoil)fenoxi]etil}-1-benzofuran-2-carboxamida

$C_{21}H_{23}N_3O_5$



amilomotidum #
amilomotide

virus like particle of bacteriophage Q-beta coat protein that is coupled to multiple copies of human beta-amyloid1-6 peptide fragment;
reaction products of bacteriophage Q-beta coat protein with human beta-amyloid protein-(1-6)-peptidylglycylglycyl-L-cysteine and 3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrole-1-yl)-*N*-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}propanamide

amilomotide

pseudo-particule virale de la capside du phage Q-bêta couplée à plusieurs copies du fragment 1-6 de la protéine bêta-amyloïde humaine;
produit obtenu par réaction de la protéine de capside du phage Q-bêta avec la protéine bêta-amyloïde humaine-(1-6)peptidylglycylglycyl-L-cystéine et le 3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrole-1-yl)-*N*-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}propanamide

amilomotida

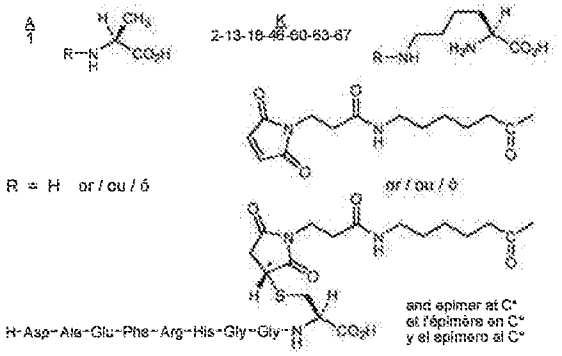
pseudo-partícula viral de cápsida del fago Q-beta acoplada a múltiples copias del fragmento 1-6 de la proteína beta-amiloide humana;
producto obtenido por reacción de la proteína de cápsida del fago Q-beta con la proteína beta-amiloide humana-(1-6)peptidilglicilglicil-L-cisteína y el 3-(2,5-dioxo-2,5-dihidro-1*H*-pirrol-1-il)-*N*-{6-[(2,5-dioxopirrolidin-1-il)oxi]-6-oxohexil}propanamida

Heavy chain / Chaîne lourde / Cadena pesada

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AKLEVTLGN IGKDGKQELV LNPKGVNPTN GVASLSQAGA VPALDKRVTV SQ
SVSQPSRNRK NYKVQVKIQN PTACTANGEC DPKVTRQAYA DVTFSFTQYS TK
TDERRAFVRT ELAALLASPL LIDAIDQLNP AY
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Disulfide bridge location / Position du pont disulfure / Posición del puente disulfuro
74–80

Modified residues / Résidus modifiés / Residuos modificados



anivamersenum
anivamersen

2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methylcytidine

anivamersen

2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-*O*-méthylcytidine

anivamersén

2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-*O*-metilctidina

$C_{157}H_{208}N_{58}O_{103}P_{14}$

(3'-5')-mC-mG-mC-mG-mG-mU-mA-mU-mA-mG-mU-mC-mC-mA-mC

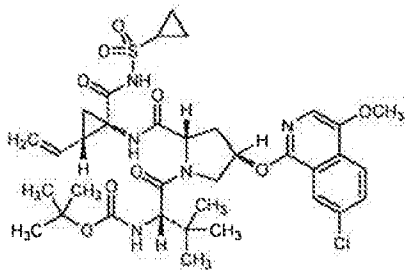
asunaprevirum

asunaprevir — *tert*-butyl {(2*S*)-1-[(2*S*,4*R*)-4-({7-chloro-4-methoxyisoquinolin-1-yl}oxy)-2-({(1*R*,2*S*)-1-[(cyclopropanesulfonyl)carbamoyl]-2-ethenylcyclopropyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

asunaprévir — (2*S*)-1-[(2*S*,4*R*)-4-({7-chloro-4-méthoxyisoquinolin-1-yl}oxy)-2-({(1*R*,2*S*)-1-[(cyclopropanesulfonyl)carbamoyl]-2-éthènylcyclopropyl}carbamoyl)pyrrolidin-1-yl]-3,3-diméthyl-1-oxobutan-2-yl}carbamate de *tert*-butyle

asunaprevir — {(2*S*)-1-[(2*S*,4*R*)-4-({7-cloro-4-metoxiisoquinolin-1-il}oxi)-2-({(1*R*,2*S*)-1-[(ciclopropanosulfonil)carbamoil]-2-etenilciclopropil}carbamoil)pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de *terc*-butilo

$C_{35}H_{46}ClN_5O_9S$



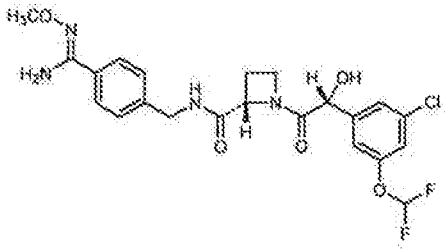
atecegatranum metoxilum

atecegatran metoxil — (2*S*)-1-{(2*R*)-2-[3-chloro-5-(difluoromethoxy)phenyl]-2-hydroxyacetyl}-*N*-({4-[(*Z*)-*N*'-methoxycarbamimidoyl]phenyl}methyl)azetidine-2-carboxamide

atécégatran métoxil — (2*S*)-1-{(2*R*)-2-[3-chloro-5-(difluorométhoxy)phényl]-2-hydroxyacétyl}-*N*-({4-[(*Z*)-*N*'-méthoxycarbamimidoyl]phényl}méthyl)azétidine-2-carboxamide

atecegatrán metoxilo — (2*S*)-1-{(2*R*)-2-[3-cloro-5-(difluorometoxi)fenil]-2-hidroxiacetil}-*N*-({4-[(*Z*)-*N*'-metoxicarbamimidoil]fenil}metil)azetidina-2-carboxamida

$C_{22}H_{23}ClF_2N_4O_5$

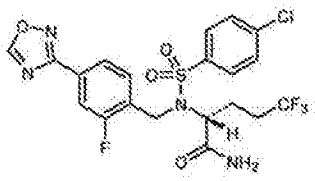


avagacestatum
avagacestat — (2*R*)-2-(4-chloro-*N*-{[2-fluoro-4-(1,2,4-oxadiazol-3-yl)phenyl]methyl}benzenesulfonamido)-5,5,5-trifluoropentanamide

avagacestat — (2*R*)-2-(4-chloro-*N*-{[2-fluoro-4-(1,2,4-oxadiazol-3-yl)phényl]méthyl}benzenesulfonamido)-5,5,5-trifluoropentanamide

avagacestat — (2*R*)-2-(4-cloro-*N*-{[2-fluoro-4-(1,2,4-oxadiazol-3-yl)fenil]metil}bencenosulfonamido)-5,5,5-trifluoropentanamida

$C_{20}H_{17}ClF_4N_4O_4S$

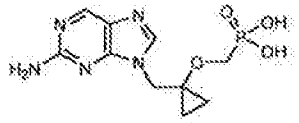


besifovirum
besifovir — [({1-[(2-amino-9*H*-purin-9-yl)methyl]cyclopropyl}oxy)methyl]phosphonic acid

bésifovir — acide [({1-[(2-amino-9*H*-purin-9-yl)méthyl]cyclopropyl}oxy)méthyl]phosphonique

besifovir — ácido [({1-[(2-amino-9*H*-purin-9-il)metil]ciclopropil}oxi)metil]fosfónico

$C_{16}H_{14}N_6O_4P$

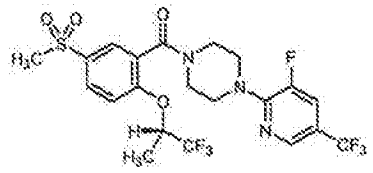


bitopertinum
bitopertin — {4-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}[5-(methanesulfonyl)-2-{[(2*S*)-1,1,1-trifluoropropan-2-yl]oxy}phenyl]methanone

bitopertine — {4-[3-fluoro-5-(trifluorométhyl)pyridin-2-yl]pipérazin-1-yl}[5-(méthanesulfonyl)-2-{[(2*S*)-1,1,1-trifluoropropan-2-yl]oxy}phényl]méthanone

bitopertina — {4-[3-fluoro-5-(trifluorometil)piridin-2-il]piperazin-1-il}[5-(metanosulfonil)-2-{[(2*S*)-1,1,1-trifluoropropan-2-il]oxy}fenil]metanona

$C_{21}H_{20}F_7N_3O_4S$



blosozumabum #
blosozumab

immunoglobulin G4-kappa, anti-[*Homo sapiens* SOST (sclerostin)], humanized monoclonal antibody;
gamma4 heavy chain (1-444) [humanized VH (*Homo sapiens* IGHV1-24*01 (85.70%) -(IGHD)-IGHJ4*01 L123>T (113)) [8.8.11] (1-118) -*Homo sapiens* IGHG4*01 hinge S10>P (226), CH3 K120>del (119-444)], (132-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-13*02 (84.00%) -IGKJ1*01 Q120>G (100)) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (224-224'':227-227'')-bisdisulfide dimer

blosozumab

immunoglobuline G4-kappa, anti-[*Homo sapiens* SOST (sclérostine)], anticorps monoclonal humanisé;
chaîne lourde gamma4 (1-444) [VH humanisé (*Homo sapiens* IGHV1-24*01 (85.70%) -(IGHD)-IGHJ4*01 L123>T (113)) [8.8.11] (1-118) -*Homo sapiens* IGHG4*01 charnière S10>P (226), CH3 K120>del (119-444)], (132-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-13*02 (84.00%) -IGKJ1*01 Q120>G (100)) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (224-224'':227-227'')-bisdisulfure

blosozumab

inmunoglobulina G4-kappa, anti-[*Homo sapiens* SOST (esclerostina)], anticuerpo monoclonal humanizado;
cadena pesada gamma4 (1-444) [VH humanizada (*Homo sapiens* IGHV1-24*01 (85.70%) -(IGHD)-IGHJ4*01 L123>T (113)) [8.8.11] (1-118) -*Homo sapiens* IGHG4*01 bisagra S10>P (226), CH3 K120>del (119-444)], (132-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizada (*Homo sapiens* IGKV1-13*02 (84.00%) -IGKJ1*01 Q120>G (100)) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (224-224'':227-227'')-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada
QVQLVQSGAE VKKPGASVKV SCKVSGFFLK DTFQHWVRQA PGKGLEWMGW 50
SDPELGDTEY ASKFQGRVTM TEDTSTDTAY MELSSLRSED TAVYYCARGD 100
TTYKFDFWGQ GTTVTVSSAS TKGPSVFPLA PCSRSTSEST AALGCLVKDY 150
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTKTYT 200
CNVDHKPSNT KVDKRVESKY GPPCPPCPAP EFLGGPSVFL FPPKPKDTLM 250
ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV 300
VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP 350
PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG 400
SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLG 444

Light chain / Chaîne légère / Cadena ligera
DIQMTQSPSS LSASVGDRVT ITCRASQDVH TAVAWYQQKP GKAPKLLIYW 50
ASTRHTGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSDYPWTFGG 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC 214

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H 22-96 145-201 259-319 365-423
22''-96'' 145''-201'' 259''-319'' 365''-423''
Intra-L 23'-88' 134'-194'
23''-88'' 134''-194''
Inter-H-L 132-214' 132''-214''
Inter-H-H 224-224'' 227-227''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
295, 295''

brodalumabum #
brodalumab

immunoglobulin G2-kappa, anti-[*Homo sapiens* IL17RA (interleukin 17 receptor A, CD217)], *Homo sapiens* monoclonal antibody; gamma2 heavy chain (1-442) [*Homo sapiens* VH (IGHV1-18*01 (98.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -*Homo sapiens* IGHG2*01 (117-442)], (130-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-15*01 (93.70%) - IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (218-218'':219-219'':222-222'':225-225'')-tetrakisdisulfide dimer

brodalumab

immunoglobuline G2-kappa, anti-[*Homo sapiens* IL17RA (récepteur A de l'interleukine 17, CD217)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma2 (1-442) [*Homo sapiens* VH (IGHV1-18*01 (98.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -*Homo sapiens* IGHG2*01 (117-442)], (130-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-15*01 (93.70%) - IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (218-218'':219-219'':222-222'':225-225'')-tétrakisdisulfure

brodalumab

inmunoglobulina G2-kappa, anti-[IL17RA (receptor A de la interleukina 17 de *Homo sapiens*, CD217)], anticuerpo monoclonal de *Homo sapiens*;
cadena pesada gamma2 (1-442) [*Homo sapiens* VH (IGHV1-18*01 (98.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -*Homo sapiens* IGHG2*01 (117-442)], (130-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-15*01 (93.70%) - IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (218-218'':219-219'':222-222'':225-225'')-tetrakisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada
QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYGISWVRQA PGQGLEWMGW 50
ISTYSGNTNY AQKLQGRVTM TTDTSTSTAY MELRSLRSDD TAVYYCARRQ 100
LYPHYYGQGT LVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP 150
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS NFGTQTYTCN 200
VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP KPKDTLMISR 250
TPEVTCVVVD VSHEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV 300
LTVVHQDWLN GKSYKCKVSN KGLPAPIEKT ISKTKGQPRE PQVYTLPPSR 350
EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PMLDSDGSFF 400
LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK 442

Light chain / Chaîne légère / Cadena ligera
EIVMTQSPAT LSVSPGERAT LSCRASQSVS SNLAWFQQKP GQAPRLLIYD 50
ASTRATGVPA RFSGSGSGTD FTLTISSLQS EDFAVYYCQQ YDNWPLTFGG 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC 214

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H 22-96 143-199 256-316 362-420
22''-96'' 143''-199'' 256''-316'' 362''-420''
Intra-L 23'-88' 134'-194'
23'''-88''' 134'''-194'''
Inter-H-L 130-214' 130''-214'''
Inter-H-H 218-218'' 219-219'' 222-222'' 225-225''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
292, 292''

cabozantinibum
cabozantinib

N-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

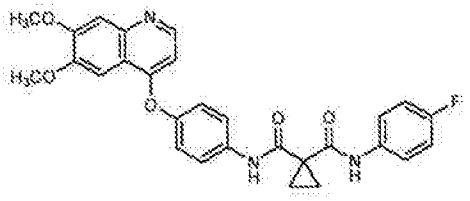
cabozantinib

N-{4-[(6,7-diméthoxyquinoléin-4-yl)oxy]phényl}-*N'*-(4-fluorophényl)cyclopropane-1,1-dicarboxamide

cabozantinib

N-{4-[(6,7-dimetoxiquinolin-4-il)oxi]fenil}-*N'*-(4-fluorofenil)ciclopropano-1,1-dicarboxamida

$C_{28}H_{24}FN_3O_5$



calaspargasum pegolum #
calaspargase pegol

pegylated *Escherichia coli* asparaginase;
[27-alanine,64-aspartic acid,252-threonine,263-asparagine]-L-asparaginase 2 (EC 3.5.1.1, L-asparagine amidohydrolase II) *Escherichia coli* (strain K12) tetramer α_4, carbamates with α-carboxy-ω-methoxypoly(oxyethylene)

calaspargase pégol

asparaginase d'*Escherichia coli* pégylée;
carbamates entre le tétramère α_4 de [27-alanine,64-acide aspartique,252-thréonine,263-asparagine]-L-asparaginase 2 (EC 3.5.1.1, L-asparagine amidohydrolase II) d'*Escherichia coli* (souche K12) et le α-carboxy-ω-méthoxypoly(oxyéthylène)

calaspargasa pegol

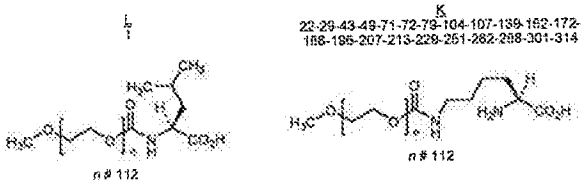
asparaginasa de *Escherichia coli* pegilada;
carbamatos entre el tetrámero α_4 de [27-alanina,64-ácido aspártico,252-treonina,263-asparagina]-L-asparaginasa 2 (EC 3.5.1.1, L-asparagina amidohidrolasa II) de *Escherichia coli* (cepa K12) y el α-carboxi-ω-metoxipoli(oxietileno)

$C_{1518}H_{2423}N_{415}O_{482}S_8$ (peptide monomer)

Monomer / Monomère / Monómero

```
LDNITILATG GTIASGDDSA TKSNYTVGKV GVENLVNAVP QLKDLANVKG 50
EQVVNIGSQD MNDNVLLTLA KINTDCDKTK GCVVTHGTDT MEETAYFLDL 100
TVKCDKPVV MVGAMRPSTS MSADGPFNLY NAVVTAADKA SANRGVLVVM 150
NDRVLSGRDV TKTNTTDVAT FKSVNYGPLG YIHNGKIDYQ RTPARKHTSD 200
TPFDVSKLTE LPKVGIVYNY ANASSLPAKA LVDAGYDGLV SAGVEMKNLY 250
SEYKDTLATA AKDAVAVVRS SKVPCATTQ NASVDNAKYG PSAECISNEQ 300
KAVLLQLAL TETSDPQDTQ QIFNQV                          326
```

approximately 9 residues are pegylated out of 23 (1 L and 22 K)
environ 9 résidus sur 23 (1 L et 22 K) sont pegylés
aproximadamente están pegilados 9 restos de 23 (1L y 22K)



Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
77-105 $77'$-$105'$ $77''$-$105''$ $77'''$-$105'''$

cantuzumabum ravtansinum # cantuzumab ravtansine	immunoglobulin G1-kappa, anti-(*Homo sapiens* MUC1 sialylated carbohydrate, tumour-associated (CA242, cancer antigen 242)], humanized monoclonal antibody conjugated to maytansinoid DM4; gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* IGHV7-4-1*02 (76.50%) -(IGHD)-IGHJ2*01 R120>Q (111), L123>T (114)) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2-28*01 (82.00%) -IGKJ3*01 V124>L (109), D125>E (110), I126>L (111)) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (228-228'':231-231'')-bisdisulfide dimer ; conjugated, on an average of 3 to 4 lysyl, to maytansinoid DM4 [$N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine] via the reducible SPDB linker [*N*-succinimidyl 4-(2-pyridyldithio)butanoate] For the *ravtansine* part, please refer to the document *"INN for pharmaceutical substances: Names for radicals, groups and others"**
cantuzumab ravtansine	immunoglobuline G1-kappa, anti-(*Homo sapiens* glycane sialylé de MUC1, associé á des tumeurs (CA242, antigène du cancer 242)], anticorps monoclonal humanisé conjugué au maytansinoide DM4; chaîne lourde gamma1 (1-449) [VH humanisé (*Homo sapiens* IGHV7-4-1*02 (76.50%) -(IGHD)-IGHJ2*01 R120>Q (111), L123>T (114)) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-219')-disulfure avec la chaîne légère kappa (1'-219') [V-KAPPA humanisé (*Homo sapiens* IGKV2-28*01 (82.00%) -IGKJ3*01 V124>L (109), D125>E (110), I126>L (111)) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dimère (228-228'':231-231'')-bisdisulfure, conjugué, sur 3 à 4 lysyl en moyenne, au maytansinoide DM4 [$N^{2'}$-déacétyl-$N^{2'}$-(4-mercapto-4-méthyl-1-oxopentyl)-maytansine] via le linker SPDB réductible [4-(2-pyridyldithio)butanoate de *N*-succinimidyle] Pour la partie *ravtansine*, veuillez vous référer au document *"INN for pharmaceutical substances: Names for radicals, groups and others"**.
cantuzumab ravtansina	inmunoglobulina G1-kappa, anti-(*Homo sapiens* glicano sialilo de MUC1, asociado al tumor (CA242, antígeno del cancer 242)] anticuerpo monoclonal humanizado conjugado con el maitansinoide DM4; cadena pesada gamma1 (1-449) [VH humanizada (*Homo sapiens* IGHV7-4-1*02 (76.50%) -(IGHD)-IGHJ2*01 R120>Q (111), L123>T (114)) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-219')-disulfuro con la cadena ligera kappa (1'-219') [V-KAPPA humanizada (*Homo sapiens* IGKV2-28*01 (82.00%) -IGKJ3*01 V124>L (109), D125>E (110), I126>L (111)) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dímero (228-228'':231-231'')-bisdisulfuro; conjugado, en 3-4 grupos lisil por término medio, con el maitansinoide DM4 [$N^{2'}$-desacetil-$N^{2'}$-(4-mercapto-4-metil-1-oxopentil)-maitansina] mediante el conector SPDB reducible [*N*-4-(2-piridilditio)butanoato de succinimidilo] Para la fracción *ravtansina*, se ruega referirse al documento *"INN for pharmaceutical substances: Names for radicals, groups and others"**.

Heavy chain / Chaîne lourde / Cadena pesada
QVQLVQSGAE VKKPGESVKI SCKASDYTFT YYGMNWVRQA PGQGLKWMGW 50
IDTYTGEPTY AQEFQGRIAF SLETSASTAY LQINSLKSED TATYFCARRG 100
PYHWYFDVWG QGTTVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK 449

Light chain / Chaîne légère / Cadena ligera
DIVMTQSPLS VPVTPGEPVS ISCRSSKSLL HSNGNTYLYW FLQRPGQSPQ 50
LLIYRMSNLV SGVPDRFSGS GSGTAFTLRI SRVEAEDVGV YYCLQHLEYP 100
FTFGPGTKLE LKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK 150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE 200
VTHQGLSSPV TKSFNRGEC 219

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H 22-96 146-202 263-323 369-427
22''-96'' 146''-202'' 263''-323'' 369''-427''
Intra-L 23'-93' 139'-199'
23''-93'' 139''-199''
Inter-H-L 222-219' 222''-219''
Inter-H-H 228-228'' 231-231''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
299, 299''

ceftolozanum
ceftolozane

(6*R*,7*R*)-3-[(5-amino-4-{[(2-aminoethyl)carbamoyl]amino}-1-methyl-1*H*-pyrazol-2-ium-2-yl)methyl]-7-[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

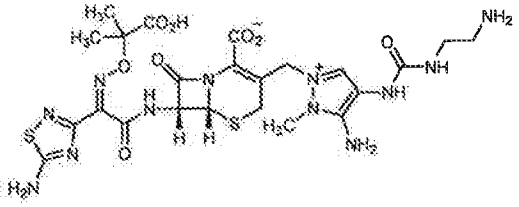
ceftolozane

(6*R*,7*R*)-3-[(5-amino-4-{[(2-aminoéthyl)carbamoyl]amino}-1-méthyl-1*H*-pyrazol-2-ium-2-yl)méthyl]-7-[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acétamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ène-2-carboxylate

ceftolozano

(6*R*,7*R*)-3-[(5-amino-4-{[(2-aminoetil)carbamoil]amino}-1-metil-1*H*-pirazol-2-io-2-il)metil]-7-[(2*Z*)-2-(5-amino-1,2,4-tiadiazol-3-il)-2-{[(2-carboxipropan-2-il)oxo]imino}acetamido]-8-oxo-5-tia-1-azabiciclo[4.2.0]oct-2-eno-2-carboxilato

$C_{23}H_{36}N_{12}O_8S_2$



cenderitidum
cenderitide

natriuretic peptide receptor type B (NPR-B) agonist; human C-type natriuretic peptide-(32-53)-peptide (CNP-22) fusion protein with eastern green mamba (*Dendroaspis angusticeps*) natriuretic peptide-(24-38)-peptide

cendéritide

agoniste du récepteur du peptide natriurétique de type B; peptide natriurétique de type-C humain-(32-53)-peptide (CNP-22) protéine de fusion avec le peptide natriurétique de *Dendroaspis angusticeps* (mamba vert)-(24-38)-peptide

cenderitida

agonista del receptor del péptido natriurético de tipo B; péptido natriurético de tipo-C humano-(32-53)-péptido (CNP-22) proteína de fusión con el péptido natriurético de *Dendroaspis angusticeps* (mamba vert)-(24-38)-péptido

$C_{156}H_{269}N_{49}O_{50}S_3$

```
GLSKGCFGLK  LDRIGSMSGL  GCPSLRDPRP  NAPSTSA  37
```

Disulfide bridge location / Position du pont disulfure / Posición del puente disulfuro
6-22

cepeginterferonum alfa-2b #
cepeginterferon alfa-2b

pegylated human interferon alpha-2b;
$N^{2,1}$-{4-[ω-methoxypoly(oxyethylene)]butyl}-human interferon alpha-2b

cépeginterféron alfa-2b

interféron alpha-2b humain pégylé;
$N^{2,1}$-{4-[ω-méthoxypoly(oxyéthylène)]butyl}-interféron alpha-2b humain

cepeginterferón alfa-2b

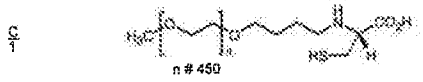
interferón alfa-2b humano pegilado;
$N^{2,1}$-{4-[ω-metoxipoli(oxietileno)]butil}-interferón alfa-2b humano

$C_{988}H_{1599}N_{229}O_{259}S_5\,[C_2H_4O]_n$

```
CDLPQTHSLG SRRTLMLLAQ MRRISLFSCL KDRHDFGFPQ EEFGNQFQKA 50
ETIPVLHEMI QQIFNLFSTK DSSAAWDETL LDKFYTELYQ QLNDLEACVI 100
QGVGVTETPL MKEDSILAVR KYFQRITLYL KEKKYSPCAW EVVRAEIMRS 150
FSLSTNLQES LRSKE                                      165
```

Disulfide bridges location / Positions des ponts disulfure / Posiciones de los puentes disulfuro
1-98 29-138

Modified residue / Résidu modifié / Residuo modificado



conberceptum #
conbercept

fusion protein for immune applications (FPIA) comprising *Homo sapiens* FLT1 (fms-related tyrosine kinase 1, vascular endothelial growth factor receptor 1, VEGFR1, vascular permeability factor receptor, tyrosine-protein kinase FRT) fragment, fused with *Homo sapiens* KDR (kinase insert domain receptor, vascular endothelial growth factor receptor 2, VEGFR2, protein-tyrosine kinase receptor FLK1, CD309) fragment, fused with *Homo sapiens* immunoglobulin G1 Fc fragment;
FLT1, 132-232 precursor fragment (1-101) -KDR, 227-421 precursor fragment (102-296) -glycyl-prolyl-glycyl (297-299) -gamma1 chain H-CH2-CH3 fragment (300-526) [*Homo sapiens* IGHG1*03 hinge 6-15 P13>L (307) (300-309), CH2 (310-419), CH3-CH-S (420-526)]; (305-305':308-308')-bisdisulfide dimer

conbercept

protéine de fusion pour applications immunitaires (FPIA) comprenant un fragment d'*Homo sapiens* FLT1 (tyrosine kinase 1 apparentée au fms, récepteur 1 du facteur de croissance de l'endothélium vasculaire, VEGFR1, récepteur du facteur de perméabilité vasculaire, tyrosine-protéine kinase FRT), fusionné à un fragment d'*Homo sapiens* KDR (récepteur à domaine kinase, récepteur 2 du facteur de croissance de l'endothélium vasculaire, VEGFR2, récepteur tyrosine-protéine kinase FLK1, CD309), fusionné au fragment Fc de l'*Homo sapiens* immunoglobuline G1;
FLT1, fragment 132-232 du précurseur (1-101) -KDR, fragment 227-421 du précurseur (102-295) - glycyl-prolyl-glycyl (297-299) - fragment H-CH2-CH3 de la chaîne gamma1 (300-526) [*Homo sapiens* IGHG1*03 charnière 6-15 P13>L (307) (300-309), CH2 (310-419), CH3-CH-S (420-526)]; dimère (305-305':308-308')-bisdisulfure

conbercept

proteína de fusión para aplicaciones inmunitarias (FPIA) que comprende un fragmento de FLT1 de *Homo sapiens* (tirosina kinasa 1 relacionada con fms, receptor 1 del factor de crecimiento del endotelio vascular, VEGFR1, receptor del factor de permeabilidad vascular, tirosina-protein kinasa FRT), fusionada a un fragmento de KDR de *Homo sapiens* (receptor con dominio kinasa, receptor 2 del factor de crecimiento del endotelio vascular, VEGFR2, receptor tirosina-protein kinasa FLK1, CD309), fusionado al fragmento Fc de la inmunoglobulina G1 de *Homo sapiens*;
FLT1, fragmento 132-232 de precursor (1-101) -KDR, fragmento 227-421 del precursor (102-295) - glicil-prolil-glicil (297-299) - fragmento H-CH2-CH3 de la cadena gamma1 (300-526) [*Homo sapiens* IGHG1*03 bisagra 6-15 P13>L (307) (300-309), CH2 (310-419), CH3-CH-S (420-526)]; dímero (305-305':308-308')-bisdisulfuro

Fused chain / chaîne fusionnée / cadena fusionada

```
GRPFVEMYSE LPSIIHMTEG RELVIPCRVT SPNIEVTLKK FPLDTLIPDG  50
KRIIWDSRKG FIISNATYKE IGLLTCEATV NGHLYKTNYL THRQTNTIID 100
VVLSPSHGIE LSVGEKLVLN CTARTELNVG IDFNWEYPSS KHQHKKLVNR 150
DLKTQSGSEM KKFLSTLTID GVTRSDQGLY TCAASSGLMT KKNSTFVRVH 200
EKDPVAFSSG MESLVEATVG ERVRIPAKYL GYPPPEIKWY KNGIPLESNH 250
TIKAGHVLTI MEVSERDTGN YTVILTNPIS KEKQSHVVSL VVYVPPQIGE 300
KSNISLVRYV VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC 400
KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN QVSLTCLVKG 450
FYPSDIAVEW ESNGQPENNY KATPPVLDSD GSFFLYSKLT VDKSRWQQGN 500
VFSCSVMHEA LHNHYTQKSL SLSPGK                           526
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-chain 27-76 121-182 340-400 446-504
27'-76' 121'-182' 340'-400' 446'-504'
Inter-chains 305-305' 308-308'

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
376, 376'

crenezumabum #
crenezumab

immunoglobulin G4-kappa, anti-(*Homo sapiens* amyloid beta (Abeta) peptides Aβ42 and Aβ40)], humanized monoclonal antibody;
gamma4 heavy chain (1-438) [humanized VH (*Homo sapiens* IGHV3-23*04 (89.70%) -(IGHD)-IGHJ4*01 L123>T (107) [8.8.5] (1-112) -*Homo sapiens* IGHG4*01 hinge S10>P (220) (113-438)], (126-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2D-29*02 (86.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')], (218-218":221-221")-bisdisulfide dimer

crénezumab

immunoglobuline G4-kappa, anti-[*Homo sapiens* peptides *beta-amyloïdes* (*Abéta*) Aβ42 et Aβ40)], anticorps monoclonal humanisé; chaîne lourde gamma4 (1-438) [VH humanisé (*Homo sapiens* IGHV3-23*04 (89.70%) -(IGHD)-IGHJ4*01 L123>T (107) [8.8.5] (1-112) -*Homo sapiens* IGHG4*01 charnière S10>P (220) (113-438)], (126-219')-disulfure avec la chaîne légère kappa (1'-219') [V-KAPPA humanisé (*Homo sapiens* IGKV2D-29*02 (86.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dimère (218-218'':221-221'')-bisdisulfure

crenezumab

inmunoglobulina G4-kappa, anti-[péptidos *beta-amiloides* (*Abeta*) Aβ42 y Aβ40 de *Homo sapiens*)], anticuerpo monoclonal humanizado;
cadena pesada gamma4 (1-438) [VH humanizada (*Homo sapiens* IGHV3-23*04 (89.70%) -(IGHD)-IGHJ4*01 L123>T (107) [8.8.5] (1-112) -*Homo sapiens* IGHG4*01 bisagra S10>P (220) (113-438)], (126-219')-disulfuro con la cadena ligera kappa (1'-219') [V-KAPPA humanizada (*Homo sapiens* IGKV2D-29*02 (86.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dímero (218-218'':221-221'')-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYWMSWVRQA PGKGLEWVAS   50
INSNGGSTYY PDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCASGD  100
YWGQGTTVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT  150
VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK  200
PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE  250
VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV  300
LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM  350
TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS  400
RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLG              438
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQSPLS LPVTPGEPAS ISCRSSQSLV YSNGDTYLHW YLQKPGQSPQ   50
LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHVP  100
WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK  150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE  200
VTHQGLSSPV TKSFNRGEC                                    219
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
Intra-H  22-96    139-195   253-313   359-417
         22''-96''  139''-195''  253''-313''  359''-417''
Intra-L  23'-93'   139'-199'
         23'''-93'''  139'''-199'''
Inter-H-L  126-219'  126''-219'''
Inter-H-H  218-218''  221-221''
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

289, 289''

crenolanibum
crenolanib

1-(2-{5-[(3-methyloxetan-3-yl)methoxy]-1*H*-benzimidazol-1-yl}quinolin-8-yl)piperidin-4-amine

crénolanib

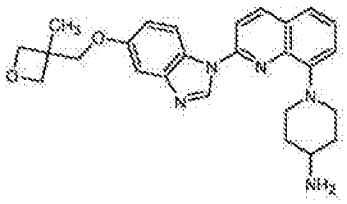
1-(2-{5-[(3-méthyloxétan-3-yl)méthoxy]-1*H*-benzimidazol-1-yl}quinoléin-8-yl)pipéridin-4-amine

crenolanib

1-(2-{5-[(3-metiloxetan-3-il)metoxi]-1*H*-benzoimidazol-1-il}quinolin-8-il)piperidin-4-amina

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$C_{26}H_{29}N_5O_2$



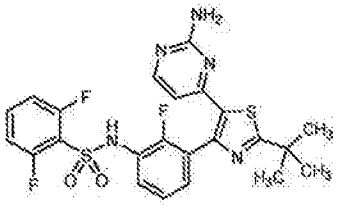
dabrafenibum

dabrafenib — *N*-{3-[5-(2-aminopyrimidin-4-yl)-2-*tert*-butyl-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide

dabrafénib — *N*-{3-[5-(2-aminopyrimidin-4-yl)-2-*tert*-butyl-1,3-thiazol-4-yl]-2-fluorophényl}-2,6-difluorobenzènesulfonamide

dabrafenib — *N*-{3-[5-(2-aminopirimidin-4-il)-2-*terc*-butil-1,3-tiazol-4-il]-2-fluorofenil}-2,6-difluorobencenosulfonamido

$C_{23}H_{20}F_3N_5O_2S_2$



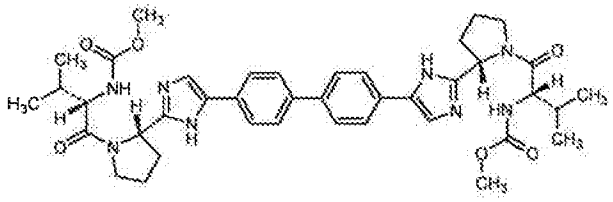
daclatasvirum

daclatasvir — dimethyl *N*,*N*′-([1,1′-biphenyl]-4,4′-diylbis{1*H*-imidazole-5,2-diyl-[(2*S*)-pyrrolidine-2,1-diyl][(1*S*)-3-methyl-1-oxobutane-1,2-diyl]})dicarbamate

daclatasvir — *N*,*N*′-([1,1′-biphényl]-4,4′-diylbis{1*H*-imidazole-5,2-diyl-[(2*S*)-pyrrolidine-2,1-diyl][(1*S*)-3-méthyl-1-oxobutane-1,2-diyl]})dicarbamate de diméthyle

daclatasvir — *N*,*N*′-([1,1′-bifenil]-4,4′-diilbis{1*H*-imidazol-5,2-diil-[(2*S*)-pirrolidina-2,1-diil][(1*S*)-3-metil-1-oxobutano-1,2-diil]})dicarbamato de dimetilo

$C_{40}H_{50}N_8O_6$



dalanterceptum #
dalantercept

fusion protein for immune applications (FPIA) comprising *Homo sapiens* ACVRL1 (activin A receptor type II-like 1, activin receptor-like kinase 1, ALK1, ALK-1, serine/threonine-protein kinase receptor R3, SKR3, transforming growth factor-beta superfamily receptor type I, TGF-B superfamily receptor type I, TSR-I, HHT2, ORW2) fragment, fused with *Homo sapiens* immunoglobulin G1 Fc fragment; ACVR2L1, 22-120 precursor fragment (1-99) -threonyl-triglycyl (100-103) -gamma1 chain H-CH2-CH3 fragment (104-328) [*Homo sapiens* IGHG1*03 hinge 8-15 (104-111), CH2 L1.3>A (115), G1>A (118), A115>V (211) (112-221), CH3 S85.3>P (284) (222-328)]; (107-107':110-110')-bisdisulfide dimer

dalantercept

protéine de fusion pour applications immunitaires (FPIA) comprenant un fragment d'*Homo sapiens* ACVRL1 (récepteur 1 de type II-like de l'activine A, kinase 1 apparentée au récepteur de l'activine, ALK1, ALK-1, récepteur R3 de type sérine/thréonine-protéine kinase, SKR3, récepteur de type I de la superfamille du facteur de croissance transformant bêta, récepteur de type I de la superfamille du TGF-B, TSR-I, HHT2, ORW2), fusionné au fragment Fc de l'*Homo sapiens* immunoglobuline G1;
ACVR2L1, fragment 22-120 du précurseur (1-99) -thréonyl-triglycyl (100-103) -fragment H-CH2-CH3 de la chaîne gamma1 (104-328) [*Homo sapiens* IGHG1*03 charnière 8-15 (104-111), CH2 L1.3>A (115), G1>A (118), A115>V (211) (112-221), CH3 S85.3>P (284) (222-328)]; dimère (107-107':110-110')-bisdisulfure

dalantercept

proteína de fusión para aplicaciones inmunitarias (FPIA) que comprende un fragmento de ACVRL1 de *Homo sapiens* (receptor 1 de tipo II-like de la activina A, kinasa 1 relacionada con el receptor de la activina, ALK1, ALK-1, receptor R3 de tipo serina/treonina-proteinkinasa, SKR3, receptor de tipo I de la superfamilia del factor de crecimiento transformador beta, receptor de tipo I de la superfamilia del TGF-B, TSR-I, HHT2, ORW2), fusionada con el fragmento Fc de la inmunoglobulina G1 de *Homo sapiens*;
ACVR2L1, fragmento 22-120 del precursor (1-99) -treonil-triglicil (100-103) -fragmento H-CH2-CH3 de la cadena gamma1 (104-328) [*Homo sapiens* IGHG1*03 bisagra 8-15 (104-111), CH2 L1.3>A (115), G1>A (118), A115>V (211) (112-221), CH3 S85.3>P (284) (222-328)]; dímero (107-107':110-110')-bisdisulfuro

Fused chain / chaîne fusionnée / cadena fusionada

```
DFVVPSRGPL VTCTCESPHC KGPTCRGAWC TVVLVREEGR HPQEHRGCGN   50
LHRELCRGRP TEFVNHYCCD SHLCRHNVSL VLEATQPPSE QPGTDGQLAT  100
GGGTHTCPPC PAPBALGAPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE  150
DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY  200
KCKVSNKALP VPIEKTISKA KGQPREPQVY TLPPSREEMT KNQVSLTCLV  250
KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGPFFLYSK LTVDKSRWQQ  300
GNVFSCSVMH EALHNHYTQK SLSLSPGK                          328
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

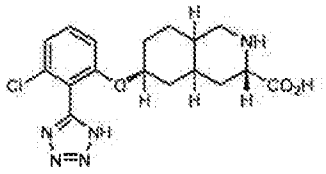
```
Intra-chain  13-30  15-20  25-48  56-68  69-74  142-202  248-306
             13'-30' 15'-20' 25'-48' 56'-68' 69'-74' 142'-202' 248'-306'
Inter-chains 107-107' 110-110'
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
77, 178, 77', 178'

dasolampanelum

dasolampanel	(3*S*,4a*S*,6*S*,8a*R*)-6-[3-chloro-2-(1*H*-tetrazol-5-yl)phenoxy]-decahydroisoquinoline-3-carboxylic acid
dasolampanel	acide (3*S*,4a*S*,6*S*,8a*R*)-6-[3-chloro-2-(1*H*-tétrazol-5-yl)phénoxy]décahydroisoquinoléine-3-carboxylique
dasolampanel	ácido (3*S*,4a*S*,6*S*,8a*R*)-6-[3-cloro-2-(1*H*-tetrazol-5-il)fenoxi]-decahidroisoquinolina-3-carboxílico

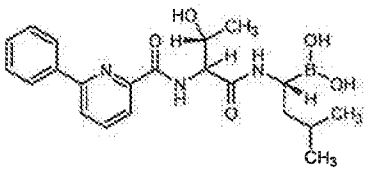
$C_{17}H_{20}ClN_5O_3$



delanzomibum

delanzomib	{(1*R*)-1-[(2*S*,3*R*)-3-hydroxy-2-(6-phenylpyridine-2-carboxamido)butanamido]-3-methylbutyl}boronic acid
délanzomib	acide {(1*R*)-1-[(2*S*,3*R*)-3-hydroxy-2-(6-phénylpyridine-2-carboxamido)butanamido]-3-méthylbutyl}boronique
delanzomib	ácido {(1*R*)-1-[(2*S*,3*R*)-3-hidroxi-2-(6-fenilpiridina-2-carboxamido)butanamido]-3-metilbutil}borónico

$C_{21}H_{28}BN_3O_5$



delcasertibum

delcasertib	human immunodeficiency virus 1 protein Tat-(46-57)-peptide (1→1')-disulfide with L-cysteinyl-[mouse protein kinase C delta type-(8-17)-peptide]
delcasertib	protéine Tat du virus 1 de l'immunodéficience humaine-(46-57)-peptide (1→1')-disulfure avec le L-cystéinyl-(protéine kinase C type delta de souris-(8-17)-peptide
delcasertib	proteína Tat del virus 1 de la inmunodeficiencia humana-(46-57)-péptido (1→1')-disulfuro con la L-cisteinil-[proteína kinasa C tipo delta de ratón-(8-17)-péptido]

$C_{120}H_{189}N_{45}O_{34}S_2$

A chain / Chaîne A / Cadena A
CYGRKKRRQR RR 12

Light chain / Chaîne légère / Cadena ligera
CSFNSYELGS L 11'

Disulfide bridge location / Position du pont disulfure / Posición del puente disulfuro
1-1'

dolutegravirum
dolutegravir

(4*R*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazine-9-carboxamide

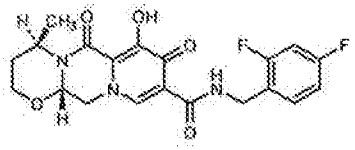
dolutégravir

(4*R*,12a*S*)-*N*-[(2,4-difluorophényl)méthyl]-7-hydroxy-4-méthyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazine-9-carboxamide

dolutegravir

(4*R*,12a*S*)-*N*-[(2,4-difluorofenil)metil]-7-hidroxi-4-metil-6,8-dioxo-3,4,6,8,12,12a-hexahidro-2*H*-pirido[1',2':4,5]pirazino[2,1-*b*][1,3]oxazina-9-carboxamida

$C_{20}H_{19}F_2N_3O_5$



encaleretum
encaleret

2'-{(1*R*)-1-[(2*R*)-3-{[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino}-2-hydroxypropoxy]ethyl}-3-methyl[1,1'-biphenyl]-4-carboxylic acid

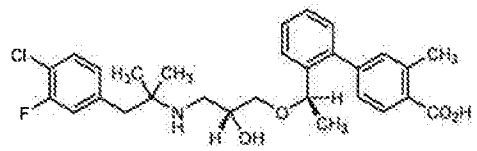
encaléret

acide 2'-{(1*R*)-1-[(2*R*)-3-{[1-(4-chloro-3-fluorophényl)-2-méthylpropan-2-yl]amino}-2-hydroxypropoxy]éthyl}-3-méthyl[1,1'-biphényl]-4-carboxylique

encaleret

ácido 2'-{(1*R*)-1-[(2*R*)-3-{[1-(4-cloro-3-fluorofenil)-2-metilpropan-2-yl]amino}-2-hidroxipropoxi]etil}-3-metil[1,1'-bifenil]-4-carboxílico

$C_{29}H_{35}ClFNO_4$

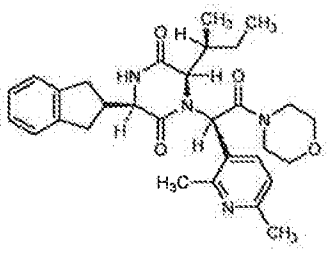


epelsibanum
epelsiban (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1*R*)-1-(2,6-dimethylpyridin-3-yl)-2-(morpholin-4-yl)-2-oxoethyl]-6-[(2*S*)-butan-2-yl]piperazine-2,5-dione

épelsiban (3*R*,6*R*)-3-(2,3-dihydro-1*H*-indén-2-yl)-1-[(1*R*)-1-(2,6-diméthylpyridin-3-yl)-2-(morpholin-4-yl)-2-oxoéthyl]-6-[(2*S*)-butan-2-yl]pipérazine-2,5-dione

epelsibán (3*R*,6*R*)-3-(2,3-dihidro-1*H*-inden-2-il)-1-[(1*R*)-1-(2,6-dimetilpiridin-3-il)-2-(morfolin-4-il)-2-oxoetil]-6-[(2*S*)-butan-2-il]piperazina-2,5-diona

$C_{30}H_{38}N_4O_4$

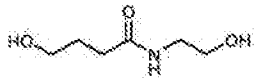


etoxybamidum
etoxybamide 4-hydroxy-*N*-(2-hydroxyethyl)butanamide

étoxybamide 4-hydroxy-*N*-(2-hydroxyéthyl)butanamide

etoxibamida 4-hidroxi-*N*-(2-hidroxietil)butanamida

$C_6H_{13}NO_3$

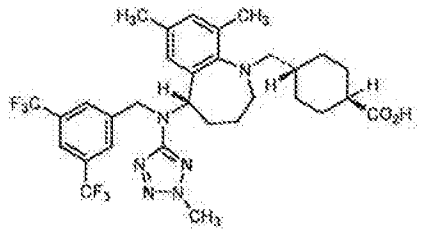


evacetrapibum
evacetrapib (1*r*,4*r*)-4-({(5*S*)-5-[{[3,5-bis(trifluoromethyl)phenyl]methyl}(2-methyl-2*H*-tetrazol-5-yl)amino]-7,9-dimethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}methyl)cyclohexane-1-carboxylic acid

évacétrapib acide (1*r*,4*r*)-4-({(5*S*)-5-[{[3,5-bis(trifluorométhyl)phényl]méthyl}(2-méthyl-2*H*-tétrazol-5-yl)amino]-7,9-diméthyl-2,3,4,5-tétrahydro-1*H*-benzazépin-1-yl}méthyl)cyclohexane-1-carboxylique

evacetrapib ácido (1*r*,4*r*)-4-({(5*S*)-5-[{[3,5-bis(trifluorometil)fenil]metil}(2-metil-2*H*-tetrazol-5-il)amino]-7,9-dimetil-2,3,4,5-tetrahidro-1*H*-1-benzazepin-1-il}metil)ciclohexano-1-carboxílico

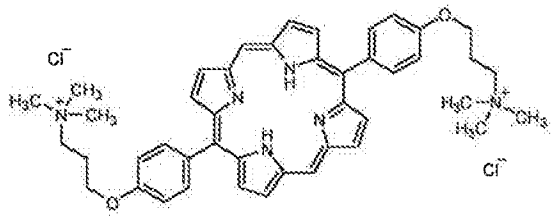
$C_{31}H_{36}F_6N_6O_2$



exeporfinii chloridum

exeporfinium chloride	3,3'-(21*H*,23*H*-porphyrin-5,15-diylbis{[(4,1-phenylene)oxy]-*N*,*N*,*N*-trimethylpropan-1-aminium}) dichloride
chlorure d'exéporfinium	dichlorure de 3,3'-[21*H*,23*H*-porphyrin-5,15-diylbis(4,1-phénylèneoxy)]bis[*N*,*N*,*N*-triméthylpropan-1-aminium]
cloruro de exeporfinio	dicloruro de 3,3'-(21*H*,23*H*-porfirin-5,15-diilbis{[(4,1-fenileno)oxi]-*N*,*N*,*N*-trimetilpropan-1-aminium})

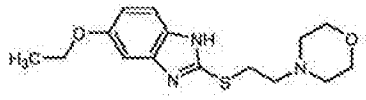
$C_{44}H_{50}Cl_2N_6O_2$



fabomotizolum

fabomotizole	5-ethoxy-2-{[2-(morpholin-4-yl)ethyl]sulfanyl}-1*H*-benzimidazole
fabomotizole	5-éthoxy-2-{[2-(morpholin-4-yl)éthyl]sulfanyl}-1*H*-benzimidazole
fabomotizol	5-etoxi-2-{[2-(morfolin-4-il)etil]sulfanil}-1*H*-benzoimidazol

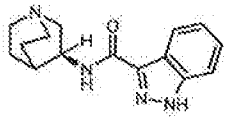
$C_{15}H_{21}N_3O_2S$



faciniclinum

facinicline	*N*-[(3*S*)-1-azabicyclo[2.2.2]octan-3-yl]-1*H*-indazole-3-carboxamide
facinicline	*N*-[(3*S*)-1-azabicyclo[2.2.2]octan-3-yl]-1*H*-indazole-3-carboxamide
faciniclina	*N*-[(3*S*)-1-azabiciclo[2.2.2]octan-3-il]-1*H*-indazol-3-carboxamida

$C_{15}H_{15}N_4O$



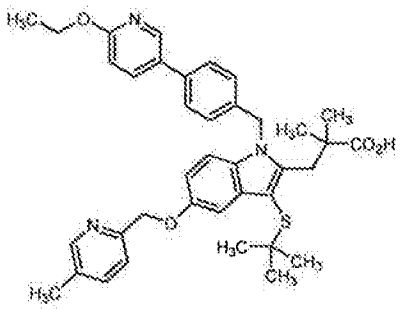
fiboflaponum

fiboflapon — 3-{3-(*tert*-butylsulfanyl)-1-{[4-(6-ethoxypyridin-3-yl)phenyl]methyl}-5-[(5-methylpyridin-2-yl)methoxy]-1*H*-indol-2-yl}-2,2-dimethylpropanoic acid

fiboflapon — acide 3-{3-(*tert*-butylsulfanyl)-1-{[4-(6-éthoxypyridin-3-yl)phényl]méthyl}-5-[(5-méthylpyridin-2-yl)méthoxy]-1*H*-indol-2-yl}-2,2-diméthylpropanoïque

fiboflapón — ácido 3-{3-(*terc*-butilsulfanil)-1-{[4-(6-etoxipiridin-3-il)fenil]metil}-5-[(5-metilpiridin-2-il)metoxi]-1*H*-indol-2-il}-2,2-dimetilpropanoico

$C_{38}H_{43}N_3O_4S$



ficlatuzumabum #

ficlatuzumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* HGF (hepatocyte growth factor, scatter factor, SF, hepatopoeitin A)], humanized monoclonal antibody;
gamma1 heavy chain (1-448) [humanized VH (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01 V124>L (114)) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03 (119-448)], (221-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV4-1*01 (73.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (227-227'':230-230'')-bisdisulfide dimer

ficlatuzumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* HGF (facteur de croissance de l'hépatocyte, facteur dispersant, SF, hépatopoïétine A)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-448) [VH humanisé (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01 V124>L (114)) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03 (119-448)], (221-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV4-1*01 (73.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (227-227'':230-230'')-bisdisulfure

ficlatuzumab

inmunoglobulina G1-kappa, anti-[HGF de *Homo sapiens* (factor de crecimiento del hepatocito, factor dispersante, SF, hepatopoyetina A)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-448) [VH humanizado (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01 V124>L (114)) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03 (119-448)], (221-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizada (*Homo sapiens* IGKV4-1*01 (73.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (227-227'':230-230'')-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada
QVQLVQPGAE VKKPGTSVKL SCKASGYTFT TYWMHWVRQA PGQGLEWIGE 50
INPTNGHTNY NQKFQGRATL TVDKSTSTAY MELSSLRSED TAVYYCARNY 100
VGSIFDYWGQ GTLLTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY 150
FPEPVTVSWN SGALPSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGPQTYI 200
CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD 250
TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST 300
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY 350
TLPPSREEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD 400
SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK 448

Light chain / Chaîne légère / Cadena ligera
DIVMTQSPDS LAMSLGERVT LNCKASENVV SYVSWYQQKP GQSPKLLIYG 50
ASNRESGVPD RFSGSGSATD FTLTISSVQA EDVADYHCGQ SYNYPYTFGQ 100
GTKLEIKRTV AAPSVFIFPP SDEQLNSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC 214

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H 22-96 145-201 262-322 368-426
22''-96'' 145''-201'' 262''-322'' 368''-426''
Intra-L 23''-88'' 134'-194'
23''-88'' 134''-194''
Inter-H-L 221-214' 221''-214''
Inter-H-H 227-227'' 230-230''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
298, 298''

galeteronum
galeterone

17-(1*H*-benzimidazol-1-yl)androsta-5,16-dien-3β-ol

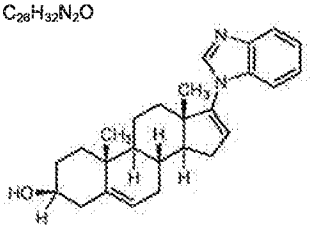
galétérone

17-(1*H*-benzimidazol-1-yl)androsta-5,16-dién-3β-ol

galeterona

17-(1*H*-benzoimidazol-1-il)androsta-5,16-dien-3β-ol

$C_{26}H_{32}N_2O$



ganetespibum
ganetespib

5-[2,4-dihydroxy-5-(propan-2-yl)phenyl]-4-(1-methyl-1*H*-indol-5-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

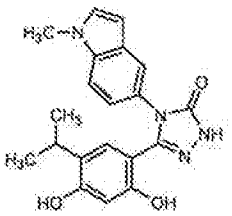
ganétespib

5-[2,4-dihydroxy-5-(propan-2-yl)phényl]-4-(1-méthyl-1*H*-indol-5-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

ganetespib

5-[2,4-dihidroxi-5-(propan-2-il)fenil]-4-(1-metil-1*H*-indol-5-il)-2,4-dihidro-3*H*-1,2,4-triazol-3-ona

$C_{20}H_{20}N_4O_3$



indatuximabum ravtansinum #

indatuximab ravtansine

immunoglobulin G4-kappa, anti-[*Homo sapiens* SDC1 (syndecan-1, CD138)], chimeric monoclonal antibody conjugated to maytansinoid DM4;
gamma4 heavy chain (1-449) [*Mus musculus* VH (IGHV1-9*01 -(IGHD)-IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG4*01 (123-449)], (136-214')-disulfide with kappa light chain (1'-214') [*Mus musculus* V-KAPPA (IGKV10-94*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (228-228":231-231")-bisdisulfide dimer; conjugated, on an average of 3 to 4 lysyl, to maytansinoid DM4 [N^2-deacetyl-N^2-(4-mercapto-4-methyl-1-oxopentyl)-maytansine] via the reducible SPDB linker [*N*-succinimidyl 4-(2-pyridyldithio)butanoate]
For the *ravtansine* part, please refer to the document *"INN for pharmaceutical substances: Names for radicals, groups and others"*

indatuximab ravtansine

immunoglobuline G4-kappa, anti-[*Homo sapiens* SDC1 (syndecan-1, CD138)], anticorps monoclonal chimérique conjugué au maytansinoïde DM4;
chaîne lourde gamma4 (1-449) [*Mus musculus* VH (IGHV1-9*01 -(IGHD)-IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG4*01 (123-449)], (136-214')-disulfure avec la chaîne légère kappa (1'-214') [*Mus musculus* V-KAPPA (IGKV10-94*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (228-228":231-231")-bisdisulfure; conjugué, sur 3 à 4 lysyl en moyenne, au maytansinoïde DM4 [N^2-déacétyl-N^2-(4-mercapto-4-méthyl-1-oxopentyl)-maytansine] via le linker SPDB réductible [4-(2-pyridyldithio)butanoate de *N*-succinimidyle]
Pour la partie *ravtansine*, veuillez vous référer au document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.

indatuximab ravtansina

inmunoglobulina G4-kappa, anti-[SDC1 de *Homo sapiens* (sindecán-1, CD138)], anticuerpo monoclonal quimérico conjugado con el maitansinoide DM4;
cadena pesada gamma4 (1-449) [*Mus musculus* VH (IGHV1-9*01 -(IGHD)-IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG4*01 (123-449)], (136-214')-disulfuro con la cadena ligera kappa (1'-214') [*Mus musculus* V-KAPPA (IGKV10-94*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (228-228":231-231")-bisdisulfuro; conjugado, en 3-4 grupos lisil por término medio con el maitansinoide DM4 [N^2-desacetil-N^2-(4-mercapto-4-metil-1-oxopentil)-maitansina] mediante el espaciador SPDB reducible [4-(2-piridilditio)butanoato de *N*-succinimidilo]
Para la fracción *ravtansina*, se ruega referirse al documento *"INN for pharmaceutical substances: Names for radicals, groups and others"*

Heavy chain / Chaîne lourde / Cadena pesada
```
QVQLQQSGSE LMMPGASVKI SCKATGYTFS NYWIEWVKQR PGHGLEWIGE  50
ILPGTGRTIY NEKFKGKATF TADTSSNTVQ MQLSSLTSED SAVYYCARRD 100
YYGNFYYAMD YWGQGTSVTV SSASTKGPSV FPLAPCSRST SESTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT 200
KTYTCNVDHK PSNTKVDKRV ESKYGPPCPS CPAPEFLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV 350
YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK  449
```

Light chain / Chaîne légère / Cadena ligera
```
DIQMTQSTSS LSASLGDRVT ISCSASQGIN NYLNWYQQKP DGTVKLLIYY  50
TSTLQSGVPS RFSGSGSGTD YSLTISNLEP EDIGTYYCQQ YSKLPWTFGG 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                         214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H 22-96 149-205 263-323 369-437
22'-96' 149'-205' 263'-323' 369'-437'
Intra-L 23'-88' 134'-194'
23''-88'' 134''-194''
Inter-H-L 136-214' 136''-214''
Inter-H-H 228-228'' 231-231''

N-glycosylation sites / Sites de N-glycosylation[7] / Posiciones de N-glicosilación
299, 299''

iofolastatum (^{123}I)
iofolastat (^{123}I)

N-[[(1*S*)-1-carboxy-5-{[(4-(^{123}I)iodophenyl)methyl]amino}pentyl]carbamoyl]-L-glutamic acid

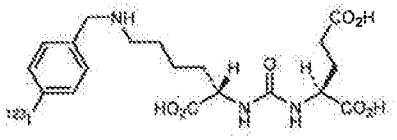
iofolastat (^{123}I)

acide *N*-[[(1*S*)-1-carboxy-5-{[(4-(^{123}I)iodophényl)méthyl]amino}pentyl]carbamoyl]-L-glutamique

iofolastat (^{123}I)

ácido *N*-[[(1*S*)-1-carboxi-5-{[(4-(^{123}I)iodofenil)metil]amino}pentil]carbamoil]-L-glutámico

$C_{19}H_{28}{}^{123}IN_3O_7$



irdabisantum
irdabisant

6-(4-{3-[(2*R*)-2-methylpyrrolidin-1-yl]propoxy}phenyl)pyridazin-3(2*H*)-one

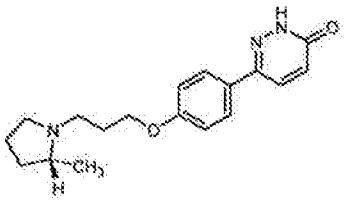
irdabisant

6-(4-{3-[(2*R*)-2-méthylpyrrolidin-1-yl]propoxy}phényl)pyridazin-3(2*H*)-one

irdabisant

6-(4-{3-[(2*R*)-2-metilpirrolidin-1-il]propoxi}fenil)piridazin-3(2*H*)-ona

$C_{18}H_{23}N_3O_2$



ixekizumabum #

ixekizumab

immunoglobulin G4-kappa, anti-[*Homo sapiens* IL17A (interleukin 17A, IL-17A)], humanized monoclonal antibody;
gamma4 heavy chain (1-445) [humanized VH (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG4*01 hinge S10>P (227), CH3 K130>del (120-445)], (133-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2D-29*02 (89.00%) -IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (225-225":228-228")-bisdisulfide dimer

ixékizumab

immunoglobuline G4-kappa, anti-[*Homo sapiens* IL17A (interleukine 17A, IL-17A)], anticorps monoclonal humanisé;
chaîne lourde gamma4 (1-445) [VH humanisé (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG4*01 charnière S10>P (227), CH3 K130>del (120-445)], (133-219')-disulfure avec la chaîne légère kappa (1'-219') [V-KAPPA humanisé (*Homo sapiens* IGKV2D-29*02 (89.00%) -IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dimère (225-225":228-228")-bisdisulfure

ixekizumab

inmunoglobulina G4-kappa, anti-[*Homo sapiens* IL17A (interleukina 17A, IL-17A)], anticuerpo monoclonal humanizado;
cadena pesada gamma4 (1-445) [VH humanizada (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG4*01 bisagra S10>P (227), CH3 K130>del (120-445)], (133-219')-disulfuro con la cadena ligera kappa (1'-219') [V-KAPPA humanizada (*Homo sapiens* IGKV2D-29*02 (89.00%) -IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dímero (225-225":228-228")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGSSVKV SCKASGYSFT DYNIHWVRQA PGQGLEWMGV   50
INPNYGTTDY NQRFKGRVTI TADESTSTAY MELSSLRSED TAVYYCARYD  100
YFTGTGVYWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD  150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY  200
TCNVDHKPSN TKVDKRVESK YGPPCPPCPA PEFLGGPSVF LFPPKPKDTL  250
MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR  300
VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL  350
PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD  400
GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLG       445
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQTPLS LSVTPGQPAS ISCRSSRSLV HSRGNTYLHW YLQKPGQSPQ   50
LLIYKVSNRF IGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHLP  100
FTFGQGTRLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK  150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE  200
VTHQGLSSPV TKSFNRGEC                                    219
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
Intra-H  22-96    146-202   260-320   366-424
         22"-96"  146"-202" 260"-320" 366"-424"
Intra-L  23'-93'   139'-199'
         23"-93"  139"-199"
Inter-H-L  133-219'  133"-219"
Inter-H-H  225-225"  228-228"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
296, 296"

ladarixinum

ladarixin

4-[(2*R*)-1-oxo-1-(methanesulfonamido)propan-2-yl]phenyl trifluoromethanesulfonate

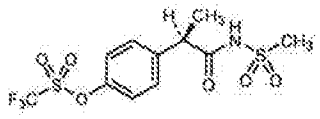
ladarixine

trifluorométhanesulfonate de 4-[(2*R*)-1-oxo-1-(méthanesulfonamido)propan-2-yl]phényle

ladarixina

trifluoromethanesulfonato de 4-[(2*R*)-1-oxo-1-(metanosulfonamido)propan-2-il]fenil

$C_{11}H_{12}F_3NO_5S_2$



lenomorelinum
lenomorelin

$O^{3,26}$-octanoylhuman appetite-regulating hormone (growth hormone-releasing peptide) precursor (protein M46)-(24-51)-peptide (ghrelin-28-C8)

lénomoréline

$O^{3,26}$-octanoylprécurseur de l'hormone humaine de régulation de l'appétit (précurseur du peptide de libération d'hormone de croissance, protéine M46)-(24-51)-peptide (ghréline-28-C8)

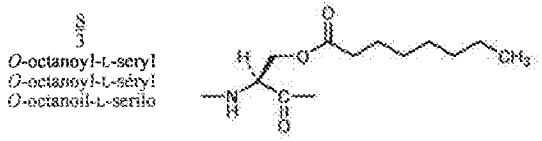
lenomorelina

$O^{3,28}$-octanoilprecursor de la hormona humana de regulación del apetito (precursor del péptido de liberación de hormona del crecimiento, proteína M46)-(24-51)-péptido (ghrelina-28-C8)

$C_{149}H_{249}N_{47}O_{42}$

GSSFLSPEHQ RVQQRKESKK PPAKLQPR 28

Modified residue / Résidu modifié / Resíduo modificado



lesinuradum
lesinurad

2-{[5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetic acid

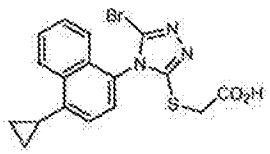
lésinurad

acide 2-{[5-bromo-4-(4-cyclopropylnaphtalén-1-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acétique

lesinurad

ácido 2-{[5-bromo-4-(4-ciclopropilnaftalen-1-il)-4*H*-1,2,4-triazol-3-il]sulfanil}acético

$C_{17}H_{14}BrN_3O_2S$



lexibulinum
lexibulin

1-ethyl-3-[2-methoxy-4-(5-methyl-4-{[(1*S*)-1-(pyridin-3-yl)butyl]amino}pyrimidin-2-yl)phenyl]urea

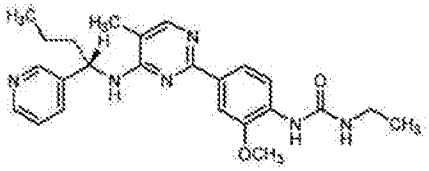
lexibuline

1-éthyl-3-[2-méthoxy-4-(5-méthyl-4-{[(1*S*)-1-(pyridin-3-yl)butyl]amino}pyrimidin-2-yl)phényl]urée

lexibulina

1-etil-3-[2-metoxi-4-(5-metil-4-{[(1*S*)-1-(piridin-3-il)butil]amino}pirimidin-2-il)fenil]urea

$C_{24}H_{30}N_8O_2$



lipegfilgrastimum #
lipegfilgrastim

pegylated granulocyte colony stimulating factor; $O^{3\,133}$-[N^6-(*N*-{[ω-methoxypoly(oxyethylene)]carbonyl}glycyl)-α-neuraminyl-(2→6)-α-D-galactopyranosyl]-L-methionyl-des-1-L-alanine-des-37-L-valine-des-38-L-serine-des-39-L-glutamic acid-human granulocyte colony-stimulating factor (G-CSF, pluripoietin)

lipegfilgrastim

facteur de stimulation de colonie de granulocytes humain pégylé; $O^{3\,133}$-[N^6-(*N*-{[ω-méthoxypoly(oxyéthylène)]carbonyl}glycyl)-α-neuraminyl-(2→6)-α-D-galactopyranosyl]-L-méthionyl-dès-1-L-alanine-dès-37-L-valine-des-38-L-sérine-dès-39-L-acide glutamique-facteur de stimulation de colonie de granulocytes humain (G-CSF, pluripoïétine)

lipegfilgrastim

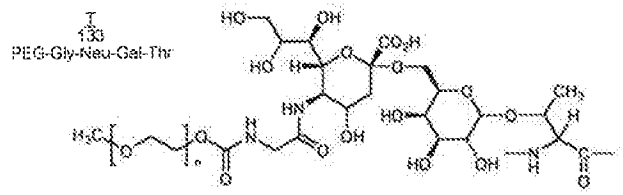
factor de estimulación de colonias de granulocitos humano pegilado; $O^{3\,133}$-[N^6-(*N*-{[ω-metoxipoli(oxietileno)]carbonil}glicil)-α-neuraminil-(2→6)-α-D-galactopiranosil]-L-metionil-des-1-L-alanina-des-37-L-valina-des-38-L-serine-des-39-L-ácido glutámico-factor de estimulación de colonias de granulocitos humanos (G-CSF, pluripoyetina)

$C_{964}H_{1568}N_{225}O_{258}S_9$ $[C_2H_4O]_n$

```
                                                                  N  0
TPLGPASSLP QSFLLFCLEQ VRKIQGDGAA LQEKLCATYK LCHPEELVLL  50
GHSLGIPWAP LSSCPSQALQ LAGCLSQLHS GLFLYQGLLQ ALEGISPELG 100
PTLDTLQLDV ADFATTIWQQ MEELGMAPAL QPTQGAMPAF ASAFQRRAGG 150
VLVASNLQSF LEVSYRVLRH LAQP                              174
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
36-42 64-74

Modified residue / Résidu modifié / Residuo modificado

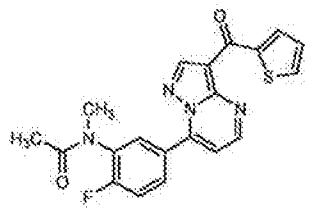


lorediplonum
loredipIon — *N*-{2-fluoro-5-[3-(thiophene-2-carbonyl)pyrazolo[1,5-*a*]pyrimidin-7-yl]phenyl}-*N*-methylacetamide

lorédiplon — *N*-{2-fluoro-5-[3-(thiophène-2-carbonyl)pyrazolo[1,5-*a*]pyrimidin-7-yl]phényl}-*N*-méthylacétamide

loredipión — *N*-{2-fluoro-5-[3-(tiofeno-2-carbonil)pirazolo[1,5-*a*]pirimidin-7-il]fenil}-*N*-metilacetamida

$C_{20}H_{15}FN_4O_2S$

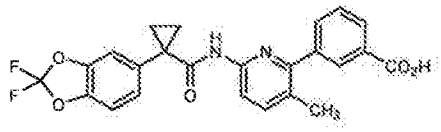


lumacaftorum
lumacaftor — 3-{6-[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropane-1-carboxamido]-3-methylpyridin-2-yl}benzoic acid

lumacaftor — acide 3-{6-[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropane-1-carboxamido]-3-methylpyridin-2-yl}benzoïque

lumacaftor — ácido 3-{6-[1-(2,2-difluoro-1,3-benzodioxol-5-il)ciclopropano-1-carboxamido]-3-metilpiridin-2-il}benzoico

$C_{24}H_{18}F_2N_2O_5$

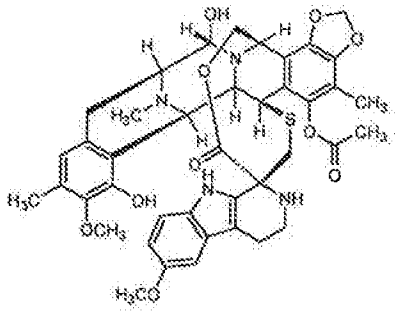


lurbinectedinum
lurbinectedin — (1′*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-8,14-dihydroxy-6′,9-dimethoxy-4,10,23-trimethyl-19-oxo-2′,3′,4′,6,7,9′,12,13,14,16-decahydro-6a*H*-spiro[7,13-azano-6,16-(epithiopropanooxymethano)[1,3]dioxolo[7,8]isoquinolino[3,2-b][3]benzazocine-20,1′-pyrido[3,4-b]indol]-5-yl acetate

lurbinectédine — acétate de (1′*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-8,14-dihydroxy-6′,9-diméthoxy-4,10,23-triméthyl-19-oxo-2′,3′,4′,6,7,9′,12,13,14,16-décahydro-6a*H*-spiro[7,13-azano-6,16-(épithiopropanooxyméthano)[1,3]dioxolo[7,8]isoquinolino[3,2-b][3]benzazocine-20,1′-pyrido[3,4-b]indol]-5-yl

lurbinectedina — acetato de (1′*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-8,14-dihidroxi-6′,9-dimetoxi-4,10,23-trimetil-19-oxo-2′,3′,4′,6,7,9′,12,13,14,16-decahidro-16*H*-spiro[7,13-azano-6,16-(epitiopropanooximetano)[1,3]dioxolo[7,8]isoquinolino[3,2-*b*][3]benzazocina-20,1′-pirido[3,4-*b*]indol]-5-ilo

$C_{41}H_{44}N_4O_{10}S$



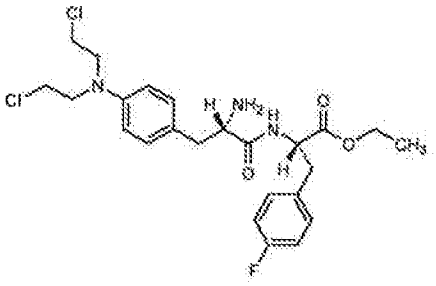
melphalanum flufenamidum

melphalan flufenamide — ethyl (2*S*)-2-[(2*S*)-2-amino-3-{4-[bis(2-chloroethyl)amino]phenyl}propanamido]-3-(4-fluorophenyl)propanoate

melphalan flufénamide — (2*S*)-2-[(2*S*)-2-amino-3-{4-[bis(2-chloroéthyl)amino]phényl}propanamido]-3-(4-fluorophényl)propanoate d'éthyle

melfalán flufenamida — (2*S*)-2-[(2*S*)-2-amino-3-{4-[bis(2-cloroetil)amino]fenil}propanamido]-3-(4-fluorofenil)propanoato de etilo

$C_{24}H_{30}Cl_2FN_3O_3$



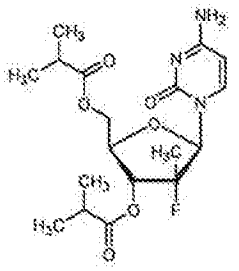
mericitabinum

mericitabine — (2'*R*)-2'-deoxy-2'-fluoro-2'-methyl-2',3'-bis-O-(2-methylpropanoyl)cytidine

méricitabine — 3',5'-bis(2-méthylpropanoate) de (2'*R*)-2'-déoxy-2'-fluoro-2'-méthylcytidine

mericitabina — (2'*R*)-2'-desoxi-2'-fluoro-2'-metil-2',3'-bis-O-(2-metilpropanoil)citidina

$C_{19}H_{26}FN_3O_6$



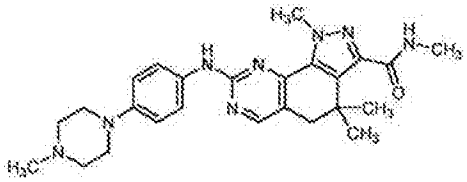
milciclibum

milciclib — *N*,1,4,4-tetramethyl-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*h*]quinazoline-3-carboxamide

milciclib — *N*,1,4,4-tétraméthyl-8-{[4-(4-méthylpipérazin-1-yl)phényl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*h*]quinazoline-3-carboxamide

milciclib — *N*,1,4,4-tetrametil-8-{[4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-1*H*-pirazolo[4,3-*h*]quinazolina-3-carboxamida

$C_{25}H_{32}N_8O$



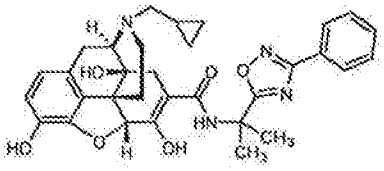
naldemedinum

naldemedine — 17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,6,14-trihydroxy-*N*-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]morphinan-7-carboxamide

naldémédine — 17-(cyclopropylméthyl)-6,7-didéhydro-4,5α-époxy-3,6,14-trihydroxy-*N*-[2-(3-phényl-1,2,4-oxadiazol-5-yl)propan-2-yl]morphinan-7-carboxamide

naldemedina — 17-(ciclopropilmetil)-6,7-didehidro-4,5α-epoxi-3,6,14-trihidroxi-*N*-[2-(3-fenil-1,2,4-oxadiazol-5-il)propan-2-il]morfinan-7-carboxamida

$C_{32}H_{34}N_4O_8$



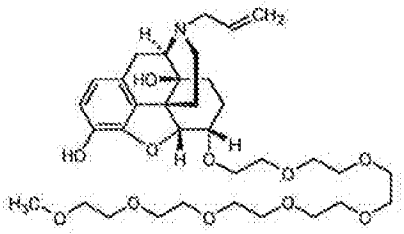
naloxegolum

naloxegol — 4,5α-epoxy-6α-[(3,6,9,12,15,18,21-heptaoxadocosan-1-yl)oxy]-17-(prop-2-en-1-yl)morphinan-3,14-diol

naloxégol — 4,5α-époxy-6α-[(3,6,9,12,15,18,21-heptaoxadocosan-1-yl)oxy]-17-(prop-2-én-1-yl)morphinane-3,14-diol

naloxegol — 4,5α-epoxi-6α-[(3,6,9,12,15,18,21-heptaoxadocosan-1-il)oxi]-17-(prop-2-en-1-il)morfinan-3,14-diol

$C_{34}H_{53}NO_{11}$



narnatumabum #

narnatumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* MST1R (macrophage stimulating 1 receptor, macrophage stimulating protein receptor, MSP receptor, c-met-related tyrosine kinase, protein-tyrosine kinase 8, PTK8, RON, p185-Ron, CD136)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-452) [*Homo sapiens* VH (IGHV3-7*01 (95.90%) -(IGHD)-IGHJ6*01 T127>I (119)) [8.8.15] (1-122) -IGHG1*03 (123-452)], (225-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (98.90%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; (231-231'':234-234'')-bisdisulfide dimer

narnatumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* MST1R (récepteur 1 stimulant le macrophage, récepteur de la protéine stimulant le macrophage, récepteur de la MSP, tyrosine kinase apparentée à c-met, protéine-tyrosine kinase 8, PTK8, RON, p185-Ron, CD136)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-452) [*Homo sapiens* VH (IGHV3-7*01 (95.90%) -(IGHD)-IGHJ6*01 T127>I (119)) [8.8.15] (1-122) -IGHG1*03 (123-452)], (225-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (98.90%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (231-231'':234-234'')-bisdisulfure

narnatumab — inmunoglobulina G1-kappa, anti-[*Homo sapiens* MST1R (receptor 1 estimulante el macrófago, receptor de la proteína estimulante el macrófago, receptor de la MSP, tirosina kinasa relacionada con c-met, proteína-tirosina kinase 8, PTK8, RON, p185-Ron, CD136)], *Homo sapiens* anticuerpo monoclonal;
cadena pesada gamma1 (1-452) [*Homo sapiens* VH (IGHV3-7*01 (95.90%) -(IGHD)-IGHJ6*01 T127>I (119)) [8.8.15] (1-122) -IGHG1*03 (123-452)], (225-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (98.90%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dímero (231-231'':234-234'')-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYLMFWVRQA PGKGLEWVAN   50
IKQDGSEKYY VDSVKGRFTI SRDNAKNSLN LQMNSLRAED TAVYYCTRDG  100
YSSGRHYGMD VWGQGTTVIV SSASTKGPSV FPLAPSSKST SGGTAALGCL  150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT  200
QTYICNVNHK PSNTKVDKRV EPKSCDKTHT CPPCPAPELL GGPSVFLFPP  250
KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ  300
YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE  350
PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP  400
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP  450
GK                                                      452
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPAT LSLSPGERAT LSCRASQSVS RYLAWYQQKP GQAPRLLIYD   50
ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPRTFGQ  100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV  150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG  200
LSSPVTKSFN RGEC                                         214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H 22-96 149-2105 266-326 372-430
22'''-96''' 149'''-205''' 266'''-326''' 372'''-430'''
Intra-L 23'-88' 134'-194'
23'''-88''' 134'''-194'''
Inter-H-L 225-214' 225'''-214'''
Inter-H-H 231-231'' 234-234''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
302, 302''

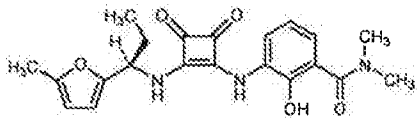
navarixinum

navarixin — 2-hydroxy-*N*,*N*-dimethyl-3-[(2-{[(1*R*)-1-(5-methylfuran-2-yl)propyl]amino}-3,4-dioxocyclobut-1-en-1-yl)amino]benzamide

navarixine — 2-hydroxy-*N*,*N*-diméthyl-3-[(2-{[(1*R*)-1-(5-méthylfuran-2-yl)propyl]amino}-3,4-dioxocyclobut-1-én-1-yl)amino]benzamide

navarixina — 2-hidroxi-*N*,*N*-dimetil-3-[(2-{[(1*R*)-1-(5-metilfuran-2-il)propil]amino}-3,4-dioxociclobut-1-en-1-il)amino]benzamida

$C_{21}H_{23}N_3O_5$



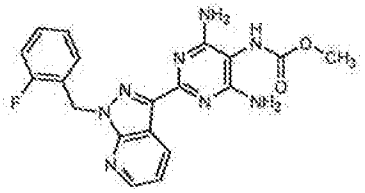
nelociguatum

nelociguat — methyl (4,6-diamino-2-{1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}pyrimidin-5-yl)carbamate

nélociguat — (4,6-diamino-2-{1-[(2-fluorophényl)méthyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}pyrimidin-5-yl)carbamate de méthyle

nelociguat — (4,6-diamino-2-{1-[(2-fluorofenil)metil]-1*H*-pirazolo[3,4-*b*]piridin-3-il}pirimidin-5-il)carbamato de metilo

$C_{15}H_{17}FN_6O_2$

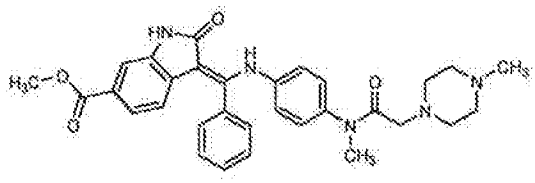


nintedanibum
nintedanib — methyl (3*Z*)-3-[({4-[*N*-methyl-2-(4-methylpiperazin-1-yl)acetamido]phenyl}amino)(phenyl)methylidene]-2-oxo-2,3-dihydro-1*H*-indole-6-carboxylate

nintédanib — (3*Z*)-3-[({4-[*N*-méthyl-2-(4-méthylpipérazin-1-yl)acétamido]phényl}amino)(phényl)méthylidène]-2-oxo-2,3-dihydro-1*H*-indole-6-carboxylate de méthyle

nintedanib — (3*Z*)-3-[({4-[*N*-metil-2-(4-metilpiperazin-1-il)acetamido]fenil}amino)(fenil)metiliden]-2-oxo-2,3-dihidro-1*H*-indol-6-carboxilato de metilo

$C_{31}H_{33}N_6O_4$

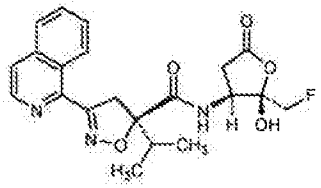


nivocasanum
nivocasan — (5*R*)-*N*-[(2*S*,3*S*)-2-(fluoromethyl)-2-hydroxy-5-oxooxolan-3-yl]-3-(isoquinolin-1-yl)-5-(propan-2-yl)-4,5-dihydro-1,2-oxazole-5-carboxamide

nivocasan — (5*R*)-*N*-[(2*S*,3*S*)-2-(fluorométhyl)-2-hydroxy-5-oxooxolan-3-yl]-3-(isoquinoléin-1-yl)-5-(propan-2-yl)-4,5-dihydro-1,2-oxazole-5-carboxamide

nivocasán — (5*R*)-*N*-[(2*S*,3*S*)-2-(fluorometil)-2-hidroxi-5-oxooxolan-3-il]-3-(isoquinolin-1-il)-5-(propan-2-il)-4,5-dihidro-1,2-oxazol-5-carboxamida

$C_{21}H_{22}FN_3O_5$



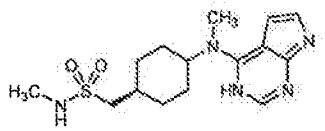
oclacitinibum

oclacitinib — *N*-methyl{*trans*-4-[methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]cyclohexyl}methanesulfonamide

oclacitinib — *N*-méthyl[*trans*-4-(méthyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamino)cyclohexyl]méthanesulfonamide

oclacitinib — *N*-metil{*trans*-4-[metil(7*H*-pirrolo[2,3-*d*]pirimidin-4-il)amino]ciclohexil}metanosulfonamida

$C_{15}H_{23}N_5O_2S$



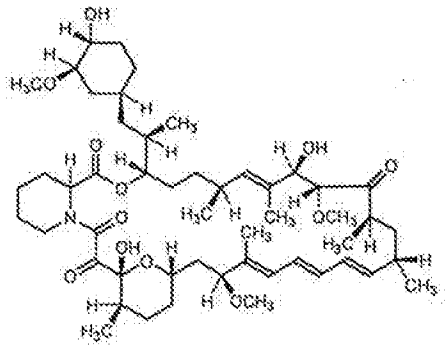
olcorolimusum

olcorolimus — (3*S*,6*S*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-dihydroxy-3-{(1*R*)-1-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]propan-2-yl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-3,4,5,6,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-icosahydro-11*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,11,28,29(31*H*)-tetrone

olcorolimus — (3*S*,6*S*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-dihydroxy-3-{(1*R*)-1-[(1*S*,3*R*,4*R*)-4-hydroxy-3-méthoxycyclohexyl]propan-2-yl}-10,21-diméthoxy-6,8,12,14,20,26-hexaméthyl-3,4,5,6,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-icosahydro-11*H*-23,27-époxypyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,11,28,29(31*H*)-tétrone

olcorolimús — (3*S*,6*S*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-dihidroxi-3-{(1*R*)-1-[(1*S*,3*R*,4*R*)-4-hidroxi-3-metoxiciclohexil]propan-2-il}-10,21-dimetoxi-6,8,12,14,20,26-hexametil-3,4,5,6,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-icosahidro-11*H*-23,27-epoxipirido[2,1-*c*][1,4]oxaazaciclohentriacontina-1,11,28,29(31*H*)-tetrona

$C_{61}H_{81}NO_{12}$



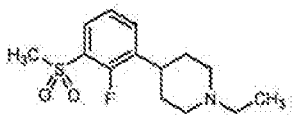
ordopidinum

ordopidine — 1-ethyl-4-[2-fluoro-3-(methanesulfonyl)phenyl]piperidine

ordopidine — 1-éthyl-4-[2-fluoro-3-(méthylsulfonyl)phényl]pipéridine

ordopidina — 1-etil-4-[2-fluoro-3-(metanosulfonil)fenil]piperidina

$C_{14}H_{20}FNO_2S$ — 871351-60-9



ozoralizumabum #

ozoralizumab — immunoglobulin single chain VH-VH'-VH, trivalent bispecific anti-[*Homo sapiens* TNF (tumor necrosis factor, TNF superfamily member 2, TNFSF2, TNFA, TNF-alpha)] VH and anti-[*Homo sapiens* ALB (albumin, human serum albumin, HAS)] VH', humanized *Lama glama* monoclonal antibody;
scVH-VH'-VH (1-363) [humanized VH (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (105)) [8.8.8] (1-115) - 9-mer linker (tetraglycyl-seryl-triglycyl-seryl) (116-124) -humanized VH' (*Homo sapiens* IGHV3-23*04 (89.60%) -(IGHD)-IGHJ1*01 W118>S (229), G119>S (230) [8.8.8] (125-239) -9-mer linker (tetraglycyl-seryl-triglycyl-seryl) (240-248) -humanized VH (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (353)(249-363)

ozoralizumab — immunoglobuline single chain VH-VH'-VH, trivalente bispécifique anti-[*Homo sapiens* TNF (facteur de nécrose tumorale, membre 2 de la superfamille du TNF, TNFSF2, TNFA, TNF-alpha)] VH et anti-[*Homo sapiens* ALB (albumine, sérum albumine humaine, SAH)] VH', anticorps monoclonal de *Lama glama* humanisé;
scVH-VH'-VH (1-363) [VH humanisé (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (105)) [8.8.8] (1-115) -9-mer linker (tétraglycyl-séryl-triglycyl-séryl) (116-124) -VH' humanisé (*Homo sapiens* IGHV3-23*04 (89.60%) -(IGHD)-IGHJ1*01 W118>S (229), G119>S (230) [8.8.8] (125-239) -9-mer linker (tétraglycyl-séryl-triglycyl-séryl) (240-248) -VH humanisé (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (353)(249-363)

ozoralizumab — inmunoglobulina de cadena sencilla VH-VH'-VH, trivalente biespecífica anti-[TNF de *Homo sapiens* (factor de necrosis tumoral, miembro 2 de la superfamilia del TNF, TNFSF2, TNFA, TNF-alpha)] VH y anti-[*Homo sapiens* ALB (albumina, albumina sérica humana SAH)] VH', anticuerpo monoclonal de *Lama glama* humanizado;
scVH-VH'-VH (1-363) [VH humanizado (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (105)) [8.8.8] (1-115) - conector nonámero (tetraglicil-seril-triglicil-seril) (116-124) -VH' humanizado (*Homo sapiens* IGHV3-23*04 (89.60%) -(IGHD)-IGHJ1*01 W118>S (229), G119>S (230) [8.8.8] (125-239) - espaciador nonámero (tetraglicil-seril-triglicil-seril) (240-248) -VH humanizado (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (353)(249-363)

scVH-VH'-VH chain / Chaine scVH-VH'-VH / Cadena scVH-VH'-VH

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS DYWMTWVRQA PGKGLEWVSE   50
INPDGLITKY PDSVKGRFTI SRDNAKNTLY LQMNSLRPED TAVYYCARSP  100
SGFNRGQGTL VTVSSGGGGS GGGSEVQLVE SGGGLVQPGN SLRLSCAASG  150
FTFSSFGMSW VRQAPGKGLE WVSSISGSGS DTLYADSVKG RFTISRDNAK  200
TTLYLQMNSL RPEDTAVYYC TIGGSLGRSS QGTLVTVSSG GGGSGGGSEV  250
QLVESGGGLV QPGGSLRLSC AASGFTFSDY WMYWVRQAPG KGLEWVSEIN  300
TNGLITKYPD SVKGRFTISR DNAKNTLYLQ MNSLRPEDTA VYYCARSPSG  350
FNRGQGTLVT VSS                                          363
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-chain 22-96 146-220 270-34

pateclizumabum #

pateclizumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* LTA (lymphotoxin alpha, TNFSF1, tumor necrosis factor superfamily member 1, LT)], humanized monoclonal antibody;
gamma1 heavy chain (1-447) [humanized VH (*Homo sapiens* IGHV3-74*01 (76.50%) -(IGHD)-IGHJ5*01) [8.9.11] (1-118) -*Homo sapiens* IGHG1*03 CH1 R120>K (215), CH3 K130>del (119-447)], (221-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (88.40%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (227-227":230-230")-bisdisulfide dimer

patéclizumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* LTA (lymphotoxine alpha, TNFSF1, membre 1 de la superfamille du facteur de nécrose tumorale, LT)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-447) [VH humanisé (*Homo sapiens* IGHV3-74*01 (76.50%) -(IGHD)-IGHJ5*01) [8.9.11] (1-118) -*Homo sapiens* IGHG1*03 CH1 R120>K (215), CH3 K130>del (119-447)], (221-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (88.40%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (227-227":230-230")-bisdisulfure

pateclizumab

inmunoglobulina G1-kappa, anti-[LTA *de Homo sapiens* (linfotoxina alfa, TNFSF1, miembro 1 de la superfamilia del factor de necrosis tumoral, LT)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-447) [VH humanizada (*Homo sapiens* IGHV3-74*01 (76.50%) -(IGHD)-IGHJ5*01) [8.9.11] (1-118) -*Homo sapiens* IGHG1*03 CH1 R120>K (215), CH3 K130>del (119-447)], (221-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizada (*Homo sapiens* IGKV1-39*01 (88.40%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (227-227":230-230")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada
```
EVQLVESGGG LVQPGGSLRL SCAASGYTFT SYVIHWVRQA PGKGLEWVGY  50
NNPYNAGTNY NEKFKGRFTI SSDKSKNTAY LQMNSLRAED TAVYYCSRFT 100
MLPWFAYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY 150
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI 200
CNVNHKPSNT KVDKKVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD 250
TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST 300
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY 350
TLPPSREEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD 400
SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPG    447
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Light chain / Chaîne légère / Cadena ligera
```
DIQMTQSPSS LSASVGDRVT ITCRASQAVS SAVAWYQQKP GKAPKLLIYS  50
ASHRYTGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQE SYSTFWTFGQ 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
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Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H 22-96 145-201 262-322 368-426
22"-96" 145"-201" 262"-322" 368"-426"
Intra-L 23'-88' 134'-194'
23"-88" 134"-194"
Inter-H-L 221-214' 221"-214"
Inter-H-H 227-227" 230-230"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
298, 298"

pegadricasum #

pegadricase

pegylated Urate Oxidase from *Candida utilis*, [198-threonine(S>T)]uricase (EC 1.7.3.3, urate oxidase) *Pichia jadinii* (Yeast) (*Candida utilis*) tetramer, 6-amino group of an average of 3 lysine residues, mostly in position 16, 19, and 85 of each monomer, are amidified with α-(3-carboxypropanoyl)-ω-methoxypoly(oxyethylene)

pégadricase

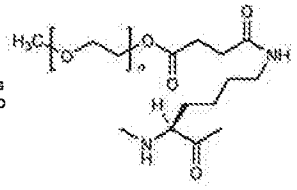
urate oxidase de *Candida utilis* pégylée, [198-thréonine(S>T)]uricase (EC 1.7.3.3, urate oxydase) *Pichia jadinii* (levure) (*Candida utilis*), tétramère, la fonction amine en 6 de certaines lysines, en moyenne 3, principalement en positions 16, 19, et 85 de chaque monomère, sont amidifiées par le α-(3-carboxypropanoyl)-ω-méthoxypoly(oxyéthylène)

pegadricasa

urato oxidasa de *Candida utilis* pegilada, [198-treonina(S>T)]uricasa (EC 1.7.3.3, urato oxidasa) *Pichia jadinii* (levadura) (*Candida utilis*), tetrámero, la función amina en 6 de ciertas lisinas, 3 por término medio, principalmente en las posiciones 16, 19, y 85 de cada monómero, está amidificada con α-(3-carboxipropanoil)-ω-metoxipoli(oxietileno)

Monomer / Monomère / Monómero
```
MSTTLSSSTY GKDNVKFLKV KKDPQNPKKQ EVMERFVFCL LSGGFDTSYT  50
EADNSSIVPT DTVMNTKLVL ANTTDEIWPI RSAAKLATHF VEKYSHVSGV 100
SVKIVQDRWV KYAVDGKPHD HSFIHEGGEK RTIDLYYKRS GDYKLSSAIK 150
DLTVLKSTGS MEYGYNKCDF TTLQPTTDRI LSTDVDATWV WDNFKICTVY 200
DIAKAADKGI FDNVYNQARE ITLTTEALEN GPSVQATMFN NAFQILEKAC 250
GVYSGVSYAL P NKHYFLTDLK WKGLENDNEL FYPSPNPNGL IKCTVVRKEK 300
TKL                                                    303
```

Modified residues / Résidus modifiés / Residuos modificados



peginterferonum lambda-1a #
peginterferon lambda-1a

pegylated interferon lambda-1; pegylated interleukin 29; *N*-{3-[α-methylpoly(oxyethylene)oxy]propyl}-L-methionyl{[171-serine]human interleukin-29 (IFN-λ-1)-(7-181)-peptide}

péginterféron lambda-1a

interféron lambda-1 pégylé; interleukine-29 pégylée; *N*-{3-[α-méthylpoly(oxyéthylène)oxy]propyl}-L-méthionyl{[171-sérine] interleukine-29 humaine (IFN-λ-1)-(7-181)-peptide}

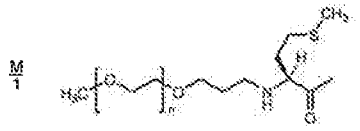
peginterferón lambda-1a

interferón lambda-1 pegilado; interleukina-29 pegilada; *N*-{3-[α-metilpoli(oxietileno)oxi]propil}-L-metionil{[171-serina] interleukina-29 humana (IFN-λ-1)-(7-181)-péptido}

$C_{876}H_{1408}N_{254}O_{251}S_5\ (C_2H_4O)_n$

```
      MKPTT TGKGCNIGRF KSLSPQELAS FKKARDALEE SLKLKNWSCS  50
SPVFPGNWDL RLLQVRERPV ALEAELALTL KVLEAAAGPA LEDVLDQPLH 100
TLHHILSQLQ ACIQPQPTAG PRPRGRLHHW LHRLQEAPKK ESAGCLEASV 150
TFNLFRLLTR DLKYVADGNL SLRTSTHPES T                     181
```

Modified residue / Résidu modifié / Residuo modificado



Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
15-112 49-185

pegnivacoginum
pegnivacogin

a ribonucleic acid aptamer which binds Factor XIa; ester of 2'-*O*-methyl-5'-*O*-phosphonoguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→3')-thimidine with 6-[(2,6-bis{*N*-[ω-methoxypoly(oxyethylene)carbonyl]}-DL-lysyl)amino]hexan-1-ol

pégnivacogin

acide ribonucleique aptamère se liant au Factor XIa;
ester de 2'-*O*-méthyl-5'-*O*-phosphonoguanylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-déoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-déoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-déoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-déoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-déoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→3')-thimidine avec 6-[(2,6-bis{*N*-[ω-méthoxypoly(oxyéthylène)carbonyl]}-DL-lysyl)amino]hexan-1-ol

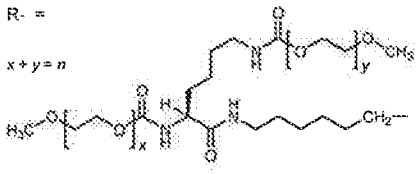
pegnivacogina

aptámero de ácido ribonucléico que se une a Factor XIa;
éster of 2'-*O*-metil-5'-*O*-fosfonoguanilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-guaniil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-*O*-metilcitidilil-(3'→3')-timidina con 6-[(2,6-bis{*N*-[ω-metoxipoli(oxietileno)carbonil]}-DL-lisil)amino]hexan-1-ol

$C_{327}H_{422}F_{11}N_{114}O_{213}P_{31}\ (C_2H_4O)_n$

(3'-5')-R-pmG-mU-mG-mG-mA-dfiC-dfiU-mA-dfiU-mA-dfiC-dfiC-mG-dfiC-mG-dfiU-mA-mA-dfiU-mG-dfiC-mU-G-mC-dfiC-dfiU-mC-mC-mA-mC3'-3'dT
Legend:
dfi = 2'-deoxy-2'-fluoro ; m = 2'-O-methyl ; p (as prefix) = 5'-phosphate

R- =



pimasertibum

pimasertib

N-[(2*S*)-2,3-dihydroxypropyl]-3-[(2-fluoro-4-iodophenyl)amino]pyridine-4-carboxamide

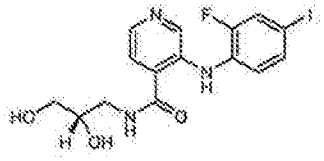
pimasertib

N-[(2*S*)-2,3-dihydroxypropyl]-3-[(2-fluoro-4-iodophényl)amino]pyridine-4-carboxamide

pimasertib

N-[(2*S*)-2,3-dihidroxipropil]-3-[(2-fluoro-4-iodofenil)amino]piridina-4-carboxamida

$C_{15}H_{15}FIN_3O_3$



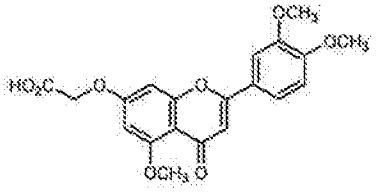
recoflavonum

recoflavone {[2-(3,4-dimethoxyphenyl)-5-methoxy-4-oxo-4*H*-chromen-7-yl]oxy}acetic acid

récoflavone acide {[2-(3,4-diméthoxyphényl)-5-méthoxy-4-oxo-4*H*-chromen-7-yl]oxy}acétique

recoflavona ácido {[2-(3,4-dimetoxifenil)-5-metoxi-4-oxo-4*H*-cromen-7-il]oxi}acético

$C_{20}H_{18}O_8$



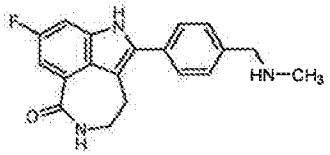
rucaparibum

rucaparib 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6*H*-pyrrolo[4,3,2-*ef*][2]benzazepin-6-one

rucaparib 8-fluoro-2-{4-[(méthylamino)méthyl]phényl}-1,3,4,5-tétrahydro-6*H*-pyrrolo[4,3,2-*ef*][2]benzazépin-6-one

rucaparib 8-fluoro-2-{4-[(metilamino)metil]fenil}-1,3,4,5-tetrahidro-6*H*-pirrolo[4,3,2-*ef*][2]benzazepin-6-ona

$C_{19}H_{16}FN_3O$



safotibantum

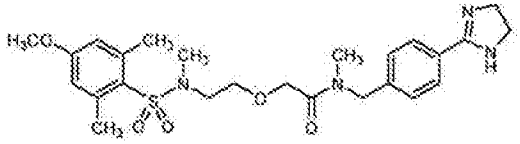
safotibant *N*-{[4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl]methyl}-2-{2-[(4-methoxy-2,6-dimethylbenzenesulfonyl)(methyl)amino]ethoxy}-*N*-methylacetamide

safotibant *N*-{[4-(4,5-dihydro-1*H*-imidazol-2-yl)phényl]méthyl}-2-{2-[(4-méthoxy-2,6-diméthylbenzènesulfonyl)(méthyl)amino]éthoxy}-*N*-méthylacétamide

safotibant

N-[[4-(4,5-dihidro-1*H*-imidazol-2-il)fenil]metil}-2-{2-[(4-metoxi-2,6-dimetilbencenosulfonil)(metil)amino]etoxi}-*N*-metilacetamido

$C_{25}H_{34}N_4O_5S$



selepressinum
selepressin

vasopressin type 1a (V1a) receptor agonist; [2-L-phenylalanine,3-L-isoleucine,4-(6-oxo-L-lysine),8-[5-*N*-(propan-2-yl)-L-ornithine]]human vasopressin

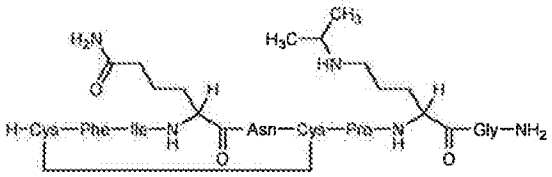
sélépressine

agoniste du récepteur de la vasopressine type 1a (V1a); [2-L-phénylalanine,3-L-isoleucine,4-(6-oxo-L-lysine),8-[5-*N*-(propan-2-yl)-L-ornithine]]vasopressine humaine

selepresina

agonista del receptor de la vasopresina tipo 1ª (V1a); [2-L-fenilalanina,3-L-isoleucina,4-(6-oxo-L-lisina),8-[5-*N*-(propan-2-yl)-L-ornitina]]vasopresina humana

$C_{46}H_{73}N_{13}O_{11}S_2$



sepantronii bromidum
sepantronium bromide

1-(2-methoxyethyl)-2-methyl-4,9-dioxo-3-[(pyrazin-2-yl)methyl]-4,9-dihydro-1*H*-naphtho[2,3-*d*]imidazolium bromide

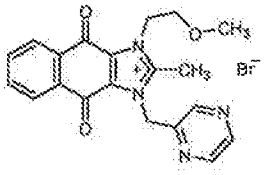
bromure de sépantronium

bromure de 1-(2-méthoxyéthyl)-2-méthyl-4,9-dioxo-3-[(pyrazin-2-yl)méthyl]-4,9-dihydro-1*H*-naphto[2,3-*d*]imidazolium

bromuro de sepantronio

bromuro de 2-metil-1-(2-metoxietil)-4,9-dioxo-3-[(pirazin-2-il)metil]-4,9-dihidro-1*H*-nafto[2,3-*d*]imidazolio

$C_{20}H_{19}BrN_4O_3$



serelaxinum

serelaxin — human relaxin 2 (relaxin H2)

sérélaxine — rélaxine 2 humaine (rélaxine H2)

serelaxina — relaxina 2 humana (relaxina H2)

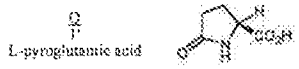
$C_{256}H_{408}N_{74}O_{74}S_8$

B chain / Chaîne B / Cadena B
DSWMEEVIKL CGRELVRAQI AICGMSTWS 29

A chain / Chaîne A / Cadena A
QLYSALANKC CHVGCTKRSL ARFC 24

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
10-15 11-11 23-24

Modified residue / Résidu modifié / Residuo modificado



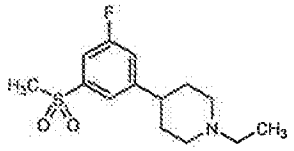
seridopidinum

seridopidine — 1-ethyl-4-[3-fluoro-5-(methanesulfonyl)phenyl]piperidine

séridopidine — 1-éthyl-4-[3-fluoro-5-(méthylsulfonyl)phényl]pipéridine

seridopidina — 1-etil-4-[3-fluoro-5-(metanosulfonil)fenil]piperidina

$C_{14}H_{20}FNO_2S$



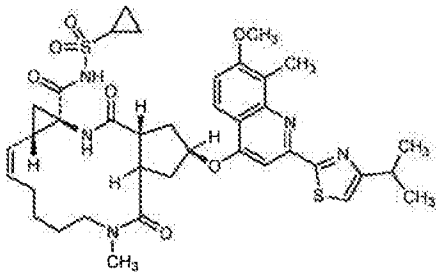
simeprevirum

simeprevir — (2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(cyclopropanesulfonyl)-2-({7-methoxy-8-methyl-2-[4-(propan-2-yl)-1,3-thiazol-2-yl]quinolin-4-yl}oxy)-5-methyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahydrocyclopenta[*c*]cyclopropa[*g*][1,6]diazacyclotetradecine-12a(1*H*)-carboxamide

siméprévir — (2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(cyclopropanesulfonyl)-2-({7-méthoxy-8-méthyl-2-[4-(propan-2-yl)-1,3-thiazol-2-yl]quinoléin-4-yl}oxy)-5-méthyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tétradécahydrocyclopenta[*c*]cyclopropa[*g*][1,6]diazacyclotétradécine-12a(1*H*)-carboxamide

simeprevir — (2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(ciclopropanosulfonil)-2-({7-metoxi-8-metil-2-[4-(propan-2-il)-1,3-tiazol-2-il]quinolin-4-il}oxi)-5-metil-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahidrociclopenta[*c*]ciclopropa[*g*][1,6]diazaciclotetradecina-12a(1*H*)-carboxamida

$C_{36}H_{47}N_5O_7S_2$



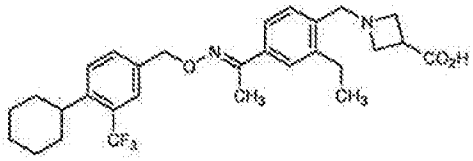
siponimodum

siponimod — 1-({4-[(1*E*)-1-({[4-cyclohexyl-3-(trifluoromethyl)phenyl]methoxy}imino)ethyl]-2-ethylphenyl}methyl)azetidine-3-carboxylic acid

siponimod — acide 1-({4-[(1*E*)-1-({[4-cyclohexyl-3-(trifluorométhyl)phényl]méthoxy}imino)éthyl]-2-éthylphényl}méthyl)azétidine-3-carboxylique

siponimod — ácido 1-({4-[(1*E*)-1-({[4-ciclohexil-3-(trifluorometil)fenil]metoxi}imino)etil]-2-etilfenil}metil)azetidina-3-carboxílico

$C_{29}H_{35}F_3N_2O_3$



sirukumabum #

sirukumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* IL6 (interleukin 6, IL-6)], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-449) [*Homo sapiens* VH (IGHV3-7*01 (87.80%) -(IGHD)-IGHJ6*01) [8.8.12] (1-119) -IGHG1*01 (120-449)], (222-213')-disulfide with kappa light chain (1'-213') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (87.40%) -IGKJ4*01) [5.3.9] (1'-107') -IGKC*01 (107'-213')]; (228-231":228-231")-bisdisulfide dimer

sirukumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* IL6 (interleukine 6, IL-6)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma1 (1-449) [*Homo sapiens* VH (IGHV3-7*01 (87.80%) -(IGHD)-IGHJ6*01) [8.8.12] (1-119) -IGHG1*01 (120-449)], (222-213')-disulfure avec la chaîne légère kappa (1'-213') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (87.40%) -IGKJ4*01) [5.3.9] (1'-107') -IGKC*01 (107'-213')]; dimère (228-228":231-231")-bisdisulfure

sirukumab

inmunoglobulina G1-kappa, anti-[IL6 de *Homo sapiens* (interleukina 6, IL-6)], anticuerpo monoclonal de *Homo sapiens*; cadena pesada gamma1 (1-449) [*Homo sapiens* VH (IGHV3-7*01 (87.80%) -(IGHD)-IGHJ6*01) [8.8.12] (1-119) -IGHG1*01 (120-449)], (222-213')-disulfuro con la cadena ligera kappa (1'-213') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (87.40%) -IGKJ4*01) [5.3.9] (1'-107') -IGKC*01 (107'-213')]; dímero (228-228":231-231")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS PFAMSWVRQA PGKGLEWVAK  50
ISPGGSWTTY SDTVTGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARQL 100
NGYYALDING QGTTVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPAT LSLSPGERAT LSCSASLSVS YMYWYQQFPG QAPRLLIYDM  50
SNLASGIPAR FSGSGSGTDF TLTISSLEPE DFAVYYCMQH SGYPYTFGGG 100
TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD 150
NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL 200
SSPVTKSFNR GEC                                         213
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
Intra-H  22-96    146-202   263-323   369-427
         22"-96"  146"-202" 263"-323" 369"-427"
Intra-L  23'-87'   133'-193'
         23"-87"" 133"-193""
Inter-H-L  222-213'  222"-213""
Inter-H-H  228-228"  231-231"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
299, 299"

solithromycinum

solithromycin

(3a*R*,4*R*,7*S*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-1-{4-[4-(3-aminophenyl)-1*H*-1,2,3-triazol-1-yl]butyl}-4-ethyl-7-fluoro-11-methoxy-3^a,7,9,11,13,15-hexamethyl-10-{[trideoxy-(dimethylamino)-β-D-hexopyranosyl]oxy}octahydro-2*H*-oxacyclotetradecino[4,3-*b*][1,3]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tetraone

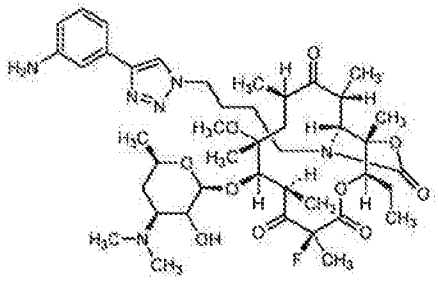
solithromycine

(3a*S*,4*R*,7*S*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-1-{4-[4-(3-aminophényl)-1*H*-1,2,3-triazol-1-yl]butyl}-4-éthyl-7-fluoro-11-méthoxy-3a,7,9,11,13,15-hexaméthyl-10-{[3,4,6-tridéoxy-3-(diméthylamino)-β-D-*xylo*-hexopyranosyl]oxy}octahydro-2*H*-oxacyclotétradécino[4,3-*d*]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tétrone

solitromicina

(3a*R*,4*R*,7*S*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-1-{4-[4-(3-aminofenil)-1*H*-1,2,3-triazol-1-il]butil}-4-etil-7-fluoro-3^a,7,9,11,13,15-hexametil-11-metoxi-10-{[tridesoxi-(dimetilamino)-β-D-hexopiranosil]oxi}octahidro-2*H*-oxaciclotetradecino[4,3-*b*][1,3]oxazol-2,6,8,14(1*H*,7*H*,9*H*)-tetraona

$C_{43}H_{65}FN_6O_{10}$ 760981-83-7



spriferminum #

sprifermin — L-methionyl[human fibroblast growth factor 18 (FGF-18, zFGF5)-(1-169)-peptide

sprifermine — L-méthionyl[facteur 18 de croissance du fibroblaste humain (FGF-18, zFGF5)-(1-169)-peptide]

esprifermina — L-metionil[factor 18 de crecimiento de fibroblastos humanos (FGF-18, zFGF5)-(1-169)-péptido]

$C_{878}H_{1396}N_{258}O_{256}S_6$

```
                                                                M
EENVDFRIHV  ENQTRARDDV  SPERQLRLYQL  YSRTGGKHIQ  VLGPRISARG  SD
EDGDMFAQLA  VETDEFGSQV  PLRGKETEFY  LCMNPKGKLV  GKPDGTSKEC  VD
VTEEKVLENN  YTALMSAKYS  GWYVGFTKKG  RPRKGPKTRE  NQQDVHFMKR  YP
YPNKQPELQK  PFKYTTVTK                                      16
```

Disulfide bridge location / Position du pont disulfure / Posición del puente disulfuro
82-100

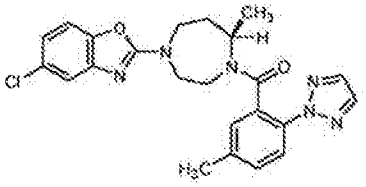
suvorexantum

suvorexant — [(7*R*)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl]methanone

suvorexant — [(7*R*)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-méthyl-1,4-diazépan-1-yl][5-méthyl-2-(2*H*-1,2,3-triazol-2-yl)phényl]méthanone

suvorexant — [(7*R*)-4-(5-cloro-1,3-benzoxazol-2-il)-7-metil-1,4-diazepan-1-il][5-metil-2-(2*H*-1,2,3-triazol-2-il)fenil]metanona

$C_{23}H_{23}ClN_6O_2$



tabalumabum #

tabalumab

immunoglobulin G4-kappa, anti-[*Homo sapiens* TNFSF13B (tumor necrosis factor superfamily member 13B, BAFF, THANK, TALL-1, TALL1, BLYS, BLyS, B cell activating factor, B lymphocyte stimulator, CD257)], *Homo sapiens* monoclonal antibody; gamma4 heavy chain (1-450) [*Homo sapiens* VH (IGHV4-34*01 (100.00%) -(IGHD)-IGHJ4*01) [8.7.17] (1-123) -IGHG4*01 hinge S10>P (231) (124-450)], (137-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (97.90%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*05 (108'-214')]; (229-229'':232-232'')-bisdisulfide dimer

tabalumab

immunoglobuline G4-kappa, anti-[*Homo sapiens* TNFSF13B (membre 13B de la superfamille du facteur de nécrose tumorale, BAFF, THANK, TALL-1, TALL1, BLYS, BLyS, facteur d'activation des cellules B, stimulateur des lymphocytes B, CD257)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma4 (1-450) [*Homo sapiens* VH (IGHV4-34*01 (100.00%) -(IGHD)-IGHJ4*01) [8.7.17] (1-123) -IGHG4*01 charnière S10>P (231) (124-450)], (137-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (97.90%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*05 (108'-214')]; dimère (229-229'':232-232'')-bisdisulfure

tabalumab

inmunoglobulina G4-kappa, anti-[TNFSF13B *de Homo sapiens* (miembro 13B de la superfamilia del factor de necrosis tumoral, BAFF, THANK, TALL-1, TALL1, BLYS, BLyS, factor de activación de células B, estimulante de linfocitos B, CD257)], *Homo sapiens* anticuerpo monoclonal;
cadena pesada gamma4 (1-450) [VH de *Homo sapiens* (IGHV4-34*01 (100.00%) -(IGHD)-IGHJ4*01) [8.7.17] (1-123) -IGHG4*01 bisagra S10>P (231) (124-450)], (137-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (97.90%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*05 (108'-214')]; dímero (229-229'':232-232'')-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQQWGAG LLKPSETLSL TCAVYGGSFS GYYWSWIRQP PGKGLEWIGE  50
INHSGSTNYN PSLKSRVTIS VDTSKNQFSL KLSSVTAADT AVYYCARGYY 100
DILTGYYYYF DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC 150
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG 200
TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP 250
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN 300
STYRVVSVLT VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ 350
VYTLPPSQEE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 400
LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLGK 450
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPAT LSLSPGERAT LSCRASQSVS RYLAWYQQKP GQAPRLLIYD  50
ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPRTFGQ 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSNTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                         214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
Intra-H  22-95    150-206    264-324    370-428
         22''-95''  150''-206''  264''-324''  370''-428''
Intra-L  23'-88'    134'-194'
         23''-88''  134''-194''
Inter-H-L  137-214'   137''-214''
Inter-H-H  229-229''  232-232''
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
306, 306''

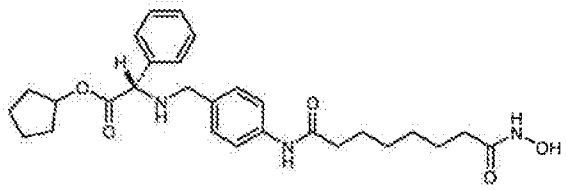
tefinostatum

tefinostat — cyclopentyl (2*S*)-2-[({4-[8-(hydroxyamino)-8-oxooctanamido]phenyl}methyl)amino]-2-phenylacetate

téfinostat — (2*S*)-2-[({4-[8-(hydroxyamino)-8-oxooctanamido]phényl}methyl)amino]-2-phénylacétate de cyclopentyle

tefinostat — (2*S*)-2-[({4-[8-(hidroxiamino)-8-oxooctanamido]fenil}metil)amino]-2-fenilacetato de ciclopentilo

$C_{28}H_{37}N_3O_5$



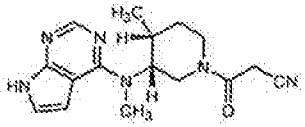
tofacitinibum

tofacitinib — 3-{(3*R*,4*R*)-4-methyl-3-[methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]piperidin-1-yl}-3-oxopropanenitrile

tofacitinib — 3-{(3*R*,4*R*)-4-méthyl-3-[méthyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]pipéridin-1-yl}-3-oxopropanenitrile

tofacitinib — 3-{(3*R*,4*R*)-4-metil-3-[metil(7*H*-pirrolo[2,3-*d*]pirimidin-4-il)amino]piperidin-1-il}-3-oxopropanonitrilo

$C_{16}H_{20}N_6O$



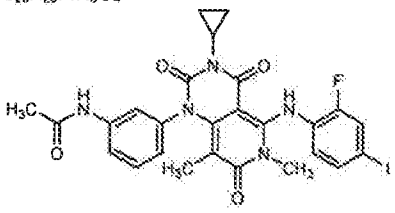
trametinibum

trametinib — *N*-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl}phenyl)acetamide

tramétinib — *N*-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophényl)amino]-6,8-diméthyl-2,4,7-trioxo-3,4,6,7-tétrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl}phényl)acétamide

trametinib — *N*-(3-{3-ciclopropil-5-[(2-fluoro-4-iodofenil)amino]-6,8-dimetil-2,4,7-trioxo-3,4,6,7-tetrahidropirido[4,3-*d*]pirimidin-1(2*H*)-il}fenil)acetamida

$C_{26}H_{23}FIN_5O_4$



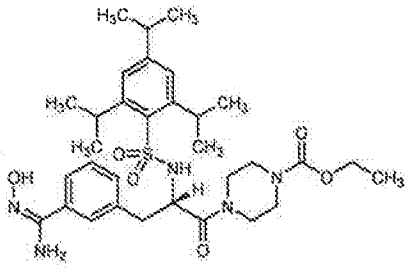
upamostatum

upamostat — ethyl 4-{(2*S*)-3-{3-[(*E*)- *N*'-hydroxycarbamimidoyl]phenyl}-2-[2,3,5-tri(propan-2-yl)benzenesulfonamido]propanoyl}piperazine-1-carboxylate

upamostat — 4-{(2*S*)-3-{3-[(*E*)- *N*'-hydroxycarbamimidoyl]phényl}-2-[2,3,5-tri(propan-2-yl)benzènesulfonamido]propanoyl}pipérazine-1-carboxylate d'éthyle

upamostat — 4-{(2*S*)-3-{3-[(*E*)- *N*'-hidroxicarbamimidoil]fenil}-2-[2,3,5-tri(propan-2-il)bencenosulfonamido]propanoil}piperazina-1-carboxilato de etilo

$C_{33}H_{47}N_5O_8S$



vatelizumabum #

vatelizumab — immunoglobulin G4-kappa, anti-[*Homo sapiens* ITGA2 (integrin alpha 2, CD49b, GPIa, subunit of the alpha2beta1 integrin (VLA-2, collagen receptor))], humanized monoclonal antibody; gamma4 heavy chain (1-446) [humanized VH (*Homo sapiens* IGHV4-59*01 (79.40%) -(IGHD)-IGHJ6*01) [8.7.13] (1-119) -*Homo sapiens* IGHG4*01 (120-446)], (133-213')-disulfide with kappa light chain (1'-213') [humanized V-KAPPA (*Homo sapiens* IGKV6D-41*01 (77.90%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; (225-225":228-228")-bisdisulfide dimer

vatélizumab — immunoglobuline G4-kappa, anti-[*Homo sapiens* ITGA2 (intégrine alpha 2, CD49b, GPIa, sous-unité de l'intégrine alpha2bêta1 (VLA-2, récepteur du collagène))], anticorps monoclonal humanisé; chaîne lourde gamma4 (1-446) [VH humanisé (*Homo sapiens* IGHV4-59*01 (79.40%) -(IGHD)-IGHJ6*01) [8.7.13] (1-119) -*Homo sapiens* IGHG4*01 (120-446)], (133-213')-disulfure avec la chaîne légère kappa (1'-213') [V-KAPPA humanisé (*Homo sapiens* IGKV6D-41*01 (77.90%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; dimère (225-225":228-228")-bisdisulfure

vatelizumab — inmunoglobulina G4-kappa, anti-[*Homo sapiens* ITGA2 (integrina alfa 2, CD49b, GPIa, subunidad de la integrina alfa2beta1 (VLA-2, receptor del colageno))], anticuerpo monoclonal humanizado; cadena pesada gamma4 (1-446) [VH humanizada (*Homo sapiens* IGHV4-59*01 (79.40%) -(IGHD)-IGHJ6*01) [8.7.13] (1-119) -*Homo sapiens* IGHG4*01 (120-446)], (133-213')-disulfuro con la cadena ligera kappa (1'-213') [V-KAPPA humanizada (*Homo sapiens* IGKV6D-41*01 (77.90%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; dímero (225-225":228-228")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQESGPG LVKPSETLSL TCTVSGFSLT NYGIHWIRQP PGKGLEWLGV  50
IWARGFTNYN SALMSRLTIS KDNSKNQVSL KLSSVTAADT AVYYCARAND 100
GVYYAMDYWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY 200
TCNVDHKPSN TKVDKRVESK YGPPCPSCPA PEFLGGPSVF LFPPKPKDTL 250
MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL 350
PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 400
GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLGK     446
```

Light chain / Chaîne légère / Cadena ligera

```
DFVMTQSPAS LSVTPGEKVT ITCSASQSVN YIHWYQQKPD QAPKKLIYDT  50
SKLASGVPSR FSGSGSGTDY TFTISSLEAE DAATYYCQQW TTNPLTFGQG 100
TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD 150
NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL 200
SSPVTKSFNR GEC                                         213
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
Intra-H  22-95    146-202   260-320   366-424
         22''-95''  146''-202''  260''-320''  366''-424''
Intra-L  23'-87'    133'-193'
         23'''-87'''  133'''-193'''
Inter-H-L  133-213'  133''-213'''
Inter-H-H  225-225''  228-228''
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

296, 296''

* *"INN for pharmaceutical substances: Names for radicals, groups & others"* document available at / document disponible à / documento disponible en :
http://www.who.int/medicines/services/inn/publication/en/index.html

Electronic structure available on Mednet: http://mednet.who.int/
Structure électronique disponible sur Mednet: http://mednet.who.int/
Estructura electrónica disponible en Mednet: http://mednet.who.int/

AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Recommended International Non Proprietary Names (Rec. INN): List 6
(Chronicle of the WHO, December 1959, Vol. 13, No. 12)

p. 468 **mecamylaminum**
mecamylamine *replace the chemical name by the following*

(1*RS*,2*SR*,4*SR*)-*N*,2,3,3-tetramethylbicyclo[2.2.1]heptan-2-amine

Denominations communes internationales recommandées (DCI Rec.): Liste 6
(Chronique de l'OMS, Vol. 13, No. 12, décembre 1959)

p. 488 **mecamylaminum**
mécamylamine *remplacer le nom chimique par le suivant*

(1*RS*,2*SR*,4*SR*)-*N*,2,3,3-tétraméthylbicyclo[2.2.1]heptan-2-amine

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 6
(Crónica de la OMS, Vol. 13, No. 12, diciembre de 1959)

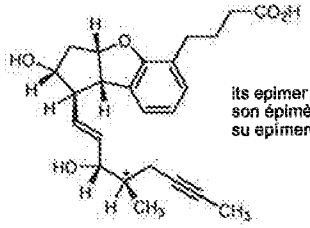
p. 501 **mecamylaminum**
mecamilamina *sustitúyase el nombre químico por el siguiente*

(1*RS*,2*SR*,4*SR*)-*N*,2,3,3-tetrametilbiciclo[2.2.1]heptan-2-amina

Recommended International Non Proprietary Names (Rec. INN): List 31
(WHO Drug Information, Vol. 5, No. 3, 1991)

p. 17 **beraprostum**
beraprost *replace the chemical name and the structure by the following ones*

rac-4-{(1*R*,2*R*,3a*S*,8b*S*)-2-hydroxy-1-[(1*E*,3*S*,4*RS*)-3-hydroxy-4-methyloct-1-en-6-ynyl]-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*][1]benzofuran-5-yl}butanoic acid



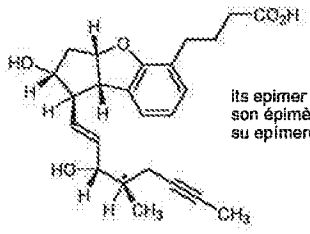
its epimer at C* and their enantiomers
son épimère en C* et leurs énantiomères
su epímero al C* y sus enantiómeros

Denominations communes internationales recommandées (DCI Rec.): Liste 31
(Informations pharmaceutiques OMS, Vol. 5, No. 3, 1991)

p. 18 **beraprostum**
béraprost

remplacer le nom chimique et la structure par les suivants

acide *rac*-4-{(1*R*,2*R*,3a*S*,8b*S*)-2-hydroxy-1-[(1*E*,3*S*,4*RS*)-3-hydroxy-4-méthyloct-1-én-6-ynyl]-2,3,3a,8b-tétrahydro-1*H*-cyclopenta[*b*][1]benzofuran-5-yl}butanoïque



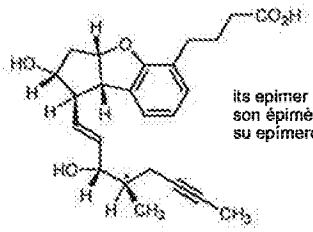
its epimer at C* and their enantiomers
son épimère en C* et leurs énantiomères
su epímero al C* y sus enantiómeros

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 31
(Información farmacéutica OMS, Vol. 5, No. 3, 1991)

p. 18 **beraprostum**
beraprost

sustitúyase el nombre químico y la estructura por los siguientes

ácido *rac*-4-{(1*R*,2*R*,3a*S*,8b*S*)-2-hidroxi-1-[(1*E*,3*S*,4*RS*)-3-hidroxi-4-metiloct-1-en-6-inil]-2,3,3a,8b-tetrahidro-1*H*-ciclopenta[*b*][1]benzofuran-5-il}butanoico



its epimer at C* and their enantiomers
son épimère en C* et leurs énantiomères
su epímero al C* y sus enantiómeros

Recommended International Non Proprietary Names (Rec. INN): List 62
Denominations communes internationales recommandées (DCI Rec.): Liste 62
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 62
(WHO Drug Information, Vol. 23, No. 3, 2009)

p. 250	*delete/supprimer/suprimáse*	*insert/insérer/insertese*
	ingenoli mebutatum	**ingenoli mebutas**

Recommended International Non Proprietary Names (Rec. INN): List 63
Denominations communes internationales recommandées (DCI Rec.): Liste 63
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 63
(WHO Drug Information, Vol. 24, No. 1, 2010)

p. 69 **olodaterolum**

olodaterol — *replace the chemical name by the following*
olodatérol — *remplacer le nom chimique par le suivant*
olodaterol — *sustitúyase el nombre químico por el siguiente*

6-hydroxy-8-[(1*R*)-1-hydroxy-2-{[1-(4-methoxyphenyl)-2-methylpropan-2-yl]amino}ethyl]-2*H*-1,4-benzoxazin-3(4*H*)-one

6-hydroxy-8-[(1*R*)-1-hydroxy-2-{[1-(4-méthoxyphényl)-2-méthylpropan-2-yl]amino}éthyl]-2*H*-1,4-benzoxazin-3(4*H*)-one

6-hidroxi-8-[(1*R*)-1-hidroxi-2-{[1-(4-metoxifenil)-2-metilpropan-2-il]amino}etil]-2*H*-1,4-benzoxazin-3(4*H*)-ona

Recommended International Non Proprietary Names (Rec. INN): List 64
Denominations communes internationales recommandées (DCI Rec.): Liste 64
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 64
(WHO Drug Information, Vol. 24, No. 3, 2010)

p. 264 **condoliasum #**

condoliase — *replace the structure by the following*
condoliase — *remplacer la structure par la suivante*
condoliasa — *sustitúyase la estructura por la siguiente*

```
ATGNPASDPK NLMQGEIYHF AQNNPLADES SDKNSILTLS OKRSIMGNQS 50
LLWKWKGGSS FTLHKKLIVP TDKEASKAWG RSSTPVFSFN LYNEKPIDGY 100
LTIDPGEKLI STSEAQAGFK VKLDFTGWFA VGVSLNNDLE NRFMTLNATN 150
TSSDGTQDSI GRSLGAKVDS IRFKAPSNVS QGEIYIGRIM FSVDDARYQW 200
SDYQVKTRLS EPEIQFHNVK PQLPVTPENL AAIDLIPQRL INEFVGGEKE 250
TNLALEENIS KLKSDPDALN IHTLANGGTQ GRHLITDKQI IIYQPENLNG 300
QDKQLFDNYV ILGNYTTLMF NISRAYVLEK DPTQKAQLKQ MYLLMTKHLL 350
DQGFVKGSAL YTTHNWGYSS RWWIISPLLM SDALKEANLQ TQVYDSLLWY 400
SREFRGSFDM EVSADSSDLD YFNTLSRQHL ALLLLEPDDQ KRINLVNTFS 450
HYITGALTQV PPGGKDGLRP DGTAWPHEGN YPGYSFFAFK NASQLIYLLR 500
DTPFSVGEGG WNNLNKAMVS AWIYSNFEVG LPLAGRHFEN SPSLKSVAQG 550
YYWLAMSAKS SPDKTLASIY LAISQKTQNE STAIFGETIT PASLPQGFYA 600
FNGGAFGIHR WQDKMVTLKA YNTNVWSSEL YNKDNRYGFY QSHGVAQIVS 650
NGSQLSQGYQ QEGWDWGRMQ GATTIHLPLK DLGSPKPHTL MQRGEEGFSG 700
TSSLEQQYGM MAFDLIYFAN LEPFDFNFTA KKSVLAAQNH LIFIGSNING 750
SDKNKNVETT LFQHAITPTL NTLWINGQKI ENMPYQFTLQ QGDWLIDSNG 800
NGYLITQAEK VNVSRQHQVS AENKNRQFTE GNFSSAWIDH STRFKDAYE 850
YMVFLDATPS KMGEMAQKFR ENNGLYQVLR KDKDVRILLD KLSNVTGYAF 900
YQPASISDKW IKKVNKFAIV MTNKQNDFLI VSAVTFDLNM TRQMAATPVT 950
INVFINGKWQ SADKNSEVKY QVSGDNTELT STSYPGIPQE IKLSPLP 997
```

Procedure and Guiding Principles / Procédure et Directives / Procedimientos y principios generales

The text of the *Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances* and *General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances* will be reproduced in proposed INN lists only.

Les textes de la *Procédure à suivre en vue du choix de dénominations communes internationales recommandées pour les substances pharmaceutiques* et des *Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques* seront publiés seulement dans les listes des DCI proposées.

El texto de los *Procedimientos de selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas* y de los *Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas* aparece solamente en las listas de DCI propuestas.

Exhibit G

SEQ ID NO: FROM U.S. Patent No. 7,767,206	Integrity Product Report for CAS registry 1174395-19-17
SEQ ID NO:14 (Heavy chain variable Region) QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYGISWVRQAPG QGLEWMGWISTYSGNTNYAQKLQGRVTMTTDTSTSTAYME LRSLRSDDTAVYYCARRQLYFDYWGQGTLVTVSS	**QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYGISWVR QAPGQGLEWMGWISTYSGNTNYAQKLQGRVTMTTDT STSTAYMELRSLRSDDTAVYYCARRQLYFDYWGQGTLV TVSS**ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGT QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNG KEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP MLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK
SEQ ID:40 (Light chain variable Region) EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWFQQKPGQ APRPLIYDASTRATGVPARFSGSGSGTDFTLTISSLQSEDFAVYY CQQYDNWPLTFGGGTKVEIK	**EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWFQQ KPGQAPRPLIYDASTRATGVPARFSGSGSGTDFTLTISSL QSEDFAVYYCQQYDNWPLTFGGGTKVEIK**RTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC
SEQ ID NO: 146 (Heavy Chain CDR 1): RYGIS	QVQLVQSGAEVKKPGASVKVSCKASGYTFT**RYGIS**WVRQ APGQGLEWMGWISTYSGNTNYAQKLQGRVTMTTDTST STAYMELRSLRSDDTAVYYCARRQLYFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGK EYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPM LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
SEQ ID NO:147 (Heavy Chain CDR 2): WISTYSGNTNYAQKLQG	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYGISWVRQ APGQGLEWMG**WISTYSGNTNYAQKLQG**RVTMTTDTST STAYMELRSLRSDDTAVYYCARRQLYFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGK EYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPM LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH

	YTQKSLSLSPGK
SEQ ID NO:148 (Heavy Chain CDR 3): RQLYFDY	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYGISWVRQ APGQGLEWMGWISTYSGNTNYAQKLQGRVTMTTDTST STAYMELRSLRSDDTAVYYCAR**RQLYFDY**WGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGK EYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPM LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
SEQ ID NO: 224 (Light Chain CDR 1): RASQSVSSNLA	EIVMTQSPATLSVSPGERATLSC**RASQSVSSNLA**WFQQK PGQAPRPLIYDASTRATGVPARFSGSGSGTDFTLTISSLQS EDFAVYYCQQYDNWPLTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC
SEQ ID NO: 225 (Light Chain CDR 2): DASTRAT	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWFQQKP GQAPRPLIY**DASTRAT**GVPARFSGSGSGTDFTLTISSLQSE DFAVYYCQQYDNWPLTFGGGTKVEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC
SEQ ID NO:226 (Light Chain CDR 3): QQYDNWPLT	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWFQQKP GQAPRPLIYDASTRATGVPARFSGSGSGTDFTLTISSLQSE DFAVYYC**QQYDNWPLT**FGGGTKVEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC

Brodalumab Heavy Chain (HC)

Full-Length HC Amino Acid Sequence (Integrity Product Report from CAS registry 1174395-19-17)

*QVQLVQSGAEVKKPGASVKVSCKASGYTFT**RYGIS**WVRQAPGQGLEWMG**WISTYSGNTNYAQKLQG**RVTMTTDTS*
*TSTAYMELRSLRSDDTAVYYCAR**RQLYFDY**WGQGTLVTVSS*ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNG
KEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
MLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Brodalumab Heavy Chain Amino Sequences Disclosed/Claimed in U.S. Patent No. 7,767,206:

SEQ ID NO: 14 HC variable domain (in italics)

SEQ ID NO: 146 HC CDR1 - **RYGIS**

SEQ ID NO: 147 HC CDR2 - **WISTYSGNTNYAQKLQG**

SEQ ID NO: 148 HC CDR3 - **RQLYFDY**

Brodalumab Light Chain (LC)

Full-Length LC Amino Acid Sequence (Integrity Product Report from CAS registry 1174395-19-17)

*EIVMTQSPATLSVSPGERATLSC**RASQSVSSNLA**WFQQKPGQAPRPLIY**DASTRAT**GVPARFSGSGSGTDFTLTISSLQS*
*EDFAVYYC**QQYDNWPLT**FGGGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Brodalumab Light Chain Amino Sequences Disclosed/Claimed in U.S. Patent No. 7,767,206:

SEQ ID NO: 40 LC variable domain (in italics)

SEQ ID NO: 224 LC CDR1 - **RASQSVSSNLA**

SEQ ID NO: 225 LC CDR2 - **DASTRAT**

SEQ ID NO: 226 LC CDR3 - **QQYDNWPLT**

Exhibit I

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104,671

IND ACKNOWLEDGEMENT

AMGEN
Attention: Shannon Shoup
Senior Manager
Regulatory Affairs
One Amgen Center Dr.
Thousand Oaks, CA 91320

Dear Ms. Shoup:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA). Please note the following identifying data:

IND NUMBER ASSIGNED: 104,671

SPONSOR: AMGEN

PRODUCT NAME(S): AMG 827 (Monoclonal Antibody Antagonist to Human IL-17R)

DATE OF SUBMISSION: August 27, 2009

DATE OF RECEIPT: August 27, 2009

You may not initiate studies in humans until 30 days after the date of receipt shown above unless we notify you sooner that you may proceed. If, on or before September 25, 2009, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will immediately notify you verbally or in writing that (1) clinical studies may not be initiated under this IND ("clinical hold") or (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). If we place your human studies on clinical hold, you will be notified in writing of the reasons and the information necessary to correct the deficiencies. In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have subsequently notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experiences associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk, in writing to this Division and to all investigators within 15 calendar days after initial receipt of this information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33]. You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) (42 USC §§ 282 (i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Prior to use of each new lot of the investigational biologic in clinical studies, submit the lot number, the results of all tests performed on the lot, and the specifications when established (i.e., the range of acceptable results).

We remind you that you may not charge for this investigational drug without prior written approval of FDA.

All laboratory or animal studies intended to support the safety of this product should be conducted in compliance with the regulations for "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 CFR Part 58). If such studies have not been conducted in compliance with these regulations, provide a statement describing in detail all differences between the practices used and those required in the regulations.

Item 7a of form FDA 1571 requests that either an "environmental assessment," or a "claim for categorical exclusion" from the requirements for environmental assessment, be included in the IND. If you did not include a response to this item with your application, please submit one. Information on environmental assessments is available in the guidance *Environmental Assessment of Human Drugs and Biologics*. This document is available at http://www.fda.gov/cder/guidance/1730fnl.pdf.

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please include three originals of all illustrations that do not reproduce well. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call Jeannine M. Helm, at (301) 796-0637.

Sincerely,

[See appended electronic signature page]

Jeannine M. Helm
Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-104671	ORIG-1	AMGEN INC	AMG 827

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEANNINE M HELM
09/04/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761032

BLA ACKNOWLEDGMENT

AstraZeneca UK Ltd.
c/o AstraZeneca Pharmaceuticals LP
Attention: Ian Hunt
CV/GI Therapy Area Vice President
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Hunt:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: brodalumab injection

Date of Application: November 16, 2015

Date of Receipt: November 16, 2015

Our Reference Number: BLA 761032

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 15, 2016, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. Additional information is available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Strother D. Dixon
Senior Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
11/25/2015

Exhibit K

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761032

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

AstraZeneca UK Ltd
c/o AstraZeneca Pharmaceuticals LP
Attention: Mary Whealy
Senior Director Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Whealy:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2015, submitted under section 351(a) of the Public Health Service Act for brodalumab injection, 210 mg.

We also refer to your amendments dated December 15, 23 (3), 2015 and January 8, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 16, 2016. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 20, 2016.
In addition, the planned date for our internal mid-cycle review meeting is April 6, 2016.

We request that you submit the following information by February 4, 2016:

Center for Devices and Radiological Health/Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices

You have provided data for the device constituent review of the 2.25 mL prefilled syringe with staked needle presentation.

1. Provide biocompatibility data for tissue communicating/limited contact for the needle component.
2. Provide biocompatibility data for skin contacting/limited for the glass syringe barrel, plunger rod, needle shield. The information may be available from the device component manufacturer.
3. If you intend to market an auto-injector, submit all relevant information. No information about an auto-injector was submitted with this application.

Division of Risk Evaluation

Your submitted Risk Evaluation and Mitigation Strategy (REMS) only includes a REMS document which refers to the following:

- Medication Guide
- Communication Plan (CP)
- Timetable for Submission of Assessments

You also indicate in your submission "specific elements to be included in the CP will be agreed upon with Agency during review." However, a complete proposed REMS submission should include a REMS document, all appended materials to be included as part of the REMS (e.g., proposed communication and educational materials), and a REMS supporting document.

Therefore, provide the following, within 10 business days:

1. A complete REMS document, including specific elements in your proposed CP;
2. All appended materials referred to in your REMS document (e.g., proposed communication and education materials and forms, including REMS Letters for Healthcare Providers, REMS Letters for Professional Societies, and REMS Program Website screenshots, etc.); and
3. A REMS Supporting Document.

For further clarification on the format and contents of a proposed REMS, see guidance for industry *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications* as well as a recently approved REMS found on the REMS@FDA website.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and Instructions for Use. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and Instructions for Use, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
01/21/2016

Exhibit L

PTO/SB/81A (12-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	7,767,206
Issue Date	08-03-2010
First Named Inventor	Joel Tocker
Title	NEUTRALIZING DETERMINANTS OF IL-17 RECEPTOR A AND ANTIBODIES THAT BIND THERETO
Attorney Docket Number	A-1116-US-NP4

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 1131

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Inventor or Patent Owner

Signature	/Stuart L. Watt/	Date	April 11, 2017
Name	Stuart L. Watt	Telephone	805-447-1000
Title and Company	Authorized Signatory, Kirin-Amgen, Inc.		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: KIRIN-AMGEN, INC.

Application No./Patent No.: 7767206 Filed/Issue Date: 08/03/2010

Titled:
NEUTRALIZING DETERMINANTS OF IL-17 RECEPTOR A AND ANTIBODIES THAT BIND THERETO

KIRIN-AMGEN, INC. , a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: TOCKER, JOEL; MEHLIN, CHRISTOPHER; To: AMGEN INC.

The document was recorded in the United States Patent and Trademark Office at
Reel 020799, Frame 0697, or for which a copy thereof is attached.

2. From: AMGEN INC. To: KIRIN-AMGEN, INC.

The document was recorded in the United States Patent and Trademark Office at
Reel 030045, Frame 0876, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Stuart L. Watt/ April 11, 2017
Signature Date

Stuart L. Watt Authorized Signatory
Printed or Typed Name Title

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Exhibit M

AMGEN
Stuart Watt
Vice President
Intellectual Property and Litigation

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Direct Dial: 805.447.7926
Fax: 805.447.2154
E-mail: swatt@amgen.com

CONFIDENTIAL

April 6, 2017

Commissioner of Patents
U.S. Patent and Trademark Office
600 Dulany Street (Madison Building)
Alexandra, VA 22314

Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re.: Patent Term Extension – SILIQ™ (brodalumab)
Investigational New Drug No. 104671

Dear Commissioners:

Amgen, Inc. (Amgen) hereby authorizes Amgen-Kirin, Inc. to rely upon the activities of Amgen before the U.S. Food and Drug Administration during the regulatory review period for brodalumab in making its application for extension of patent terms of U.S. Patent Nos. 7,767,206, 7,939,070, 8,435,518 and 8,545,842. Kirin-Amgen, Inc. is the assignee of the entire right, title and interest in U.S. Patent Nos. 7,767,206, 7,939,070, 8,435,518 and 8,545,842. Amgen further grants the Commissioner for Patents and the Secretary for Health and Human Services and Commissioner of Food and Drugs the right to refer to the above-referenced Investigational New Drug application (IND), which was used in the approval for Biologic License Application (BLA) No. 761032, in determining the eligibility of Amgen-Kirin for such extension.

Amgen began the clinical investigation of brodalumab under IND No.104671. Amgen transferred ownership of IND 104671 to AstraZeneca UK Ltd. (AstraZeneca) on August 12, 2015. Subsequently, AstraZeneca became the marketing authorization applicant for SILIQ™ (brodalumab) under Biologic License Application No. 761032, which was first submitted on

November 16, 2015. Thereafter, AstraZeneca transferred the Biologics License Application for SILIQ™ (brodalumab) to Valeant Pharmaceuticals Luxembourg S.a.r.l (VPL) (Valeant). Valeant is the current holder of Biologic License Application No. 761032 for SILIQ™ (brodalumab), which was approved by FDA on February 15, 2017.

Sincerely,

AMGEN INC.

By: Stuart L. Watt

Name: Stuart L. Watt

Title: Vice President, Law and Intellectual Property Officer

Date: April 6, 2017

Thereafter, AstraZeneca transferred the BLA for SILIQ™ (brodalumab) to Valeant Pharmaceuticals Luxembourg S.a.r.l (VPL) (Valeant). Valeant is the current holder of BLA Application No. 761032 for Siliq™ (brodalumab), which was approved by FDA on February 15, 2017.

Sincerely,

ASTRAZENECA UK LTD.

By: _____

Name: GREG MUELLER

Title: DGC, International

Date: 27.03.17

AstraZeneca UK Limited
1 Francis Crick Avenue
Cambridge Biomedical Campus
Cambridge, CB2 0AA
United Kingdom
T: +44 (0) 20 3749 5000

astrazeneca.com

CONFIDENTIAL

March 24, 2017

Commissioner of Patents
U.S. Patent and Trademark Office
600 Dulany Street (Madison Building)
Alexandra, VA 22314

Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Patent Term Extension – SILIQ™ (brodalumab)
Biologic License Application No. 761032

Dear Commissioners:

AstraZeneca UK Ltd. (AstraZeneca) hereby authorizes Amgen-Kirin, Inc. to rely upon the activities of AstraZeneca before the U.S. Food and Drug Administration during the regulatory review period for brodalumab in making its application for extension of patent terms of U.S. Patent Nos. 7,767,206, 7,939,070, 8,435,518 and 8,545,842. Kirin-Amgen, Inc. is the assignee of the entire right, title and interest in U.S. Patent Nos. 7,767,206, 7,939,070, 8,435,518 and 8,545,842. AstraZeneca further grants the Commissioner for Patents and the Secretary for Health and Human Services and Commissioner of Food and Drugs the right to refer to the above-approved Biologic License Application (BLA) in determining the eligibility of Amgen-Kirin for such extension.

AstraZeneca was the original marketing authorization applicant for SILIQ™ (brodalumab) under BLA No. 761032, which was first submitted on November 16, 2015.

AstraZeneca UK Limited is a subsidiary of AstraZeneca PLC
Registered in England No. 3674842
Registered office: 1 Francis Crick Avenue
Cambridge Biomedical Campus
Cambridge, CB2 0AA
United Kingdom

VALEANT
Pharmaceuticals Luxembourg S.a.r.l.

CONFIDENTIAL

March 27, 2017

Commissioner of Patents
U.S. Patent and Trademark Office
600 Dulany Street (Madison Building)
Alexandra, VA 22314

Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re.: Patent Term Extension – SILIQ™ (brodalumab)
Biologic License Application No. 761032

Dear Commissioners:

Valeant Pharmaceuticals Luxembourg S.a.r.l. (Valeant) hereby authorizes Amgen-Kirin, Inc. to rely upon the activities of Valeant before the U.S. Food and Drug Administration during the regulatory review period for brodalumab in making its application for extension of patent terms of U.S. Patent Nos. 7,767,206, 7,939,070, 8,435,518 and 8,545,842. Kirin-Amgen, Inc. is the assignee of the entire right, title and interest in U.S. Patent Nos. 7,767,206, 7,939,070, 8,435,518 and 8,545,842. Valeant further grants the Commissioner for Patents and the Secretary for Health and Human Services and Commissioner of Food and Drugs the right to refer to the above-approved Biologic License Application (BLA) in determining the eligibility of Amgen-Kirin for such extension.

AstraZeneca UK Ltd. was the original marketing authorization applicant for SILIQ™ (brodalumab) under BLA No. 761032, which was first submitted on November 16, 2015. Thereafter, AstraZeneca transferred the BLA for SILIQ™ (brodalumab) to Valeant. Valeant is the current holder of BLA No. 761032 for Siliq™ (brodalumab), which was approved by FDA on February 15, 2017.

Sincerely,

VALEANT PHARMACEUTICALS LUXEMBOURG S.A.R.L.

By: _____

Name: Michael Kennan

Title: A Manager

Date: Mar 27, 2017

By: _____

Name: Franck Deconinck

Title: B Manager

Date: March 27, 2017

Exhibit N

IND Period

Sequence	Date	Document
0000	8/27/09	Original Application
0001	9/11/09	Amendment - New Investigator
0002	9/23/09	Response to Questions
0003	9/28/09	Meeting Minutes
0005	11/11/09	Periodic Safety Reporting
0004	11/24/09	Protocol Amendment and New Protocol
0006	12/10/09	Amendment - New Investigator
0007	1/8/10	Amendment - New Investigator
0008	1/14/10	Official Representative Change
0009	1/14/10	Adverse Event Report
0010	1/20/10	Adverse Event Report
0011	1/22/10	Non-Clinical Study Report
0012	1/25/10	Adverse Event Report
0013	2/2/10	Adverse Event Report
0014	2/4/10	Amendment - New Investigator
0015	2/5/10	Quarterly Safety Update Report
0016	2/12/10	Adverse Event Report
0018	3/2/10	Adverse Event Report
0017	3/4/10	Amendment - New Investigator
0019	3/9/10	Adverse Event Report
0020	3/25/10	Protocol Amendments
0021	4/2/10	Protocol Amendments
0022	4/29/10	Protocol Amendments
0023	5/6/10	Quarterly Safety Update Report
0024	5/14/10	Investigator Brochure
0026	5/27/10	Protocol Amendments
0027	5/27/10	Adverse Event Report
0025	6/10/10	Response to Questions
0028	6/24/10	Protocol Amendments
0029	7/21/10	Protocol Amendments
0031	8/12/10	Quarterly Safety Update Report
0030	8/18/10	Annual Report
0032	8/20/10	Protocol Amendments
0033	9/16/10	Protocol Amendments
0034	9/21/10	Clinical Study Report
0035	9/28/10	Meeting Request

Sequence	Date	Document
0036	9/30/10	Adverse Event Report
0037	10/7/10	Adverse Event Report
0038	10/14/10	Protocol Amendments
0039	10/25/10	Adverse Event Report
0041	10/28/10	Adverse Event Report
0042	11/8/10	Quarterly Safety Update Report
0040	11/16/10	Briefing Document
0043	11/17/10	Adverse Event Report
0044	11/22/10	CMC Meeting Request
0045	11/23/10	Adverse Event Report
0046	12/9/10	Protocol Amendments
0048	1/13/11	Official Representative Change
0047	1/30/11	Briefing Document
0049	2/4/11	Adverse Event Report
0050	2/9/11	Quarterly Safety Update Report
0052	2/10/11	Protocol Amendments
0051	2/11/11	Official Representative Change
0053	2/17/11	Adverse Event Report
0054	3/1/11	Meeting Request
0055	3/3/11	Protocol Amendments
0056	3/25/11	Meeting Request
0056	3/25/11	Meeting Request
0058	4/18/11	Adverse Event Report
0059	5/6/11	Briefing Document
0061	5/11/11	Meeting Minutes
0060	5/12/11	Quarterly Safety Update Report
0062	5/13/11	Investigator Brochure
0063	5/20/11	Adverse Event Report
0057	5/27/11	Meeting Request
0064	6/17/11	Clinical Study Report
0065	6/17/11	Non-Clinical Study Report
0066	6/21/11	Amendment - New Investigator
0067	6/22/11	Clinical Study Report
0068	6/30/11	Annual Report
0070	7/1/11	Meeting Request
0072	8/10/11	Adverse Event Report
0071	8/11/11	Quarterly Safety Update Report
0073	9/16/11	Protocol Amendments
0074	9/20/11	Amendment
0076	9/29/11	Adverse Event Report

Sequence	Date	Document
0075	9/30/11	New Protocols
0077	10/14/11	Protocol Amendments
0078	11/1/11	Investigator Brochure
0079	11/10/11	Quarterly Safety Update Report
0080	11/10/11	Adverse Event Report
0081	11/30/11	Adverse Event Report
0082	12/7/11	Protocol Amendments
0083	12/9/11	Adverse Event Report
0084	12/29/11	Adverse Event Report
0085	1/11/12	Adverse Event Report
0086	1/25/12	Protocol Amendments
0087	2/2/12	Investigator Documents
0088	2/14/12	Quarterly Safety Update Report Amendment
0089	3/8/12	Protocol Amendments
0090	3/29/12	Investigator Documents
0093	4/4/12	Adverse Event Report
0091	4/6/12	Response to Questions
0094	4/13/12	CMC Correspondence
0095	5/8/12	Quarterly Safety Update Report Amendment
0096	5/30/12	Protocol Amendments
0097	5/31/12	Non-Clinical Study Report
0098	6/22/12	Official Representative Change
0100	7/19/12	Investigator Documents
0099	7/20/12	Protocol Amendments
0092	7/26/12	Official Representative Change
0101	8/3/12	Investigator Brochure
0103	8/3/12	Protocol Amendments
0106	8/14/12	Quarterly Safety Update Report Amendment
0105	8/15/12	Investigator Documents
0102	8/20/12	Annual Report
0107	9/6/12	Adverse Event Report
0108	9/13/12	Investigator Documents
0109	9/27/12	Adverse Event Report
0104	10/8/12	Meeting Request
0069	10/12/12	Briefing Document
0110	10/12/12	Investigator Documents
0111	10/12/12	Adverse Event Report
0112	10/17/12	Official Representative Change
0113	10/24/12	Adverse Event Report
0114	11/8/12	Official Representative Change

Sequence	Date	Document
0116	11/9/12	Investigator Documents
0115	11/13/12	Quarterly Safety Update Report
0117	11/14/12	Adverse Event Report
0118	12/7/12	Briefing Document
0119	12/7/12	Investigator Documents
0120	12/14/12	Adverse Event Report
0121	12/18/12	Adverse Event Report
0123	12/21/12	Response to Questions
0124	12/26/12	Adverse Event Report
0122	1/4/13	Investigator Documents
0125	1/11/13	Investigator Brochure
0127	1/17/13	Adverse Event Report
0126	1/24/13	Protocol Amendments
0129	1/31/13	Adverse Event Report
0128	2/1/13	Investigator Documents
0130	2/5/13	Meeting Minutes
0131	2/6/13	Quarterly Safety Update Report Amendment
0132	2/18/13	Adverse Event Report
0134	2/22/13	New Protocols
0135	2/28/13	Adverse Event Report
0133	3/1/13	Investigator Documents
0136	3/4/13	Adverse Event Report
0137	3/11/13	Protocol Amendments
0139	3/25/13	Adverse Event Report
0141	3/28/13	Adverse Event Report
0138	3/29/13	Investigator Documents
0142	4/2/13	Adverse Event Report
0140	4/9/13	Protocol Amendments
0143	4/12/13	Adverse Event Report
0145	4/19/13	Adverse Event Report
0144	4/26/13	Investigator Documents
0147	5/1/13	Adverse Event Report
0148	5/13/13	Adverse Event Report
0149	5/14/13	Adverse Event Report
0152	5/16/13	Adverse Event Report
0146	5/21/13	Quarterly Safety Update Report Amendment
0150	5/24/13	Investigator Documents
0153	5/24/13	Adverse Event Report
0151	5/28/13	New Protocols
0154	5/30/13	Adverse Event Report

Sequence	Date	Document
0155	6/6/13	Adverse Event Report
0157	6/13/13	Adverse Event Report
0158	6/18/13	Adverse Event Report
0156	6/21/13	Investigator Documents
0159	6/21/13	Adverse Event Report
0160	6/24/13	Adverse Event Report
0161	6/28/13	Adverse Event Report
0162	7/2/13	Adverse Event Report
0163	7/3/13	Adverse Event Report
0164	7/9/13	Adverse Event Report
0166	7/15/13	Adverse Event Report
0165	7/19/13	Investigator Documents
0168	7/23/13	Adverse Event Report
0169	7/25/13	Adverse Event Report
0167	7/31/13	Adverse Event Report
0173	8/2/13	Adverse Event Report
0171	8/5/13	Response to Questions
0172	8/7/13	Non-Clinical Study Report
0174	8/7/13	Adverse Event Report
0170	8/8/13	Response to Questions
0177	8/12/13	Adverse Event Report
0178	8/14/13	Adverse Event Report
0176	8/16/13	Investigator Documents
0179	8/21/13	Adverse Event Report
0175	8/22/13	Annual Report
0181	8/26/13	Adverse Event Report
0182	9/3/13	Adverse Event Report
0183	9/4/13	Adverse Event Report
0185	9/9/13	Adverse Event Report
0184	9/13/13	Investigator Documents
0186	9/16/13	Adverse Event Report
0187	9/18/13	Adverse Event Report
0188	9/26/13	Adverse Event Report
0180	10/1/13	Protocol Amendments
0189	10/1/13	Adverse Event Report
0191	10/8/13	Adverse Event Report
0190	10/11/13	Investigator Documents
0193	10/11/13	Adverse Event Report
0192	10/18/13	Investigator Brochure
0194	10/23/13	Adverse Event Report

Sequence	Date	Document
0195	10/28/13	Adverse Event Report
0197	11/4/13	Adverse Event Report
0198	11/5/13	Adverse Event Report
0196	11/11/13	Investigator Documents
0199	11/11/13	Adverse Event Report
0200	11/14/13	Adverse Event Report
0202	11/21/13	Adverse Event Report
0201	11/25/13	Protocol Amendments
0203	11/27/13	Development Safety Update Reports
0204	11/27/13	Adverse Event Report
0207	12/5/13	Adverse Event Report
0205	12/6/13	Investigator Documents
0208	12/11/13	Adverse Event Report
0211	12/17/13	Adverse Event Report
0212	12/19/13	Adverse Event Report
0209	12/20/13	Adverse Event Report
0213	12/23/13	Adverse Event Report
0214	12/30/13	Adverse Event Report
0215	1/2/14	Adverse Event Report
0206	1/8/14	New Protocols and Protocol Amendments
0216	1/9/14	Adverse Event Report
0210	1/10/14	Protocol Amendments
0217	1/15/14	Adverse Event Report
0219	1/22/14	Adverse Event Report
0220	1/29/14	Adverse Event Report
0221	2/3/14	Adverse Event Report
0218	2/4/14	Investigator Documents
0223	2/5/14	Adverse Event Report
0224	2/6/14	Adverse Event Report
0222	2/7/14	Safety Risk Communication
0225	2/10/14	Adverse Event Report
0226	2/11/14	Safety Risk Communication
0227	2/12/14	Adverse Event Report
0229	2/13/14	Adverse Event Report
0230	2/17/14	Adverse Event Report
0231	2/19/14	Adverse Event Report
0232	2/19/14	Adverse Event Report
0228	2/20/14	Clinical Study Report
0233	2/21/14	Adverse Event Report
0234	2/25/14	Adverse Event Report

Sequence	Date	Document
0235	2/27/14	Adverse Event Report
0237	3/4/14	Adverse Event Report
0238	3/6/14	Adverse Event Report
0241	3/10/14	Adverse Event Report
0242	3/11/14	Adverse Event Report
0243	3/12/14	Adverse Event Report
0244	3/17/14	Adverse Event Report
0245	3/19/14	Adverse Event Report
0239	3/20/14	Investigator Brochure
0236	3/21/14	Cross Reference
0246	3/24/14	Adverse Event Report
0248	3/25/14	Adverse Event Report
0249	3/26/14	Safety Risk Communication
0250	3/27/14	Adverse Event Report
0240	3/28/14	Investigator Documents
0251	3/28/14	Response to Questions
0252	3/28/14	Adverse Event Report
0254	4/1/14	Adverse Event Report
0247	4/2/14	Adverse Event Report
0253	4/3/14	Protocol Amendments
0255	4/3/14	Adverse Event Report
0257	4/7/14	Adverse Event Report
0256	4/8/14	Response to Questions
0259	4/9/14	Adverse Event Report
0258	4/11/14	Response to Questions
0260	4/11/14	Adverse Event Report
0261	4/15/14	Adverse Event Report
0264	4/16/14	Adverse Event Report
0262	4/18/14	Protocol Amendments
0268	4/18/14	Adverse Event Report
0269	4/23/14	Adverse Event Report
0263	4/25/14	Investigator Documents
0270	4/28/14	Adverse Event Report
0271	4/30/14	Adverse Event Report
0273	5/2/14	Adverse Event Report
0274	5/5/14	Adverse Event Report
0265	5/6/14	Protocol Amendments
0267	5/7/14	New Protocols
0275	5/7/14	Adverse Event Report
0272	5/9/14	Meeting Request

Sequence	Date	Document
0279	5/12/14	Adverse Event Report
0280	5/13/14	Adverse Event Report
0276	5/15/14	Response to Questions
0281	5/15/14	Adverse Event Report
0277	5/16/14	Protocol Amendments
0282	5/19/14	Adverse Event Report
0283	5/21/14	Adverse Event Report
0278	5/22/14	Pre-BLA Activities
0266	5/23/14	Protocol Amendments
0284	5/23/14	Adverse Event Report
0285	5/28/14	Adverse Event Report
0286	6/2/14	Adverse Event Report
0287	6/4/14	Adverse Event Report
0288	6/6/14	Adverse Event Report
0290	6/11/14	Adverse Event Report
0291	6/13/14	Adverse Event Report
0289	6/20/14	Investigator Documents
0292	6/24/14	Monthly Safety Report
0294	6/25/14	Adverse Event Report
0293	6/27/14	Pediatric Study Plan
0298	7/2/14	Adverse Event Report
0299	7/8/14	Pediatric Study Plan
0300	7/8/14	Adverse Event Report
0295	7/10/14	Correspondence
0301	7/10/14	Adverse Event Report
0296	7/11/14	Clinical Data Submission
0302	7/14/14	Adverse Event Report
0304	7/18/14	Adverse Event Report
0305	7/22/14	Adverse Event Report
0306	7/24/14	Adverse Event Report
0303	7/28/14	Monthly Safety Report
0307	7/28/14	Adverse Event Report
0310	7/30/14	Adverse Event Report
0309	7/31/14	Meeting Request
0311	8/4/14	Adverse Event Report
0312	8/6/14	Adverse Event Report
0308	8/7/14	Pre-BLA Activities
0314	8/8/14	Adverse Event Report
0316	8/13/14	Adverse Event Report
0317	8/14/14	Adverse Event Report

Sequence	Date	Document
0313	8/15/14	Investigator Documents
0318	8/15/14	Adverse Event Report
0319	8/19/14	Adverse Event Report
0321	8/21/14	Adverse Event Report
0315	8/22/14	Amendment
0323	8/22/14	Adverse Event Report
0324	8/26/14	Adverse Event Report
0322	8/27/14	Monthly Safety Report
0320	8/29/14	Briefing Document
0326	8/29/14	Adverse Event Report
0327	9/2/14	Adverse Event Report
0329	9/3/14	Adverse Event Report
0330	9/8/14	Adverse Event Report
0328	9/12/14	Investigator Documents
0331	9/12/14	Adverse Event Report
0332	9/15/14	Adverse Event Report
0333	9/18/14	Adverse Event Report
0334	9/24/14	Adverse Event Report
0335	9/29/14	Adverse Event Report
0337	10/3/14	Monthly Safety Report
0338	10/3/14	Adverse Event Report
0339	10/7/14	Adverse Event Report
0336	10/10/14	Investigator Documents
0340	10/10/14	Pre-BLA Activities
0341	10/10/14	Adverse Event Report
0342	10/13/14	Adverse Event Report
0343	10/16/14	Official Representative Change
9000	10/16/14	Adverse Event Report
9001	10/20/14	Adverse Event Report
9002	10/24/14	Adverse Event Report
0345	10/27/14	Risk Assessment Report
0346	10/28/14	Monthly Safety Report
9003	10/29/14	Adverse Event Report
0344	10/30/14	Protocol Amendments
9004	11/6/14	Adverse Event Report
0347	11/7/14	Investigator Documents
0348	11/10/14	Meeting Request
9005	11/10/14	Adverse Event Report
9006	11/13/14	Adverse Event Report
0349	11/17/14	Protocol Amendments

Sequence	Date	Document
9007	11/18/14	Adverse Event Report
9008	11/20/14	Adverse Event Report
0350	11/24/14	Protocol Amendments
0351	11/25/14	Request for Proprietary Name Review
9009	11/25/14	Adverse Event Report
0352	11/26/14	Development Safety Update Reports
0353	12/1/14	Official Representative Change
0355	12/2/14	Briefing Document
9010	12/2/14	Adverse Event Report
0356	12/5/14	Investigator Documents
9011	12/8/14	Adverse Event Report
0354	12/10/14	Official Representative Change
9012	12/12/14	Adverse Event Report
0357	12/17/14	Pediatric Study Plan
0358	12/17/14	Monthly Safety Report
9013	12/18/14	Adverse Event Report
0359	12/19/14	Aggregate Safety Report
9014	12/22/14	Adverse Event Report
9015	12/23/14	Adverse Event Report
9016	12/26/14	Adverse Event Report
9017	12/29/14	Adverse Event Report
9018	1/2/15	Adverse Event Report
0360	1/16/15	New Protocols
0362	1/23/15	Monthly Safety Report
9019	1/23/15	Adverse Event Report
9020	1/26/15	Adverse Event Report
9021	1/27/15	Adverse Event Report
9022	1/29/15	Adverse Event Report
0361	1/30/15	Investigator Documents
0363	1/30/15	Meeting Request
9023	2/4/15	Adverse Event Report
0364	2/5/15	Monthly Safety Report
9024	2/5/15	Adverse Event Report
0365	2/6/15	Clinical Study Report
9025	2/6/15	Adverse Event Report
9026	2/13/15	Adverse Event Report
0367	2/17/15	Clinical Study Report
9027	2/17/15	Adverse Event Report
0368	2/19/15	Briefing Document
9028	2/19/15	Adverse Event Report

Sequence	Date	Document
9029	2/20/15	Adverse Event Report
9030	2/23/15	Adverse Event Report
9031	2/24/15	Adverse Event Report
0370	2/25/15	Clinical Study Report
9032	2/25/15	Adverse Event Report
0369	2/27/15	Investigator Documents
9033	2/27/15	Adverse Event Report
9034	3/3/15	Adverse Event Report
9035	3/5/15	Adverse Event Report
0366	3/6/15	Monthly Safety Report
9036	3/6/15	Adverse Event Report
9037	3/10/15	Adverse Event Report
9038	3/12/15	Adverse Event Report
9039	3/13/15	Adverse Event Report
9040	3/17/15	Adverse Event Report
9041	3/18/15	Adverse Event Report
9042	3/19/15	Adverse Event Report
0371	3/20/15	Protocol Amendments
9043	3/20/15	Adverse Event Report
9044	3/24/15	Adverse Event Report
9045	3/30/15	Adverse Event Report
0373	4/1/15	Response to Questions
9046	4/2/15	Adverse Event Report
9047	4/3/15	Adverse Event Report
9048	4/6/15	Adverse Event Report
0372	4/9/15	Monthly Safety Report
9049	4/9/15	Adverse Event Report
0375	4/10/15	Clinical Study Report
0376	4/10/15	Questions to FDA
9050	4/10/15	Adverse Event Report
9051	4/13/15	Adverse Event Report
0374	4/17/15	Meeting Minutes
9052	4/17/15	Adverse Event Report
9053	4/22/15	Adverse Event Report
9054	4/23/15	Adverse Event Report
0377	4/24/15	Investigator Documents
9055	4/24/15	Adverse Event Report
9056	4/29/15	Adverse Event Report
9057	5/4/15	Adverse Event Report
9058	5/5/15	Adverse Event Report

Sequence	Date	Document
9059	5/6/15	Adverse Event Report
9060	5/7/15	Adverse Event Report
0378	5/8/15	Clinical Study Report
9061	5/8/15	Adverse Event Report
9062	5/11/15	Adverse Event Report
9063	5/12/15	Adverse Event Report
9064	5/18/15	Adverse Event Report
9065	5/20/15	Adverse Event Report
0379	5/22/15	Monthly Safety Report
0380	5/22/15	Investigator Documents
9066	5/22/15	Adverse Event Report
9067	5/26/15	Adverse Event Report
9068	5/28/15	Adverse Event Report
9069	5/28/15	Adverse Event Report
0381	5/29/15	Clinical Trial Terminations
9070	6/1/15	Adverse Event Report
9071	6/2/15	Adverse Event Report
9072	6/4/15	Adverse Event Report
0382	6/5/15	Clinical Study Report
9073	6/5/15	Adverse Event Report
9074	6/8/15	Adverse Event Report
9075	6/11/15	Adverse Event Report
9076	6/12/15	Adverse Event Report
9077	6/15/15	Adverse Event Report
9078	6/17/15	Adverse Event Report
0385	6/18/15	Protocol Amendments
0384	6/19/15	Investigator Documents
0383	6/25/15	Monthly Safety Report
9079	6/25/15	Adverse Event Report
9080	6/26/15	Adverse Event Report
9081	6/30/15	Adverse Event Report
9082	7/7/15	Adverse Event Report
9083	7/8/15	Adverse Event Report
9084	7/15/15	Adverse Event Report
9085	7/16/15	Adverse Event Report
9086	7/17/15	Adverse Event Report
9087	7/21/15	Adverse Event Report
9088	7/22/15	Adverse Event Report
9089	7/27/15	Adverse Event Report
9090	7/28/15	Adverse Event Report

Sequence	Date	Document
0386	7/30/15	Monthly Safety Report
9091	7/30/15	Adverse Event Report
9092	7/31/15	Adverse Event Report
9093	8/3/15	Adverse Event Report
9094	8/7/15	Adverse Event Report
0387	8/12/15	Notice of Change in Ownership
9095	8/12/15	Adverse Event Report
9096	8/14/15	Adverse Event Report
9097	8/18/15	Adverse Event Report
9098	8/20/15	Adverse Event Report
9099	8/21/15	Adverse Event Report
9100	8/25/15	Adverse Event Report
9101	8/27/15	Adverse Event Report
9102	8/31/15	Adverse Event Report
9103	9/1/15	Adverse Event Report
9104	9/4/15	Adverse Event Report
9105	9/8/15	Adverse Event Report
9106	9/9/15	Adverse Event Report
9107	9/10/15	Adverse Event Report
9108	9/11/15	Adverse Event Report
9109	9/18/15	Adverse Event Report
9110	9/21/15	Adverse Event Report
9111	9/23/15	Adverse Event Report
9112	9/30/15	Adverse Event Report
9113	10/1/15	Adverse Event Report
9114	10/6/15	Adverse Event Report
9115	10/12/15	Adverse Event Report
9116	10/13/15	Adverse Event Report
9117	10/20/15	Adverse Event Report
9118	10/21/15	Adverse Event Report
9119	10/22/15	Adverse Event Report
9120	10/27/15	Adverse Event Report
9121	10/28/15	Adverse Event Report
9122	10/30/15	Adverse Event Report
9123	11/3/15	Adverse Event Report
9124	11/5/15	Adverse Event Report
9125	11/12/15	Adverse Event Report
9126	11/13/15	Adverse Event Report
9127	11/17/15	Adverse Event Report
9128	11/18/15	Adverse Event Report

Sequence	Date	Document
9129	12/8/15	Adverse Event Report
9130	12/10/15	Adverse Event Report
9131	12/23/15	Adverse Event Report
9132	12/28/15	Adverse Event Report
9133	1/6/16	Adverse Event Report
9134	1/20/16	Adverse Event Report
9135	2/12/16	Adverse Event Report
9136	4/4/16	Adverse Event Report
9137	4/12/16	Adverse Event Report
9138	7/6/16	Adverse Event Report

Exhibit O

BLA Period

Sequence	Date	Document
0000	11/16/15	BLA 761032 Brodalumab BLA Submission
	11/25/15	BLA 761032 Brodalumab BLA Acknowledgement Letter
0003	12/15/15	Module 1 - proprietary name request
0002	12/15/15	Module 1 - change in regulatory contact
0001	12/15/15	CMC - stability update
0004	12/23/15	Clinical - Response to Information Request 20151216, Subject level safety data
0005	1/8/16	CMC - Response to Information Request 20160107, Manufactutring Schedule for Amgen RI for DS
0007	1/26/16	Clinical - Response to Information Request 20160113, SIB information: SIB categories, variables, datasets, clarification
0008	2/2/16	Clinical - Response to Information Request 20160112, PK/PD datasets and information
0009	2/4/16	Clinical CMC - Response to Information Request 20160121 Filing Communication, REMS Dose, auto-injector
0010	2/23/16	Clinical - Response to Information Request 20160212, CIOMS
0012	3/11/16	Clinical - Response to Information Request 20160212, Patient Profiles
0006	3/15/16	Clinical - 4MSU
0011	3/16/16	Clinical - Response to Information Request 20160212, CRFs
0013	3/23/16	Clinical - 4MSU Errata
0014	3/31/16	Clinical - Response to Information Request 20160324, SIB
0016	4/1/16	Module 1 - Acceptance of Ownership
0015	4/1/16	Module 1 - Transfer of Ownership
0017	4/12/16	Clinical - Response to Information Request 20160405, ADSIB4 dataset - (Part 1 of 2)
0018	4/14/16	CMC - Response to Information Request 20160407
0019	4/19/16	Clinical - Response to Information Request 20160413, MACE Tabular Data; cytokine (Part 1 of 2)
0020	4/20/16	CMC - Response to Information Request 20160407, Needle insertion test report - Tolerance analysis report
	4/20/16	Mid-cycle Meeting
0021	4/21/16	Clinical - Response to Information Request 20160418, Appendices for Investigator training for eC-SSRS and PHQ-8.
0022	4/27/16	Clinical - Response to Information Request 20160413, Draft labeling text updated information (Part 2 of 2)
0023	4/29/16	CMC - Response to Information Request 20160415, Module 3 update (Part 1 of 2)

Sequence	Date	Document
0024	5/2/16	CMC - Response to Information Request 20160414, Manufacturing plans for DS at Amgen Rhode Island postlicensure
0026	5/3/16	CMC - Response to Information Request 20160415, Module 3 update (Part 2 of 2)
0025	5/3/16	Clinical - Response to Information Request 20160429, Label - Word version of response document as a Follow up request to SN0022.
0027	5/11/16	CMC - Response to Information Request 20160415, Q6 errata data – Append
0028	5/25/16	CMC - Response to Information Request 20160416, CMC update
0029	5/27/16	CMC - Response to Information Request 20160520, CMC update (Part 1 of 2)
0030	5/31/16	Clinical - Response to Information Request 20160524, DB inconsistencies
0032	6/1/16	Clinical - Response to Information Request 20160526 (received via email), Adjudicated MACE numbers
0031	6/2/16	Clinical - Response to Information Request 20160525, DSMB Meeting minutes
0033	6/10/16	CMC - Response to Information Request 20160520, CMC Update (Part 2 of 2)
0034	6/16/16	CMC - Response to Information Request 20160609, CMC update (Part 1 of 2)
0037	6/17/16	Clinical - Response to Information Request 20160615, Carton and Container Labels – Revised due to Change in Ownership
0036	6/17/16	Clinical - Response to Information Request 20160603, Follow-up for DSMB Mtg Minutes (SN0031) to provide Open & Closed session MM
0035	6/17/16	CMC - Response to Information Request 201606014, Needle information
0038	6/24/16	Clinical - Response to Information Request 20160621, Cardiovascular Events Committee (CEC) charter etal
0039	6/27/16	CMC - Response to Information Request 20160621, CMC Amendment (Part 1 of 2)
	6/28/16	Late-cycle Meeting
0040	7/6/16	Clinical - Response to Information Request 20160628, Clinical information on Pharmacovigilance PSI
0041	7/8/16	CMC - Response to Information Request 20160609 & Response to Information Request 20160621, CMC Update (Part 2 of 2)
0042	7/12/16	Clinical - Response to Information Request 20160711, Clinical Information on SIB subject IDs
0043	7/13/16	Clinical - Response to Information request 20160712, Clinical Information regarding clarification of Sponsor BD Errata question
0044	7/15/16	Clinical - Late Cycle Meeting Minutes - Sponsor Comments
	7/19/16	Advisory Committee Meeting

Sequence	Date	Document
0045	8/10/16	Clinical - Response to Information request 20160727, Label - request for boxed warning for suicide, and suicidal ideation, and possible mitigation of these events.
0046	8/12/16	Clinical - Response to Information request 20160811, Request for red-lined MS Word version of the label
0048	8/22/16	CMC - Response to Information Request 20160808, CMC Update - Follow up to previous responses
	8/22/16	Meeting to discuss REMS
0049	8/23/16	Clinical - Response to Information Request 20160812, PV Plan Clarifications
0047	8/23/16	Clinical - Response to Information request 20160405, CEC Report and ECGs (Part 2 of 2)
0050	8/26/16	Clinical - Response to Information Request 8/22/2016, Response to FDA Request for Revisions to Label and REMS, Follow-up response to August 22, 2016 meeting
	8/31/16	Meeting to discuss REMS
0051	9/2/16	Clinical - Response to Information Request 20160831, C-reactive protein levels in completed suicides
0052	9/16/16	Clinical - Response to Information Request 20160727, Response to FDA Request for Revisions to Label and REMS, Follow-up response to August 31, 2016 meeting.
	9/21/16	Meeting to discuss REMS
0053	9/22/16	Clinical - Submission of Sponsor Meeting Minutes 9/21/2106 teleconference), Meeting to discuss submission dated 9/16/2016, seq 0052, which contained Sponsor proposals for labeling and REMS (without ETASU)
0054	9/28/16	CMC - Response to Information Request 20160919, CMC Update - Follow up to previous responses
0055	10/4/16	Clinical - Response to FDA Request for Revisions to the REMS, Follow-up response to September 21, 2016 meeting, REMS
	10/5/16	Meeting to discuss REMS
0056	10/6/16	Clinical - Response to FDA request to submit the meeting request letter sent via FedEx to the BLA, Sponsor request for informal meeting
0057	10/17/16	Clinical - Response to Information Request 20160727 and 20160822, REMS
0058	10/25/16	CMC - Response to FDA Information Request (Update Letters of Authorization)
	10/25/16	Review Extension – Major Amendment
0059	11/4/16	Clinical - Notification of unauthorized marketing materials, Unauthorized marketing materials related to product discovered on website.

Sequence	Date	Document
0060	12/12/16	Clinical - Response to FDA Request for PMC and PMR, Sponsor concurrence with and/or your proposed dates for final protocol submission, study/trial initiation, and final report submission for the required postmarketing studies.
0061	12/13/16	Clinical - Response to Agency-proposed labeling, Agency proposed labeling (Prescribing Information, Medication Guide and Instructions for Use) as well as the recommended edits for the carton and container labeling
0062	12/16/16	Clinical - Response to FDA request for revisions to REMS, Agency proposed revisions to REMS materials (appended materials, supporting document)
0063	12/22/16	Clinical - Draft REMS & REMS Correspondence; 2nd Response to PMC & PMR Requests, Submission contains the remaining documents from the response submitted in seq 0062; draft REMS Program forms and website screenshots. Submission also contains the 2nd response to the Agency proposed PMC/PMRs submitted in seq 0060.
0064	12/23/16	Clinical - Draft REMS & REMS Correspondence; Additional PMR , Response to Agency proposed PMR #6 (malignancy). Sponsor concurrence with all Agency proposed REMS elements (in response to seq 0062)
0065	1/17/17	Clinical - Draft REMS & REMS Correspondence, Valeant response to Agency proposed REMS documents (noting that FDA comments are on outdated versions; i.e. version control issue at Agency).
0066	1/19/17	Clinical - Response to Agency-proposed labeling
0067	1/20/17	Clinical - Draft REMS
	1/23/17	Meeting to discuss REMS
0068	1/25/17	Clinical - Response to Agency comments on Pharmacovigilance Plan
0070	2/1/17	Clinical - Response to Agency-proposed Labeling
0069	2/3/17	Clinical - Draft REMS & REMS Correspondence
0072	2/9/17	Clinical - Response to Agency proposed labeling, Agency proposed labeling (Prescribing Information, Medication Guide and Instructions for Use).
0073	2/10/17	Clinical - Draft REMS & REMS Correspondence, Response to Agency request for minor revisions to Prescriber Enrollment Form
0071	2/10/17	Clinical - Draft REMS & REMS Correspondence, Response to Agency proposed comments to REMS elements
	2/15/17	BLA 761032 Siliq (brodalumab) Approval letter