PTO/SB/21 (07-09)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

		Application Number	Patent No. 7,601,740
		Filing Date	Issue Date: October 13, 2009
		First Named Inventor	David M. Weiner
		Art Unit	1617
		Examiner Name	Jennifer M. Kim
Total Number of Pages in This Submission	348	Attorney Docket Number	12560-016-999

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Application of Extension of Patent Term + 2 copies (45 pgs)
Power of Attorney + 2 copies (3 pgs)
Statement under 3.73(b) +2 copies (3 pgs)
See Remarks

Remarks

Exhibit A + 2 copies (84 pgs); Exhibit B + 2 copies (39 pgs); Exhibit C + 2 copies (2 pgs); Exhibit D + 2 copies (24 pgs); Exhibit E + 2 copies (6 pgs); Exhibit F + 2 copies (6 pgs); Exhibit G +2 copies (6 pgs); Exhibit H + 2 copies (72 pgs); Return Receipt Postcard

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Jones Day		
Signature	Roger C. Rich		
Printed name	Roger C. Rich for Anthony M. Insogna, Reg. No. 35,203		
Date	June 22, 2016	Reg. No.	54,398

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature	K. Chaffin-Penny		
Typed or printed name	Krista Chaffin-Penny (Express Mail No. EM 0934344838 US)	Date	June 22, 2016

This collection of information is required by 37 CFR 1.5. 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 and1.14. This collection is estimated to 2 hours 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.**

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FEE TRANSMITTAL

Complete if known	
Application Number	Patent No. 7,601,740
Filing Date	Issue Date: October 13, 2009
First Named Inventor	David M. Weiner
Examiner Name	Jennifer M. Kim
Art Unit	1617
Practitioner Docket No.	12560-016-999

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($) 1,120.00

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 50-3013 Deposit Account Name: Jones Day

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☐ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☐ Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	Fees Paid ($)
Utility	280	140*	70	600	300	150	720	360	180	
Design	180	90	45	120	60	30	460	230	115	
Plant	180	90	45	380	190	95	580	290	145	
Reissue	280	140	70	600	300	150	2,160	1,080	540	
Provisional	260	130	65	0	0	0	0	0	0	

* The $140 small entity status filing fee for a utility application is further reduced to $70 for a small entity status applicant who files the application via EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	Undiscounted Fee ($)	Small Entity Fee ($)	Micro Entity Fee ($)
Each claim over 20 (including Reissues)	80	40	20
Each independent claim over 3 (including Reissues)	420	210	105
Multiple dependent claims	780	390	195

Total Claims		Extra Claims		Fee ($)		Fee Paid ($)
_____	-20 or HP =	_____	x	_____	=	_____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims		Fee ($)		Fee Paid ($)
_____	-3 or HP =	_____	x	_____	=	_____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	_____

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3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
_____	- 100 =	_____	/ 50 =	_____ (round up to a whole number)	x	_____	=	_____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English specification, $130 fee (no small or micro entity discount)	
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)	
Other (e.g., late filing surcharge): Extension of Term of Patent	1,120.00

SUBMITTED BY

Signature	Roger C. Rich	Registration No. (Attorney/Agent) 54,398	Telephone
Name (Print/Type)	Roger C. Rich for Anthony M. Insogna, Reg. No. 35,203)	Date	June 22, 2016

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PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	7,601,740
Issue Date	October 13, 2009
First Named Inventor	David M. Weiner
Title	SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS ...
Attorney Docket Number	12560-016-999

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: 20583

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			

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OPLA

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	R R	Date	June 22, 2016
Name	Ryan Brown	Telephone	
Title and Company	Vice President, Compliance, ACADIA Pharmaceuticals 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 1 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.**

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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

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: ACADIA Pharmaceuticals Inc.

Application No./Patent No.: 7,601,740 Filed/Issue Date: October 13, 2009

Titled: SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES

ACADIA Pharmaceuticals 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: D. M. Weiner, R. E. Davis, M. R. Brann To: ACADIA Pharmaceuticals Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 015548, Frame 0274, or for which a copy thereof is attached.

2. From: C. A. Andersson, A. K. Uldam To: ACADIA Pharmaceuticals Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 021247, Frame 0176, 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.

R K
Signature

June 22, 2016
Date

Ryan Brown
Printed or Typed Name

VP, Compliance
Title

Express Mail No.: EM 093434038 US

10/759,561

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 7,601,740 B2 **Attorney Docket No.: 12560-016-999**

Issue Date: October 13, 2009

Inventors: David M. Weiner, Robert E. Davis, Mark R. Brann, Carl-Magnus A. Andersson and Allan K. Uldam

Title: SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES

MAIL STOP HATCH-WAXMAN PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156(d) AND 37 C.F.R. § 1.740

Sir:

In accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740, ACADIA Pharmaceuticals Inc. ("ACADIA"), represents that it is the owner of record of United States Patent No. 7,601,740 B2 ("the '740 patent"), attached hereto as **Exhibit A**, and hereby requests an extension of the patent term thereof. Copies of the assignments and assignment recordations from the '740 patent, which were recorded at Reel 015548 and frame 0274, Reel 019218 and frame 0633, and Reel 021247 and frame 0176, confirming that all right, title and interest resides in ACADIA are attached hereto as **Exhibit B**.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740. The sections of this application are numbered in a manner corresponding with

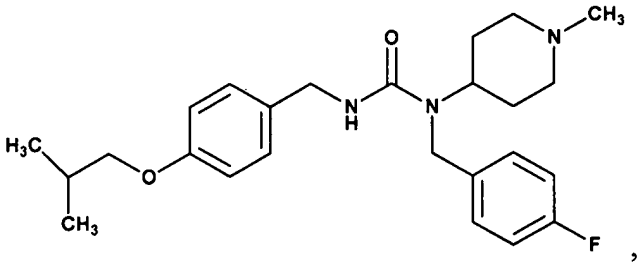
the numbering of subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a) and follow the format set forth therein.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

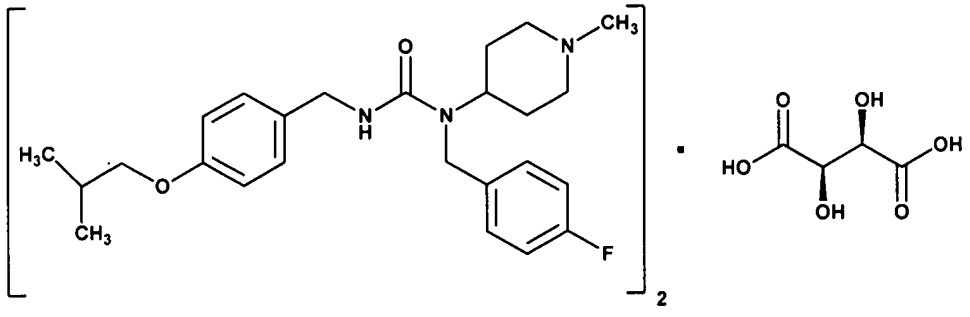
The approved product is NUPLAZID™ (pimavanserin) tablets, for oral use, in which the active ingredient is pimavanserin, which is present as pimavanserin tartrate salt. A chemical name of the tartrate salt of pimavanserin is:

urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N'*-[[4-(2-methylpropoxy)phenyl]methyl]-, (2R,3R)-2,3-dihydroxybutanedioate (2:1).

The chemical structure of pimavanserin is



and its tartrate salt can be depicted as:



A copy of the approved labeling is provided in **Exhibit C**. The molecular weight of pimavanserin is 427.5 g/mol, and the molecular weight of pimavanserin tartrate salt is 1005.2 g/mol, which has the empirical formula of $(C_{25}H_{34}FN_3O_2)_2 \cdot C_4H_6O_6$. (*See* **Exhibit C**, page 7).

As currently approved, NUPLAZID™ is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. (*See* **Exhibit C**, page 2). The approved product is available in the form of a tablet for oral administration containing 20 mg of pimavanserin tartrate, which is equivalent to 17 mg of pimavanserin. (*See* **Exhibit C**, pages 7-8). The recommended dose is 34 mg, taken orally as two 17 mg tablets once daily, without titration. (*See* **Exhibit C**, pages 1-2).

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

NUPLAZID™ was subject to regulatory review for an investigational new drug application ("IND") and a new drug application ("NDA") under section 505 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355 ("FFDCA"). Section 505(b) of the FFDCA, 21 U.S.C. §355(b), authorizes the filing of an NDA for a new drug, which was filed in accordance with 21 C.F.R. § 314.50. The Food and Drug Administration ("FDA") subsequently approved the NUPLAZID™ NDA 207-318 under the authority granted by section 505(c) of the FFDCA, 21 U.S.C. § 355(c).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

The FDA approved NDA 207-318 for NUPLAZID™ for commercial marketing or use under 21 U.S.C. § 355(b), on April 29, 2016. A copy of the FDA approval letter is attached as **Exhibit D**.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

NUPLAZID™ is a human drug product with pimavanserin, which is present as a tartrate salt, being the sole active ingredient. Neither pimavanserin nor any salt thereof has been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted.

This application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The last day for submission of this Application is June 27, 2016.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

The patent for which extension is being requested is:

Named Inventors:	David M. Weiner, Robert E. Davis, Mark R. Brann, Carl-Magnus A. Andersson Allan K. Uldam
Patent No.:	7,601,740 B2
Issue Date:	October 13, 2009
Expiration Date:	June 17, 2027 (20 years from January 15, 2004, plus 1,249 days for patent term adjustment (PTA))

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings.

A copy of the '740 patent, including the specification, claims and drawings is attached as **Exhibit A**.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent.

No disclaimer was filed for the '740 patent.

A copy of a Certificate of Correction issued April 27, 2010, is attached as **Exhibit E**.

A copy of a Certificate of Correction issued August 25, 2015, is attached as **Exhibit F**.

A copy of the Maintenance Fee Statement, indicating that the first maintenance fee was paid on April 18, 2013, is attached as **Exhibit G**; thus, no maintenance fee is currently due. The second maintenance fee is not due until October 2016.

The '740 patent has never been subjected to a reexamination proceeding.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

(i) The approved product, if the listed claims include any claim to the approved product;

(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

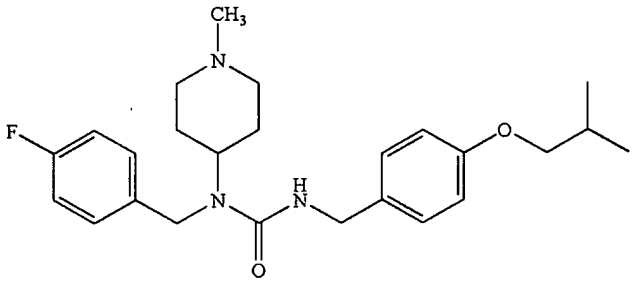
(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.

The '740 patent claims, *inter alia*, the approved product and the active ingredient thereof, *i.e.*, pimavanserin or salts thereof. The '740 patent includes 26 claims, with independent claim 1 and at least dependent claims 9 and 11-17 claiming compositions containing pimavanserin; and independent claim 22 and at least dependent claims 23-24 and 26 claiming pimavanserin.

Applicable patent claims of the '740 patent include the following:

1. A composition comprising a compound of Formula (I):

(I)



or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

9. The composition of claim 1, wherein the compound of formula (I) is the free base.

11. The composition of claim 1, wherein the salt is a tartrate salt.

12. The composition of claim 1, wherein the composition is in a single unit dosage form.

13. The composition of claim 12, wherein the composition is in a single unit dosage form suitable for oral administration to a human.

14. The composition of claim 12, wherein the dosage form is solid.

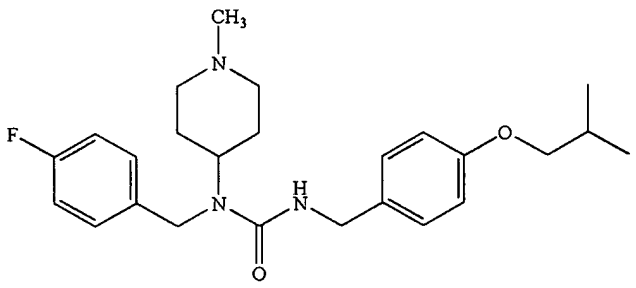
15. The composition of claim 13, wherein the composition is in the form of a tablet or a capsule.

16. The composition of claim 15, wherein the composition is in the form of a tablet.

17. The composition of claim 12, wherein the amount of the compound of Formula (I), or a salt thereof, is from about 0.001 mg to about 50 mg.

22. A compound having the structure of Formula (I):

(I)



or a pharmaceutically acceptable salt thereof.

23. A compound of claim 22, wherein the compound of formula (I) is in solid form.

24. A compound of claim 22, wherein the compound of formula (I) is the free base.

26. A compound of claim 22, wherein the salt is a tartrate salt.

The approved label for NUPLAZID™ (pimavanserin) describes the active ingredient in the product as pimavanserin, which is present as pimavanserin tartrate salt. (*See* **Exhibit C**, page 7). Formula I recited in claims 1 and 22 is the same as the formula for pimavanserin depicted in the approved label, and both claims recite "or a pharmaceutically acceptable salt thereof." The composition of claim 1 also includes "a pharmaceutically acceptable carrier," which is found in the approved product as one or more of the inactive ingredients listed in the approved label. (*See* **Exhibit C**, pages 7). Dependent claims 9 and 24 recite "wherein the compound of formula (I) is the free base." Dependent claims 11 and 26 recite "wherein the salt is a tartrate salt."

The approved label further states that the product is in the form of a tablet for oral administration containing 20 mg of pimavanserin tartrate. (*See* **Exhibit C**, pages 7-8). The recommended dose is 34 mg, taken orally as two 17 mg tablets once daily, without titration (*See* **Exhibit C**, pages 1-2). Thus, the claim composition is in a single unit dosage form (claim 12) suitable for oral administration to a human (claim 13), wherein the dosage form is solid

(claims 14 and 23), specifically in the form of a tablet (claims 15 and 16), and, with 20 mg pimavanserin tartrate (equivalent to 17 mg pimavanserin) per tablet, is within the range from about 0.001 mg to about 50 mg (claim 17).

(10) A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) or a Produce License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued.

The '740 patent claims a human drug.

Investigational New Drug Application (IND) No. 68,384 was received by the FDA on October 10, 2003 and became effective on November 9, 2003 which is 30 days after the receipt of the IND by the FDA.

The New Drug Application (NDA) was submitted on September 1, 2015, and later assigned NDA 207-318.

NDA 207-318 was approved by the FDA on April 29, 2016 (**Exhibit D**).

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

Exhibit H provides a Brief Description of Significant Activities during the Regulatory Review Period.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined.

Applicant is of the opinion that the '740 patent is eligible for an extension. Applicant calculates the extension to be **1316 days**, subject to an applicable reduction in days pursuant to the fourteen (14) year limitation set forth in 37 C.F.R. § 1.775(d)(2)-(4), the calculation of which is described below.

A. Eligibility:

(a) Pursuant to 35 U.S.C. § 156(a), the '740 patent claims the approved product and active ingredient thereof;

(b) Pursuant to 35 U.S.C. § 156(a)(1), the term of the '740 patent has not expired before submission of this application for extension;

(c) Pursuant to 35 U.S.C. § 156(a)(2), the term of the '740 patent has never been extended;

(d) Pursuant to 35 U.S.C. § 156(a)(3), the application for extension is submitted by the owners of record of the '740 patent;

(e) Pursuant to 35 U.S.C. § 156(a)(4), the approved product, NUPLAZID™, has been subject to a regulatory review period before its commercial marketing or use;

(f) Pursuant to 35 U.S.C. § 156(a)(5)(A), the permission for the commercial marketing or use of NUPLAZID™ after the regulatory review period is the first permitted commercial marketing or use of this product;

(g) Pursuant to 35 U.S.C. § 156(c)(4), no other patent has been extended for the same regulatory review period for any product.

B. Regulatory Review Period:

(a) Pursuant to 37 C.F.R. § 1.775(c)(1), the period from November 9, 2003 (the date IND application number 68,384 became effective) to September 1, 2015 (the date the NDA was initially submitted) is 4,314 days. Accordingly, Applicant calculates the "Testing Phase" as 4,314 days.

(b) Pursuant to 37 C.F.R. § 1.775(c)(2), the period from September 1, 2015 (the date the NDA was initially submitted) to April 29, 2016 (the date of NDA approval) is 241 days. Accordingly, Applicant calculates the "Approval Phase" as 241 days.

C. Extended Patent Term:

(a) The number of days in the regulatory review period which were on and before October 13, 2009, the date on which the '740 patent issued, is 2,165 days. Accordingly, 2,165 days are subtracted from the regulatory review pursuant to 37 C.F.R. § 1.775(d)(1)(i). Thus, Applicant calculates the "Adjusted Testing Phase" to be 2,149 days (4,314 days minus 2,165 days).

(b) As demonstrated in **Exhibit H**, the Applicant acted with due diligence during the regulatory review period. Accordingly, zero (0) days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(ii).

(c) One half of the number of days remaining in the Adjusted Testing Phase after the above reductions is 1074 days (a half day is ignored and is not subtracted from the regulatory review period). Accordingly, 1074 days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(iii) with 1075 days remaining in the Test Phase (2,149 days minus 1074 days). After the above adjustments, the total remaining Testing Phase and Approval Phase is **1,316** days (1075 days plus 241 days), which is the period of extension subject to reductions as explained below.

(d) The date that is **1,316** days after the expiration date of the '740 patent is January 23, 2031 (the '740 patent expiration date is June 17, 2027). April 29, 2030 is the date that is 14 years from the date of approval of NUPLAZID™ (April 29, 2016). Accordingly, the fourteen (14) year limitation set forth in 37 C.F.R. § 1.775(d)(2)-(4) should operate to reduce the period of extension, by 269 days, that is, from January 23, 2031 (*i.e.*, the expiration date of the '740 patent plus the period of extension) to April 29, 2030 (*i.e.*, the date that is fourteen years after the date of approval of NUPLAZID ™ on April 29, 2016). Accordingly, the period of extension of **1,316 days** subject to the fourteen year limitation should be **1047** days (1316 days minus 269 days).

(e) The period of extension (1047 days) is less than five (5) years. Accordingly, the five (5) year limitation set forth in 37 C.F.R. § 1.775(d)(5)(i)(ii) does not operate to further reduce the regulatory review period.

(13) A statement that applicant acknowledges a 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 any determination of entitlement to the extension sought.

Applicant and the undersigned acknowledge a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. § 1.765.

Applicant notes that it is also filing an application for patent term extension for U.S. Patent Nos. 7,732,615 and 7,659,285 based upon the same regulatory review as disclosed herein with the understanding that Applicant will select only one patent for term extension before a patent term is granted.

(14) The prescribed fee for receiving and acting upon the application for extension.

The prescribed fee for receiving and acting upon this application is believed to be $1,120.00 pursuant to 37 C.F.R. § 1.20(j)(1). The Director is authorized to charge this fee and any additional required fees, or credit any overpayment, to Deposit Account No. 50-3013

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Please direct all inquiries relating to this application to:

Anthony M. Insogna
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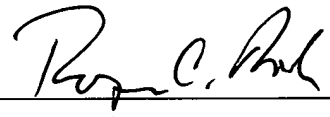
A power of attorney is also enclosed so that the record will reflect correspondence should be addressed to Customer No. 20583.

(16) The application under this section must be accompanied by two additional copies of such application (for a total of three copies).

This Application is accompanied by two additional copies of such application for a total of three copies as required by 37 C.F.R. § 1.740(b). The undersigned attorney for Applicant hereby states that these copies are accurate and true duplicates of the original.

Respectfully submitted,

Date: **June 22, 2016**



54,398

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EXHIBIT A—Copy of U.S. Patent No. 7,601,740 B2

US007601740B2

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

(10) **Patent No.: US 7,601,740 B2**
(45) **Date of Patent: Oct. 13, 2009**

(54) **SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES**

(75) Inventors: **David M. Weiner**, San Diego, CA (US); **Robert E. Davis**, San Diego, CA (US); **Mark R. Brann**, Rye, NH (US); **Carl-Magnus A. Andersson**, Hjärup (SE); **Allan K. Uldam**, Ballerup (DK)

(73) Assignee: **Acadia Pharmaceuticals, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 899 days.

(21) Appl. No.: **10/759,561**

(22) Filed: **Jan. 15, 2004**

(65) **Prior Publication Data**

US 2004/0213816 A1 Oct. 28, 2004

Related U.S. Application Data

(60) Provisional application No. 60/441,406, filed on Jan. 16, 2003, provisional application No. 60/479,346, filed on Jun. 17, 2003.

(51) **Int. Cl.**
A61K 31/47 (2006.01)
A61K 31/445 (2006.01)
C07D 211/56 (2006.01)

(52) **U.S. Cl.** **514/310**; 514/317; 546/224

(58) **Field of Classification Search** 514/310, 514/317; 546/224

See application file for complete search history.

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Primary Examiner—Jennifer M Kim
(74) *Attorney, Agent, or Firm*—Jones Day

(57) **ABSTRACT**

Behavioral pharmacological data with the compound of formula (I), a novel and selective 5HT2A/2C receptor inverse agonist, demonstrate in vivo efficacy in models of psychosis and dyskinesias. This includes activity in reversing MK-801 induced locomotor behaviors, suggesting that this compound may be an efficacious anti-psychotic, and activity in an MPTP primate model of dyskinesias, suggesting efficacy as an anti-dyskinesia agent. These data support the hypothesis that 5HT2A/2C receptor inverse agonism may confer antipsychotic and anti-dyskinetic efficacy in humans, and indicate a use of the compound of formula (I) and related agents as novel therapeutics for Parkinson's Disease, related human neurodegenerative diseases, and psychosis.

26 Claims, 4 Drawing Sheets

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Dopamine D_2 Receptor

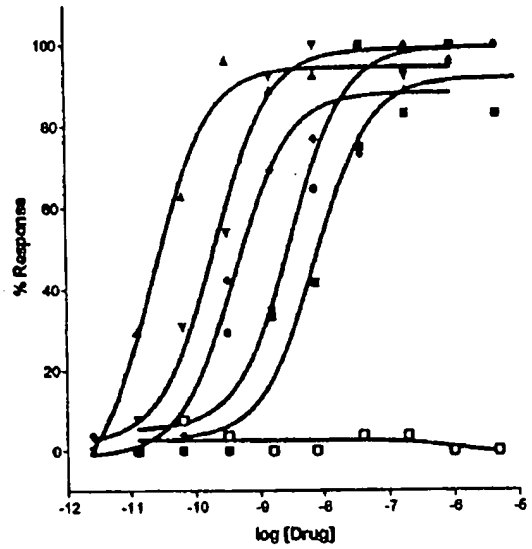


Figure 1A

Serotonin 2A Receptor

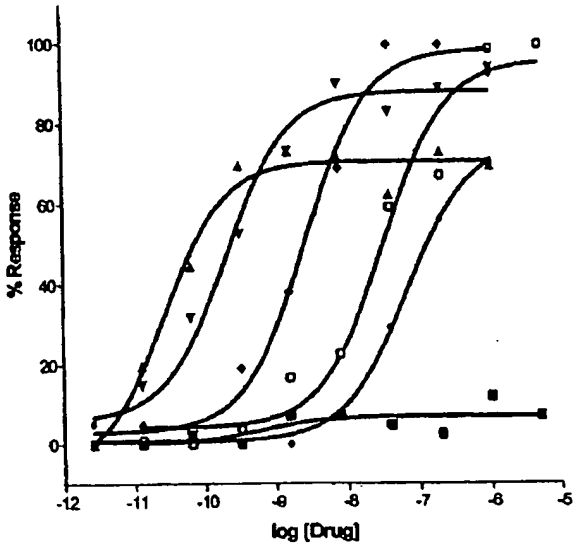


Figure 1B

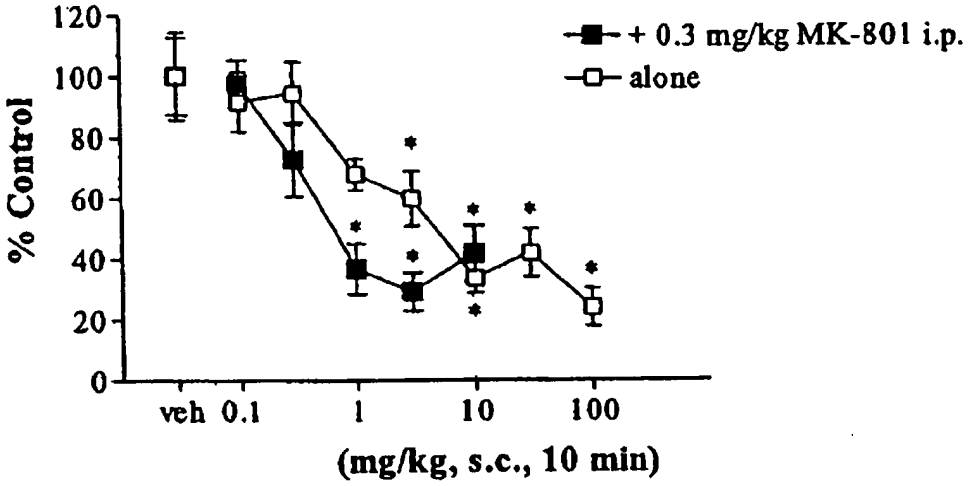


Figure 2A

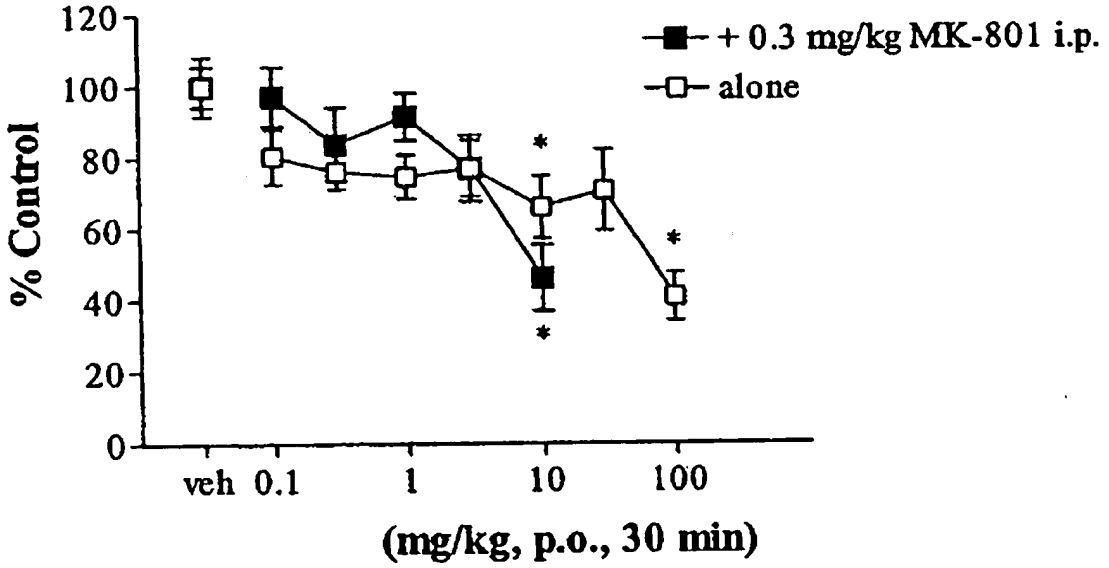


Figure 2B

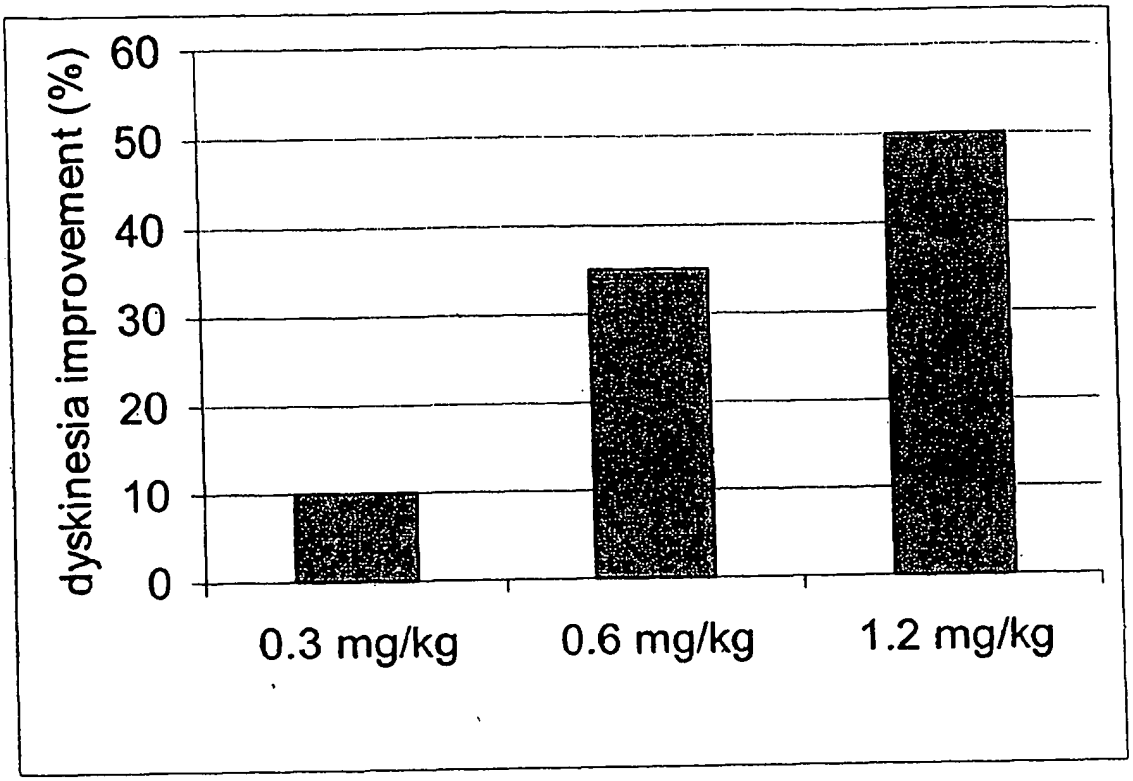

dyskinesia improvement (%)
60
50
40
30
20
10
0
0.3 mg/kg
0.6 mg/kg
1.2 mg/kg

Figure 3

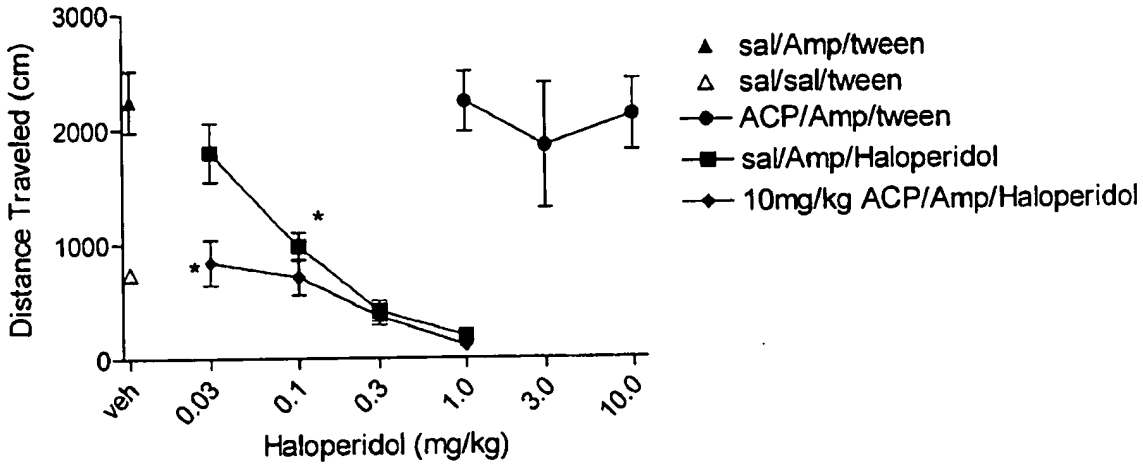

3000
2000
1000
0
Distance Traveled (cm)
veh
0.03
0.1
0.3
1.0
3.0
10.0
Haloperidol (mg/kg)
sal/Amp/tween
sal/sal/tween
ACP/Amp/tween
sal/Amp/Haloperidol
10mg/kg ACP/Amp/Haloperidol

Figure 4

SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/441,406, filed Jan. 16, 2003, and U.S. Provisional Application No. 60/479,346, filed Jun. 17, 2003, both by Weiner et al. and entitled "SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES," both of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to the therapeutic use of N-(1-methylpiperidin-4-yl)-N-(4-flourophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide and related serotonin 2A/2C receptor inverse agonists to treat a variety of human neurodegenerative diseases including Parkinson's Disease, Huntington's Disease, Lewy Body Dementia, and Alzheimer's Disease. Specifically, these agents improve motor function in Parkinson's Disease, and Huntington's Disease. Specifically, N-(1-methylpiperidin-4-yl)-N-(4-flourophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide and related compounds can be used to control the behavioral and neuropsychiatric manifestations present in all of these disease states. Pharmaceutical compositions comprised of a combination of N-(1-methylpiperidin-4-yl)-N-(4-flourophenylmethyl)-N'-(4-(2-methylpropyloxy) phenylmethyl)carbamide and existing therapeutic agents are also disclosed.

BACKGROUND OF THE INVENTION

Neurodegenerative disorders (NDs) are a group of related human maladies that share a common pathophysiological feature, the progressive degeneration of selective neuronal populations over the course of time. These neurodegenerative diseases include but are not limited to Alzheimer's Disease and related dementias, Parkinson's Disease, Huntington's Disease, Lewy Body Disease and related movement disorders, and Friedrich's Ataxia and related Spinocerebellar Ataxia's. Each of these disorders has unique clinical aspects including age of onset, time course of progression, neurological signs and symptoms, neuropsychiatric symptoms, and sensitivity to known therapeutic agents. In addition, the pathophysiological basis of each of these disorders is caused by genetic mechanisms unique to each disease.

Despite significant progress in elucidating the genetic causes underlying these disparate disorders, relatively little is known about the biochemical mechanisms that cause the selective neuronal degeneration common to all of them. In addition, for the most common of these disorders, including Parkinson's Disease and Alzheimer's Disease, the genetic factors that cause the rare familial forms of these diseases have been discovered, but the pathophysiological basis of the vast majority of sporadic cases is still unknown. Because of this, no specific therapeutic agents currently exist that can directly modify disease progression. Instead, clinicians utilize a variety of existing agents to provide symptomatic relief of the motor, cognitive, and neuropsychiatric manifestations that characterize these disorders. None of these existing agents were designed and developed to specifically treat patients with NDs.

Of the various neurological symptoms that characterize the NDs, abnormalities of motor function, including bradykinesias, dyskinesias and chorea, and the emergence of neuropsychiatric symptoms, including psychosis, and affective symptoms such as anxiety and depression, are common and severely impact upon the patient's functional status and quality of life. Unfortunately, most existing therapeutic agents, including antipsychotics and antidepressants, often demonstrate efficacy, yet are very poorly tolerated in these patients. In addition, the available therapeutic agents for Parkinson's Disease, including L-dopa and dopamine agonists, while generally effective, cause the emergence of severe treatment-limiting side effects that are currently intractable to pharmacotherapy.

Multiple factors, both disease and drug related, are primarily responsible for the limited tolerability of these agents. First, patients with neurodegenerative disease are particularly sensitive to most therapeutic agents that are designed to cross the blood-brain barrier and interact with neuronal targets that confer efficacy against adverse motoric or neuropsychiatric symptoms. For instance, atypical antipsychotics are generally well tolerated by healthy volunteers, or in patients with primary psychiatric disorders like schizophrenia; brain states that are not characterized by neuronal degeneration. In contrast, when these agents are administered to patients with Parkinson's or Huntington's Disease, they display severe, treatment-limiting adverse effects on motor function, cause severe sedation, and can worsen cognitive functioning. The direct effects of the neuronal loss characteristic of NDs, and the adaptive changes that occur secondarily to this are both posited to create a neurochemical and/or neurophysiological state in ND patients that confer this extra sensitivity.

Second, the known mechanisms of action of these drugs, including antagonism of dopamine receptors, is not tolerated in some patient populations secondary to specific alterations in distinct neuronal systems. For instance, Parkinson's patients have a relatively selective degeneration of the ascending dopaminergic neuronal systems, and as a consequence of this they are deficient in central dopamine neurotransmission. It is therefore not surprising that drugs that further attenuate dopaminergic neurotransmission, by blocking dopamine receptors, are not well tolerated.

Lastly, nearly all presently known therapeutic agents lack specificity in their mechanisms of action. Antipsychotic and antidepressant drugs possess a multitude of pharmacologically relevant interactions with critical neuronal proteins including a host of cell surface receptors, ion channels, and re-uptake transporters. This lack of drug target specificity is known to confer a variety of adverse effects in non-ND patient populations, which are qualitatively and quantitatively worse in ND patients.

These observations highlight the need to develop novel therapeutic agents that are specifically designed to not only demonstrate efficacy against these particular disabling symptoms but to also possess tolerability in these specific patient populations. This can be achieved by improving the selectivity of the drug target interactions of new therapeutic agents. Specifically, the development of agents with novel mechanisms of action that avoid the known pitfalls associated with existing agents is desired. In addition, improved selectivity can avoid the known adverse effects associated with interactions with non-efficacy conferring drug targets.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows plots of D_2 and 5-HT2A receptor agonist activity of Parkinson's Disease therapeutics as determined by

the physiologicaly predictive, cell-based, in vivo R-SAT assay. FIG. 1A plots drug activity at human D_2 receptors. FIG. 1B plots drug activity at human Serotonin 2A receptors.

FIG. 2A is a plot of the efficacy of the compound of formula (I) in reducing MK-801 induced locomotor behaviors in rats against a control after s.c. administration over a ten (10) minute time period. FIG. 2B is a plot of the efficacy of the compound of formula (I) in reducing MK-801 induced locomotor behaviors in rats against a control after oral administration over a thirty (30) minute time period.

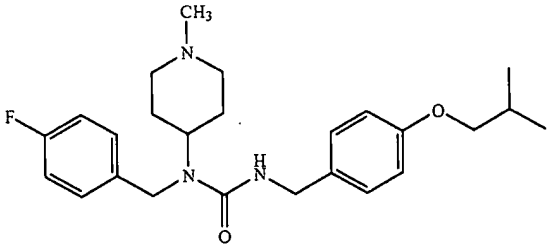
FIG. 3 shows a bar graph that indicates three dosage levels of the compound of formula (I) and the effect of each dosage on reducing dyskinesia in a primate model.

FIG. 4 shows the affect of the compound of formula (I) on amphetamine induced hyperactivity in mice when used in combination with varying doses of Haloperidol.

SUMMARY OF THE INVENTION

Disclosed herein is a composition comprising a compound of Formula (I):

(I)



and a pharmaceutically acceptable carrier. In some embodiments, the composition further comprises an additional therapeutic agent. In some embodiments the additional therapeutic agent is selected from levodopa (SINEMET™, SINEMET-CR™, bromocriptine (PARLODEL™), pergolide (PERMAX™), ephenedrine sulfate (EPHEDRINE™), pemoline CYLERT™), mazindol (SANOREX™), d,1-α-methylphenethylamine (ADDERALL™), methylphenydate (RITALIN™), pramipexole (MIRAPEX™), modafinil (PROVIGIL™), and ropinirole (REQUIP™). In other embodiments, the additional therapeutic agent is an anti-dyskinesia agent selected from baclofen (Lioresal™), botulinum toxin (Botox™), clonazepam (Klonopin™), and diazepam (Valium™). In other embodiments, the additional therapeutic agent is an anti-dystonia, anti-myoclonus, or anti-tremor agent selected from baclofen (LIORESAL™), botulinum toxin (BOTOX™), clonazepam (KLONOPIN™), and diazepam (VALIUM™). In other embodiments, the additional therapeutic agent is an anti-psychotic agent with dopaminergic receptor antagonism. In other embodiments, the additional therapeutic agent is an anti-psychotic agent selected from chlorpromazine (THORAZINE™), haloperodol (HALDOL™), molindone (MOBAN™), thioridazine (MELLARIL™), a phenothiazine, a butyrophenome, diphenulbutylpiperinde (pimozide), thioxanthines (fluphenthixol), substituted benzamides (sulpiride), sertindole, amisulpride, risperidone, clozapine, olanzapine, ziprasidone, aripiprazole, and their active metabolites (N-desmethylclozapine, N-desmethylolanzapine, 9-OH-risperdone)).

Also disclosed herein is a method for treating a neurodegernative disease comprising: identifying a patient suffering from a neurodegenerative disease and administering to the patient an effective amount of an inverse agonist selective for a serotonin receptor; whereby the dopaminergic therapy associated dyskinesia is reduced. In some embodiments, the neurodegenerative disease is Parkinson's disease, Huntington's disease, Alzheimer's disease, Spinocerebellar Atrophy, Tourette's Syndrome, Friedrich's Ataxia, Machado-Joseph's disease, Lewy Body Dementia, Dystonia, Progressive Supranuclear Palsy, or Frontotemporal Dementia. In one embodiment, the serotonin receptor is a 5HT2A receptor. In another embodiment, the serotonin receptor is a 5HT2C receptor. In some embodiments, the inverse agonist binds to a 5HT2A receptor or a 5HT2C receptor. In some embodiments, the inverse agonist is the compound of formula (I). One embodiment further comprises administering a dopaminergic agent in combination with the compound of formula (I). In some embodiments, the reagent increases dopaminergic activity and is selected from the group consisting of levodopa, SINAMET™, SINAMETCR™, bromocriptine (PARLODEL™), pergolide (PERMAX™), ephenedrine sulfate (EPHEDRINE™), pemoline CYLERT™), mazindol (SANOREX™), d,1-α-methylphenethylamine (ADDERALL™), methylphenydate (RITALIN™), pramipexole (MIRAPEX™), modafinil (PROVIGIL™), and ropinirole (REQUIP™).

Also disclosed herein is, a method for treating dyskinesia associated with dopaminergic therapy comprising: identifying a patient suffering from dopaminergic therapy associated dyskinesia and administering to the patient an effective amount of an inverse agonist selective for a serotonin receptor; whereby the dopaminergic therapy associated dyskinesia is reduced. In one embodiment the serotonin receptor is a 5HT2A receptor. In another embodiment the serotonin receptor is a 5HT2C receptor. In some embodiments, the inverse agonist binds to a 5HT2A receptor and a 5HT2C receptor. In one embodiment, the inverse agonist is the compound of formula (I). Some embodiments further comprise administering an anti-dyskinesia agent in combination with the compound of formula (I). In some embodiments, the anti-dyskinesia agent is selected from the group consisting of baclofen (Lioresal™), botulinum toxin (Botox™), clonazepam (Klonopin™), and diazepam (Valium™). In some embodiments, the patient suffers from a neurodegenerative disease selected from the group consisting of Parkinson's disease, Huntington's disease, Alzheimer's disease, Spinocerebellar Atrophy, Tourette's Syndrome, Friedrich's Ataxia, Machado-Joseph's disease, Lewy Body Dementia, Dystonia, Progressive Supranuclear Palsy, and Frontotemporal Dementia.

Further disclosed herein is a method for treating dystonia, myoclonus, or tremor associated with dopaminergic therapy comprising: identifying a patient suffering from dopaminergic therapy associated dystonia, myoclonus, or tremor; and administering to the patient an effective amount of an inverse agonist selective for a serotonin receptor; whereby the dopaminergic therapy associated dystonia, myoclonus, or tremor is reduced. In one embodiment the serotonin receptor is a 5HT2A receptor. In another embodiment, the serotonin receptor is a 5HT2C receptor. In some embodiments, the inverse agonist binds to a 5HT2A receptor and a 5HT2C receptor. In some embodiments, the inverse agonist is the compound of formula (I). Some embodiments further comprise an anti-dystonia, anti-myoclonus, or anti-tremor agent in combination with the compound of formula (I). In some embodiments, the anti-dystonia, anti-myoclonus, or anti-tremor agent is selected from the group consisting of baclofen

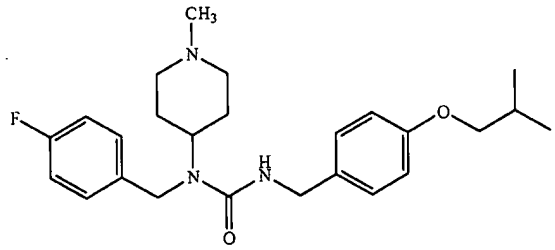
(LIORESAL™), botulinum toxin (BOTOX™), clonazepam (KLONOPIN™), and diazepam (VALIUM™).

Also disclosed herein is a method for treating psychosis associated with dopaminergic therapy comprising: identifying a patient suffering from dopaminergic therapy associated psychosis; and administering to the patient an effective amount of an inverse agonist selective for a serotonin receptor; whereby symptoms of dopaminergic therapy associated psychosis is reduced. In one embodiment the serotonin receptor is a 5HT2A receptor. In another embodiment the serotonin receptor is a 5HT2C receptor. In some embodiments the inverse agonist binds to a 5HT2A receptor and a 5HT2C receptor. In some embodiments the inverse agonist is the compound of formula (I). Some embodiments further comprise an anti-psychotic agent in combination with the compound of formula (I). In some embodiments, the anti-psychotic agent is selected from the group consisting of chlorpromazine (THORAZINE™), haloperodol (HALDOL™), molindone (MOBAN™), thioridazine (MELLARIL™), a phenothiazine, a butyrophenome, diphenulbutylpiperinde (pimozide), thioxanthines (fluphenthixol), substituted benzamides (sulpiride), sertindole, amisulpride, risperidone, clozapine, olanzapine, ziprasidone, aripiprazole, and their active metabolites (N-desmethylclozapine, N-desmethylolanzapine, 9-OH-risperdone)). In some embodiments, the patient suffers from a neurodegenerative disease selected from the group consisting of Parkinson's disease, Huntington's disease, Alzheimer's disease, Spinocerebellar Atrophy, Tourette's Syndrome, Friedrich's Ataxia, Machado-Joseph's disease, Lewy Body Dementia, Dystonia, Progressive Supranuclear Palsy, and Frontotemporal Dementia.

Also disclosed herein is a method for treating a neuropsyhiatric disease comprising: identifying a patient suffering from a neuropsyhiatric disease; and administering to the patient an effective amount of an inverse agonist selective for a serotonin receptor. In some embodiments, the neuropsychiatric disease is selected from the group consisting of schizophrenia, schizoaffective disorders, mania, behavioral disturbances associated with dementia and psychotic depression. In some embodiments the serotonin receptor is a 5HT2A receptor. In some embodiments the serotonin receptor is a 5HT2C receptor. In some embodiments the inverse agonist binds to a 5HT2A receptor or a 5HT2C receptor. In one embodiment, the inverse agonist is the compound of formula (I). Some embodiments further comprise administering an antipsychotic agent in combination with the inverse agonist, the anti-psychotic agent selected from the group consisting of chlorpromazine (THORAZINE™), haloperodol (HALDOL™), molindone (MOBAN™), thioridazine (MELLARIL™), a phenothiazine, a butyrophenome, diphenulbutylpiperinde (pimozide), thioxanthines (fluphenthixol), substituted benzamides (sulpiride), sertindole, amisulpride, risperidone, clozapine, olanzapine, ziprasidone, aripiprazole, and their active metabolites (N-desmethylclozapine, N-desmethylolanzapine, 9-OH-risperdone)).

Also disclosed herein is a compound having the structure of Formula (I):

(I)



Additionally disclosed herein is a method of inhibiting an activity of a monoamine receptor comprising contacting the monoamine receptor or a system containing the monoamine receptor with an amount of the compound of formula (I) that is effective in inhibiting the activity of the monoamine receptor. In some embodiments, the monoamine receptor is a serotonin receptor. In one embodiment the serotonin receptor is the 5-HT2A subclass. In some embodiments the serotonin receptor is in the central nervous system. In some embodiments the serotonin receptor is in the peripheral nervous system. In some embodiments the serotonin receptor is in blood cells or platelets. In some embodiments the serotonin receptor is mutated or modified. In some embodiments the activity is signaling activity. In some embodiments the activity is constitutive. In some embodiments the activity is associated with serotonin receptor activation.

Also disclosed herein is a method of inhibiting an activation of a monoamine receptor comprising contacting the monoamine receptor or a system containing the monoamine receptor with an amount of the compound of formula (I) that is effective in inhibiting the activation of the monoamine receptor. In some embodiments, the activation is by an agonistic agent. In some embodiments the agonistic agent is exogenous. In some embodiments the agonistic agent is endogenous. In some embodiments the activation is constitutive. In some embodiments the monoamine receptor is a serotonin receptor. In some embodiments the serotonin receptor is the 5-HT2A subclass. In some embodiments the serotonin receptor is in the central nervous system. In some embodiments the serotonin receptor is in the peripheral nervous system. In some embodiments the serotonin receptor is in blood cells or platelets. In some embodiments the serotonin receptor is mutated or modified.

Also disclosed herein is a method of treating a disease condition associated with a monoamine receptor comprising administering to a subject in need of such treatment a therapeutically effective amount of the compound of formula (I). In some embodiments the disease condition is selected from the group consisting of schizophrenia, psychosis, migraine, hypertension, thrombosis, vasospasm, ischemia, depression, anxiety, sleep disorders and appetite disorders. In some embodiments the disease condition is associated with dysfunction of a monoamine receptor. In some embodiments, the disease condition is associated with activation of a monoamine receptor. In some embodiments, the disease condition is associated with increased activity of monoamine receptor. In some embodiments, the monoamine receptor is a serotonin receptor. In some embodiments the serotonin receptor is the 5-HT2A subclass. In some embodiments the serotonin receptor is in the central nervous system. In some embodiments the serotonin receptor is in the peripheral nervous system. In some embodiments the serotonin receptor is in blood cells or platelets. In some embodiments, the serotonin receptor is mutated or modified.

Also disclosed herein is a method of treating schizophrenia comprising administering to a subject in need of such treatment a therapeutically effective amount the compound of formula (I).

Also disclosed herein is a method of treating migraine comprising administering to a subject in need of such treatment a therapeutically effective amount of the compound of formula (I).

Also disclosed herein is a method of treating psychosis comprising administering to a subject in need of such treatment a therapeutically effective amount of the compound of formula (I).

Also disclosed herein is a method for identifying a genetic polymorphism predisposing a subject to being responsive the compound of formula (I), comprising: administering to a subject a therapeutically effective amount of said compound; measuring the response of said subject to said compound, thereby identifying a responsive subject having an ameliorated disease condition associated with a monoamine receptor; and identifying a genetic polymorphism in the responsive subject, wherein the genetic polymorphism predisposes a subject to being responsive to said compound. In some embodiments the ameliorated disease condition is associated with the 5-HT class or 5-HT2A subclass of monoaminergic receptors.

Additionally disclosed herein is a method for identifying a subject suitable for treatment with the compound of formula (I), comprising detecting the presence of a polymorphism in a subject wherein the polymorphism predisposes the subject to being responsive to the compound, and wherein the presence of the polymorphism indicates that the subject is suitable for treatment with the compound of formula (I).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

For the purpose of the current disclosure, the following definitions shall in their entireties be used to define technical terms, and shall also, in their entireties, be used to define the scope of the composition of matter for which protection is sought in the claims.

"Constitutive activity" is defined as the elevated basal activity of a receptor that is independent of the presence of an agonist. Constitutive activity of a receptor may be measured using a number of different methods, including cellular (e.g., membrane) preparations (see, e.g., Barr &. Manning, *J. Biol. Chem.* 272:32979-87 (1997)), purified reconstituted receptors with, or without the associated G-protein in phospholipid vesicles (Cerione et al., *Biochemistry* 23:4519-25 (1984)), and functional cellular assays (U.S. Patent Application Ser. No. 60/103,317) or any other method known in the art.

"Agonist" is defined as a compound that increases the basal activity of a receptor when it contacts the receptor.

An "antagonist" is defined as a compound that competes with an agonist or inverse agonist for binding to a receptor, thereby blocking the action of an agonist or inverse agonist on the receptor. However, an antagonist (also known as a "neutral" antagonist) has no effect on constitutive receptor activity.

An "inverse agonist" is defined as a compound that decreases the basal activity of a receptor (i.e., signaling mediated by the receptor). Such compounds are also known as negative antagonists. An inverse agonist is a ligand for a receptor that causes the receptor to adopt an inactive state relative to a basal state occurring in the absence of any ligand. Thus, while an antagonist can inhibit the activity of an agonist, an inverse agonist is a ligand that can alter the conformation of the receptor in the absence of an agonist. The concept of an inverse agonist has been explored by Bond et al. in *Nature* 374:272 (1995). More specifically, Bond et al. have proposed that unliganded β_2-adrenoceptor exists in an equilibrium between an inactive conformation and a spontaneously active conformation. Agonists are proposed to stabilize the receptor in an active conformation. Conversely, inverse agonists are believed to stabilize an inactive receptor conformation. Thus, while an antagonist manifests its activity by virtue of inhibiting an agonist, an inverse agonist can additionally manifest its activity in the absence of an agonist by inhibiting the spontaneous conversion of an unliganded receptor to an active conformation.

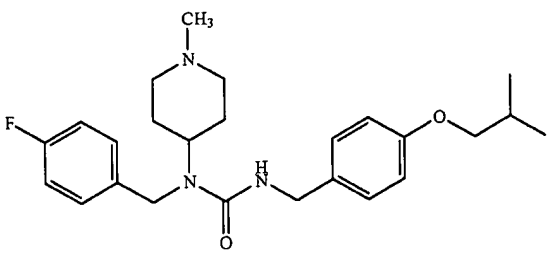
The "5-HT2A receptor" is defined as a receptor, having an activity corresponding to the activity of the human serotonin receptor subtype, which was characterized through molecular cloning and pharmacology as detailed in Saltzman et al., *Biochem. Biophys. Res. Comm.* 181:1469-78; and Julius et al., *Proc. Natl. Acad. Sci. USA* 87:928-932, the disclosures of which are incorporated herein by reference in their entireties.

The term "subject" refers to an animal, preferably a mammal, most preferably a human, who is the object of treatment, observation or experiment.

"Selective" is defined as a property of a compound whereby an amount of the compound sufficient to effect a desired response from a particular receptor type, subtype, class or subclass with significantly less or substantially little or no effect upon the activity other receptor types. For example, a selective compound may have at least a 10-fold greater effect on activity of the desired receptor than on other receptor types. In some cases, a selective compound may have at least a 20-fold greater effect on activity of the desired receptor than on other receptor types, or at least a 50-fold greater effect, or at least a 100-fold greater effect, or at least a 1000-fold greater effect, or at least a 10,000-fold greater effect, or at least a 100,000-fold greater effect, or more than a 100,000-fold greater effect. "Selectivity" or "selective," as an inverse agonist is understood as a property of the compound of the invention whereby an amount of compound that effectively inversely agonizes the 5-HT2A receptor, and thereby decreases its activity, causes little or no inverse agonistic or antagonistic activity at other, related or unrelated, receptors. In particular, in one embodiment, a compound has surprisingly been found not to interact strongly with other serotonin receptors (5-HT 1A, 1B, 1D, 1E, 1F, 2B, 2C, 4A, 6, and 7) at concentrations where the signaling of the 5-HT2A receptor is strongly or completely inhibited. In one embodiment, the compound is also selective with respect to other monoamine-binding receptors, such as the dopaminergic, histaminergic, adrenergic and muscarinic receptors. Compounds that are highly selective for 5-HT2A receptors may have a beneficial effect in the treatment of psychosis, schizophrenia or similar neuropsychiatric disorders, while avoiding adverse effects associated with drugs hitherto suggested for this purpose.

Some embodiments described herein relate to serotonin 2A or 2C receptor inverse agonists, including compositions and methods for treating certain side-effects caused or exacerbated by dopaminergenic agent-associated therapies commonly used in treating neurodegenerative diseases. For example, the compounds disclosed herein have utility in reducing dyskinesia and psychosis associated with dopaminergenic therapies used in treating Parkinson's disease, a neurodegenerative disease. According to one embodiment, the compound N-(1-methylpiperidin-4-yl)-N-(4-flourophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide having the structure of formula (I) is provided:

(I)



One embodiment relates to a composition comprising the compound of formula (I) and a pharmaceutically acceptable carrier. The composition may also contain other compounds such as compounds for treating dyskinesia, dystonia, or psychosis.

According to one embodiment, the tartrate salt of the compound, N-(1-methylpiperidin-4-yl)-N-(4-flourophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide is a potent, selective, orally bioavailable 5-HT2A receptor inverse agonist. One embodiment includes the hydrochloride salt of N-(1-methylpiperidin-4-yl)-N4-flourophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide. The compound of formula (I) also possesses lesser potency as a 5-HT2C receptor inverse agonist and lacks intrinsic activity at the remaining monoaminergic receptor subtypes. Perhaps most notably, the compound of formula (I) lacks activity at dopamine receptor subtypes. (See U.S. patent application Ser. No. 09/800,096, which is hereby incorporated by reference in its entirety). Extensive behavioral pharmacological profiling of the compound of formula (I), including pre-clinical models of antipsychotic and anti-dyskinetic drug actions, support the therapeutic use of the compound in Parkinson's Disease and related human neurodegenerative diseases.

Parkinson's Disease (PD) is a common and progressive neurodegenerative disease. Current estimates suggest that nearly 900,000 individuals in the United States have PD and that the prevalence is increasing as the US population ages. Dopamine receptor agonists are used to alleviate the symptoms of PD, such as motoric dysfunction. Unfortunately, the protracted use of these dopaminergenic agents causes, over time, neuropsychiatric (psychosis) and troublesome motor (dyskinesia)side effects in 30 to 80% of patients, respectively.

Antipsychotics and dopamine receptor antagonists can be effective in ameliorating these adverse effects. Unfortunately, many of these compounds significantly worsen motor function in PD patients secondary to their hypo-dopaminergic state. Biochemical and pharmacological data support the hypothesis that potentiation of serotonergic neurotransmission may be pathophysiologically related to the development of dyskinesias and psychosis in these patients. While not being bound by this theory, the compounds disclosed herein were selected to exploit the relationship of serotonergic activity and the negative side-effects associated with dopaminergenic therapy.

L-dopa is a typical dopaminergic compound used to treat PD. L-dopa has been shown to increase central serotonin release, turnover, and metabolite concentrations in rodent brain. Direct acting dopamine receptor agonists like pergolide possess, in additional to their dopamine receptor agonist properties, potent agonist activity at serotonin 2A (5-HT2A) and 2C (5-HT2C) receptors as demonstrated by various in vitro pharmacological assays.

In one embodiment, the compounds disclosed herein can be used to treat many side-effects that arise from dopaminergenic therapy. For example, the disclosed compounds are also useful for treatment of dyskinesia or psychosis caused or exacerbated as a side-effect of other therapeutic agents such as L-dopa. In one embodiment, the compounds are preferably used for the treatment of dyskinesia or psychosis associated with L-dopa treatment.

The compounds may be used to treat existing dyskinesia or psychosis or may be used prophylactic fashion when for example, it is considered necessary to initiate L-dopa therapy and it is feared that dyskinesia or psychosis may develop.

The compounds may be used to treat dyskinesia or psychosis as a monotherapy or as an adjunct to medicaments to prevent or treat dyskinesia or psychosis side-effects caused by the medicament or alternatively the compounds may be given in combination with other compounds which also reduce dyskinesia.

In some embodiments, the compounds described herein can be formulated into compositions for administration to patients in need thereof. Appropriate compositions can take a number of different forms depending on how the composition is to be used. For example, the composition may be in the form of a powder, tablet, capsule, liquid, ointment, cream, gel, hydrogel, aerosol. spray, micelle, liposome or any other pharmaceutically acceptable form. One of ordinary skill in the art would readily appreciate that an appropriate vehicle for use with the disclosed compounds of the invention should be one that is well tolerated by a recipient of the composition. The vehicle should also readily enable the delivery of the compounds to appropriate target receptors. For example, one of ordinary skill in the art would know to consult *Pharmaceutical Dosage Forms and Drug Delivery Systems*, by Ansel, et al., Lippincott Williams & Wilkins Publishers; 7th ed. (1999) or a similar text for guidance regarding such formulations.

The composition of the invention may be used in a number of ways. For instance, systemic administration may be required in which case the disclosed compounds can be formulated into a composition that can be ingested orally in the form of a tablet, capsule or liquid. Alternatively the composition may be administered by injection into the blood stream. Injections may be intravenous (bolus or infusion) or subcutaneous (bolus or infusion). The disclosed compounds can also be administered centrally by means of intracerebral, intracerebroventricular, or intrathecal delivery.

The compound may also be used with a time delayed release device. Such devices may, for example, be inserted under the skin and the compound may be released over weeks or months. Such a device may be particularly useful for patients with long term dyskinesia such as patients on continuous L-dopa therapy for the treatment of PD. The devices may be particularly advantageous when a compound is used which would normally require frequent administration (e.g., frequent injection).

It will be readily appreciated that the amount of a compound required is determined by biological activity and bioavailability which in turn depends on the mode of administration, the physicochemical properties of the compound employed and whether the compound is being used as a monotherapy or in a combined therapy. The frequency of administration will also be influenced by the above mentioned factors and particularly the half-life of the compound within the subject being treated.

One of ordinary skill in the art would appreciate that specific formulations of compositions and precise therapeutic regimes (such as daily doses of the compounds and the frequency of administration) can be determined using known procedures. Such procedures conventionally employed by the pharmaceutical industry include in vivo experimentation and clinical trials.

Generally, a daily dose of between 0.01 μg/kg of body weight and 1.0 g/kg of body weight of a serotonin 2A/2C receptor inverse agonist can be used with the methods disclosed herein. In one embodiment, the daily dose is between 0.01 mg/kg of body weight and 100 mg/kg of body weight, or any milligram or half-milligram quantity in this disclosed range, e.g., 1.5, 2, 2.5, etc.

Daily doses may be given as a single administration (e.g. a daily tablet for oral consumption or as a single daily injection). Alternatively the compound used may require administration twice or more times during a day, depending on the

kinetics of the drug associated with the individual patient. Alternatively a slow release device may be used to provide optimal doses to a patient without the need to administer repeated doses.

Biochemical Evidence

The cornerstone of current pharmacological intervention in PD remains L-dopa based therapies. L-dopa readily crosses the blood brain barrier, is taken up by neurons and undergoes rapid enzymatic conversion to dopamine, via L-aromatic acid decarboxylase (LAAD) activity in dopaminergic neurons. The increased availability and release of dopamine from these neurons clearly leads to increased dopaminergic transmission, and clinical efficacy in reversing the motoric effects of the hypo-dopaminergic state observed in PD. However, L-dopa lacks specificity for dopaminergic systems, and LAAD is widely expressed in brain. Early biochemical observations in rat brain noted that L-dopa substantially reduced central serotonergic stores, and increased the concentration of the principle serotonin metabolite of 5-hydroxyindoleacetic acid (5-HIAA) (1). Histochemical approaches have demonstrated that L-dopa accumulates in serotonergic neurons, and neurotransmitter release experiments have demonstrated that L-dopa markedly increased the release of both dopamine and serotonin, that release of serotonin is dependent upon LAAD activity, and that it is not eliminated by the selective destruction of dopaminergic neurons (2,3). These observations suggest that the administration of L-dopa to PD patients results in marked increases in the release of central serotonin, potentiating serotonergic neurotransmission. Finally, post-mortem biochemical analysis of PD patients that developed psychosis, when compared to a matched group that did not develop neuropsychiatric disturbances, found that the patients with psychosis had significant elevations in serotonin and 5-HIAA levels in multiple cortical and sub-cortical structures, most notably various mesencephalic nuclei including the red nucleus (4).

Serotonin or 5-hydroxytryptamine (5-HT) plays a significant role in the functioning of the mammalian body. In the central nervous system, 5-HT is an important neurotransmitter and neuromodulator that is implicated in such diverse behaviors and responses as sleeping, eating, locomotion, perceiving pain, learning and memory, sexual behavior, controlling body temperature and blood pressure. In the spinal column, serotonin plays an important role in the control systems of the afferent peripheral nociceptors (Moulignier, *Rev. Neurol.* 150:3-15, (1994)). Peripheral functions in the cardiovascular, hematological, and gastrointestinal systems have also been ascribed to 5-HT. 5-HT has been found to mediate a variety of contractile, secretory, and electrophysiologic effects including vascular and nonvascular smooth muscle contraction, and platelet aggregation. (Fuller, *Biology of Serotonergic Transmission,* 1982; Botillin, *Serotonin In Mental Abnormalities* 1:316 (1978); Barchas, et al., *Serotonin and Behavior*, (1973)). The 5-HT2A receptor subtype (also referred to as subclass) is widely yet discretely expressed in the human brain, including many cortical, limbic, and forebrain regions postulated to be involved in the modulation of higher cognitive and affective functions. This receptor subtype is also expressed on mature platelets where it mediates, in part, platelet aggregation, one of the initial steps in the process of vascular thrombosis.

Given the broad distribution of serotonin within the body, it is understandable that tremendous interest in drugs that affect serotonergic systems exists (Gershon, et at, *The Peripheral Actions of 5-Hydroxytryptamine,* 246 (1989); Saxena, et at, *J. Cardiovascular Pharmacol.* 15: Supp. 7 (1990)). Serotonin receptors are members of a large human gene family of membrane-spanning proteins that function as transducers of intercellular communication. They exist on the surface of various cell types, including neurons and platelets, where, upon their activation by either their endogenous ligand serotonin or exogenously administered drugs, they change their conformational structure and subsequently interact with downstream mediators of cellular signaling. Many of these receptors, including the 5-HT2A subclass, are G-protein coupled receptors (GPCRs) that signal by activating guanine nucleotide binding proteins (G-proteins), resulting in the generation, or inhibition of, second messenger molecules such as cyclic AMP, inositol phosphates, and diacylglycerol. These second messengers then modulate the function of a variety of intracellular enzymes, including kinases and ion channels, which ultimately affect cellular excitability and function.

At least 15 genetically distinct 5-HT receptor subtypes have been identified and assigned to one of seven families (5-HT1-7). Each subtype displays a unique distribution, preference for various ligands, and functional correlate(s). Serotonin may be an important component in various types of pathological conditions such as certain psychiatric disorders (depression, aggressiveness, panic attacks, obsessive compulsive disorders, psychosis, schizophrenia, suicidal tendency), certain neurodegenerative disorders (Alzheimer-type dementia, Parkinsonism, Huntington's chorea), anorexia, bulimia, disorders associated with alcoholism, cerebral vascular accidents, and migraine (Meltzer, *Neuropsychopharmacology,* 21:106S-115S (1999); Barnes & Sharp, *Neuropharmacology,* 38:1083-1152 (1999); Glennon, *Neurosci. Biobehavioral Rev.,* 14:35 (1990)). Recent evidence strongly implicates the 5-HT2 receptor subtype in the etiology of such medical conditions as hypertension, thrombosis, migraine, vasospasm, ischemia, depression, anxiety, psychosis, schizophrenia, sleep disorders and appetite disorders.

Schizophrenia is a particularly devastating neuropsychiatric disorder that affects approximately 1% of the human population. It has been estimated that the total financial cost for the diagnosis, treatment, and lost societal productivity of individuals affected by this disease exceeds 2% of the gross national product (GNP) of the United States. Current treatment primarily involves pharmacotherapy with a class of drugs known as antipsychotics. Antipsychotics are effective in ameliorating positive symptoms (e.g., hallucinations and delusions), yet they frequently do not improve negative symptoms (e.g., social and emotional withdrawal, apathy, and poverty of speech).

Currently, nine major classes of antipsychotics are prescribed to treat psychotic symptoms. Use of these compounds is limited, however, by their side effect profiles. Nearly all of the "typical" or older generation compounds have significant adverse effects on human motor function. These "extrapyramidal" side effects, so termed due to their effects on modulatory human motor systems, can be both acute (e.g., dystonic reactions, a potentially life threatening but rare neuroleptic malignant syndrome) and chronic (e.g., akathisias, tremors, and tardive dyskinesia). Drug development efforts have, therefore, focused on newer "atypical" agents free of these adverse effects.

Antipsychotic drugs have been shown to interact with a large number of central monoaminergic neurotransmitter receptors, including dopaminergic, serotonergic, adrenergic, muscarinic, and histaminergic receptors. It is likely that the therapeutic and adverse effects of these drugs are mediated by distinct receptor subtypes. The high degree of genetic and pharmacological homology between these receptor subtypes has hampered the development of subtype-selective com-

pounds, as well as the determination of the normal physiologic or pathophysiologic role of any particular receptor subtype. Thus there is a need to develop drugs that are selective for individual receptor classes and subclasses amongst monoaminergic neurotransmitter receptors.

The prevailing theory for the mechanism of action of antipsychotic drugs involves antagonism of dopamine D2 receptors. Unfortunately, it is likely that antagonism of dopamine D2 receptors also mediates the extrapyramidal side effects. Antagonism of 5-HT2A is an alternate molecular mechanism for drugs with antipsychotic efficacy, possibly through antagonism of heightened or exaggerated signal transduction through serotonergic systems. 5-HT2A antagonists are therefore good candidates for treating psychosis without extrapyramidal side effects.

Traditionally, these receptors have been assumed to exist in a quiescent state unless activated by the binding of an agonist (a drug that activates a receptor). It is now appreciated that many, if not most, of the GPCR monoamine receptors, including serotonin receptors, can exist in a partially activated state in the absence of their endogenous agonists. This increased basal activity (constitutive activity) can be inhibited by compounds called inverse agonists. Both agonists and inverse agonists possess intrinsic activity at a receptor, in that they alone can activate or inactivate these molecules, respectively. In contrast, classic or neutral antagonists compete against agonists and inverse agonists for access to the receptor, but do not possess the intrinsic ability to inhibit elevated basal or constitutive receptor-responses.

We have elucidated an important aspect of 5-HT2A receptor function by applying the Receptor Selection and Amplification Technology (U.S. Pat. No. 5,707,798, 1998; *Chem. Abstr.* 128:111548 (1998) and citations therein), to the study of the 5-HT2 subclass of serotonin receptors. R-SAT is a phenotypic assay of receptor function that involves the heterologous expression of receptors in mammalian fibroblasts. Using this technology we were able to demonstrate that native 5-HT2A receptors possess significant constitutive, or agonist-independent, receptor activity (U.S. patent application Ser. No. 60/103,317, herein incorporated by reference). Furthermore, by directly testing a large number of centrally acting medicinal compounds with known clinical activity in neuropsychiatric disease, we determined that compounds with antipsychotic efficacy all shared a common molecular property. Nearly all of these compounds, which are used by psychiatrists to treat psychosis, were found to be potent 5-HT2A inverse agonists. This unique clinico-pharmacologic correlation at a single receptor subtype is compelling evidence that 5-HT2A receptor inverse agonism is a molecular mechanism of antipsychotic efficacy in humans.

Detailed pharmacological characterization of a large number of antipsychotic compounds revealed that they possess broad activity at multiple related receptor subtypes. Most of these compounds display agonist, competitive antagonist, or inverse agonist activity at multiple monoaminergic receptor subtypes, including serotoninergic, dopaminergic, adrenergic, muscarinic and histaminergic receptors. This broad activity is likely responsible for the sedating, hypotensive, and motor side effects of these compounds. It would therefore be of great advantage to develop compounds that are selective inverse agonists of the 5-HT2A receptor, but which have little or no activity on other monamine receptor subtypes, especially dopamine D2 receptors. Such compounds may be useful in the treatment of human disease (e.g., as anti-psychotics), and may avoid the adverse side effects associated with non-selective receptor interactions.

The compound of formula (I) is active at monoamine receptors, specifically serotonin receptors. In one embodiment, the compound acts as inverse agonist at the 5-HT2A receptor. Thus, experiments performed on cells transiently expressing the human phenotype of said receptor have shown that the compound of formula (I) attenuates the signaling of such receptors in the absence of additional ligands acting upon the receptor. The compound has thus been found to possess intrinsic activity at this receptor and is able to attenuate the basal, non-agonist-stimulated, constitutive signaling responses that the 5-HT2A receptor displays. The observation that the compound of formula (I) is an inverse agonist also indicates that the compound has the ability to antagonize the activation of 5-HT2A receptors that is mediated by endogenous agonists or exogenous synthetic agonist ligands.

In one embodiment, the compound of formula (I) shows a relatively high degree of selectivity towards the 5-HT2A subtype of serotonin receptors relative to other subtypes of the serotonin (5-HT) family of receptors as well as to other receptors, most particularly the monoaminergic G-protein coupled receptors, such as dopamine receptors.

The compound of formula (I) may therefore be useful for treating or alleviating symptoms of disease conditions associated with impaired function, in particular elevated levels of activity, of especially 5-HT2A receptors, whether this impaired function is associated with improper levels of receptor stimulation or phenotypical aberrations.

Others have previously hypothesized that certain neuropsychological diseases might be caused by altered levels of constitutive activity of monoamine receptors. Such constitutive activity might be modified via contacting the relevant receptor with a synthetic inverse agonist. By directly testing a large number of centrally acting medicinal compounds with known clinical activity in neuropsychiatric disease, we determined that compounds with antipsychotic efficacy all shared a common molecular property. Nearly all of these compounds that are used by psychiatrists to treat psychosis were found to be potent 5-HT2A inverse agonists. This correlation is compelling evidence that 5-HT2A receptor inverse agonism is a molecular mechanism of antipsychotic efficacy in humans.

Detailed pharmacological characterization of a large number of antipsychotic compounds in our laboratory revealed that they possess broad activity at multiple related receptor subtypes. Most of these compounds display either agonist, competitive antagonist, or inverse agonist activity at multiple monoaminergic receptor subtypes including serotoninergic, dopaminergic, adrenergic, muscarinic and histaminergic receptors. This broad activity is likely responsible for the sedating, hypotensive, and motor side effects of these compounds. In one embodiment, the compound of formula (I) possesses efficacy as, for example, a novel antipsychotic, but will have fewer or less severe side effects than existing compounds.

In one embodiment a method is provided to inhibit activity of a monoamine receptor. This method comprises contacting a monoamine receptor or a system containing the monamine receptor, with an effective amount of the compound of formula (I). According to one embodiment, the monamine receptor is a serotonin receptor. In one embodiment, the compound is selective for the 5-HT2A receptor subclass. In another embodiment, the compound has little or substantially no activity to other types of receptors, including other serotonergic receptors and most particularly, monoaminergic G-protein coupled receptors, such as dopaminergic receptors.

The system containing the monoamine receptor may, for example, be a subject such as a mammal, non-human primate

or a human. The receptor may be located in the central or peripheral nervous system, blood cells or platelets.

The system may also be an in vivo or in vitro experimental model, such as a cell culture model system that expresses a monamine receptor, a cell-free extract thereof that contains a monoamine receptor, or a purified receptor. Non-limiting examples of such systems are tissue culture cells expressing the receptor or extracts or lysates thereof. Cells that may be used in the present method include any cells capable of mediating signal transduction via monoamine receptors, especially the 5-HT2A receptor, either via endogenous expression of this receptor (e.g., certain types of neuronal cells lines, for example, natively express the 5-HT2A receptor), or following transfection of cells with plasmids containing the receptor gene. Such cells are typically mammalian cells (or other eukaryotic cells, such as insect cells or Xenopus oocytes), because cells of lower organisms generally lack the appropriate signal transduction pathways for the present purpose. Examples of suitable cells include: the mouse fibroblast cell line NIH 3T3 (ATCC CRL 1658), which responds to transfected 5-HT2A receptors by stimulating growth; RAT 1 cells (Pace et al., *Proc. Natl. Acad. Sci. USA* 88:7031-35 (1991)); and pituitary cells (Vallar et al., *Nature* 330:556-58 (1987). Other useful mammalian cells for the present method include HEK 293 cells, CHO cells, and COS cells.

One embodiment provides methods of inhibiting activity of a native, mutated or modified monoamine receptor. Also provided are kits for performing the same. In one embodiment, the activity of the receptor is a signaling activity. In another embodiment, the activity of the receptor is the constitutive basal activity of the receptor.

In one embodiment, the activity of the receptor is a response, such as a signaling response, to an endogenous agonist, such as 5-HT, or an exogenous agonistic agent, such as a drug or other synthetic ligand. The compound of formula (I) may act by either inversely agonizing or antagonizing the receptor.

In one embodiment, the compound of formula (I) is an inverse agonist selective for the 5-HT2A receptor and the compound has little or substantially no activity toward other serotonergic or other monoaminergic receptors, such as dopaminergic receptors.

In a further embodiment, a method is provided for inhibiting an activation of a monoamine receptor comprising contacting the monoamine receptor, or a system containing the monoamine receptor, with the compound of formula (I). The activation of the receptor may be due to an exogenous or endogenous agonist agent, or may be the constitutive activation associated with a native, mutated or modified receptor. The receptor may be purified or present in an in vitro or in vivo system. The receptor may also be present in the central or peripheral nervous system, blood cells or platelets of a non-human or human subject. Also provided are kits for performing the same.

In one embodiment, the compound of formula (I) is selective for 5-HT class serotonin receptors, such as the 5-HT2A subclass of serotonin receptors. In another embodiment, the compound has little or substantially no anti-dopaminergic activity.

One embodiment provides methods of treating a disease condition associated with a monoamine receptor comprising administering to a mammal in need of such treatment an effective amount of the compound of formula (1). One embodiment provides methods for treating or alleviating disease conditions associated with improper function or stimulation of native, as well as mutated or otherwise modified, forms of central serotonin receptors, particularly the 5-HT class of such receptors, comprising administration of an effective amount of a selective inverse agonist of formula (I) to a host in need of such treatment. Also provided are kits for performing the same.

In one embodiment, the receptor is the 5-HT2A subclass. In one embodiment, the disease condition is associated with dysfunction of the serotonin receptor. In another embodiment, the disease condition is associated with activation of the serotonin receptor, for instance, inappropriately elevated or constitutive activation, elevated serotonergic tone, as well as disease conditions associated with secondary cellular functions impaired by such pathologies.

Examples of diseases for which such treatment using the compound of formula (I) is useful include, but are not limited to, neuropsychiatric diseases such as schizophrenia and related idiopathic psychoses, anxiety, sleep disorders, appetite disorders, affective disorders such as major depression, bipolar disorder, and depression with psychotic features, and Tourette's Syndrome, drug-induced psychoses, psychoses secondary to neurodegenerative disorders such as Alzheimer's or Huntington's Disease. It is anticipated that the compound of formula (I), a particularly selective inverse agonist of 5-HT2A that shows little or no activity on dopaminergic receptors, may be especially useful for treating schizophrenia. Treatment using the compound of formula (I) may also be useful in treating migraine, vasospasm, hypertension, various thrombotic conditions including myocardial infarction, thrombotic or ischemic stroke, idiopathic and thrombotic thrombocytopenic purpura, and peripheral vascular disease.

In a further embodiment the present invention provides methods for treating or alleviating a disease condition associated with improper function, dysfunction, or stimulation of native, as well as mutated or otherwise modified, forms of central or peripheral monoamine receptors, such methods comprising administration of an effective amount of a compound of formula (I) to a host in need of such treatment. In one embodiment, the monamine receptor is serotonin receptor in the peripheral nervous system, blood or platelets. In some embodiments, the serotonin receptor is a 5-HT2A subclass receptor. In additional embodiments, the disease condition is associated with increased activity or activation of a serotonin receptor. Also provided are kits for performing the same.

Some embodiments also pertain to the field of predictive medicine in which pharmacogenomics is used for prognostic (predictive) purposes. Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See e.g., Eichelbaum, *Clin Exp Pharmacol. Physiol.*, 23:983-985 (1996), and Linder, *Clin. Chem.* 43:254-66 (1997). In general, two types of pharmacogenetic conditions can be differentiated: genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action), and genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur as naturally occurring polymorphisms.

One pharmacogenomics approach to identifying genes that predict drug response, known as "a genome-wide association," relies primarily on a high-resolution map of the human genome consisting of already known gene-related markers (e.g., a "bi-allelic" gene marker map that consists of 60,000-100,000 polymorphic or variable sites on the human genome, each of which has two variants). Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a

particular observed drug response or side effect. Alternatively, such a high-resolution map can be generated from a combination of some ten-million known single nucleotide polymorphisms (SNPs) in the human genome. As used herein, a "SNP" is a common alteration that occurs in a single nucleotide base in a stretch of DNA. For example, a SNP may occur once per every 1,000 bases of DNA. A SNP may be involved in a disease process; however, the vast majority may not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that may be common among such genetically similar individuals.

Alternatively, a method termed the "candidate gene approach" can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drug's target is known (e.g., a protein or a receptor of the present invention), all common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

Alternatively, a method termed the "gene expression profiling", can be utilized to identify genes that predict drug response. For example, the gene expression of an animal dosed with a drug (e.g., a molecule or modulator of the present invention) can give an indication whether gene pathways related to toxicity have been turned on.

Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment of an individual. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a molecule or modulator of the invention, such as a modulator identified by one of the exemplary screening assays described herein. As we have described previously, this approach can also be used to identify novel candidate receptor or other genes suitable for further pharmacological characterization in vitro and in vivo.

Accordingly, one embodiment provides methods and kits for identifying a genetic polymorphism predisposing a subject to being responsive to the compound of formula (I). The method comprises administering to a subject an effective amount of the compound; identifying a responsive subject having an ameliorated disease condition associated with a monamine receptor; and identifying a genetic polymorphism in the responsive subject, wherein the genetic polymorphism predisposes a subject to being responsive to the compound. It is anticipated that this method may be useful both for predicting which individuals are responsive to therapeutic effects of the compound and also for predicting those likely to experience adverse side effect responses. This approach may be useful for identifying, for example, polymorphisms in a serotonin receptor that lead to constitutive activation and are thus amenable to inverse agonist therapy. In addition, this method may be useful for identifying polymorphisms that lead to altered drug metabolism whereby toxic byproducts are generated in the body. Such a mechanism has been implicated in the rare, but potentially life threatening side effects of the atypical antipsychotic, clozapine.

In a related embodiment, a method for identifying a subject suitable for treatment with the compound of formula (I) is provided. According to the method, the presence of a polymorphism that predisposes the subject to being responsive to the compound is detected, the presence of the polymorphism indicating that the subject is suitable for treatment. Also provided are kits for performing the same.

The compound of formula (I) preferably shows selective inverse agonist activity towards the 5-HT2A receptor. Such activity is defined by an ability of the ligand to attenuate or abolish the constitutive signaling activity of this receptor. Selectivity in the present context is understood as a property of a compound of the invention whereby an amount of compound that effectively inversely agonizes the 5-HT2A receptor and thereby decreases its activity causes little or no inverse agonistic or antagonistic activity at other, related or unrelated, receptors. In particular, the compound of formula (I) has surprisingly been found not to interact strongly with other serotonin receptors (5-HT 1A, 1B, 1D, 1E, 1F, 2B, 2C, 4A, 6, and 7) at concentrations where the signaling of the 5-HT2A receptor is strongly or completely inhibited. In one embodiment, the compound is also selective with respect to other monoamine-binding receptors, such as the dopaminergic, histaminergic, adrenergic and muscarinic receptors.

One embodiment of the present invention relates to a method of alleviating or treating a disease condition in which modification of monoamine receptor activity, in particular 5-HT2A serotonergic receptor activity, has a beneficial effect by administering a therapeutically effective amount of the compound of formula (I) to a subject in need of such treatment. Such diseases or conditions may, for instance arise from inappropriate stimulation or activation of serotonergic receptors. It is anticipated that by using a compound that is selective for a particular serotonin receptor subtype, in particular 5-HT2A, the problems with adverse side effects observed with the known antipsychotic drugs, such as extrapyramidal effects, may be avoided substantially.

The term "therapeutically effective amount" as used herein means an amount of an active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation, amelioration, or lessening of the symptoms of the disease being treated, or prevents or slows the progress of the disease or increase of the symptoms.

In one embodiment, the compound of formula (I) may be administered in a single daily dose, or the total daily dosage may be administered in divided doses, for example, two, three or four times daily. Furthermore, the compound of formula (I) may be administered in intranasal form via topical use of suitable intranasal vehicles, via transdermal routes, using those forms of transdermal skin patches well known to persons skilled in the art, by implantable pumps; or by any other suitable means of administration. To be administered in the form of a transdermal delivery system, for example, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The dosage regimen utilizing the compound of formula (I) is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the disease or disorder that is being treated.

For oral administration, compositions containing the compound of formula (I) are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0 or 50.0 mg of the active ingredient for the symptomatic

adjustment of the dosage to the patient to be treated. In one embodiment, a unit dose contains from about 0.001 mg to about 50 mg of the active ingredient. In another embodiment a unit dose contains from about 1 mg to about 10 mg of active ingredient.

The compound of formula (I) may be used alone at appropriate dosages defined by routine testing in order to obtain optimal pharmacological effect on a monoaminergic receptor, in particular the 5-HT2A serotonergic receptor subtype, while minimizing any potential toxic or otherwise unwanted effects. In addition, co-administration or sequential administration of other agents that improve the effect of the compound may, in some cases, be desirable.

In one embodiment, the compound of formula (I) may be combined with an additional therapeutic agent. Additional therapeutic agents may include: levodopa (SINEMET™, SINEMET-CR™, bromocriptine (PARLODEL™), pergolide (PERMAX™), ephenedrine sulfate (EPHEDRINE™), pemoline CYLERT™), mazindol (SANOREX™), d,1-α-methylphenethylamine (ADDERALL™), methylphenydate (RITALIN™), pramipexole (MIRAPEX™), modafinil (PROVIGIL™), ropinirole (REQUIP™), an anti-dyskinesia agent, an anti-dystonia, an anti-myoclonus, an anti-tremor agent, or an anti-psychotic agent. In some embodiments, the anti-dyskinesia agent is selected from baclofen (Lioresal™), botulinum toxin (Botox™), clonazepam (Klonopin™), or diazepam (Valium™). In some embodiments, the anti-dystonia, anti-myoclonus, or anti-tremor agents are selected from baclofen (LIORESAL™), botulinum toxin (BOTOX™), clonazepam (KLONOPIN™), or diazepam (VALIUM™). In some embodiments, the anti-psychotic agent is selected from chlorpromazine (THORAZINE™), haloperodol (HALDOL™), molindone (MOBAN™), thioridazine (MELLARIL™), a phenothiazine, a butyrophenome, diphenulbutylpiperinde (pimozide), thioxanthines (fluphenthixol), substituted benzamides (sulpiride), sertindole, amisulpride, risperidone, clozapine, olanzapine, ziprasidone, aripiprazole, or their active metabolites (N-desmethylclozapine, N-desmethylolanzapine, 9-OH-risperdone)).

The pharmacological properties and the selectivity of the compound of formula (I) for specific serotonergic receptor subtypes may be demonstrated by a number of different assay methods using recombinant receptor subtypes, preferably of the human receptors if these are available, e.g. conventional second messenger or binding assays. A particularly convenient functional assay system is the receptor selection and amplification assay disclosed in U.S. Pat. No. 5,707,798, which describes a method of screening for bioactive compounds by utilizing the ability of cells transfected with receptor DNA, e.g., coding for the different serotonergic subtypes, to amplify in the presence of a ligand of the receptor. Cell amplification is detected as increased levels of a marker also expressed by the cells.

Treatment of Neuropsychiatric Disorders

In one embodiment, the compound of formula (I) and related serotonin 2A and/or 2C receptor inverse agonists alone or in combination with other antipsychotic drugs, particularly those with dopamine antagonist properties, are used to treat a variety of human neuropsychiatric diseases including schizophrenia, schizoaffective disorders, mania and psychotic depression. Specifically, the compound of formula (I) and related serotonin 2A/2C receptor inverse agonists can improve psychotic symptoms (feelings of being controlled by outside forces, hearing, seeing, smelling or feeling things which are not there, hallucinations and unusual beliefs, delusions), negative symptoms (loss of normal behavior including tiredness, loss of concentration and lack of energy and motivation, and cognitive function in psychotic patients when used alone or in combination with other antipsychotic drugs. These agents also reduce the side-effects associated with the use of existing antipsychotic drugs and reduce the dose of exisiting agent that is required to achieve antipsychotic efficacy. Specifically, the compound of formula (I) and related compounds alone or in combination with existing antipsychotic drugs can be used to control the behavioral and neuropsychiatric manifestations present in all of these disease states. In some embodiments, pharmaceutical compositions comprised of a combination of the compound of formula (I) and existing antipsychotic agents are used.

Neuropsychiatric disorders associated with psychosis affect a large proportion of the human population. Psychosis appears as a dominating symptom in diverse disorders, including schizophrenia, schizoaffective states, mania, psychotic depression among others. Current treatment options primarily involve pharmacotherapy with a class of drugs known as antipsychotics. Antipsychotics are effective in ameliorating positive symptomotology of these disorders, yet they frequently do not improve and may worsen negative and cognitive symptoms. Signitifcant treatment limiting side effects are common with the use of antipsychotic drugs.

Drugs that possess antipsychotic properties have been in clinical use since the early 1950's. Antipsychotic drugs are widely prescribed to treat psychotic symptoms irrespective of their etiology. Clinical use of these compounds is limited, however, by their side effect profiles. Nearly all of the "typical" or first generation compounds have significant adverse effects on human motor function. These "extrapyramidal" side effects, so termed due to their effects on human motor systems, can be both acute and chronic in nature. Acute effects include dystonic reactions, and a potentially life threatening but rare symptom constellation; neuroleptic malignant syndrome. Chronic side effects include akathisias, tremors, and tardive dyskinesia. Due in large part to these disabling side effects, antipsychotic drug development has been focused on newer "atypical" agents (clozapine, olanzapine, quetiapine, risperidal, arapiprazole) that appear to have reduced liability for inducing adverse motoric effects. These newer "atypical" antipsychotic drugs, however, suffer from other limiting side-effects, including induction of cardiovascular abnormalities, extreme sedation, morbid obesity, type II diabetes, blood dyscrasias and pancreatitis among others.

While the precise molecular mechanisms mediating antipsychotic drug action remain to be elucidated, antipsychotic drugs have been shown, by both in vitro and in vivo methods, to interact with a large number of central monoaminergic neurotransmitter receptors, including dopaminergic, serotonergic, adrenergic, muscarinic, and histaminergic receptors. It is likely that the therapeutic and adverse effects of these drugs are separable and are mediated by distinct receptor subtypes.

Currently, it is thought that antipsychotic drugs reduce the positive symptoms in these disorders by blocking dopamine D2 receptors. This is based on the observation that these all antipsychotic drugs have reasonable affinity for this receptor in vitro, and that a correlation exists between their potency to block D2 receptors and their ability to reduce the psotive symptoms of these disorders. Unfortunately, it is likely that antagonism of dopamine D2 receptors also mediates the disabling extrapyramidal side effects.

The only other consistent receptor interaction that these drugs as a class display is inverse agonism of 5-HT2A receptors, suggesting that inverse agonism of these receptors is an alternate molecular mechanism that confers antipsychotic

efficacy. This theory is bolstered by a number of basic scientific and clinical observations regarding serotonergic systems and the 5-HT2A receptor in particular (U.S. Pat. No. 6,358,698 incorporated by reference).

However, nearly all known antipsychotic agents lack specificity in their mechanisms of action. In addition to possessing activity at dopamine D2 receptors and 5-HT2A receptors, these drugs as a class have a multitude of pharmacologically relevant interactions with critical neuronal proteins including a host of cell surface receptors, ion channels, and re-uptake transporters. This lack of drug target specificity likely contributes to the multiplicity of adverse effects associated with use of existing antipsychotic agents.

These observations highlight the need to develop novel therapeutic regimens that are specifically designed to not only demonstrate efficacy against these particular disabling symptoms but to also possess tolerability in these specific patient populations. This can be achieved by improving the selectivity of the drug target interactions of new therapeutic agents. Specifically, the development of agents with novel mechanisms of action that avoid the known pitfalls associated with existing agents is desired. In addition, improved selectivity avoids the known adverse effects associated with interactions with non-efficacy off-target receptor interaction. For example many antipsychotic drugs possess high affinity interactions with H1 receptors. H1 antagonism is associated with sedation. Further, other antipsuchotic drugs have affinity interactions with alpha receptors. Antagonism of alpha-1 receptors is associated with orthostasis. Improvements in therapeutic efficacy and safety also can be achieved by combining two or more agents each with selective target interactions to achieve additive or synergistic benefits. Specifically, by combining one drug that specifically interacts with D2 receptors as an antagonist and another drug like the compound of formula (I) that interacts with specifically with 5-HT2A/2C receptors as antagonist or inverse agonist, the multitude of off-target interactions of existing antipsychotic drugs can be avoided.

In one embodiment, serotonin 2A and/or 2C receptor inverse agonists are used to treat a variety of human neuropsychiatric diseases including schizophrenia, schizoaffective disorders, mania, behavioral disturbances associated with dementia and psychotic depression. For example, the compounds disclosed herein have utility in reducing the positive symptoms, improving negative symptoms and enhancing cognitive function in patients with certain neuropsychiatric diseases.

Antipsychotics and dopamine receptor antagonists can be effective in ameliorating positive symptoms in schizophrenia and related diseases. Unfortunately, many of these compounds significantly worsen motor function and increase negative symptoms or leave these and other symptoms untreated in these patients. Biochemical and pharmacological data support the hypothesis that potentiation of serotonergic neurotransmission may be pathophysiologically important in the development of these unwanted effects and conversely blockade of serotonergic neurotransmission may reduced the side-effects associated with antipsychotic drug therapy. While not being bound by this theory, the compound of formula (I) was selected to exploit the relationship of serotonergic activity and the limiting effects associated with antipsychotic therapy.

Haloperidol is a typical antipsychotic with specificity as a D2 receptor antagonist. This compound commonly is used to treat the positive symptoms associated with acute exacerbations of schizophrenia. Unfortunately, the use of this compound is associated with a plethora of unwanted motoric side effects, including akathisia, parkinsonism, tardive dyskinesia and neuroleptic maliginant syndrome. This compound also does not alter or worsens negative symptoms and cognitive function in these patients.

In one embodiment, the compound of formula (I) can be used to treat many side-effects that arise from antipsychotic therapy. For example, the compound of formula (I) may be useful for treatment of motoric side-effects of other antipsychotic agents such as haloperidol. In one embodiment, the compound of formula (I) is used for the treatment of motoric side-effects associated with haloperidol treatment.

In one embodiment, the compound of formula (I) may be used prophylactically when for example, it is considered necessary to initiate haloperidol therapy and it is feared that motoric deficits may develop.

In some embodiments, the compound of formula (I) may be used to treat psychosis as a monotherapy or as an adjunct to medicaments to prevent or treat antipsychotic drug side-effects caused by the medicament. Alternatively, the compound of formula (I) may be given in combination with other compounds, which also reduce antipsychotic drug side-effects.

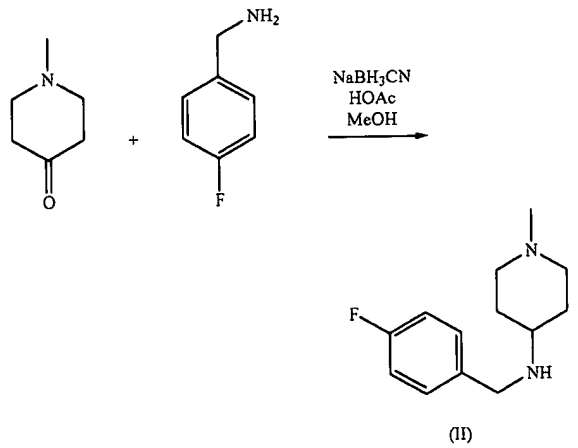
In one embodiment, the compound of formula (I) may used to treat the negative symptoms of certain neuropsychiatric disease including schizophrenia as a monotherapy or as an adjunct to medicaments used to treat the positive symptom of these diseases.

In some embodiments, the compound of formula (I) also may used to improve cognitive function in certain neuropsychiatric disease including schizophrenia as a monotherapy or as an adjunct to medicaments used to treat the positive symptom of these diseases.

Methods of Preparation

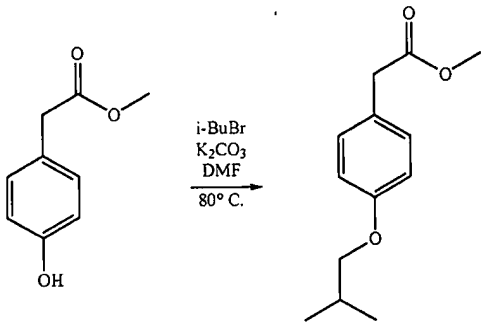
The compound of formula (I) may be synthesized by methods described below, or by modification of these methods. Ways of modifying the methodology include, among others, modification in temperature, solvent, reagents, etc.

The first step of the synthesis, illustrated below, is conducted in the presence of acetic acid, $NaBH_3CN$, and methanol to produce the compound of formula (II):



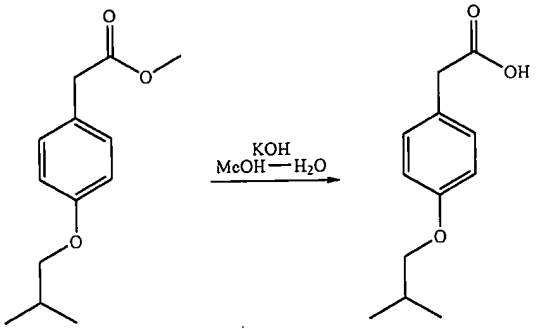
(II)

The compound of formula (IV) can be synthesized by treatment of the compound of formula (III) with isobutyl bromide and potassium carbonate in dimethyl formamide (DMF) at about 80° C.:



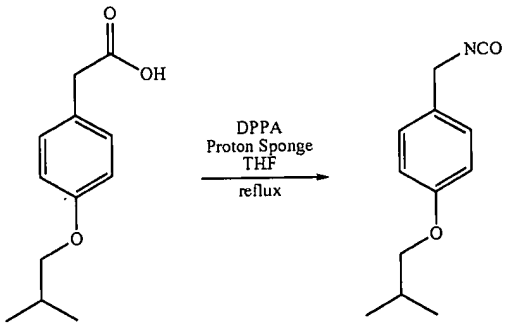
(III) (IV)

The compound of formula (IV) can be converted to the compound of formula (V) by reaction with potassium hydroide in methanol/water:



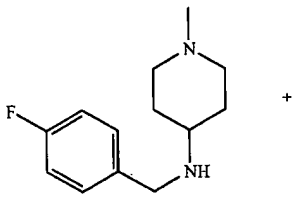
(IV) (V)

The compound of formula (V) is heated to reflux with diphenylphosphonyl azide (DPPA) and a proton sponge in tetrahydrofuran (THF) to produce the compound of formula (VI):

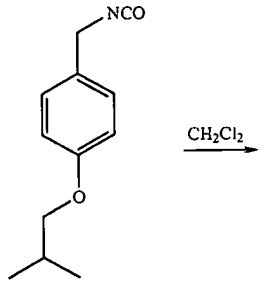


(V) (VI)

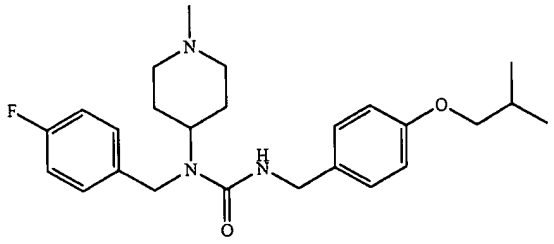
Finally, reaction of the compound of formula (II) with the compound of formula (VI) in methylene chloride produces the compound of formula (I):



(II)

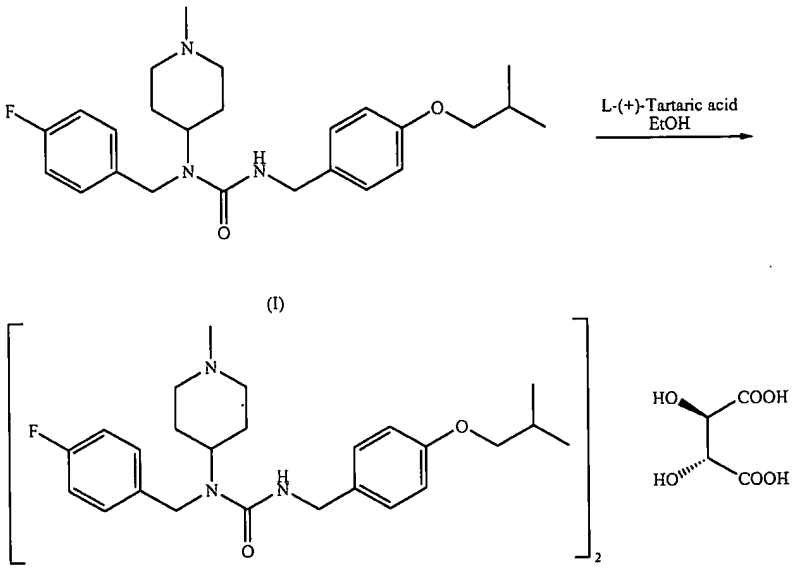


(VI)



(I)

The tartrate salt of the compound of formula (I) may be produced by mixing with L-(+)-Tartaric acid in ethanol:



EXAMPLES

The examples below are non-limiting and are set forth to illustrate some of the embodiments disclosed herein.

Example 1

Agonist Studies

Parkinson's disease is typically managed using direct acting dopamine agonists. Examples of this class of compounds include pergolide, bromocriptine, pramipexole and ropinirole. These drugs are thought to be effective because of their agonist activity at the dopamine D_2, D_3, and D_4 receptors located in striatal and forebrain regions. This activity may compensate for the progressive loss of forebrain dopaminergic innervation that characterizes the PD. However, these drugs are not specific for these dopaminergic receptors and also possess potent agonist activity at other receptors, including 5HT2A and 5HT2C receptors. Using a physiologically predictive in vitro functional assay, it is shown below that pergolide, lisuride, and bromocriptine display agonist potencies at human 5HT2A receptors that are equivalent to those observed at the human D_2 receptor. (FIGS. 1A and 1B, and Table 1).

Using the R-SAT assay, the activity of common dopeaminergic compounds against dopamine and serotonin receptor types was studied. (See U.S. Pat. Nos. 5,912,132 and 5,955, 281, both of which are hereby incorporated by reference.) In FIG. 1, data were plotted as percentage agonist response as determined for a reference full agonist (100%) versus drug concentration. The reference full agonist used for the D_2 receptor was quinpirole, while serotonin was used for the 5HT2A receptor. Compounds tested include dopamine (filled squares), quinpirole (filled circles), lisuride (filled triangles), bromocriptine (filled diamonds), serotonin (open squares), and pergolide (filled inverted triangles). Potencies of representative dose response curves using dopamine D_2 receptors were determined and are shown in FIG. 1A; (pergolide-0.21 nM, dopamine-8.0 nM, lisuride-0.023 nM, quinpirole-3.3 nM, bromocriptine-0.43 nM, and serotonin-no response). FIG. 1B shows compound potency against the serotonin 5-HT2A receptor; (dopamine-no response, quinpirole-174 nM, lisuride-0.028 nM, bromocriptine-2.7 nM, serotonin-33 nM, and pergolide-0.22 nM).

Because these drugs are administered in the clinic to achieve D_2 receptor occupancy, these data argue that direct acting dopamine agonists are also behaving as 5HT2A receptor agonists in vivo when administered in therapeutic doses to PD patients.

TABLE 1

Serotonin Receptor Agonist Activity of Dopaminergic Agents Used in PD

Drug	Dopamine D2	Serotonin 2A	Serotonin 2C
Dopamine	8.40 +/- 0.32	NA	NA
Serotonin	NA	7.73 +/- 0.04	7.29 +/- 0.10
Lisuride	11.00 +/- 0.36	10.65 +/- 0.10	7.61 +/- 0.13
Pergolide	9.45 +/- 0.06	8.05 +/- 0.22	6.66 +/- 0.08
Bromocriptine	9.30 +/- 0.31	8.75 +/- 0.14	5.80 +/- 0.05
Ropinirole	8.19 +/- 0.58	6.85 +/- 0.77	NT
Pramipexole	8.15 +/- 0.38	5.93 +/- 0.74	NT
Apomorphine	6.24 +/- 0.11	NA	NA

Data are derived from R-SAT assays. As shown, all compounds displayed full (>75%) relative agonist efficacies. Data are reported as $-\text{Log}(EC_{50})$ values +/- standard deviation of three to eight separate determinations. The VGV isoform of the 5HT2C receptor, and the short form of the D_2 receptor were utilized for these studies. NA denotes no activity, NT denotes not tested.

The agonist activity of these anti-parkinsonian agents at human 5HT2A/C receptors has particular implications for the generation and treatment of human hallucinations and psychosis. That certain natural and synthetic chemical compounds can induce hallucinatory states in humans has led to detailed investigations of the mechanisms of action of these hallucinogenic or psychotomimetic drugs. These efforts have implicated a number of molecular activities of these classes of

drugs as being relevant to their ability to induce hallucinations, particularly visual hallucinations, in normal healthy individuals. Hallucinogens fall into two distinct chemical classes, the phenylethanolamines, and the substituted tryptamines, both of which are structurally related to serotonin. Many in vitro studies, utilizing radioligand binding techniques, as well as functional pharmacological assays, have repeatedly demonstrated that these drugs are potent 5HT2A and 5HT2C receptor agonists (5). More recent in vivo studies, in which normal volunteers are administered the hallucinogen MDMA (Ecstasy) and then evaluated for clinical response, as well as anatomical measures of brain activation utilizing functional neuro-imaging technologies, have demonstrated that the psychometric and pharmacological activities of hallucinogens can be blocked by anti-psychotic drugs as well as the compound ketanserin (6,7). These drugs share a common molecular property, 5HT2A receptor inverse agonism.

Example 2

Inverse Agonist Studies

Once treatment-induced motoric and neuropsychiatric symptoms develop in PD patients, few viable therapeutic options exist to manage these disturbances. Treatment strategies differ for these two classes of symptoms, but one uniformly clinically efficacious, yet poorly tolerated approach, involves the use of antipsychotic agents. Antipsychotics are known to possess high affinity for the dopamine D_2 subclass of dopamine receptors and neutral antagonism of these receptors underlie the therapeutic efficacy of these drugs in human psychosis. In addition to dopamine D_2 receptor antagonism, these agents possess a wide range of additional potent and pharmacologically relevant activities at many of the other monoaminergic receptor subtypes including serotonin, adrenergic, muscarinic and histaminergic receptors. Of these additional molecular actions, 5HT2A receptor interactions have been the subject of significant study. That antipsychotics have high affinity for multiple receptor subtypes, including serotonin 2 receptors, was demonstrated by the application of radioligand binding techniques (8). The methodologies used to document this cannot define the nature of the interaction between an anti-psychotic antipsychotic and a given receptor. For example, the methods are unable to distinguish as to whether a drug possesses positive (agonist) or negative (inverse agonist) intrinsic activity, or if it lacks intrinsic activity and functions as a neutral antagonist. Recently, this class of drugs was profiled using a functional assay that can discriminate the mechanistic nature of a drug-target interaction (9).

This approach revealed a number of novel aspects of antipsychotic drug action (See U.S. Pat. No. 6,358,698, which is hereby incorporated by reference in its entirety). It confirmed that these drugs as a class possess potent neutral antagonistic activity at the D_2 receptor. Importantly, it also revealed that nearly all antipsychotic drugs, with the exception of the substituted benzamides, possess potent negative intrinsic activity (inverse agonism) at the 5HT2A receptor. These efforts have identified inverse agonist activity at the 5HT2A receptor as being a critical molecular component of anti-psychotic drug action, and suggest that compounds that are selective 5HT2A receptor inverse agonists may have antipsychotic efficacy, even in the absence of D_2 receptor activity.

None of the older typical antipsychotics, exemplified by haloperidol, can be administered to PD patients because of severe worsening in their motor states. The more recent development of newer atypical agents, namely those with reduced (but clearly not absent) liability to induced motoric side effects, suggested that perhaps these agents could be used in PD patients to control dyskinesias and hallucinosis. Unfortunately, the majority of these agents are not tolerated in PD patients secondary to worsening of motor function (10). Of the atypical agents, only one, clozapine, has shown efficacy in treating these adverse treatment-induced side effects in PD patients without untoward motoric liabilities. As such, an improved understanding of the in vitro molecular profile of clozapine can provide critical insights into the design of novel agents for these difficult to treat indications.

The demonstration that clozapine is tolerated in PD patients comes from studies on treatment-induced psychosis. Two well-designed placebo controlled, double blind clinical trials have shown that clozapine is efficacious in psychotic PD patients, and does not worsen parkinsonism, at doses in the 25-35 mg/day range (11,12). Similarly, two open label studies of clozapine in L-dopa and apomorphine induced dyskinesias also demonstrate efficacy and tolerability of low doses of clozapine, on the order of 50-100 mgs/day in these patients (13,14). The dosages used in these PD patients are much lower than the typical 600-900 mg/day range of doses used in treatment refractory schizophrenia. Commensurate with this lower dosing, plasma levels of clozapine in PD patients with psychosis ranged from 4.5 to 16.1 ng/ml (15). This is dramatically lower than the ≧250 ng/ml average serum levels that are associated with therapeutic response in refractory schizophrenic patients.

Not surprisingly, the administration of low dose clozapine, and the commensurate plasma levels obtained at these doses, are well below those necessary for D_2 receptor occupancy, providing a mechanistic understanding of why these dosages are tolerated with respect to motoric liability in these patients. (Positron emission tomography (PET) studies in schizophrenic patients have defined steady state plasma concentrations of clozapine that are required to generate high occupancy of striatal dopamine D_2 receptors). These data also argue that efficacy in dyskinesia and psychosis is mediated by one or more of the non-D_2 receptor targets of this drug. Since rank orders of receptor potencies, as determined by in vitro pharmacological assays, has repeatedly been shown to be a reliable predictor of in vivo receptor action, the receptor sites for which clozapine display a higher potency than D_2 receptors would be predicted to potentially mediate its clinical efficacy in this indication. Detailed functional profiling of clozapine against over 30 of the known monoaminergic receptor subtypes has identified only five sites with higher affinity than dopamine D_2 receptors, histamine H_1, muscarinic m1 and m4, and serotonin 2A, 2B, and 6 receptors. Table 2 reports the absolute and relative potencies of clozapine at some of these monoamine receptor targets as determined by the physiologically predictive in vitro R-SAT assay. These data suggest that at the clinical dosing and serum levels of clozapine observed in PD, two receptor sites are preferentially occupied, the histamine H_1 and 5HT2A receptors.

Conversely, plasma levels achieved with 50 mgs/day of clozapine result in full occupancy of cortical 5HT2A receptors, and extrapolation to the plasma levels observed in PD patients treated for psychosis suggest near complete occupancy of 5HT2A receptors at these dosages as well (16). Whereas central occupancy of 5HT2A receptors, coupled with negative intrinsic activity, may mediate efficacy in these states, central occupancy of histamine H_1 receptors is known to cause sedation, an effect that was observed in the majority of PD patients treated with low dose clozapine. Taken together these data suggest that clozapine is acting primarily as a 5HT2A receptor inverse agonist in this clinical setting.

TABLE 2

Antagonist and Inverse Agonist Potencies of Clozapine at Monoamine Receptors

	D_2	5HT2A	5HT2B	5HT2C	H_1
Clozapine	72 +/- 56	6.4 +/- 1.0	20 +/- 9	250 +/- 60	0.40 +/- 0.07
Ratio to D_2		11	3.6	0.3	180

Data are derived from (9) and are reported as Ki values for the D2 receptor determined as a competitive antagonist, and EC_{50} values for the remaining receptors determined as inverse agonists, in nanomolar unit's +/- standard deviation of three to eight separate determinations.

Behavioral Pharmacological Evidence

The tartrate salt of the compound, N-(1-methylpiperidin-4-yl)-N-(4-flourophenylmethyl)-N'-(4-(2-methylpropyloxy) phenylmethyl)carbamide (compound of formula (I)), is a potent, selective, orally bioavailable 5HT2A receptor inverse agonist. The compound of formula (I) also possesses lesser potency as a 5-HT2C receptor inverse agonist and lacks intrinsic activity at the remaining monoaminergic receptor subtypes. Perhaps most notably, the compound of formula (I) lacks activity at dopamine receptor subtypes. (See U.S. patent application Ser. No. 09/800,096, which is hereby incorporated by reference in its entirety). Extensive behavioral pharmacological profiling of this agent, including pre-clinical models of antipsychotic and anti-dyskinetic drug actions support the therapeutic use of the compound of formula (I) in Parkinson's Disease and related human neurodegenerative diseases.

Example 3

Animal Studies

To determine potential in vivo antipsychotic activity, we studied the compound of formula (I) in an animal model that predicts such efficacy in humans. The compound of formula (I) attenuates hyperactivity induced by the non-competitive N-methyl-d-aspartate (NMDA) antagonist MK-801 (dizocilpine) with a minimum effective dose of 1 mg/kg s.c. (FIG. 2A), and 10 mg/kg p.o. (FIG. 2B). The compound of formula (I) also reduced spontaneous locomotion at 3 mg/kg and higher s.c. doses (FIG. 2A), and at oral doses between 10 and 100 mg/kg (FIG. 2B). In FIG. 2A and 2B, asterisks indicate statistical significance ($p<0.05$) compared to respective vehicle control. Inhibition of MK-801 is a property shared by most atypical antipsychotic agents, and after i.p. administration, the compound of formula (I) attenuated MK-801 hyperactivity at 1 mg/kg, in a manner similar to the atypical antipsychotic clozapine.

Example 4

Primate Animal Studies

To determine the potential in vivo anti-dyskinetic activity, we studied the compound of formula (I) in an animal model that predicts such efficacy in humans. The use of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrilidine (MPTP) to induce parkinsonism in monkeys, coupled with prolonged administration of L-dopa induces severe dyskinesias. The compound of formula (I), when administered s.c., to dyskinetic primates was found to significantly diminish L-dopa induced dyskinesias in a dose dependent manner as determined by the reduction of observable dyskinetic movements scored as a percentage of those present in placebo injected animals (FIG. 3).

Example 5

5HT2A/C Serotonin Antagonist Treatment of Parkinson's Disease

The present example demonstrates that blockage of 5HT2A/C receptors with the compound of formula (I) in parkinsonian patients reduces levodopa-associated dyskinesias and motor response fluctuations. Additionally, the compound of formula (I) is shown to be safe and tolerated at effective doses and potentiates the beneficial effects of levodopa on parkinsonian symptoms.

The compound of formula (I) is administered orally in a group of 21 parkinsonian patients in a double blind, placebo controlled study lasting approximately 5 weeks. An unbalanced parallel-group dose escalation design is used involving an initial placebo run-in, followed by a randomized (active) phase of the compound of formula (I) or placebo. The compound of formula (I) is administered once daily for four weeks, with the dose escalating once each week. Assessments are made on the first day of each dose escalation.

The study is conducted on an outpatient basis. Studies of the compound of formula (I) effect on the motor response to levodopa are conducted in accordance with the standard Experimental Therapeutics Branch (ETB) paradigm, which makes use of a steady state infusion of dopaminomimetics in order to maximize the reliability of data acquisition as well as to permit determination of the anti-parkinsonian efficacy half-time.

Patients who participate in the study have particular characteristics. The patients are between 30 and 80 years of age, inclusively. The patients had been diagnosed with idiopathic Parkinson's disease based on the presence of a characteristic clinical history and neurological findings. The patients displayed relatively advanced disease symptoms with levodopa-associated motor response complications, including peak-dose dyskinesias and wearing-off fluctuations.

The sample size is calculated for the primary endpoint: the Unified Parkinson's Disease Rating Scale (UPDRS) part III motor examination. A sample size of 17 provides 80% power to detect predicted differences, a 40% reduction, with a standardized effect size of 1, using a two-tailed t-test at the 0.05 significance. This assumes an anti-dyskinetic effect of the compound of formula (I) to be compared to that of amantadine (as observed in previous ETB studies), and a linear dose-response of the compound of formula (I). In this phase 2 study we will accept a two-sided alpha at a 0.05 significance level. Four patients will be added for the placebo group, totaling 21 subjects enrolled in the study.

Patients enter the levodopa infusion optimal rate determination (dose finding) portion of the study as soon as all prohibited medication has been withdrawn for at least four weeks. If the patient has had an intravenous dosing rate for levodopa optimized within the past three months, these doses may be used for the study.

Intravenous infusion of levodopa is conducted in an in-patient ward. On the night prior to all infusions, subjects' usual anti-parkinsonian medications are withheld (levodopa by 12 AM, dopamine agonists by 6 PM). During the first and second days of optimal rate determination, two baseline UPDRS ratings are performed prior to levodopa infusion. Initially, the "optimal" rate of levodopa infusion is carefully titrated for each individual to determine the minimum dose needed to achieve a stable "on" state characterized by an "optimal" reduction in parkinsonian signs and mild but ratable dyskinesias (comparable to patient's usual "on" state). Dyskinesia severity is similar to that experienced with each

patient's usual therapeutic regimen. Levodopa will be administered by means of an indwelling intravenous catheter. The initial infusion rate of levodopa will not exceed 80 mg/hr. Subsequent infusion rates may be gradually increased until the optimal rate is found, up to a maximum of 2 mg/kg/hour.

Levodopa infusions will ordinarily last up to 8 hours, but may be continued uninterrupted for several days or be repeated on other days to obtain reliable assessment of motor function. The peripheral decarboxylase inhibitor carbidopa (50 mg, given every 3 hours) is administered orally starting at least one hour prior to intravenous administration of levodopa and continuing until levodopa effects have worn off. After the initial "optimal" rate finding for levodopa infusion, all subsequent infusions are given at the predetermined "optimal rate". As an intravenous levodopa formulation is not commercially available in this country, is administered under ETB IND 22,663.

Patients are dosed according to Table 3:

TABLE 3

Patient group	Week 1	Week 2	Week 3	Week 4	Week 5
I	Placebo	Placebo	Placebo	Placebo	Placebo
II	Placebo	30 mg Compound (I)	70 mg Compound (I)	150 mg Compound (I)	300 mg Compound (I)

Patients proceed through this dose escalation scheme until week 5 or until maximum tolerated dose is attained.

Throughout the study, patients are evaluated weekly for drug safety and tolerability during their inpatient admission and two weeks after treatment for an outpatient follow-up visit. During each inpatient admission, patients remain under close medical monitoring by staff physicians and nurses. If, at any time during the treatment period, the staff physician determines that a patient does not tolerate any given dose, the patient will be considered to have attained maximum tolerated dose and will not receive any additional doses of the compound of formula (I). Patients are encouraged to contact study staff between study days to report any adverse experiences.

Patients are observed in the hospital and will not be discharged until free of all significant adverse effects, if any. Safety assessments, which are performed on study days, include adverse experiences, monitoring vital signs, standard safety monitoring, and cardiac monitoring.

Subjects in Patient Group II show a reducing in levodopa-associated dyskinesias and motor response fluctuations. The subjects in Patient Group II tolerate the compound of formula (I) at all doses administered. The compound of formula (I) therapy also potentiates the benefical effects of levodopa on parkinsonian symptoms.

Example 6

R-SAT Assay

The functional receptor assay Receptor Selection and Amplification Technology (R-SAT) was used to investigate the activity of the compound of formula (I) as an inverse agonist at 5HT2A receptors. The compound of formula (I) exhibited high potency (pIC50 of 9.1) and high efficacy (98%) at 5HT2A receptors.

Example 7

Anti-Psychotic Activity Study

To determine potential in vivo antipsychotic activity, we studied the compound of formula (I) in an animal model that predicts such efficacy against positive symptoms in humans (FIG. 4). In FIG. 4, ACP refers to the compound of formula (I). The compound of formula (I) did not reduce hyperactivity induced by 3.0 mg/kg I.P. of the indirect dopamine agonist d-amphetamine when administered alone at doses of 10.0 mg/kg P.O. and below to mice. As expected, haloperidol dose-dependently reduced amphetamine hyperactivity with a minimally significant effect seen at 0.1 mg/kg, s.c. When a 10.0 mg/kg P.O. dose of the compound of formula (I) was administered in combination with various s.c. doses of haloperidol, the minimally significant dose of haloperidol was decreased to 0.03 mg/kg. With this combination, amphetamine hyperactivity is completely reversed. Thus, an inactive dose of the compound of formula (I), when combined with an inactive dose of haloperidol produces a complete reversal of amphetamine hyperactivity. This suggests that the antipsychotic activity of haloperidol may be significantly enhanced when it is combined with the compound of formula (I). Equally important, when the compound of formula (I) is combined with haloperdiol, the dose of haloperidol can be lowered without a loss of efficacy. This would be expected to improve the safety margin for the clinical use of haloperidol in neuropsychiatric diseases.

Literature Cited

The following references are incorporated herein by reference in their entireties.

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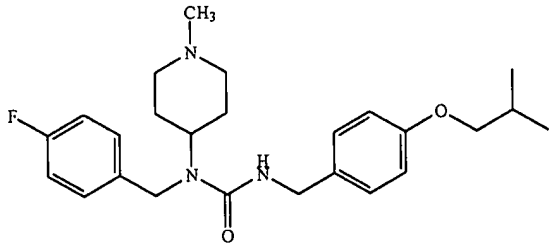
What is claimed is:

1. A composition comprising a compound of Formula (I):

(I)



or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

2. The composition of claim **1**, further comprising an additional therapeutic agent.

3. The composition of claim **2**, wherein the additional therapeutic agent is selected from the group consisting of levodopa bromocriptine, pergolide, ephenedrine sulfate, pemoline, mazindol, d,l-α-methylphenethylamine, methylphenidate, pramipexole, modafinil, and ropinirole.

4. The composition of claim **2**, wherein the additional therapeutic agent is an anti-dyskinesia agent.

5. The composition of claim **4**, wherein the additional therapeutic agent is an anti-dyskinesia agent selected from the group consisting of baclofen, botulinum toxin, clonazepam, and diazepam.

6. The composition of claim **2**, wherein the additional therapeutic agent is an anti-dystonia, anti-myoclonus, or anti-tremor agent selected from the group consisting of baclofen, botulinum toxin, clonazepam, and diazepam.

7. The composition of claim **2**, wherein the additional therapeutic agent is an anti-psychotic agent with dopaminergic receptor antagonism.

8. The composition of claim **2**, wherein the additional therapeutic agent is an anti-psychotic agent selected from the group consisting of chlorpromazine, haloperodol, molindone, thiordazine, a phenothiazine, a butyrophenone, diphenylbutylpiperidine (pimozide), thioxanthines (fluphenthixol), substituted benzamides (sulpiride), sertindole, amisulpride, ziprasidone, aripiprazole, clozapine, olanzapine, riserpidone, N-desmethylclozapine, N-desmethylolanzapine, and 9-OH-respirdone.

9. The composition of claim **1**, wherein the compound of formula (I) is the free base.

10. The composition of claim **1**, wherein the salt is a hydrochloride salt.

11. The composition of claim **1**, wherein the salt is a tartrate salt.

12. The composition of claim **1**, wherein the composition is in a single unit dosage form.

13. The composition of claim **12**, wherein the composition is in a single unit dosage form suitable for oral administration to a human.

14. The composition of claim **12**, wherein the dosage form is solid.

15. The composition of claim **13**, wherein the composition is in the form of a tablet or a capsule.

16. The composition of claim **15**, wherein the composition is in the form of a tablet.

17. The composition of claim **12**, wherein the amount of the compound of Formula (I), or a salt thereof, is from about 0.001 mg to about 50 mg.

18. The composition of claim **12**, wherein the amount of the compound of Formula (I), or a salt thereof, is from about 1 mg to about 10 mg.

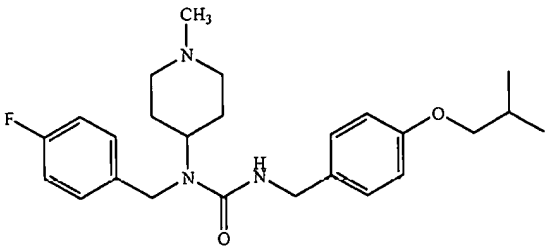
19. The composition of claim **12**, wherein the amount of the compound of Formula (I), or a salt thereof, is about 10 mg.

20. The composition of claim **12**, wherein the amount of the compound of Formula (I), or a salt thereof, is about 25 mg.

21. The composition of claim **12**, wherein the amount of the compound of Formula (I), or a salt thereof, is about 50 mg.

22. A compound having the structure of Formula (I):

(I)



or a pharmaceutically acceptable salt thereof.

23. A compound of claim **22**, wherein the compound of formula (I) is in solid form.

24. A compound of claim **22**, wherein the compound of formula (I) is the free base.

25. A compound of claim **22**, wherein the salt is a hydrochloride salt.

26. A compound of claim **22**, wherein the salt is a tartrate salt.

* * * * *

EXHIBIT B—Copies of Relevant Assignments

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 3

Patent #: 7601740 **Issue Dt:** 10/13/2009 **Application #:** 10759561 **Filing Dt:** 01/15/2004

Publication #: US20040213816 **Pub Dt:** 10/28/2004

Inventors: David M. Weiner, Robert E. Davis, Mark R. Brann, Carl-Magnus A Andersson, Allan K Uldam

Title: SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES

Assignment: 1

Reel/Frame: 015548 / 0274 **Recorded:** 07/09/2004 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: WEINER, DAVID M. **Exec Dt:** 05/24/2004

DAVIS, ROBERT E. **Exec Dt:** 06/02/2004

BRANN, MARK R. **Exec Dt:** 05/24/2004

Assignee: ACADIA PHARMACEUTICALS INC.
3911 SORRENTO VALLEY BLVD.
SAN DIEGO, CALIFORNIA 92121-1402

Correspondent: KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

Assignment: 2

Reel/Frame: 019218 / 0633 **Recorded:** 04/25/2007 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: NASH, NORMAN **Exec Dt:** 04/04/2007

Assignee: ACADIA PHARMACEUTICALS INC.
3911 SORRENTO VALLEY BOULEVARD
SAN DIEGO, CALIFORNIA 92121-1402

Correspondent: KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET, 14TH FLOOR
IRVINE, CALIFORNIA 92614

Assignment: 3

Reel/Frame: 021247 / 0176 **Recorded:** 07/15/2008 **Pages:** 5

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: ANDERSSON, CARL-MAGNUS A. **Exec Dt:** 01/18/2008

ULDAM, ALLAN K. **Exec Dt:** 12/28/2007

Assignee: ACADIA PHARMACEUTICALS, INC.
3911 SORRENTO VALLEY BLVD.
SAN DIEGO, CALIFORNIA 92121-1402

Correspondent: KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

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07-13-2004

Client Code: ACADIA.030A 1

7/9/04

102789927

To the Director, U.S. Patent and Trader... record the attached original documents or copy thereof.

1. Name of conveying party(ies): (List using letters or numbers for multiple parties)

   1. David M. Weiner 5/24/04
   2. Robert E. Davis 6/2/04
   3. Mark R. Brann 5/24/04

   Additional name(s) of conveying party(ies) attached?

   ( ) Yes (X) No

2. Name and address of receiving party(ies):

   Name: ACADIA Pharmaceuticals Inc.
   Internal Address:
   Street Address: 3911 Sorrento Valley Blvd.
   City: San Diego **State:** CA
   ZIP: 92121-1402

   Additional name(s) of receiving party(ies) attached?

   ( ) Yes (X) No

3. Nature of conveyance:

   (X) Assignment ( ) Security Agreement
   ( ) Merger ( ) Change of Name
   ( ) Other:

   Execution Date: (List as in section 1 if multiple signatures)
   See Section 1

4. Application number(s) or Patent number(s):

   (X) Patent Application No.: 10/759,561
   Filing Date: January 15, 2004

   Additional numbers attached?

   ( ) Yes (X) No

5. Name and address of party to whom correspondence concerning document should be mailed:

   Name: Sam K. Tahmassebi
   KNOBBE MARTENS OLSON & BEAR LLP
   2040 Main Street
   Fourteenth Floor
   Irvine, CA 92614
   Customer No. 20,995
   Return Fax: (949) 760-9502
   Attorney's Docket No.: ACADIA.030A

6. Total number of applications and patents involved:
   1

7. Total fee (37 CFR 1.21(h)): $40
   (X) Enclosed

8. Deposit account number: 11-1410
   Please charge this account for any additional fees which may be required, or credit any overpayment to this account.

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9. Statement and signature.

   To the best of my knowledge and belief, the foregoing information is true and correct, and any attached copy is a true copy of the original document.

   Sam K. Tahmassebi
   Name of Person Signing

   Signature

   July 6, 2004
   Date

   45,151
   Registration No.

   Total number of pages including cover sheet, attachments and document: 3

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ASSIGNMENT

WHEREAS, We, David M. Weiner, a United States citizen, residing at 4915 Muir Avenue, San Diego, California 92107, Robert E. Davis, 13272 Glencliff Way, San Diego, California 92130, and Mark R. Brann, 2950 Racetrack View Drive, Del Mar, California 92014-2460, have invented certain new and useful improvements in a SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES for which we have filed an application for Letters Patent in the United States, Application No. 10/759,561, Filed on January 15, 2004;

AND WHEREAS, ACADIA Pharmaceuticals Inc. (hereinafter "ASSIGNEE"), a Delaware Corporation, with its principal place of business at 3911 Sorrento Valley Boulevard, San Diego, California 92121-1402, desires to acquire the entire right, title, and interest in and to the said improvements and the said Application:

NOW, THEREFORE, in good and valuable consideration, the receipt of which is hereby acknowledged, we, the said inventors, do hereby acknowledge that we have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over, unto the said ASSIGNEE, its successors, legal representatives and assigns, the entire right, title, and interest throughout the world in, to and under the said improvements, and the said application and all provisional applications relating thereto, and all divisions, renewals and continuations thereof, and all Letters Patent of the United States which may be granted thereon and all reissues and extensions thereof, and all rights of priority under International Conventions and applications for Letters Patent which may hereafter be filed for said improvements in any country or countries foreign to the United States, and all Letters Patent which may be granted for said improvements in any country or countries foreign to the United States and all extensions, renewals and reissues thereof; and we hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said improvements to the said ASSIGNEE, its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND WE DO HEREBY sell, assign, transfer, and convey to ASSIGNEE, his successors, legal representatives, and assigns all claims for damages and all remedies arising out of any violation of the rights assigned hereby that may have accrued prior to the date of assignment to ASSIGNEE, or may accrue hereafter, including, but not limited to, the right to sue for, collect, and retain damages for past infringements of the said Letters Patent before or after issuance.

AND WE HEREBY covenant and agree that we will communicate to the said ASSIGNEE, its successors, legal representatives and assigns, any facts known to us respecting said improvements, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything possible to aid the said ASSIGNEE, its successors, legal representatives and assigns, to obtain and enforce proper patent protection for said improvements in all countries.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 24 day of MAY, 2004

David M. Weiner

STATE OF CA }
} ss.
COUNTY OF San Diego }

On 5/24/04, before me, M C Gomez, personally appeared David M. Weiner personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL] M. C. GOMEZ
COMM. #1272984
NOTARY PUBLIC-CALIFORNIA
SAN DIEGO COUNTY
My Comm. Expires August 23, 2004

Notary Signature

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 2 day of June, 2004.

Robert E Davis
Robert E. Davis

STATE OF CA
COUNTY OF San Diego } ss.

On 6/2/04, before me, MC Gomez, personally appeared Robert E. Davis personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL]

M. C. GOMEZ
COMM. #1272984
NOTARY PUBLIC-CALIFORNIA
SAN DIEGO COUNTY
My Comm. Expires August 28, 2004

MC Gomez
Notary Signature

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 24th day of May, 2004.

Mark R. Brann

STATE OF CA
COUNTY OF San Diego } ss.

On 5/24/04, before me, MC Gomez, personally appeared Mark R. Brann personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL]

MC Gomez
Notary Signature

M. C. GOMEZ
COMM. #1272984
NOTARY PUBLIC-CALIFORNIA
SAN DIEGO COUNTY
My Comm. Expires August 28, 2004

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Client Code: ACADIA.030A

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To the Director, U.S. Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies): (List using letters or numbers for multiple parties)

   Norman Nash

   Additional name(s) of conveying party(ies) attached?

   ( ) Yes (X) No

2. Name and address of receiving party(ies):

   Name: ACADIA Pharmaceuticals Inc.

   Internal Address:

   Street Address: 3911 Sorrento Valley Boulevard

   City: San Diego **State**: CA

   ZIP: 92121-1402

   Additional name(s) of receiving party(ies) attached?

   ( ) Yes (X) No

3. Nature of conveyance:

   (X) Assignment ( ) Security Agreement
   ( ) Merger ( ) Change of Name
   ( ) Other:

   Execution Date: (List as in section 1 if multiple signatures)

   April 4, 2007

4. US or PCT Application number(s) or US Patent number(s):

   (X) Patent Application No.: 10/759,561
   Filing Date: January 15, 2004

   Additional numbers attached?

   ( ) Yes (X) No

5. Party to whom correspondence concerning document should be mailed:

   Customer No. 20,995

   Address: Knobbe, Martens, Olson & Bear, LLP
   2040 Main Street, 14th Floor
   Irvine, CA 92614

   Return Fax: (949) 760-9502

   Attorney's Docket No.: ACADIA.030A

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 1.21(h)): $40

   (X) Authorized to be charged to deposit account

8. Deposit account number: 11-1410

   Please charge this account for any additional fees which may be required, or credit any overpayment to this account.

9. Statement and signature.

   To the best of my knowledge and belief, the foregoing information is true and correct, and any attached copy is a true copy of the original document.

   Ryan E. Melnick
   Name of Person Signing

   Ryan Melnick
   Signature

   4-25-07
   Date

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   Registration No.

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PATENT
Application No.: 10/759,561 Client Code: ACADIA.030A
Filing Date: January 15, 2004 Page 1

ASSIGNMENT

WHEREAS, I, Norman Nash, a Canadian citizen, residing at 10994 W. Ocean Air Drive #384, San Diego, CA 92130, have invented certain new and useful improvements for SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES as a joint inventor, for which an application for Letters Patent in the United States, Application No. 10/759,561, was filed January 15, 2004;

AND WHEREAS, ACADIA Pharmaceuticals Inc. (hereinafter "ASSIGNEE"), a Delaware Corporation, with its principal place of business at 3911 Sorrento Valley Blvd., San Diego, California 92121-1402, desires to acquire the entire right, title, and interest in and to the said improvements and the said Application:

NOW, THEREFORE, in consideration of the sum of One Dollar ($1.00) to me in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, I, the said inventor, do hereby acknowledge that I have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over, unto the said ASSIGNEE, its successors, legal representatives and assigns, my entire right, title, and interest throughout the world in, to and under the said improvements, and the said application and all provisional applications relating thereto, and all divisions, renewals and continuations thereof, and all Letters Patent of the United States which may be granted thereon and all reissues and extensions thereof, and all rights of priority under International Conventions and applications for Letters Patent which may hereafter be filed for said improvements in any country or countries foreign to the United States, and all Letters Patent which may be granted for said improvements in any country or countries foreign to the United States and all extensions, renewals and reissues thereof; and I hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said improvements to the said ASSIGNEE, its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND I DO HEREBY sell, assign, transfer, and convey to ASSIGNEE, its successors, legal representatives, and assigns all claims for damages and all remedies arising out of any violation of the rights assigned hereby that may have accrued prior to the date of assignment to ASSIGNEE, or may accrue hereafter, including, but not limited to, the right to sue for, collect, and retain damages for past infringements of the said Letters Patent before or after issuance.

AND I HEREBY covenant and agree that I will communicate to the said ASSIGNEE, its successors, legal representatives and assigns, any facts known to me respecting said improvements, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything possible to aid the said ASSIGNEE, its successors, legal representatives and assigns, to obtain and enforce proper patent protection for said improvements in all countries.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 4 day of April, 2007

Norman Nash

STATE OF California }
} ss.
COUNTY OF San Diego }

On April 4th 2007, before me, Kenneth C Shook, Notary Public personally appeared Norman Nash ~~personally known to me~~ (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Kenneth C Shook
Notary Signature

[SEAL]

OFFICIAL SEAL
KENNETH C. SHOOK
NOTARY PUBLIC-CALIFORNIA
COMM. NO. 1550095
SAN DIEGO COUNTY
MY COMM. EXP. FEB. 5, 2009

2766637:sad
071906

Client Code: **ACADIA.030A**
ACADIA.030C1
ACADIA.030C2
ACADIA.030C3

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Director, U.S. Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies): (List using letters or numbers for multiple parties)

   a. Carl-Magnus A. Andersson
   b. Allan K. Uldam

   Additional name(s) of conveying parties attached?

   ( ) Yes (X) No

2. Name and address of receiving party(ies):

   Name: Acadia Pharmaceuticals, Inc.
   Street Address: 3911 Sorrento Valley Blvd.
   City: San Diego **State:** CA
   ZIP: 92121-1402

   Additional name(s) of receiving party(ies) attached?

   ( ) Yes (X) No

3. Nature of conveyance:

   (X) Assignment ( ) Security Agreement
   ( ) Merger ( ) Change of Name
   ( ) Other:

   Execution Date: (List as in section 1 if multiple signatures)

   a. January 18, 2008
   b. December 28, 2007

4. US or PCT Application number(s) or US Patent number(s):

   (X) Patent Application No.: 10/759,561
   Filing Date: January 15, 2004

   Additional numbers attached?

   (X) Yes ( ) No

5. Party to whom correspondence concerning document should be mailed:

   Customer No. 20,995
   Address: Knobbe, Martens, Olson & Bear, LLP
   2040 Main Street, 14th Floor
   Irvine, CA 92614
   Return Fax: (949) 760-9502
   Attorney's Docket Nos.: ACADIA.030A, ACADIA.030C1, ACADIA.030C2, ACADIA.030C3

6. Total number of applications and patents involved: Four (4)

7. Total fee (37 CFR 1.21(h)): $160

   (X) Authorized to be charged to deposit account

8. Deposit account number: 11-1410

   Please charge this account for any additional fees which may be required, or credit any overpayment to this account.

CH $160.00 111410 10759561

9. Statement and signature.

   To the best of my knowledge and belief, the foregoing information is true and correct, and any attached copy is a true copy of the original document.

   Ryan E. Melnick
   Name of Person Signing

   Ryan Melnick
   Signature

   7-15-08
   Date

   58,621
   Registration No.

Total number of pages including cover sheet, attachments and document: **Five (5)**

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4. US or PCT Application number(s) or US Patent number(s):

Additional numbers attached?
(X) Yes ( ) No

Patent Application No.: 11/416,527
Filing Date: May 3, 2006

Patent Application No.: 11/416,855
Filing Date: May 3, 2006

Patent Application No.: 11/416,594
Filing Date: May 3, 2006

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070308

PATENT
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Application No.: 10/759,561
Filing Date: January 15, 2004

ASSIGNMENT

WHEREAS, we, Carl-Magnus A. Andersson, a Swedish citizen, residing at Ferievägen 3, SE-245 64 Hjärup, Sweden, and Allan K. Uldam, a citizen of Denmark, residing at Skotteparken 172, 2750 Ballerup, Denmark, have invented certain new and useful improvements for SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES as a joint inventor, for which an application for Letters Patent in the United States, Application No. 10/759,561, was filed January 15, 2004;

AND WHEREAS, ACADIA Pharmaceuticals Inc. (hereinafter "ASSIGNEE"), a Delaware Corporation, with its principal place of business at 3911 Sorrento Valley Blvd., San Diego, California 92121-1402, desires to acquire the entire right, title, and interest in and to the said improvements and the said Application:

NOW, THEREFORE, in consideration of the sum of One Dollar ($1.00) to me in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, I, the said inventor, do hereby acknowledge that I have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over, unto the said ASSIGNEE, its successors, legal representatives and assigns, my entire right, title, and interest throughout the world in, to and under the said improvements, and the said application and all provisional applications relating thereto, and all divisions, renewals and continuations thereof, and all Letters Patent of the United States which may be granted thereon and all reissues and extensions thereof, and all rights of priority under International Conventions and applications for Letters Patent which may hereafter be filed for said improvements in any country or countries foreign to the United States, and all Letters Patent which may be granted for said improvements in any country or countries foreign to the United States and all extensions, renewals and reissues thereof; and I hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said improvements to the said ASSIGNEE, its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND I DO HEREBY sell, assign, transfer, and convey to ASSIGNEE, its successors, legal representatives, and assigns all claims for damages and all remedies arising out of any violation of the rights assigned hereby that may have accrued prior to the date of assignment to ASSIGNEE, or may accrue hereafter, including, but not limited to, the right to sue for, collect, and retain damages for past infringements of the said Letters Patent before or after issuance.

AND I HEREBY covenant and agree that I will communicate to the said ASSIGNEE, its successors, legal representatives and assigns, any facts known to me respecting said improvements, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything possible to aid the said ASSIGNEE, its successors, legal representatives and assigns, to obtain and enforce proper patent protection for said improvements in all countries.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 18 day of January, 2008

Carl-Magnus A. Andersson

STATE OF SWEDEN)
) ss.
COUNTY OF Scania)

On January 18, 2008, before me, Notary Public of Malmö, personally appeared Carl-Magnus A. Andersson ~~personally known to me~~ (or proved to me on the basis of satisfactory evidence) to be the person(~~s~~) whose name(~~s~~) is/~~are~~ subscribed to the within instrument, and acknowledged to me that he executed the

Application No.: 10/759,561
Filing Date: January 15, 2004

same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), ~~or the entity upon behalf of which the person(s) acted~~, executed the instrument.

WITNESS my hand and official seal.

[SEAL]

Exp.no. 080264
Fee SEK 310:-

NOTARIUS PUBLICUS • MALMÖ •

Notary Signature
Christopher Lagström
Notary Public of Malmö, Sweden

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this _____ day of _____, 20__.

Allan K. Uldam

STATE OF)
} ss.
COUNTY OF)

On _____, before me, _____, personally appeared Allan K. Uldam personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL]

Notary Signature

4547626:ssd
111607

same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL]

Notary Signature

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 28 day of DECEMBER, 2007

Allan K. Uldam

STATE OF)
} ss.
COUNTY OF)

Lis Schoustrup-Thomsen
Notar

On 12-28, before me, _____, personally appeared Allan K. Uldam personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL]

Lis Schoustrup-Thomsen
Notar

Notary Signature

RETTEN I LYNGBY
DANMARKS DOMSTOLE
PUBLICUS

NOTARIUS PUBLICUS

Lis Schoustrup-Thomsen
Notar

4547626:sad
111607

EXHIBIT C—Copy of Approved Label for NUPLAZID™

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

NUPLAZID™ (pimavanserin) tablets, for oral use
Initial U.S. Approval: 2016

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis. (5.1)**

----------INDICATIONS AND USAGE----------

NUPLAZID is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. (1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dose is 34 mg, taken orally as two 17 mg tablets once daily, without titration. (2)
- Can be taken with or without food. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 17 mg. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- QT Interval Prolongation: Increases in QT interval; avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥5% and twice the rate of placebo): peripheral edema and confusional state. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ACADIA Pharmaceuticals Inc. at 1-844-422-2342 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong CYP3A4 Inhibitors (e.g., ketoconazole): Reduce NUPLAZID dose by one-half. (2.2, 7.1)
- Strong CYP3A4 Inducers: Monitor for reduced efficacy. Increase in NUPLAZID dosage may be needed. (2.2, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Renal Impairment: No dosage adjustment for NUPLAZID is needed in patients with mild to moderate renal impairment. Use of NUPLAZID is not recommended in patients with severe renal impairment. (8.6)
- Hepatic Impairment: Use of NUPLAZID is not recommended in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

NUPLAZID™ is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The recommended dose of NUPLAZID is 34 mg, taken orally as two 17 mg strength tablets once daily, without titration.

NUPLAZID can be taken with or without food.

2.2 Dosage Modifications for Concomitant Use with CYP3A4 Inhibitors and Inducers

- Coadministration with Strong CYP3A4 Inhibitors
  The recommended dose of NUPLAZID when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole) is 17 mg, taken orally as one tablet once daily *[see Drug Interactions (7.1)]*.
- Coadministration with Strong CYP3A4 Inducers
  Monitor patients for reduced efficacy if NUPLAZID is used concomitantly with strong CYP3A4 inducers; an increase in NUPLAZID dosage may be needed *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

NUPLAZID (pimavanserin) is available as 17 mg strength tablets. The white to off-white, round, coated tablets are debossed on one side with a "P" and "17" on the reverse side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Antipsychotic drugs increase the all-cause risk of death in elderly patients with dementia-related psychosis. Analyses of 17 dementia-related psychosis placebo-controlled trials (modal duration of 10 weeks and largely in patients taking atypical antipsychotic drugs) revealed a risk of death in the drug-treated patients of between 1.6- to 1.7-times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. NUPLAZID is not approved for the treatment

of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis *[see Boxed Warning]*.

5.2 QT Interval Prolongation

NUPLAZID prolongs the QT interval. The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin) *[see Drug Interactions (7.1)]*. NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval *[see Clinical Pharmacology (12.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials 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 clinical trial database for NUPLAZID consists of over 1200 subjects and patients exposed to one or more doses of NUPLAZID. Of these, 616 were patients with hallucinations and delusions associated with Parkinson's disease psychosis (PDP). In the placebo-controlled setting, the majority of experience in patients comes from studies evaluating once-daily NUPLAZID doses of 34 mg (N=202) compared to placebo (N=231) for up to 6 weeks. In the controlled trial setting, the study population was approximately 64% male and 91% Caucasian, and the mean age was about 71 years at study entry. Additional clinical trial experience in patients with hallucinations and delusions associated with PDP comes from two open-label, safety extension studies (total N=497). The majority of patients receiving long-term treatment received 34 mg once-daily (N=459). Over 300 patients have been treated for more than 6 months; over 270 have been treated for at least 12 months; and over 150 have been treated for at least 24 months.

The following adverse reactions are based on the 6-week, placebo-controlled studies in which NUPLAZID was administered once daily to patients with hallucinations and delusions associated with PDP.

Common Adverse Reactions (incidence ≥5% and at least twice the rate of placebo): peripheral edema (7% NUPLAZID 34 mg vs. 2% placebo) and confusional state (6% NUPLAZID 34 mg vs. 3% placebo).

Adverse Reactions Leading to Discontinuation of Treatment

A total of 8% (16/202) of NUPLAZID 34 mg-treated patients and 4% (10/231) of placebo-treated patients discontinued because of adverse reactions. The adverse reactions that occurred in more than one patient and with an incidence at least twice that of placebo were hallucination (2% NUPLAZID vs. <1% placebo), urinary tract infection (1% NUPLAZID vs. <1% placebo), and fatigue (1% NUPLAZID vs. 0% placebo).

Adverse reactions that occurred in 6-week, placebo-controlled studies and that were reported at an incidence of ≥2% and >placebo are presented in **Table 1**.

Table 1 Adverse Reactions in Placebo-Controlled Studies of 6-Week Treatment Duration and Reported in ≥2% and >Placebo

Percentage of Patients Reporting Adverse Reaction		
	NUPLAZID 34 mg	**Placebo**
	N=202	N=231
Gastrointestinal disorders		
Nausea	7%	4%
Constipation	4%	3%
General disorders		
Peripheral edema	7%	2%
Gait disturbance	2%	<1%
Psychiatric disorders		
Hallucination[a]	5%	3%
Confusional state	6%	3%

[a] Hallucination includes visual, auditory, tactile, and somatic hallucinations.

Adverse Reactions in Demographic Subgroups

Examination of population subgroups in the 6-week, placebo-controlled studies did not reveal any differences in safety on the basis of age (≤75 vs. >75 years) or sex. Because the study population was predominantly Caucasian (91%; consistent with reported demographics for PD/PDP), racial or ethnic differences in the safety profile of NUPLAZID could not be assessed. In addition, in the 6-week, placebo-controlled studies, no clinically relevant differences in the incidence of adverse reactions were observed among those with a Mini-Mental State Examination (MMSE) score at entry of <25 versus those with scores ≥25.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with NUPLAZID

Table 2 Clinically Important Drug Interactions with NUPLAZID

QT Interval Prolongation	
Clinical Impact:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of NUPLAZID and increase the risk of cardiac arrhythmia.
Intervention:	Avoid the use of NUPLAZID in combination with other drugs known to prolong QT interval *[see Warnings and Precautions (5.2)]*.
Examples:	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide; Class 3 antiarrhythmics: amiodarone, sotalol; Antipsychotics: ziprasidone, chlorpromazine, thioridazine; Antibiotics: gatifloxacin, moxifloxacin
Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of NUPLAZID with a strong CYP3A4 inhibitor increases pimavanserin exposure *[see Clinical Pharmacology (12.3)]*.
Intervention:	If NUPLAZID is used with a strong CYP3A4 inhibitor, reduce the dosage of NUPLAZID *[see Dosage and Administration (2.2)]*.
Examples:	itraconazole, ketoconazole, clarithromycin, indinavir
Strong CYP3A4 Inducers	
Clinical Impact:	Concomitant use of a strong CYP3A4 inducer may reduce pimavanserin exposure resulting in a potential decrease in efficacy.
Intervention:	Patients should be monitored for reduced efficacy and an increase in dosage may be needed if NUPLAZID is used concomitantly with strong CYP3A4 inducers *[see Dosage and Administration (2.2)]*.
Examples:	rifampin, carbamazepine, phenytoin, St. John's wort

7.2 Drugs Having No Clinically Important Interactions with NUPLAZID

Based on pharmacokinetic studies, no dosage adjustment of carbidopa/levodopa is required when administered concomitantly with NUPLAZID *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on NUPLAZID use in pregnant women that would allow assessment of the drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, no adverse developmental effects were seen when pimavanserin was administered orally to rats or rabbits during the period of organogenesis at doses up to 10- or 12-times the maximum recommended human dose (MRHD) of 34 mg/day, respectively. Administration of pimavanserin to pregnant rats during pregnancy and lactation resulted in maternal toxicity and lower pup survival and body weight at doses which are 2-times the MRHD of 34 mg/day *[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 2-4% and 15-20%, respectively.

Data

Animal Data

Pimavanserin was not teratogenic in pregnant rats when administered during the period of organogenesis at oral doses of 0.9, 8.5, and 51 mg/kg/day, which are 0.2- and 10-times the maximum recommended human dose (MRHD) of 34 mg/day based on AUC at mid and high doses, respectively. Maternal toxicity included reduction in body weight and food consumption at the highest dose.

Administration of pimavanserin to pregnant rats during pregnancy and lactation at oral doses of 8.5, 26, and 51 mg/kg/day, which are 0.14- to 14-times the MRHD of 34 mg/day based on AUC, caused maternal toxicity, including mortality, clinical signs including dehydration, hunched posture, and rales, and decreases in body weight, and/or food consumption at doses ≥26 mg/kg/day (2-times the MRHD based on AUC). At these maternally toxic doses there was a decrease in pup survival, reduced litter size, and reduced pup weights, and food consumption. Pimavanserin had no effect on sexual maturation, neurobehavioral function including learning and memory, or reproductive function in the first generation pups up to 14-times the MHRD of 34 mg/day based on AUC.

Pimavanserin was not teratogenic in pregnant rabbits during the period of organogenesis at oral doses of 4.3, 43, and 85 mg/kg/day, which are 0.2- to 12-times the MHRD of 34 mg/day based on AUC. Maternal toxicity, including mortality, clinical signs of dyspnea and rales, decreases in body weight and/or food consumption, and abortions occurred at doses 12-times the MRHD of 34 mg/day based on AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of pimavanserin in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUPLAZID and any potential adverse effects on the breastfed infant from NUPLAZID or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of NUPLAZID have not been established in pediatric patients.

8.5 Geriatric Use

No dose adjustment is required for elderly patients.

Parkinson's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the 6-week clinical studies with NUPLAZID *[see Adverse Reactions (6.1)]* was 71 years, with 49% 65-75 years old and 31% >75 years old. In the pooled population of patients enrolled in 6-week, placebo-controlled studies (N=614), 27% had MMSE scores from 21 to 24 compared to 73% with scores ≥25. No clinically meaningful differences in safety or effectiveness were noted between these two groups.

8.6 Renal Impairment

No dosage adjustment for NUPLAZID is needed in patients with mild to moderate (CrCL ≥30 mL/min, Cockcroft-Gault) renal impairment *[see Clinical Pharmacology (12.3)]*.

Use of NUPLAZID is not recommended in patients with severe renal impairment (CrCL <30 mL/min, Cockcroft-Gault). NUPLAZID has not been evaluated in this patient population.

8.7 Hepatic Impairment

Use of NUPLAZID is not recommended in patients with hepatic impairment. NUPLAZID has not been evaluated in this patient population.

8.8 Other Specific Populations
No dosage adjustment is required based on patient's age, sex, ethnicity, or weight. These factors do not affect the pharmacokinetics of NUPLAZID *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
NUPLAZID is not a controlled substance.

9.2 Abuse
NUPLAZID has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence.

While short-term, placebo-controlled and long-term, open-label clinical trials did not reveal increases in drug-seeking behavior, the limited experience from the clinical trials do not predict the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.

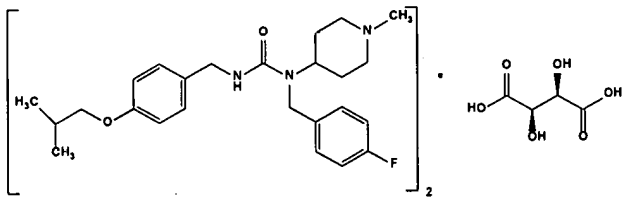
10 OVERDOSAGE

10.1 Human Experience
The pre-marketing clinical trials involving NUPLAZID in approximately 1200 subjects and patients do not provide information regarding symptoms with overdose. In healthy subject studies, dose-limiting nausea and vomiting were observed.

10.2 Management of Overdose
There are no known specific antidotes for NUPLAZID. In managing overdose, cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias *[see Warnings and Precautions (5.2)]*. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of NUPLAZID *[see Drug Interactions (7.1)]*. Consider the long plasma half-life of pimavanserin (about 57 hours) and the possibility of multiple drug involvement. Consult a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice.

11 DESCRIPTION

NUPLAZID contains pimavanserin, an atypical antipsychotic, which is present as pimavanserin tartrate salt with the chemical name, urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N'*-[[4-(2-methylpropoxy)phenyl]methyl]-,(2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1). Pimavanserin tartrate is freely soluble in water. Its molecular formula is $(C_{25}H_{34}FN_3O_2)_2 \cdot C_4H_6O_6$ and its molecular weight is 1005.20 (tartrate salt). The chemical structure is:



The molecular formula of pimavanserin free base is $C_{25}H_{34}FN_3O_2$ and its molecular weight is 427.55.

NUPLAZID tablets are intended for oral administration only. Each round, white to off-white, immediate-release, film-coated tablet contains 20 mg of pimavanserin tartrate, which is equivalent to 17 mg of

pimavanserin free base. Inactive ingredients include pregelatinized starch, magnesium stearate, and microcrystalline cellulose. Additionally, the following inactive ingredients are present as components of the film coat: hypromellose, talc, titanium dioxide, polyethylene glycol, and saccharin sodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of pimavanserin in the treatment of hallucinations and delusions associated with Parkinson's disease psychosis is unknown. However, the effect of pimavanserin could be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors and to a lesser extent at serotonin 5-HT_{2C} receptors.

12.2 Pharmacodynamics

In vitro, pimavanserin acts as an inverse agonist and antagonist at serotonin 5-HT_{2A} receptors with high binding affinity (K_i value 0.087 nM) and at serotonin 5-HT_{2C} receptors with lower binding affinity (K_i value 0.44 nM). Pimavanserin shows low binding to sigma 1 receptors (K_i value 120 nM) and has no appreciable affinity (K_i value >300 nM), to serotonin 5-HT_{2B}, dopaminergic (including D_2), muscarinic, histaminergic, or adrenergic receptors, or to calcium channels.

Cardiac Electrophysiology

The effect of NUPLAZID on the QTc interval was evaluated in a randomized placebo- and positive-controlled double-blind, multiple-dose parallel thorough QTc study in 252 healthy subjects. A central tendency analysis of the QTc data at steady-state demonstrated that the maximum mean change from baseline (upper bound of the two-sided 90% CI) was 13.5 (16.6) msec at a dose of twice the therapeutic dose. A pharmacokinetic/ pharmacodynamic analysis with NUPLAZID suggested a concentration-dependent QTc interval prolongation in the therapeutic range.

In the 6-week, placebo-controlled effectiveness studies, mean increases in QTc interval of ~5-8 msec were observed in patients receiving once-daily doses of NUPLAZID 34 mg. These data are consistent with the profile observed in a thorough QT study in healthy subjects. Sporadic QTcF values ≥500 msec and change from baseline values ≥60 msec were observed in subjects treated with NUPLAZID 34 mg; although the incidence was generally similar for NUPLAZID and placebo groups. There were no reports of torsade de pointes or any differences from placebo in the incidence of other adverse reactions associated with delayed ventricular repolarization in studies of NUPLAZID, including those patients with hallucinations and delusions associated with PDP *[see Warnings and Precautions (5.2)]*.

12.3 Pharmacokinetics

Pimavanserin demonstrates dose-proportional pharmacokinetics after single oral doses from 17 to 255 mg (0.5- to 7.5-times the recommended dosage). The pharmacokinetics of pimavanserin are similar in both the study population and healthy subjects. The mean plasma half-lives for pimavanserin and the active metabolite (*N*-desmethylated metabolite) are approximately 57 hours and 200 hours, respectively.

Absorption

The median T_{max} of pimavanserin was 6 (range 4-24) hours and was generally unaffected by dose.
The bioavailability of pimavanserin oral tablet and pimavanserin solution was essentially identical.
The formation of the major circulating *N*-desmethylated metabolite AC-279 (active) from pimavanserin occurs with a median T_{max} of 6 hours.

Ingestion of a high-fat meal had no significant effect on rate (C_{max}) and extent (AUC) of pimavanserin exposure. C_{max} decreased by about 9% while AUC increased by about 8% with a high-fat meal.

Distribution

Pimavanserin is highly protein bound (~95%) in human plasma. Protein binding appeared to be dose-independent and did not change significantly over dosing time from Day 1 to Day 14. Following administration of a single dose of NUPLAZID (34 mg), the mean (SD) apparent volume of distribution was 2173 (307) L.

Elimination

Metabolism

Pimavanserin is predominantly metabolized by CYP3A4 and CYP3A5 and to a lesser extent by CYP2J2, CYP2D6, and various other CYP and FMO enzymes. CYP3A4 is the major enzyme responsible for the formation of its major active metabolite (AC-279). Pimavanserin does not cause clinically significant CYP inhibition or induction of CYP3A4. Based on *in vitro* data, pimavanserin is not an irreversible inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4).

Based on *in vitro* studies, transporters play no significant role in the disposition of pimavanserin.

AC-279 is neither a reversible or irreversible (metabolism-dependent) inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). AC-279 does not cause clinically significant CYP3A induction and is not predicted to cause induction of any other CYP enzymes involved in drug metabolism.

Excretion

Approximately 0.55% of the 34 mg oral dose of ^{14}C-pimavanserin was eliminated as unchanged drug in urine and 1.53% was eliminated in feces after 10 days.

Less than 1% of the administered dose of pimavanserin and its active metabolite AC-279 were recovered in urine.

Specific Populations

Population PK analysis indicated that exposure of pimavanserin in patients with mild to moderate renal impairment was similar to exposure in patients with normal renal function. Age, sex, ethnicity, and weight do not have clinically relevant effect on the pharmacokinetics of pimavanserin.

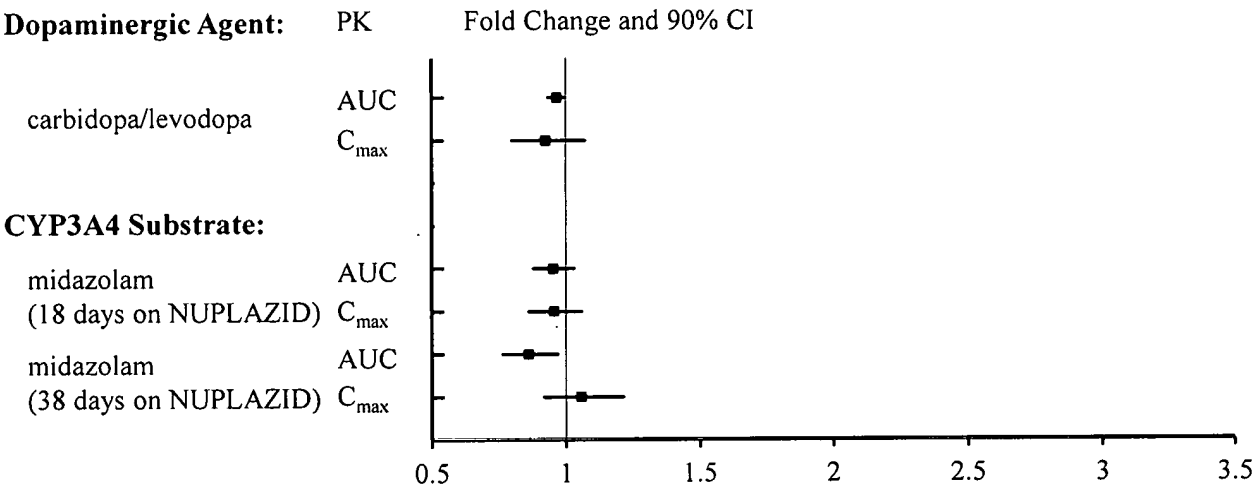
Pimavanserin has not been studied in patients with severe renal impairment or mild to severe hepatic impairment *[see Use in Specific Populations (8.6, 8.7)]*.

Drug Interaction Studies

CYP3A4 Inhibitor: ketoconazole, a strong inhibitor of CYP3A4, increased pimavanserin C_{max} by 1.5-fold and AUC by 3-fold *[see Dosage and Administration (2.2) and Drug Interactions (7.1)]*.

The effect of pimavanserin on other drugs is shown in **Figure 1**.

Figure 1 The Effects of Pimavanserin on the Pharmacokinetics of Other Drugs



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There was no increase in the incidence of tumors following daily oral administration of pimavanserin to mice or rats for 2 years. Mice were administered pimavanserin at oral doses of 2.6, 6, and 13 (males)/8.5, 21, and 43 mg/kg/day (females) which are 0.01- to 1- (males)/0.5- to 7- (females) times the MRHD of 34 mg/day based on AUC. Rats were administered pimavanserin at oral doses of 2.6, 8.5, and 26 (males)/4.3, 13, and 43 mg/kg/day (females) which are 0.01- to 4- (males)/0.04- to 16- (females) times the MRHD of 34 mg/day based on AUC.

Mutagenesis

Pimavanserin was not mutagenic in the *in vitro* Ames reverse mutation test, or in the *in vitro* mouse lymphoma assay, and was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

Pimavanserin was administered orally to male and female rats before mating, through mating, and up to Day 7 of gestation at doses of 8.5, 51, and 77 mg/kg/day, which are approximately 2-, 15-, and 22-times the maximum recommended human dose (MRHD) of 34 mg/day based on mg/m^2, respectively. Pimavanserin had no effect on fertility or reproductive performance in male and female rats at doses up to 22-times the MRHD of 34 mg based on mg/m^2. Changes in uterine parameters (decreases in the number of corpora lutea, number of implants, viable implants, and increases in pre-implantation loss, early resorptions and post-implantation loss) occurred at the highest dose which was also a maternally toxic dose. Changes in sperm parameters (decreased density and motility) and microscopic findings of cytoplasmic vacuolation in the epididymis occurred at doses approximately 15-times the MRHD of 34 mg/day based on mg/m^2.

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (foamy macrophages and/or cytoplasmic vacuolation) was observed in multiple tissues and organs of mice, rats, and monkeys as early as 14 days following oral daily administration of pimavanserin. The most severely affected organs were the lungs and kidneys. The occurrence of phospholipidosis was both dose- and duration-dependent. Diffuse phospholipidosis with focal/multifocal chronic inflammation was

observed in the lungs of rats treated for ≥3 months at doses ≥10-times the maximum recommended human dose (MRHD) of 34 mg/day based on AUC. As a result of chronic inflammation, inflammatory lung fibrosis was observed in rats treated for 3 and 6 months at doses ≥18-times the MRHD of 34 mg/day based on AUC. The findings in the lungs correlated with increased lung weights (up to 3-times those of controls) and respiratory-related clinical signs including rales, labored breathing, and gasping. Phospholipidosis in lungs of rats caused mortality at doses ≥16-times the MRHD of 34 mg/day based on AUC. The estimated No Observed Effect Level (NOEL) for chronic lung inflammation in rats is 5-fold the MRHD of 34 mg/day based on AUC. Phospholipidosis was associated with increased kidney weights and tubular degeneration in rats at doses ≥10-times the MRHD of 34 mg/day based on AUC. The relevance of these findings to human risk is not known.

14 CLINICAL STUDIES

The efficacy of NUPLAZID 34 mg as a treatment of hallucinations and delusions associated with Parkinson's disease psychosis was demonstrated in a 6-week, randomized, placebo-controlled, parallel-group study. In this outpatient study, 199 patients were randomized in a 1:1 ratio to NUPLAZID 34 mg or placebo once daily. Study patients (male or female and aged 40 years or older) had a diagnosis of Parkinson's disease (PD) established at least 1 year prior to study entry and had psychotic symptoms (hallucinations and/or delusions) that started after the PD diagnosis and that were severe and frequent enough to warrant treatment with an antipsychotic. At entry, patients were required to have a Mini-Mental State Examination (MMSE) score ≥21 and to be able to self-report symptoms. The majority of patients were on PD medications at entry; these medications were required to be stable for at least 30 days prior to study start and throughout the study period.

The PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) was used to evaluate the efficacy of NUPLAZID 34 mg. SAPS-PD is a 9-item scale adapted for PD from the Hallucinations and Delusions domains of the SAPS. Each item is scored on a scale of 0-5, with 0 being none and 5 representing severe and frequent symptoms. Therefore, the SAPS-PD total score can range from 0 to 45 with higher scores reflecting greater severity of illness. A negative change in score indicates improvement. Primary efficacy was evaluated based on change from baseline to Week 6 in SAPS-PD total score.

As shown in **Table 3**, **Figure 2**, and **Figure 3**, NUPLAZID 34 mg (n=95) was statistically significantly superior to placebo (n=90) in decreasing the frequency and/or severity of hallucinations and delusions in patients with PDP as measured by central, independent, and blinded raters using the SAPS-PD scale. An effect was seen on both the hallucinations and delusions components of the SAPS-PD.

Table 3 Primary Efficacy Analysis Result Based on SAPS-PD (N=185)

Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
SAPS-PD	NUPLAZID	15.9 (6.12)	-5.79 (0.66)	-3.06* (-4.91, -1.20)
	Placebo	14.7 (5.55)	-2.73 (0.67)	--
SAPS-PD Hallucinations[b]	NUPLAZID	11.1 (4.58)	-3.81 (0.46)	-2.01 (-3.29, -0.72)
	Placebo	10.0 (3.80)	-1.80 (0.46)	--
SAPS-PD Delusions[b]	NUPLAZID	4.8 (3.59)	-1.95 (0.32)	-0.94 (-1.83, -0.04)
	Placebo	4.8 (3.82)	-1.01 (0.32)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
[b] Supportive analysis.
* Statistically significantly superior to placebo.

The effect of NUPLAZID on SAPS-PD improved through the six-week trial period, as shown in **Figure 2**.

Figure 2 SAPS-PD Change from Baseline through 6 Weeks Total Study Treatment

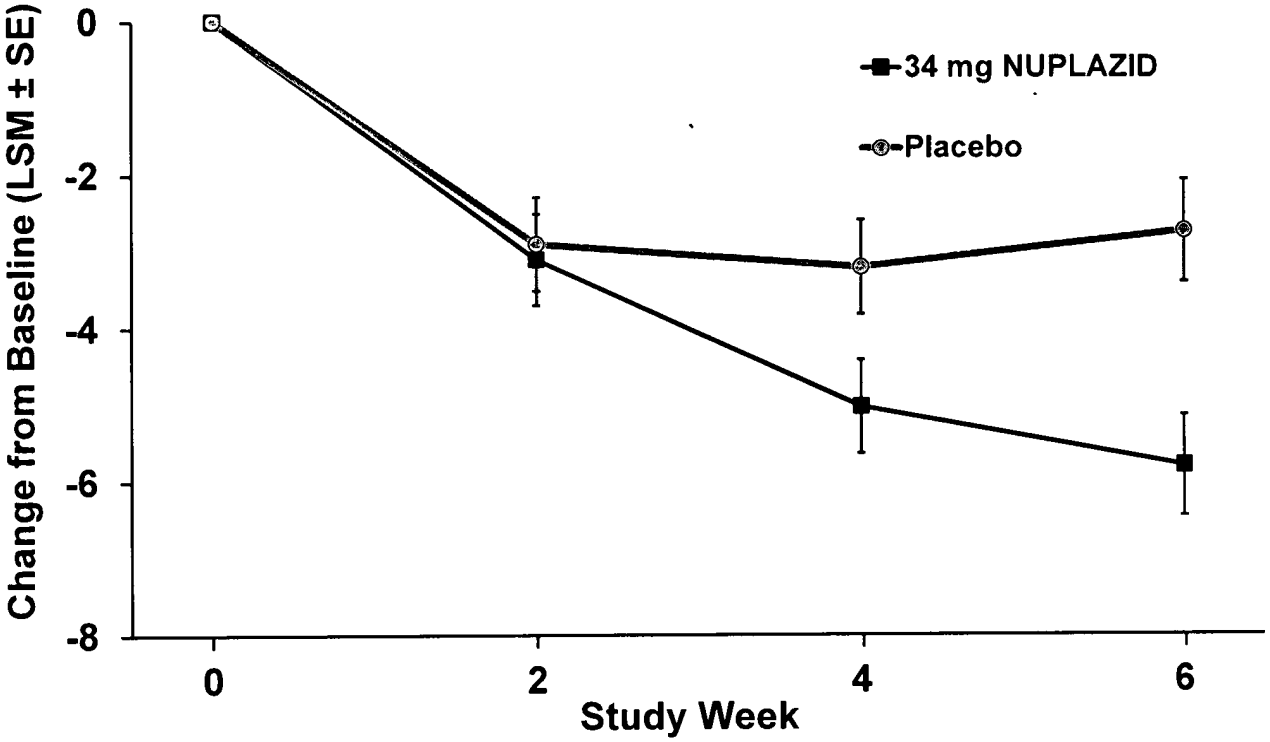
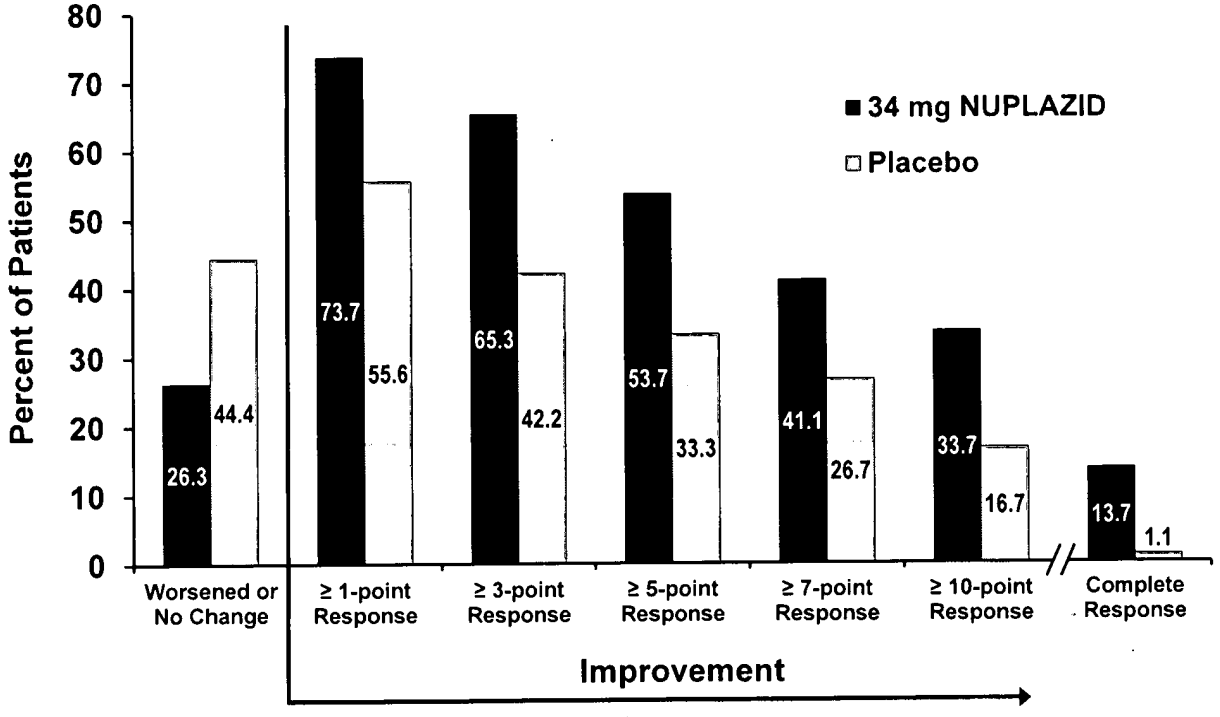


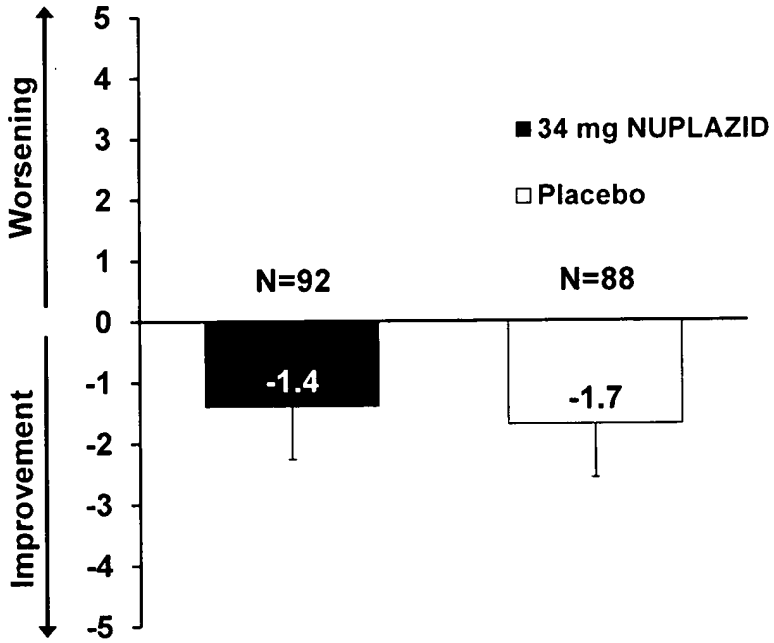
Figure 3 Proportion of Patients with SAPS-PD Score Improvement at the End of Week 6 (N=185)



Complete response = SAPS-PD score reduced to zero from baseline value.
Patients with missing values were counted as non-responders.

Motor Function in Patients with Hallucinations and Delusions Associated with Parkinson's Disease Psychosis
NUPLAZID 34 mg did not show an effect compared to placebo on motor function, as measured using the Unified Parkinson's Disease Rating Scale Parts II and III (UPDRS Parts II+III) (**Figure 4**). A negative change in score indicates improvement. The UPDRS Parts II+III was used to assess the patient's Parkinson's disease state during the 6-week double-blind treatment period. The UPDRS score was calculated as the sum of the 40 items from activities of daily living and motor examination, with a range of 0 to 160.

Figure 4 Motor Function Change from Baseline to Week 6 in UPDRS Parts II+III (LSM - SE)



LSM: least-squares mean; SE: standard error. The error bars extend one SE below the LSM.

16 HOW SUPPLIED/STORAGE AND HANDLING

NUPLAZID (pimavanserin) tablets are available as:

17 mg Tablet:
White to off-white, round, coated tablet debossed with "P" on one side and "17" on the reverse.
Bottle of 60: NDC 63090-170-60

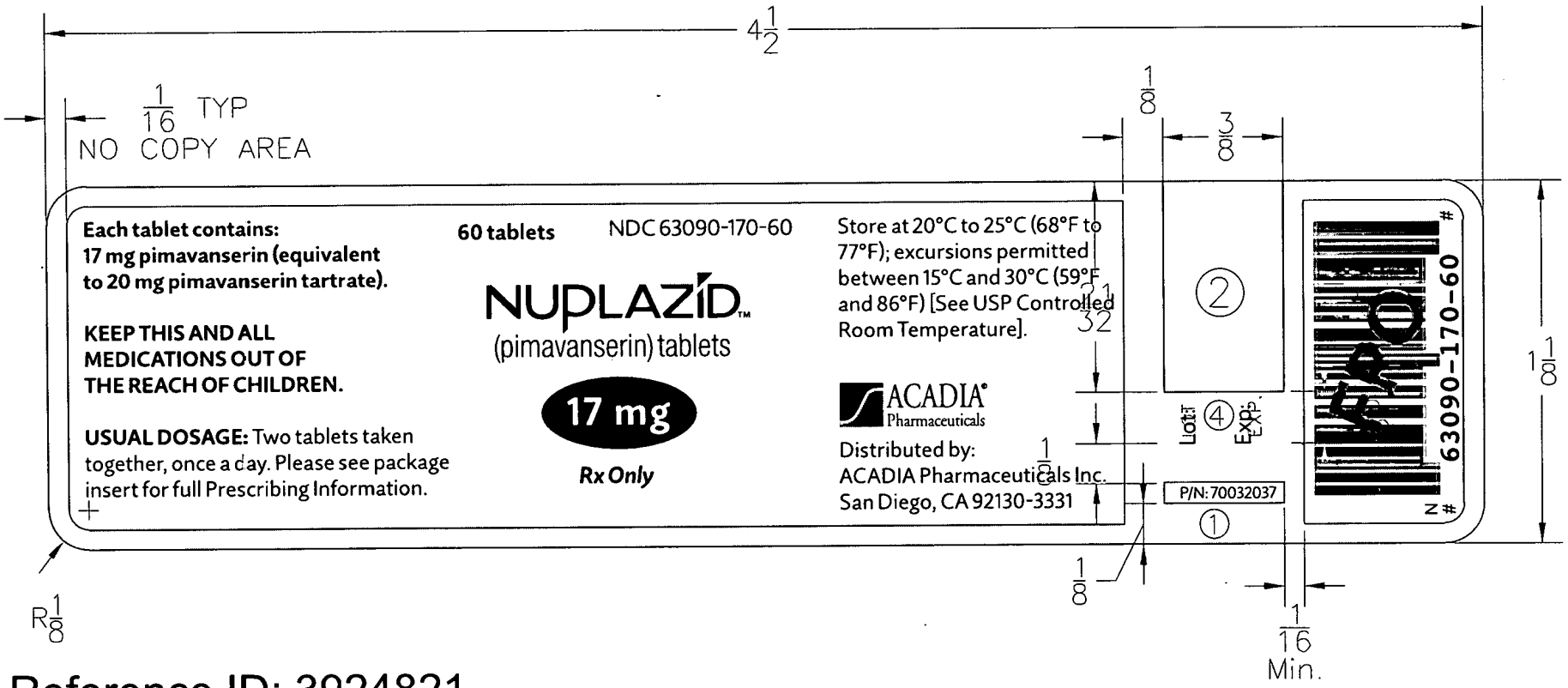
Storage
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

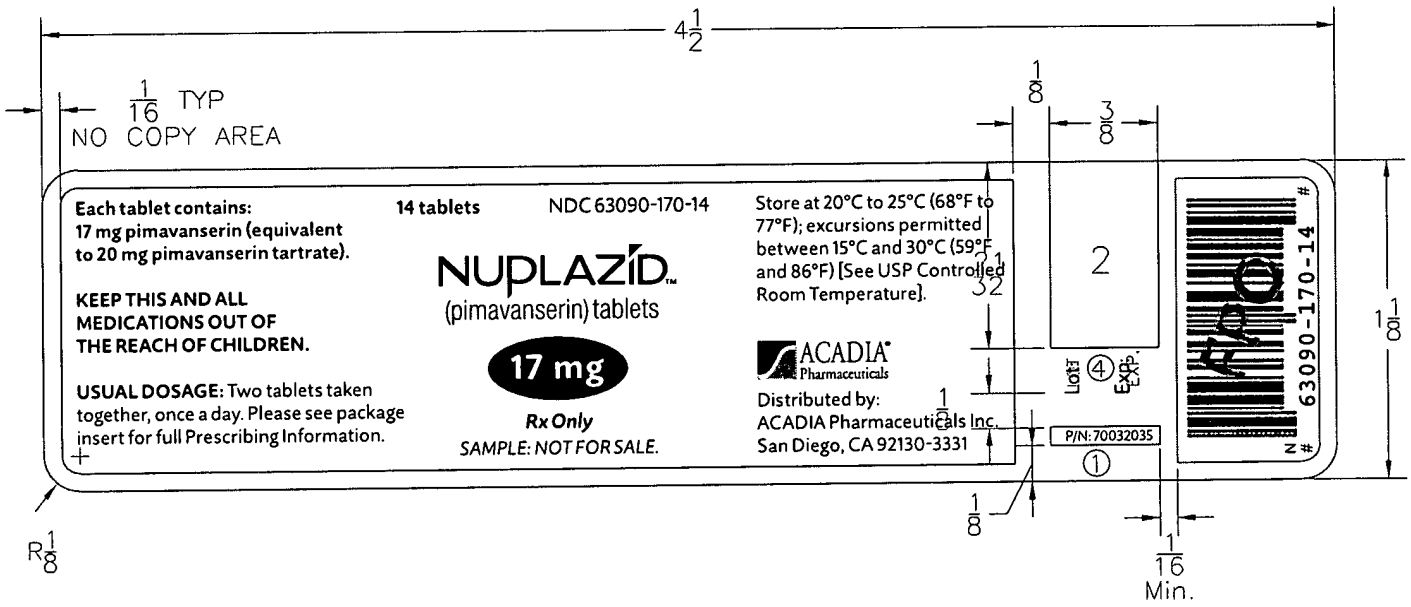
Concomitant Medication
Advise patients to inform their healthcare providers if there are any changes to their current prescription or over-the-counter medications, since there is a potential for drug interactions *[see Warnings and Precautions (5.2), Drug Interactions (7)]*.

Distributed by:
ACADIA Pharmaceuticals Inc.
San Diego, CA 92130 USA

NUPLAZID™ is a trademark of ACADIA Pharmaceuticals Inc.



Reference ID: 3924821


4 1/2
1/16 TYP
NO COPY AREA
1/8
3/8
Each tablet contains:
17 mg pimavanserin (equivalent to 20 mg pimavanserin tartrate).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
USUAL DOSAGE: Two tablets taken together, once a day. Please see package insert for full Prescribing Information.
14 tablets
NDC 63090-170-14
NUPLAZID™
(pimavanserin) tablets
17 mg
Rx Only
SAMPLE: NOT FOR SALE.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].
11/32
ACADIA Pharmaceuticals
Distributed by:
ACADIA Pharmaceuticals Inc.
San Diego, CA 92130-3331
1/8
2
Lot#
④
EXP.
P/N: 70032035
①
63090-170-14
N #
1 1/8
1/8
R 1/8
1/16
Min.


14 tablets
NDC 63090-170-14
NUPLAZID™
(pimavanserin) tablets
17 mg
Rx only
SAMPLE: NOT FOR SALE.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
Rx only
NDC 63090-170-14
Each tablet contains:
17 mg pimavanserin (equivalent to 20 mg pimavanserin tartrate).
USUAL DOSAGE: Two tablets taken together once a day. Please see package insert for full Prescribing Information.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].
SAMPLE: NOT FOR SALE.
ACADIA Pharmaceuticals
©2016 ACADIA Pharmaceuticals Inc.
All rights reserved. COM-001
NUPLAZID™
(pimavanserin) tablets
14 tablets
NDC 63090-170-14
17 mg
Rx only
SAMPLE: NOT FOR SALE.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
Rx only
NDC 63090-170-14
Lot:
Exp:
SAMPLE: NOT FOR SALE.
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San Diego, CA 92130-3331
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EXHIBIT D—Copy of FDA Approval Letter for NUPLAZID™

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207318

NDA APPROVAL

ACADIA Pharmaceuticals Inc.
Attention: Blake Burrell, MS, RAC
Sr. Director, Regulatory Affairs
3611 Valley Centre Drive, Suite 300
San Diego, CA 92130

Dear Mr. Burrell:

Please refer to your New Drug Application (NDA) dated and received September 1, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nuplazid (pimavanserin) 17 mg immediate-release, film-coated oral tablets.

This new drug application provides for the use of Nuplazid (pimavanserin) immediate-release, film-coated oral tablets for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

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.

We note that your April 28, 2016, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), 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. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your April 8, 2016, submission containing final printed carton and container labels.

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 this application because necessary studies are impossible or highly impracticable, as the disease does not exist in pediatric patients.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3069-1 Conduct a randomized withdrawal trial comparing pimavanserin 34 mg/day to placebo.

The timetable you submitted on April 28, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2017
Trial Completion:	12/2020
Final Report Submission:	12/2021

3069-2 Conduct a randomized placebo-controlled trial or trials with predominantly frail and elderly subjects that would involve exposure of at least 500 subjects to pimavanserin 34 mg daily for a minimum of 8 weeks.

The timetable you submitted on April 28, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2017
Trial Completion:	05/2021
Final Report Submission:	05/2022

3069-3 Conduct an in vivo drug-drug interaction study to measure the effect of strong CYP3A4 inducers (e.g. rifampin) on the exposure to pimavanserin. Depending on the results of the study, a maximum dose could be recommended when CYP3A4 inducers are co-administered with pimavanserin.

The timetable you submitted on April 28, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2017
Study Completion:	06/2018
Final Report Submission:	12/2018

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3069-4 Perform microscopic re-evaluation of lung tissue samples using special stains to detect collagen from high dose (30 mg/kg/day male and female groups) of the 6-month rat study (SNBL.146.02), the high dose groups (30 mg/kg/day male and 50 mg/kg/day female) from the 2-year rat carcinogenicity study (WIL-6160004), and also the high dose groups (25/60 mg/kg/day) from the 12-month monkey study (SNBL.146.01). If drug-related inflammation is detected in the lungs of any of the re-evaluated high dose groups from a particular study, then re-evaluation of lung tissue samples from the low and mid dose groups of that study should be conducted in order to identify a No Observed Effect Level (NOEL) for inflammation in the lungs of animals.

The timetable you submitted on April 28, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission:	12/2017
Final Data Submission:	12/2017

Submit clinical protocols to your IND 068384 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. 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."**

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, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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).

As required under 21 CFR 314.81(b)(3)(i), 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

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V 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 assessments. 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 these assessments.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has also 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, contact Dr. Brendan Muoio, Regulatory Project Manager, at (240) 402-4518 or brendan.muoio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director, Office of Drug Evaluation I and
Deputy Center Director for Clinical Science
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

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

/s/

ROBERT TEMPLE
04/29/2016

EXHIBIT E—Copy of Certification of Correction issued April 27, 2010, for the '740 Patent

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,601,740 B2
APPLICATION NO. : 10/759561
DATED : October 13, 2009
INVENTOR(S) : Weiner et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page,

Item [*] Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 USC 154(b) by (899) days

Delete the phrase "by 899 days" and insert -- by 1,259 days --

Signed and Sealed this

Twenty-seventh Day of April, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT F—Copy of Certification of Correction issued August 25, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,601,740 B2
APPLICATION NO. : 10/759561
DATED : October 13, 2009
INVENTOR(S) : Weiner et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1,249 days.

Signed and Sealed this
Twenty-fifth Day of August, 2015

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

EXHIBIT G—Copy of Maintenance Fee Statement

United States Patent and Trademark Office

Office of the Commissioner for Patents

Maintenance Fee Statement

KNOBBE MARTENS OLSON & BEAR LLP 2040 MAIN STREET FOURTEENTH FLOOR IRVINE, US 92614	20995	SMALL	06/21/2016 18:04:43

Invention

SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES

7601740	10759561	01/15/2004	10/13/2009

Payment Details

04/18/2013	041813RAMBULKS00006495032641	ACADI ACADIA.030 (A)	$800.00

2551	MAINTENANCE FEE DUE AT 3.5 YEARS	041813RAMBULKS00006495	$800.00

EXHIBIT H—Brief Description of Significant Activities

TABLE 1: IND 68,384

Date	From	To	Classification	Description
9-Oct-2003	ACADIA	FDA	Initial IND	IND submission
17-Oct-2003	FDA	ACADIA	fax	Official FDA 7/2/03 pre-IND meeting minutes.
17-Oct-2003	ACADIA	FDA	letter	Response to FDA Request for 10 desk copies of Vol. 1 of IND.
20-Oct-2003	FDA	ACADIA	letter	Letter from Teresa Wheelous (FDA) to F. Attarchi acknowledging submission of 10/9/03 (received on 10/10/03) and assigned the project to IND 68,384.
7-Nov-2003	FDA	ACADIA	fax	FDA fax to confirm verbal changes being requested for study.
10-Nov-2003	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-005
14-Nov-2003	ACADIA	FDA	General Correspondence	Meeting minutes from 12-Nov-03 teleconference
17-Dec-2003	FDA	ACADIA	fax	CMC comments.
17-Dec-2003	ACADIA	FDA	Protocol Amendment	New Protocol ACP-103-006
5-Jan-2004	ACADIA	FDA	Protocol Amendment	ACP-103-005 Amend. 2
23-Jan-2004	ACADIA	FDA	Protocol Amendment, Information Amendment	Change in protocol: ACP-103-006 Response to FDA request (CMC); Transfer of Regulatory Obligations
6-Feb-2004	ACADIA	FDA	Information Amendment	Summary of changes to ACP-103-002 CSR
19-Mar-2004	ACADIA	FDA	Protocol Amendment	New investigator ACP-103-005
30-Apr-2004	ACADIA	FDA	General Correspondence	IND access authorization letter for NIH/NINDS
21-May-2004	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-006
28-May-2004	ACADIA	FDA	Other	Revisions to 1572 for ACP-103-005
9-Jul-2004	ACADIA	FDA	General Correspondence	Question to Division re: safety extension studies
15-Jul-2004	ACADIA	FDA	IND Safety Report	Mfr report # ACP-103-006-SAE001
9-Aug-2004	ACADIA	FDA	Protocol Amendment	New investigator for ACP-103-006
16-Aug-2004	ACADIA	FDA	Protocol Amendment	New Protocol: ACP-103-010
29-Sep-2004	ACADIA	FDA	IND Safety Report	Mfr report #ACP-103-006-SAE001 F/U #1
4-Jan-2005	ACADIA	FDA	Annual Report	Reporting period 11/10/03 - 11/9/04
11-Jan-2005	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-010
14-Jan-2005	ACADIA	FDA	IND Safety Report	Mfr report # ACP-103-006-SAE002
20-Jan-2005	ACADIA	FDA	Information Amendment	CMC
26-Jan-2005	ACADIA	FDA	Protocol Amendment	New investigator: 1572 revision for 103-006
8-Feb-2005	ACADIA	FDA	IND Safety Report	Mfr report # ACP-103-006-SAE002 FU #1

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
18-Feb-2005	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-010
22-Feb-2005	ACADIA	FDA	Protocol Amendment	New investigator and revised 1572s for 103-006
8-Apr-2005	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-006
24-Aug-2005	ACADIA	FDA	IND Safety Report	Mfr reports
9-Sep-2005	ACADIA	FDA	Protocol Amendment	New investigator and revised 1572s for 103-006
16-Sep-2005	ACADIA	FDA	IND Safety Report	Mfg report # ACP-103-010-SAE004
4-Nov-2005	ACADIA	FDA	Protocol Amendment	New investigator for 103-010
2-Dec-2005	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-006
23-Dec-2005	ACADIA	FDA	IND Safety Report	Mfg report # ACP-103-010-SAE006
4-Jan-2006	ACADIA	FDA	Annual Report	Reporting period 11/10/04 - 11/9/05
7-Feb-2006	ACADIA	FDA	Protocol Amendment	New investigator for 103-010
10-May-2006	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-103-008-SAE00004
25-May-2006	ACADIA	FDA	Other	Briefing Package for Type C Meeting on June 29, 2006
27-May-2006	ACADIA	FDA	Letter	Type C Meeting briefing package desk copies (10).
19-Jun-2006	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-103-008-SAE00004 – follow up to written report
30-Jun-2006	ACADIA	FDA	Other	EOPII Clinical and Preclinical Meeting Request
30-Jun-2006	FDA	ACADIA	Email	Confirmation of attendees of the Type C telecon.
10-Jul-2006	FDA	ACADIA	Letter	FDA meeting minutes for Type C telecon on June 29, 2006.
12-Jul-2006	FDA	ACADIA	Email	eCopy of FDA meeting minutes for Type C telecon on June 29, 2006.
9-Aug-2006	ACADIA	FDA	Protocol Amendment	New investigator and revised 1572s, ACP-103-010
10-Aug-2006	ACADIA	FDA	Other	ACADIA's 29 June 2006 Type C Teleconference Minutes
18-Aug-2006	ACADIA	FDA	Email	EOPII draft preclinical section
24-Aug-2006	ACADIA	FDA	Other	EOPII Clinical/Preclinical Meeting Briefing Package
24-Aug-2006	ACADIA	FDA	email	Complete EOP2 Briefing Pkg and Questions
25-Aug-2006	ACADIA	FDA	letter	EOP2 Meeting briefing package desk copies (10) with correction - (includes corrected Pages 66-67).
1-Sep-2006	ACADIA	FDA	IND Safety Report	Mfg Report #2006ACP103000019
18-Sep-2006	FDA	ACADIA	email	FDA Pharm/Tox reviewer requested that the 3-month rat and monkey tox reports summarized in the EOP2 briefing package be submitted to the IND ASAP.
18-Sep-2006	ACADIA	FDA	email	Request for FDA's preliminary comments to EOP2 questions.
19-Sep-2006	ACADIA	FDA	Information Amendment	Preclinical: 3-month Tox Rat and Monkey

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
20-Sep-2006	ACADIA	FDA	IND Safety Report	Mfg Report # 2006ACP103000021
21-Sep-2006	ACADIA	FDA	email	Questions regarding EOP2 meeting logistics.
22-Sep-2006	FDA	ACADIA	email	Agency's preliminary comments to EOP2 questions.
24-Sep-2006	ACADIA	FDA	email	Points of Discussion for EOP2 Telecon
29-Sep-2006	FDA	ACADIA	letter	Official FDA meeting minutes for EOP2 telecon on Sept. 25, 2006.
9-Oct-2006	ACADIA	FDA	Other	EOPII Clinical/Preclinical CMC Meeting Request
12-Oct-2006	ACADIA	FDA	IND Safety Report	Mfg Report #2006ACP103000021 follow up to a written report
13-Oct-2006	ACADIA	FDA	IND Safety Report	Mfg Report #2006ACP103000028
18-Oct-2006	ACADIA	FDA	email	Copy of the EOP2 CMC meeting request submission.
23-Oct-2006	ACADIA	FDA	letter	Grant of EOPII CMC meeting request.
31-Oct-2006	ACADIA	FDA	Other	General Correspondence: Provision of Draft Diagnostic Criteria for Psychosis in Parkinson's Disease: Report of an NINDS/NIMH Working Group
7-Nov-2006	ACADIA	FDA	Other	EOPII CMC Meeting Briefing Package
7-Nov-2006	ACADIA	FDA	Other	EOPII Clin/Preclin Meeting Sponsor Minutes
10-Nov-2006	ACADIA	FDA	IND Safety Report	Mfg Report #2006ACP103000028
10-Nov-2006	ACADIA	FDA	IND Safety Report	Mfg Report # 006ACP103000036
30-Nov-2006	FDA	ACADIA	email	FDA preliminary responses to EOP2 CMC meeting questions.
1-Dec-2006	ACADIA	FDA	email	Call-in information for EOP2 CMC meeting telecon.
13-Dec-2006	FDA	ACADIA	letter	Official FDA meeting minutes for EOP2 CMC telecon on 04 Dec 2006.
20-Dec-2006	ACADIA	FDA	IND Safety Report	Mfg Report # 006ACP103000036
5-Jan-2007	ACADIA	FDA	General Correspondence	NINDS acceptance of PDP criteria paper
29-Jan-2007	ACADIA	FDA	IND Safety Report	Mfg Report # 2006ACP103000036 F/U #2
9-Feb-2007	ACADIA	FDA	IND Safety Report	Mfg Report # 2006ACP103000021 F/U #2
13-Feb-2007	ACADIA	FDA	Other	12/4/06 EOPII CMC Meeting Minutes
21-Feb-2007	ACADIA	FDA	Information Amendment	CMC: Updated for Form C
16-May-2007	ACADIA	FDA	Annual Report	Annual report, reporting period 09 November 2005 through 31 March 2007
17-May-2007	ACADIA	FDA	Protocol Amendment	New protocol: ACP-103-012
21-May-2007	ACADIA	FDA	Information Amendment	CMC: (for ACP-103-012)
7-Jun-2007	ACADIA	FDA	Protocol Amendment	New protocol: ACP-103-016; New investigator.
7-Jun-2007	ACADIA	FDA	Information Amendment	CMC (for ACP-103-016)
15-Jun-2007	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
12-Jul-2007	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-012 Amend. 2; New investigator.

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
20-Jul-2007	ACADIA	FDA	Protocol Amendment	New protocol: ACP-103-015 (Amend. 1), New investigator
24-Jul-2007	ACADIA	FDA	General Correspondence	NINDS published paper
26-Jul-2007	ACADIA	FDA	IND Safety Report	Mfg Report # 2006ACP103000028 F/U #2
8-Aug-2007	FDA	ACADIA	Email	Follow-up e-mail to provide FDA telecon attendees.
8-Aug-2007	ACADIA	FDA	Protocol Amendment	New protocol: ACP-103-017, New investigator
20-Aug-2007	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
30-Aug-2007	ACADIA	FDA	Other	08/07/2007 Telecon Sponsor Meeting Minutes
30-Aug-2007	ACADIA	FDA	Email	Informed consent form for ACP-103-015.
6-Sep-2007	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-015 Amend. 2
6-Sep-2007	FDA	FDA	Email	Updegraff responding to questions regarding informed consent form
10-Sep-2007	ACADIA	FDA	Information Amendment	SPA Carcinogenicity - Rat
14-Sep-2007	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
14-Sep-2007	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015
24-Sep-2007	ACADIA	FDA	Information Amendment	Final Repro Toxicology Reports
17-Oct-2007	FDA	ACADIA	Fax	Response to CAC SPA Assessment Request.
17-Oct-2007	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
17-Oct-2007	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015
31-Oct-2007	ACADIA	FDA	Information Amendment	14-day, 13-week Mouse Toxicology Reports
31-Oct-2007	ACADIA	FDA	Information Amendment	SPA Carcinogenicity - Mouse
9-Nov-2007	ACADIA	FDA	IND Safety Report	Mfg Report # 2521AC000001
16-Nov-2007	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
5-Dec-2007	ACADIA	FDA	Email	Follow-up regarding submission of IND safety reports.
13-Dec-2007	FDA	ACADIA	Fax	Response to CAC SPA Assessment Request.
21-Dec-2007	ACADIA	FDA	Information Amendment	12-month Primate Tox Report
21-Dec-2007	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-015 Amend. 3
17-Jan-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
17-Jan-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015
15-Feb-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
17-Mar-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015
19-Mar-2008	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-012 Amend 3
19-Mar-2008	ACADIA	FDA	Protocol Amendment	New protocol: ACP-103-014; New investigator
26-Mar-2008	ACADIA	FDA	Information Amendment	CMC (for ACP-103-014)

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
4-Apr-2008	ACADIA	FDA	IND Safety Report	Mfg Report #2521AC000002
17-Apr-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012 Waldman
28-Apr-2008	ACADIA	FDA	IND Safety Report	Mfg Report #2521AC000002 F/U #1
5-May-2008	ACADIA	FDA	Information Amendment	GLP hERG Report
8-May-2008	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-015 Amend 4; New investigator: US
16-May-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-014
3-Jun-2008	ACADIA	FDA	Information Amendment	General Correspondence: Follow-up info as requested in EOP2 meeting minutes
16-Jun-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
17-Jun-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015: US
17-Jul-2008	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-012 Amend 4, New investigator: EU
18-Jul-2008	ACADIA	FDA	Annual Report	Reporting period 01 April 2007 through 31 March 2008
25-Jul-2008	ACADIA	FDA	Information Amendment	CMC - Update for clinical supply material
28-Jul-2008	ACADIA	FDA	Information Amendment	CMC - Support ACP-103-018
29-Jul-2008	ACADIA	FDA	Protocol Amendment	New protocol: ACP-103-018; New investigator
6-Aug-2008	ACADIA	FDA	IND Safety Report	Mfg Report # 2521AC000005
13-Aug-2008	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-014 Amend. 1; New investigator
17-Sep-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
17-Sep-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-014; US, Austria, Poland, Spain
18-Sep-2008	ACADIA	FDA	Protocol Amendment	Change in protocol & New investigator: ACP-103-015 Amend. 5; US, UK, Ukraine
19-Sep-2008	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-018 Amend. 1
24-Sep-2008	ACADIA	FDA	IND Safety Report	Mfg Report # 2521AC000005 F/U #1
1-Oct-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-018
16-Oct-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-014; US, Spain
16-Oct-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015: US
24-Oct-2008	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-19
12-Nov-2008	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-19 F/U #1
17-Nov-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
17-Nov-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-014; US
17-Nov-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015; US
21-Nov-2008	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-22

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
15-Dec-2008	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-22 F/U #1
16-Dec-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
16-Dec-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-014; US, Italy, Poland, Portugal
16-Dec-2008	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015: US
16-Jan-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
16-Jan-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015; US
16-Feb-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
16-Feb-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-014; Italy
16-Feb-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015; US
5-Mar-2009	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-30
6-Mar-2009	ACADIA	FDA	General Correspondence	Statistical Analysis Plan for ACP-103-012
18-Mar-2009	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-30 F/U #1
19-Mar-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-014; US, Belgium, Italy, Sweden
26-Mar-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-010 (PI replaced)
30-Mar-2009	FDA	ACADIA	Email	Request for Functional testing list from Sedative Hypnotic Sponsors
9-Apr-2009	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-30 F/U #2
16-Apr-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-014; US (change in site address), Belgium, Italy, Portugal
29-Apr-2009	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-30 F/U #3
29-Apr-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012; India
29-Apr-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015
30-Apr-2009	FDA	ACADIA	Email	FDA response to statistical analysis plan for ACP-103-012
1-May-2009	FDA	ACADIA	Email	Inquiry on status of Study ACP-103-018
12-May-2009	ACADIA	FDA	IND Safety Report	7-day Expedited Mfg Report # ACP-39
28-May-2009	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-39 F/U #1
4-Jun-2009	ACADIA	FDA	Email	Copy of SN0148, Revised SAP
6-Jun-2009	ACADIA	FDA	General Correspondence	Response to FDA comments on ACP-103-012 SAP
16-Jun-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-014; Serbia
16-Jun-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015; UK
24-Jun-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-012
16-Jul-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-014; Spain
31-Jul-2009	FDA	ACADIA	letter	Response to Revised SAP

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
17-Aug-2009	FDA	ACADIA	Email	Copy of SN0153, Carc rat study information
17-Aug-2009	FDA	ACADIA	Email	Response to carc rat study request (SN0153)
17-Aug-2009	ACADIA	FDA	Information Amendment	Dosing/Termination Proposal for Rat Carcinogenicity Study
21-Aug-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-014; US, Austria, Italy, Serbia, Spain, Turkey
21-Aug-2009	ACADIA	FDA	Annual Report	Reporting period 01 April 2008 through 31 March 2009
25-Aug-2009	ACADIA	FDA	Email	Follow-up on carc rat study request (SN0153)
16-Sep-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015; Austria, France, Italy, Poland, Portugal, Russia, Serbia, Sweden, UK, US
29-Sep-2009	ACADIA	FDA	Email	Copy of SN0157, Carc mice study information
29-Sep-2009	ACADIA	FDA	Information Amendment	Dosing/Termination Proposal for Mice Carcinogenicity Study
1-Oct-2009	FDA	ACADIA	Email	Response to carc mice study request (SN0157)
8-Oct-2009	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-62
14-Oct-2009	ACADIA	FDA	General Correspondence	Notification of ACP-103-014 concluding
28-Oct-2009	ACADIA	FDA	Protocol Amendment	New investigator: ACP-103-015; US, India
15-Jan-2010	ACADIA	FDA	General Correspondence	Statistical Analysis Plan for ACP-103-014
15-Jan-2010	ACADIA	FDA	Email	Copy of SN0161, ACP-103-014 Statistical Analysis Plan
19-Jan-2010	FDA	ACADIA	Email	Response from K. Kiedrow - acknowledging receipt of the email, SN0161 and noting that Sue Larkin is Project Manager for IND 68,384
11-Feb-2010	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-010 Amendment 3, Change in Investigator, and Updated 1572
11-Feb-2010	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-62, F/U #1
11-Feb-2010	ACADIA	FDA	Email	Copy of SN0164, Type C Meeting Request
17-Feb-2010	FDA	ACADIA	Email	Written confirmation of the 26 April 2010 scheduled teleconference.
23-Feb-2010	FDA	ACADIA	Email	Official letter from the Division granting the Typc C meeting.
24-Mar-2010	ACADIA	FDA	Other	Briefing Package for Type C Meeting on 26 April 2010
23-Apr-2010	FDA	ACADIA	Email	Copy of FDA's Preliminary Comments for the 26 April meeting.
26-Apr-2010	ACADIA	FDA	Email	Request for confirmation that cancellation email was received and that meeting was cancelled.
26-Apr-2010	FDA	ACADIA	Email	Response to H. Williams' email confirming that the meeting was cancelled, the Division expects the written responses to be submitted to the IND, and noted that as of May 3, she will change Divisions. Email to T. Harrison when the written responses have been submitted and he will handle appropriately.

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
10-May-2010	ACADIA	FDA	Other	Response to FDA Preliminary Comments (prior to Type C teleconference)
19-May-2010	FDA	ACADIA	Email	Email from K. Kiedrow acknowledging receipt of the electronic copy of SN0166 and stating that he has distributed the information to the team.
21-Jun-2010	ACADIA	FDA	New Protocol	ACP-103-020, New investigators
29-Jun-2010	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-62, F/U #2
21-Jul-2010	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-015 Amendment 6, Change in investigator and Updated 1572s (clinical site address); France change in PI, Updated site addresses: US, Serbia
30-Jul-2010	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-020
20-Aug-2010	ACADIA	FDA	New Protocol	ACP-103-019, & Pre-IND Mtg Minutes
24-Aug-2010	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-110
31-Aug-2010	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-020
4-Oct-2010	ACADIA	FDA	Protocol Amendment	New investigaors: ACP-103-020
29-Oct-2010	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-015; Change in PI & updated site address
21-Dec-2010	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-020; Change in site address
22-Dec-2010	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-015
25-Jan-2011	ACADIA	FDA	Email	Email to K. Kiedrow providing electronic copy of SN0178.
25-Jan-2011	ACADIA	FDA	Annual Report	Reporting period 01 April 2009 through 31 March 2010
9-Feb-2011	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-012
22-Feb-2011	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-020
22-Feb-2011	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-015, Change in Investigator: India change in PI
15-Apr-2011	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-020
15-Apr-2011	ACADIA	FDA	Protocol Amendment	New investigators & CII: ACP-103-015
27-Apr-2011	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-110, F/U #1
27-May-2011	ACADIA	FDA	Annual Report	Reporting period 01 April 2010 through 31 March 2011
31-May-2011	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-020
28-Jul-2011	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-015
1-Nov-2011	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-015
1-Nov-2011	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-020
8-Nov-2011	ACADIA	FDA	General Correspondence	Updated Pimavanserin IB (Edition 7.0, August 2011)
22-Dec-2011	ACADIA	FDA	Protocol Amendment	Change in protocol: ACP-103-020, Protocol Amendment 1, New investigators

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
7-Feb-2012	ACADIA	FDA	Development Safety Update Report (DSUR)	1st Pimavanserin DSUR (2010-2011); submitted concurrently with Schizophrenia IND submission and worldwide DSUR submissions
16-Feb-2012	ACADIA	FDA	General Correspondence	Statistical Analysis Plan for ACP-103-020
17-Feb-2012	ACADIA	FDA	Email	Provided electronic copy of SN0193, the SAP for study ACP-103-020
10-Apr-2012	ACADIA	FDA	Information Amendment	Final reports of 24-mo Carcinogenicity studies in Rats & Mice
5-Jun-2012	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-235
13-Jun-2012	FDA	ACADIA	Email	Provided the Agency's comments on the ACP-103-020 SAP
3-Jul-2012	ACADIA	FDA	Email	Provided electronic copy of SN0196
3-Jul-2012	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-241
15-Aug-2012	ACADIA	FDA	Information Amendment	CMC Update - DS, DP, Placebo & Labeling - comprehensive update to Sections 7.1-7.4
15-Aug-2012	ACADIA	FDA	Protocol Amendment	New investigators: ACP-103-020
29-Aug-2012	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-235, Follow-up report
6-Sep-2012	ACADIA	FDA	Protocol Amendment	ACP-103-015, Change in Investigators
17-Sep-2012	ACADIA	FDA	General Correspondence	Response to FDA's Comments on ACP-103-020 SAP
19-Sep-2012	ACADIA	FDA	Email	Provided electronic copy of SN0201, our response to the FDA's comments on ACP-103-020 SAP.
4-Oct-2012	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-258
22-Oct-2012	FDA	ACADIA	Email	Provided two more comments from the Agency on the 020 SAP.
8-Nov-2012	ACADIA	FDA	Email	Provided ACADIA responses to the Agency's Oct. 22 comments on 020 SAP.
4-Jan-2013	ACADIA	FDA	Development Safety Update Report (DSUR)	2nd Pimavanserin DSUR (2011-2012); submitted concurrently with Schizophrenia IND submission and worldwide DSUR submissions
29-Jan-2013	ACADIA	FDA	Email	Request for approval to submit a Type A meeting request.
30-Jan-2013	FDA	ACADIA	Email	Meeting request approved, but change to Type C.
31-Jan-2013	ACADIA	FDA	Other	Type C Meeting Request + complete Briefing Package
1-Feb-2013	FDA	ACADIA	Email	Confirmed receipt of 1/31/13 email.
1-Feb-2013	ACADIA	FDA	Email	Notifying him that the 15 desk copies have been sent, and that while preparing them, an error was identified, and a page was revised, which is reflected in the desk copies.
1-Feb-2013	FDA	ACADIA	Email	Confirmed that the revision should be submitted to the IND.
4-Feb-2013	ACADIA	FDA	Email	Notifying him that an error was found in the desk copy and asking if he had already distributed the desk copies yet. If not, we would like to send a revised submission today.

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
4-Feb-2013	FDA	ACADIA	Email	Noting that he had not yet distributed the desk copies and asked to send the revised versions so he can distribute the revised versions.
5-Feb-2013	ACADIA	FDA	Other	Revised Type C Briefing Package
6-Feb-2013	FDA	ACADIA	Email	Desk copies received and he will let us know once he has a meeting date.
8-Feb-2013	FDA	ACADIA	Email	Provided list of FDA attendees.
8-Feb-2013	ACADIA	FDA	Email	Provided list of ACADIA attendees
12-Feb-2013	FDA	ACADIA	Email	Official notification that meeting is granted by the Agency, scheduled for April 9, 3:00-4:00pm EST.
1-Apr-2013	ACADIA	FDA	New Protocol	ACP-103-023 and New Investigator documents; Updated Pimavanserin IB (Edition 8.0, December 2012) and Summary of Changes document
3-Apr-2013	FDA	ACADIA	Email	Provided the Agency's preliminary comments for the April 9 Type C meeting.
4-Apr-2013	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-295
4-Apr-2013	FDA	ACADIA	Email	Email asking confirmation that the preliminary comments had been received, and attaching a document to bring to the meeting for checking-in at the FDA office.
5-Apr-2013	ACADIA	FDA	Email	Sent clarifications to the background information in the Agency prelim comments.
5-Apr-2013	ACADIA	FDA	Information Amendment	CMC Update - DP spec change - method for dissolution spec change
10-Apr-2013	FDA	ACADIA	Email	Emails between S.Saini & H.Williams requesting & providing an electronic copy of SN0207, submitted April 4, 2013.
12-Apr-2013	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-295, follow-up report
19-Apr-2013	FDA	ACADIA	Email	Provided the Agency minutes of the April 9 Type C meeting.
22-Apr-2013	ACADIA	FDA	Email	Provided e-copy of SN0210 (Sponsor meeting minutes).
22-Apr-2013	ACADIA	FDA	General Correspondence	Sponsor Minutes of April 9 Type C Meeting
25-Apr-2013	ACADIA	FDA	New Protocol	ACP-103-024; new investigator documents.
29-Apr-2013	FDA	ACADIA	Email	Emails between S.Saini & M.Roger requesting & providing an electronic copy of SN0211, submitted April 25, 2013.
22-Aug-2013	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-326
27-Aug-2013	FDA	ACADIA	Email	S. Parihar introduced herself and replied that she would like an electronic copy of all submissions, if we are submitting paper submissions.
27-Sep-2013	ACADIA	FDA	Email	Request to complete the brand name submission in advance of the NDA
30-Sep-2013	FDA	ACADIA	Email	Response to complete the brand name submission in advance of the NDA, including Tradename Guidance as attachment

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
6-Nov-2013	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-326, Follow-up report
13-Nov-2013	ACADIA	FDA	Protocol Amendment	Change in protocol (Amendment 1) & New Investigator (Study ACP-103-019)
26-Nov-2013	FDA	ACADIA	Email	S. Parihar emailed requests for an electronic copy of the IB, as well as requesting information about the start of the 019 study (i.e. start of enrollment, etc.). She noted that the review division had comments and would provide them shortly.
26-Nov-2013	ACADIA	FDA	Email	M. Jones responded to S. Parihar's email providing an e-copy of the IB, noting that start-up activities have begun (IM, identification of potential patients), but no patients have begun screening. We requested the comments from the division, noting that given these communications, we would refrain from screening patients until we've heard from the Division.
27-Nov-2013	ACADIA	FDA	Information Amendment	Request for Proprietary Name Review - NUPLAZID
4-Dec-2013	FDA	ACADIA	Email	S. Parihar provided an Information Request/Advice Letter from the Division regarding the 019 protocol amendment 1.
13-Dec-2013	ACADIA	FDA	Information Amendment	Response to Request for Information: Protocol ACP-103-019 Amdmt 1
19-Dec-2013	FDA	ACADIA	Email	Email with additional Agency comments regarding the 019 study, specifically about the subjects on concomitant antipsychotic drugs.
19-Dec-2013	FDA	ACADIA	Email	Email - the 019 study may proceed under current protocol, as the issues addressed in the Agency letter are review issues.
20-Dec-2013	ACADIA	FDA	IND Safety Report	Mfr. Rpt. No. ACP-326, Follow Up #2 - Written Safety Report
2-Jan-2014	ACADIA	FDA	Development Safety Update Report (DSUR)	3rd Pimavanserin DSUR (2012-2013); submitted concurrently with Schizophrenia IND submission and worldwide DSUR submissions
4-Feb-2014	ACADIA	FDA	Protocol Amendment	Change in protocol (Amendment 2 for Study ACP-103-019)
17-Mar-2014	FDA	ACADIA	Email	S. Parihar emailed Agency comments on the 019 protocol amendment 2.
21-Mar-2014	ACADIA	FDA	General Correspondence	Request for Type B Pre-NDA Meeting (Clinical/Nonclinical)
21-Mar-2014	FDA	ACADIA	Email	S. Parihar emailed that they had scheduled a tcon with us for Tuesday, March 25 for 11:00 - 12:00pm EDT.
21-Mar-2014	ACADIA	FDA	Email	Email containing an electronic copy of Serial 0220, submission of Request for Type B Meeting (Pre-NDA, Clinical/Nonclinical).
26-Mar-2014	FDA	ACADIA	Email	Official Type B Pre-NDA meeting (Clinical/nonclinical) request granted. (Letter received attached to email.)
31-Mar-2014	ACADIA	FDA	General Correspondence	Request for Type B Pre-NDA Meeting (CMC)

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Date	From	To	Classification	Description
1-Apr-2014	FDA	ACADIA	Email	Email re: assigning Ms. Teshara Bouie as the main point of contact for the Pre-NDA CMC Mtg
1-Apr-2014	FDA	ACADIA	Email	Email re: FDA's statistical comments for IND 68384 (re: primary efficacy variable, key efficacy endpoints, sensitivity analysis, & missing item scores)
15-Apr-2014	FDA	ACADIA	Email	Email re: meeting request granted for Pre-NDA CMC
23-Apr-2014	FDA	ACADIA	Email	Email re: FDA issuing Pre-Assigned NDA #207318
1-May-2014	ACADIA	FDA	General Correspondence	Pre-NDA Meeting (Clinical/Nonclinical - Full Briefing Package
2-May-2014	ACADIA	FDA	General Correspondence	Pre-NDA Meeting (CMC) - Full Briefing Package
8-May-2014	FDA	ACADIA	Letter	Response - Proposed proprietary name "Nuplazid" was reviewed and accepted
12-May-2014	ACADIA	FDA	New Protocol	ACP-103-027, Midazolam DDI study
14-May-2014	ACADIA	FDA	Information Amendment	Response to FDA Request for Information (Protocol ACP-103-019)
30-May-2014	FDA	ACADIA	Email	Email re: FDA Pre-NDA CMC Preliminary Comments (with letter attached to email)
30-May-2014	ACADIA	FDA	Form	Health Authority contact form
31-May-2014	ACADIA	FDA	Email	Email re: ACADIA Responses to FDA Pre-NDA Clin-nonclin Preliminary Comments (with ACADIA responses attached to email)
3-Jun-2014	ACADIA	FDA	Email	Emails post Clin-nonclin Pre-NDA Mtg re: sending S Parihar e-copy of SN0224
3-Jun-2014	ACADIA	FDA	Email	Emails re: FDA Response to CMC Pre-NDA Question #8 & Cancellation of CMC Pre-NDA Mtg
9-Jun-2014	ACADIA	FDA	General Correspondence	Request for waiver of pediatric assessment
11-Jun-2014	FDA	ACADIA	Email	Emails re: insufficiency of SN0226 & preparing for Initial Pediatric Study Plan
16-Jun-2014	FDA	ACADIA	Email	Email re: recommended study design changes - ACP-103-027
17-Jun-2014	ACADIA	FDA	Email	Email re: acceptance of study design changes, including CYP3A4 in ACP-103-027
18-Jun-2014	ACADIA	FDA	Email	Email re: e-copy of SN0227 - Request for Breakthrough Designation
18-Jun-2014	ACADIA	FDA	Email	Emails re: pending Change in protocol for ACP-103-027 (orig submitted in SN0224)
23-Jun-2014	ACADIA	FDA	Other	Initial pediatric study plan
24-Jun-2014	ACADIA	FDA	IND Safety Report	Mfg Report # ACP-373, Initial report
24-Jun-2014	ACADIA	FDA	Email	Email re: e-copy of SN0229
2-Jul-2014	FDA	ACADIA	Email	Email w/ attachment of copy of Type B Pre-NDA Meeting Minutes from teleconference held on June 2, 2014

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
23-Jul-2014	ACADIA	FDA	New Protocol	ACP-103-029 (Midazolam)
29-Jul-2014	ACADIA	FDA	Email	Email re: e-copy of SN0231 Sponsor Minutes from 02 Jun Type B Pre-NDA Mtg
6-Aug-2014	FDA	ACADIA	Email	Emails re: questions about 3.2.P.4 Granularity and 3.2.P Header Expectations
15-Aug-2014	FDA	ACADIA	Email	Email w/ letter attached re: FDA granting Breakthrough Designation Therapy for PIM in PDP
22-Aug-2014	ACADIA	FDA	Email	Email w/ e-copy of SN0232 - Protocol Amend #1 for ACP-103-029 (Midazolam)
3-Sep-2014	FDA	ACADIA	Email	Email re: the FDA response to the Protocol Amend #2 for ACP-103-019 that was submitted in SN0225 back on May 14, 2014
11-Sep-2014	ACADIA	FDA	Email	Email re: adding Day 40 assessment of M36 to the ACP-103-029 Protocol
12-Sep-2014	FDA	ACADIA	Email	Email w/ letter attached re: FDA acceptance of iPSP & M. Jones confirming that ACADIA will proceed with waiver request
22-Sep-2014	ACADIA	FDA	Email	Email w/ e-copy of SN0233 - Protocol Amend #2 for ACP-103-029 (Midazolam)
9-Oct-2014	ACADIA	FDA	Protocol Amendment & General Correspondence	New Investigator & updated IB (Edition 9.0)
16-Oct-2014	ACADIA	FDA	Email	Email w/ e-copies of a) PDP SN0234 - New Investigator (ACP-103-015) & Updated IB, Edition 9, hard copy sent on 10/09/14 & b) Schiz SN0076 - Updated IB, Edition 9, hard copy sent on 10/08/14
31-Oct-2014	ACADIA	FDA	Email	Email re: delay in submitting the NDA for pimavanserin - submission deadline changed from 4Q2014 to 1Q2015
5-Jan-2015	ACADIA	FDA	Development Safety Update Report (DSUR)	DSUR #4 (2013-2014); period from 08NOV2013 - 07NOV2014; submitted concurrently with Schizophrenia IND submission and worldwide DSUR submissions
14-Jan-2015	ACADIA	FDA	Email	Email re: e-copies of SN0235 & SN0077 (originally submitted via FedEx on 01/05/15), submission of the pimavanserin DSUR #4 (08 Nov 2013 - 07 Nov 2014).
29-Jan-2015	ACADIA	FDA	Email	Email re: updated NDA submission timelines - plannings to submit NDA by end of February 2015 due to adding 12-month stability data & midazolam drug-drug interaction study data
30-Jan-2015	ACADIA	FDA	New Protocol	Email w/ e-copy of SN0236, new protocol ACP-103-025 (Hepatic); new investigators
30-Jan-2015	ACADIA	FDA	New Protocol	Email w/ e-copy of SN0237, new protocol ACP-103-026 (Renal) and change of investigator (for -015 and -020))

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Date	From	To	Classification	Description
11-Mar-2015	ACADIA	FDA	Email	Email re: NDA submission is delayed further to 2nd half of 2015 due to preparations for PAI readiness (our Quality Systems need additional work)
5-Jun-2015	FDA	ACADIA	Email	V. Gooding's response to L. Jones request re: BIMO structure for the NDA. Includes BIMO data submission instructions & specs for preparing/submitting summary level clinical site data for CDER inspection planning.
17-Jul-2015	ACADIA	FDA	Letter	Letter requesting extension of PDUFA fee waiver (original waiver will expire on 7 Aug 2015).
20-Aug-2015	ACADIA	FDA	Email	Email to FDA indicating the intent to submit the NDA within the 1st half of Sept. 2015. S. Parihar confirmed receipt of email from H. Williams on 21 Aug 2015.
29-Sep-2015	ACADIA	FDA	General Correspondence	eCTD Anchor submission
2-Oct-2015	ACADIA	FDA	New Protocol/Transfer of Regulatory Obligation	Protocol ACP-103-036 (Expanded Access)
5-Oct-2015	ACADIA	FDA	General Correspondence	ACP-103-019 Statistical Analysis Plan Final Draft
5-Oct-2015	FDA	ACADIA	Email	Email from FDA with 4th NDA RFI, requesting Word version of annotated draft label (RFI deadline 07 Oct 2015); Brendan also indicated that he will now be project manager for the IND instead of Simran Parihar going forward
6-Oct-2015	ACADIA	FDA	Email	Emails re: 1st e-submission to the PDP IND of ACP-103-019 SAP, Sequence 0239
13-Oct-2015	ACADIA	FDA	Email	Email re: closing out ACP-103-015 study and begin compassionate use program; requested informal t-con
13-Oct-2015	ACADIA	FDA	Information Amendment	CMC Update
20-Oct-2015	FDA	ACADIA	Email	FDA declines informal t-con and recommends submitting request for Type C meeting; FDA also indicates that ACP-103-015 participants need to be moved to an open-label extension and not an access protocol
20-Oct-2015	ACADIA	FDA	Email	H. Williams requested clarification re: treatment protocol since ACP-103-015 is already an open-label extension study; notified FDA re: planned MAA submission in the EU in 2016
21-Oct-2015	FDA	ACADIA	Email	FDA thinks it "appears acceptable" to move ACP-103-015 patients into a treatment protocol but formal 30-day review of the treatment protocol is needed
20-Nov-2015	ACADIA	FDA	Protocol Amendment	Email w/ e-copy of SN0242 - Protocol Amend #3 for ACP-103-019
25-Nov-2015	ACADIA	FDA	Protocol Amendment	Email w/ e-copy of SN0243 - Protocol Amend #1 for ACP-103-025
25-Nov-2015	ACADIA	FDA	Protocol Amendment	Email w/ e-copy of SN0244 - Protocol Amend #1 for ACP-103-026

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Date	From	To	Classification	Description
25-Nov-2015	FDA	ACADIA	Email	FDA response to EAP protocol indicates that immediate changes need to be addressed to prevent a clinical hold, inc. revising the IB and the ACP-103-036 ICF (due by 27 Nov 2015)
25-Nov-2015	ACADIA	FDA	Email	Email to FDA requesting to submit response by 30 Nov 2015 due to holiday and vendor limitations
27-Nov-2015	ACADIA	FDA	Response to Request for Information	Response to Request for updated IB and -036 ICF
27-Nov-2015	FDA	ACADIA	Email	FDA indicates that EAP protocol response may be submitted by 30 Nov 2015
27-Nov-2015	ACADIA	FDA	Email	Email w/ e-copy of SN0245 - response to FDA review issues with ACP-103-026 EAP protocol; inc. IB v9.1 & draft updated ICF
3-Dec-2015	FDA	ACADIA	Email	FDA sent "Study May Proceed" letter with additional comments for ACP-103-036 EAP protocol
6-Jan-2016	ACADIA	FDA	Email	Email to FDA inc. SN0246, DSUR #5 (08Nov2014 - 07Nov2015)
29-Feb-2016	ACADIA	FDA	Information Amendemnt	WIL-616007 PWG Report to Further evaluate the Lung Fibrosis Observed in WIL-616007
9-Mar-2016	ACADIA	FDA	Protocol Amendment	ACP-103-036 Protocol Amendment 1
10-Mar-2016	ACADIA	FDA	Information Amendment	Addendum to Investigator Brochure v9.1
10-Mar-2016	ACADIA	FDA	Email	Sent FDA Serial 0248 - Protocol Amend #1 ACP-103-036 expanded access program
10-Mar-2016	ACADIA	FDA	Email	Sent FDA Serial 0249 - Addendum to the PIM IB 9.1

TABLE 2: NDA 207-318

Date	From	To	Classification	Description
31-Aug-2015	ACADIA	FDA	Email	Final validation and submission of the NDA, Sequence 0000
1-Sep-2015	ACADIA	FDA	Email	Email re: delay in NDA transmittal due to technical difficulties (validation errors)
2-Sep-2015	ACADIA	FDA	Email	Email to FDA indicating the NDA is being delivered through the gateway
2-Sep-2015	FDA	ACADIA	Email	Email from S Parihar confirming the NDA submission is being processed by FDA
15-Sep-2015	FDA	ACADIA	Email	Email from FDA acknowledging receipt of the NDA submission for PDP received on 01 Sept 2015 and 1st NDA request for information (RFI) of clin pharm & cardiac safety info and ECG waveforms for ACP-103-018
21-Sep-2015	ACADIA	FDA	Email	Email with ACADIA responses to 1st RFI, inc. clin pharm & cardiac info and ACP-103-018 waveform data (electronically submitted in Sequence 0001)
21-Sep-2015	ACADIA	FDA	Responses to Questions	Response to Information Request - Clinical Pharmacology/Cardiac Safety Summary and ECG Waveforms
22-Sep-2015	ACADIA		Information Amendment	Updated Patent Information
24-Sep-2015	FDA	ACADIA	Email	Email from FDA with 2nd RFI, requesting analysis data and programs for 2 study reports
29-Sep-2015	ACADIA	FDA	Responses to Questions	Response to Information Request - SAS Datasets and Programs for AE and SAPS studies
30-Sep-2015	FDA	ACADIA	Email	Email from FDA indicating that sponsor is encouraged to submit a Pharmacovigilance Plan to address safety risks following market approval
1-Oct-2015	FDA	ACADIA	Email	3rd NDA RFI, 6 nonclinical questions
1-Oct-2015	ACADIA	FDA	Email	Responses to 2nd RFI, including SAS datasets for exposure response studies (electronically submitted in Sequence 0003)
1-Oct-2015	FDA	ACADIA	Email	Email re: validation report for NDA Sequence 0000 shows two low severity errors
5-Oct-2015	FDA	ACADIA	Email	4th NDA RFI, requesting Word version of annotated draft label.
5-Oct-2015	ACADIA	FDA	Responses to Questions	Responses to FDA Request for Word Version of Annotated Label
6-Oct-2015	ACADIA	FDA	Email	Emails re: 1st e-submission to the PDP IND of ACP-103-019 SAP, Sequence 0239, and FDA acknowledgement of receipt

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Date	From	To	Classification	Description
6-Oct-2015	FDA	ACADIA	Email	Email indicating FDA receipt of annotated draft labeling; FDA response indicating there are several formatting issues with the labeling and submitting 5th NDA RFI for resubmission of labeling.
6-Oct-2015	ACADIA	FDA	Responses to Questions	Responses to FDA Request for PLR Word and PDF Versions of Annotated Label
9-Oct-2015	ACADIA	FDA	Email	Email indicating that ACADIA has formatted the annotated draft label and updated it in the NDA (electronically submitted in Sequence 0005 on 08 Oct 2015)
13-Oct-2015	ACADIA	FDA	Email	Email w/ preliminary response to FDA's recommendation to submit a Pharmacovigilance Plan - discusses opportunity to continue to assess safety of PIM and acknowledges potential for QTc prolongation
13-Oct-2015	ACADIA	FDA	Email	ACADIA preliminary response to Pharmacovigilance Plan forwarded to the old IND PM, Simran Parihar, for informational purposes because Brendan Muoio was out of the office
14-Oct-2015	ACADIA	FDA	Responses to Questions	Responses to FDA Non-Clinical Questions Dated 2015-10-01
20-Oct-2015	FDA	ACADIA	Email	Email from FDA re: receipt of NDA nonclin responses and update for the pharmacovigilance plan; FDA also responded re: PDP IND udpate for new treatment protocol for ACP-103-015 study participants
30-Oct-2015	FDA	ACADIA	Email	6th NDA RFI re: nonclinical information
30-Oct-2015	FDA	ACADIA	Email	FDA granted NDA Priority Review; PDUFA date set for 01 May 2016; review issues will be sent to ACADIA by 14 Nov 2015; FDA internal mid-cycle review is 23 Nov 2015; proposed labeling will be sent by 19 Feb 2016
4-Nov-2015	FDA	ACADIA	Email	7th NDA RFI re: statistical information (computer programs & SDTM datasets)
9-Nov-2015	FDA	ACADIA	Letter	Letter indicating that FDA has conditionally accepted the proprietary name request for NUPLAZID
10-Nov-2015	FDA	ACADIA	Email	FDA notification re: post-mid-cycle t-con to be held on 03 Dec 2015
10-Nov-2015	ACADIA	FDA	Responses to Questions	Responses to FDA Non-Clinical Questions Dated 2015-10-30
11-Nov-2015	ACADIA	FDA	Email	Email to FDA confirming that the mid-cycle meeting date (03 Dec 2015) works for ACADIA and indicated that response to statistics request will be delayed to 20 Nov 2015 (instead of originial due date of 13 Nov 2015)

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Date	From	To	Classification	Description
11-Nov-2015	ACADIA	FDA	Email	Email to FDA w/ cover letter and notification of electronic submission of Sequence 0007 - response to nonclinical information request
12-Nov-2015	ACADIA	FDA	Email	ACADIA notified FDA of NDA issue with CYP3A4/5 and Cmax will be increased based on a single dose of PIM
13-Nov-2015	FDA	ACADIA	Email	FDA sent day 74 letter with review issues and acknowledged CYP inhibitor issues in the NDA
13-Nov-2015	ACADIA	FDA	Email	Requested from FDA the draft labeling in Word with tracked changes
16-Nov-2015	FDA	ACADIA	Email	FDA sent draft labeling in tracked changes
20-Nov-2015	ACADIA	FDA	Email	Email to FDA w/ cover letter and notification of electronic submission of Sequence 0008 - response to statistics information request
20-Nov-2015	ACADIA	FDA	Responses to Questions	Response to Information Request - Statistical Programs
24-Nov-2015	ACADIA	FDA	Responses to Questions	Responses to FDA Clinical Questions Dated 13-Nov-2015: Updated Annotated Draft Labeling
25-Nov-2015	ACADIA	FDA	Email	Email to FDA w/ cover letter and notification of electronic submission of Sequence 0009 - partial response to Day 74 Letter that requested annotated labeling
25-Nov-2015	FDA	ACADIA	Email	FDA notification of Late-Cycle meeting to be held on 15 Mar 2016, requested call-in info for Mid-Cycle mtg, and requested updated on ACADIA response to SAPS-PD review issues identified in Day 74 Letter
27-Nov-2015	FDA	ACADIA	Email	FDA requested Word version of the annotated labeling that was submitted in Sequence 0009
27-Nov-2015	ACADIA	FDA	Email	Email to FDA with the Word version of the annotated labeling that was submitted in Sequence 0009 (redlined and clean copies provided)
4-Dec-2015	FDA	ACADIA	Email	9th NDA RFI for nonclinical info re: rationale for the acute inhalation toxicity study in rates (study no. 18244-14)
7-Dec-2015	FDA	ACADIA	Email	10th NDA RFI for additional statistics info based on the responses submitted in Sequence 0008. Requested ACP-103-020 info re: tx assignment and randomization schedule
7-Dec-2015	FDA	ACADIA	Email	Email from D. Woody to H. Williams, inc. letter from D. Claffey, re: FDA's 11th NDA RFI for CMC info
8-Dec-2015	FDA	ACADIA	Email	12th NDA RFI - Office of Scientific Investigations (OSI) requested database lock info, MedAvante manual, data listings, & list of "important" protocol deviations

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Date	From	To	Classification	Description
8-Dec-2015	ACADIA	FDA	Email	Email to FDA re: Sequence 0011 - complete response to review issues identified in Day 74 Letter (clinical responses)
8-Dec-2015	ACADIA	FDA	Responses to Questions	Response to Questions from Day 74 Letter - Clinical
9-Dec-2015	ACADIA	FDA	Email	Email to FDA re: Sequence 0012 - response to nonclinical questions sent by FDA on 04 Dec 2015
9-Dec-2015	ACADIA	FDA	Responses to Questions	Responses to Non-clinical Questions
14-Dec-2015	ACADIA	FDA	Email	Email to FDA re: Sequence 0013 - response to CMC questions
14-Dec-2015	ACADIA	FDA	Responses to Questions	Responses to FDA Questions - CMC
15-Dec-2015	FDA	ACADIA	Email	FDA sent meeting minutes from the Mid-Cycle Meeting that was held on 03 Dec 2015
17-Dec-2015	ACADIA	FDA	Email	Email to FDA re: Sequence 0014 - response to statistical questions
17-Dec-2015	ACADIA	FDA	Email	Email to FDA re: Sequence 0015 - response to OSI questions
17-Dec-2015	ACADIA	FDA	Responses to Questions	Responses to FDA Questions - Statistical Dated 2015-12-07
17-Dec-2015	ACADIA	FDA	Responses to Questions	Response to FDA Questions - OSI Dated 2015-12-08
21-Dec-2015	FDA	ACADIA	Email	FDA response to Sequence 0015 indicating difficulty in accessing files - need to resubmit files for access
21-Dec-2015	ACADIA	FDA	Email	Email to FDA re: updating file names in Sequence 0015 - all files should be accessible now
21-Dec-2015	FDA	ACADIA	Email	FDA sent the sponsor letter and AdComm timelines.
29-Dec-2015	FDA	ACADIA	Email	FDA's 2nd response to Sequence 0015 indicating difficulty in accessing files again - need to resubmit files for access asap
29-Dec-2015	ACADIA	FDA	Email	Email to FDA with Sequence 0015 files attached
29-Dec-2015	ACADIA	FDA	Email	Email to FDA with Sequence 0010 - 120-Day Update
29-Dec-2015	ACADIA	FDA	Information Amendment	120 Day Update
5-Jan-2016	ACADIA	FDA	Email	Email to FDA re: Sequence 0016 - re-submitted the file that was inaccessible from Sequence 0015 (a PDF of this file was emailed to FDA on 29 Dec2015)
5-Jan-2016	ACADIA	FDA	Information Amendment	RFI Replacement BioStats File
8-Jan-2016	ACADIA	FDA	Email	Sent FDA the requested list of investigators, per the deliverables for the upcoming PDAC meeting

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Date	From	To	Classification	Description
15-Jan-2016	FDA	ACADIA	Email	13th RFI for CMC info re: tightening drug substance particle size acceptance criteria & adding stratified content uniformity evaluation during process validatio
21-Jan-2016	ACADIA	FDA	Email	Sent FDA Sequence 0017 - CMC info
21-Jan-2016	ACADIA	FDA	Responses to Questions	Responses to FDA Questions - CMC
25-Jan-2016	ACADIA	FDA	Email	Fwd Sequence 0017 to OSI - containing response to CMC info request
26-Jan-2016	FDA	ACADIA	Email	14th RFI - request for further statistical info in addition to what was submitted in Sequence 0014; due 03 Feb 2016
28-Jan-2016	FDA	ACADIA	Email	15th RFI for info re: colon cancer subjects in the open label tx program. Email response acceptable, due 29 Jan 2016
29-Jan-2016	ACADIA	FDA	Email	Email to FDA requesting to align terms with Division for upcomong PDAC meeting (i.e. 40mg vs 34 mg PIM, mITT vs ITT, & weeks vs days for labeling)
29-Jan-2016	ACADIA	FDA	Responses to Questions	Response to 15th FDA RFI re: SAEs for 4 colon cancer subjects (034-008, 060-004, 169-002, 301-103)
29-Jan-2016	ACADIA	FDA	Email	Sent FDA request for tcon re: mortality cases in the PIM long-term studies with ACADIA & FDA Clinical Reviewer, Paul Andreason
31-Jan-2016	FDA	ACADIA	Email	FDA will consider ACADIA's suggested terms for the PDAC meeting & confirmed receipt of SAEs for colon cancer subjects
31-Jan-2016	FDA	ACADIA	Email	FDA suggests tcon on mortality cases to be held on 04 Feb 2016; also requests update on renal & hepatic studies (ACP-103-025 & ACP-103-026)
2-Feb-2016	ACADIA	FDA	Email	Sent FDA Sequence 0018 - stats info
2-Feb-2016	ACADIA	FDA	Responses to Questions	Responses to FDA Questions - Statistical Dated 2016-01-26
3-Feb-2016	FDA	ACADIA	Email	16th RFI re: status of renal & hepatic impairment studies (original request was on 31 Jan 2016) (ACP-103-025 & ACP-103-026)
3-Feb-2016	ACADIA	FDA	Email	Send FDA PPT slides for tcon on mortality cases to be held on 04 Feb 2016
3-Feb-2016	ACADIA	FDA	Email	Sent FDA update on renal & hepatic studies, along with estimated completion dates for the CSRs (ACP-103-025 & ACP-103-026)
4-Feb-2016	FDA	ACADIA	Email	17th RFI for nonclinical info
8-Feb-2016	FDA	ACADIA	Email	18th RFI for nonclinical info re: steady-state exposure (AUC)
8-Feb-2016	FDA	ACADIA	Email	FDA responded to terms for PDAC meeting
9-Feb-2016	ACADIA	FDA	Email	Sent FDA Sequence 0019 - response to nonclinical request

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Date	From	To	Classification	Description
9-Feb-2016	ACADIA	FDA	Responses to Questions	Response to Non-clinical Information Request Dated 04Feb2016
15-Feb-2016	ACADIA	FDA	Email	Sent FDA Sequence 0020 - response to steady-state exposure nonclinical questions
15-Feb-2016	ACADIA	FDA	Responses to Questions	Response to Non-clinical Information Request Dated 08Feb2016
16-Feb-2016	FDA	ACADIA	Email	19th RFI for CMC request to change postapproval stability protocol, due 19 Feb 2016
18-Feb-2016	ACADIA	FDA	Email	Sent FDA Sequence 0021 - response to CMC request
18-Feb-2016	ACADIA	FDA	Responses to Questions	Response to CMC Information Request Dated 16Feb2016
19-Feb-2016	ACADIA	FDA	Email	Sent FDA corrected Core ID for Sequence 0021
19-Feb-2016	FDA	ACADIA	Email	FDA sent letter indicating there are deficiencies that preclude the discussion of labeling or postmarketing requirements
23-Feb-2016	FDA	ACADIA	Email	FDA requests Foreign Visitor Forms and list of ACADIA attendees for the late cycle meeting
26-Feb-2016	ACADIA	FDA	Email	Sent FDA Sequence 0022 - briefing book for the PDAC meeting
26-Feb-2016	ACADIA	FDA	Information Amendment	AdCom Briefing Package
1-Mar-2016	FDA	ACADIA	Email	FDA confirmed that the late cycle meeting can be held via teleconference
1-Mar-2016	FDA	ACADIA	Email	20th RFI for nonclinical information & requested that any information sent to the IND be submitted to the NDA as an amendment
4-Mar-2016	ACADIA	FDA	Email	Sent FDA Sequence 0023 - response to nonclinical information request
4-Mar-2016	ACADIA	FDA	Responses to Questions	Responses to Non-Clinical Questions Dated 01Mar2016
8-Mar-2016	FDA	ACADIA	Email	FDA requested teleconference info for late cycle meeting & indicated FDA will send background package by 11 Mar 2016
8-Mar-2016	ACADIA	FDA	Email	Sent FDA teleconference info for the late cycle meeting to be held on 15 Mar 2016
17-Mar-2016	FDA	ACADIA	Email	FDA sent list of attendees for the late cycle meeting & requested ACADIA's list of attendees
18-Mar-2016	ACADIA	FDA	Email	Sent FDA Serial 0024 - toxicological study report WIL-616007 Amendment #2
18-Mar-2016	ACADIA	FDA	Information Amendment	WIL-616007 Amendment 2
21-Mar-2016	FDA	ACADIA	Email	FDA requesting Advisory Committee info that was agreed upon at the late-cycle meeting

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
22-Mar-2016	ACADIA	FDA	Email	Sent FDA draft ACADIA core presentation slides for the upcoming PDAC meeting to be held on 29 March 2016
28-Mar-2016	FDA	ACADIA	Email	FDA indicated the Division's PDAC presentation slides will be available on the morning of 29 Mar 2016
31-Mar-2016	FDA	ACADIA	Email	FDA sent their late-cycle meeting minutes
1-Apr-2016	ACADIA	FDA	Email	Sent FDA additional labeling language for section 5.1
4-Apr-2016	ACADIA	FDA	Email	ACADIA requested timing of FDA's labeling comments
5-Apr-2016	FDA	ACADIA	Email	21st NDA RFI re: carton and container labeling changes, due 08 April 2016
8-Apr-2016	ACADIA	FDA	Email	Sent FDA Sequence 0025 - response to labeling changes
13-Apr-2016	FDA	ACADIA	Email	22nd NDA RFI re: un-annoted draft labeling changes, due 15 April 2016
15-Apr-2016	ACADIA	FDA	Email	Sent FDA un-annoted draft labeling response with ACADIA rationale for changes & requested a teleconference to discuss the proposed indication language ASAP
15-Apr-2016	ACADIA	FDA	Response to Questions	Response to FDA PI Label comments dated 13-Apr-2016
18-Apr-2016	FDA	ACADIA	Email	FDA denied labeling teleconference but the Division will consider the ACADIA rationale and send a labeling response by the end of the week (by ≈ 22 April 2016)
21-Apr-2016	ACADIA	FDA	Information Amendment	Updated Patent Information
22-Apr-2016	FDA	ACADIA	Email	23rd RFI - revised labeling and requested updated label by 25 April 2016; FDA will send post-approval commitments by early next week
25-Apr-2016	ACADIA	FDA	Response to Questions	Response to FDA Labeling Comments on Package Insert dated 22-Apr-2016
27-Apr-2016	FDA	ACADIA	Email	24th RFI - additional labeling changes and post-marketing commitments - response due 28 April 2016
28-Apr-2016	ACADIA	FDA	Email	Sent FDA revised un-annotated labeling and response to post-marketing commitments and suggested teleconference for further changes (email refers to "tomorrow" as April 28th since email was sent at 12:05 am)
28-Apr-2016	FDA	ACADIA	Email	FDA agreed with the need for a teleconference and requested dial-in information

EXHIBIT H — Activities During Regulatory Review Period for NUPLAZID™

Date	From	To	Classification	Description
29-Apr-2016	FDA	ACADIA	Email	25th RFI - revised post-marketing commitments, response due same day by noon EST
29-Apr-2016	ACADIA	FDA	Email	Sent FDA PMC response - ACADIA agreed to all revised post-marketing commitments