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Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
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UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES AND THE FOOD AND DRUG ADMINISTRATION

**PETITION FOR STAY OF ACTION :
REGARDING PHASE II AND III : Docket No. FDA-2020-P-1770
CLINICAL TRIAL OF BNT162b :
- NCT04368728 :**

ADMINISTRATIVE STAY OF ACTION

This petition for a stay of action is submitted on behalf of the Informed Consent Action Network¹ (“**Petitioner**”) pursuant to 21 CFR § 10.35 and related and relevant provisions of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act to request the Commissioner of Food and Drugs (the “**Commissioner**”) stay the Phase III trial of BNT162b² (NCT04368728), and not approve this product, unless its Phase III trial design is amended to conform with the requests in the “Action Requested” section below.

Because of the compelling need to ensure the safety and efficacy of any COVID-19 vaccine licensed by the FDA, and to allow Petitioner the opportunity to seek emergency judicial relief should the Commissioner deny its Petition, **Petitioner respectfully requests that FDA act on the instant Petition by August 26, 2020.**

¹ Including, but not limited to, on behalf of its members that work for the Petitioner.

² As used herein, “BNT162b” refers to BNT162b1 and BNT162b2.

A. DECISION INVOLVED

1. Approval of trial design for Phase III trial of BNT162b.³

B. ACTION REQUESTED

2. Stay the Phase III trial of BNT162b (NCT04368728) until its study design is amended to provide that:
 - a. any and all adverse events and reactions⁴ will be documented for the entire duration of the trial;
 - b. such documenting of adverse events and reactions shall last at least twelve months for adults, thirty-six months for children, and sixty months for infants and toddlers;
 - c. it uses an adequate sample size, appropriately powered, in order to (i) detect an increase in rare adverse events or, any untoward medical occurrence, whether or not considered vaccine related and (ii) determine that the rate of adverse events from the vaccine will not exceed the rate of adverse events known to occur from SARS-CoV-2 in the group under review;⁵ and
 - d. participants are tested for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination.

C. STATEMENT OF GROUNDS

3. As detailed herein, (i) without the requested stay, the Petitioner will suffer irreparable harm, (ii) the request is not frivolous and is being pursued in good faith, (iii) the request demonstrates sound public policy, and (iv) the public interest favors granting a stay.⁶

4. The current study design for the Phase III clinical trial for BNT162b provides that, despite reviewing efficacy for at least 2 years, it will only capture “adverse events” for 1 month

³ NCT04368728 available at <https://www.clinicaltrials.gov/ct2/show/NCT04368728> (last visited August 11, 2020).

⁴ Including, but not limited to, systemic adverse reactions, adverse events, non-serious adverse event, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue of any degree or type arising or exacerbated post-vaccination, whether suspected, unexpected, expected or otherwise, and whether or not considered related to the vaccine.

⁵ For example, for children, the clinical trial should be properly sized and powered to determine that the vaccine is safer than a child having a SARS-CoV-2 infection.

⁶ The Petitioner hereby incorporates by reference as if fully set forth herein the Statement of Grounds from its Amended Citizen’s Petition, dated July 20, 2020, available at, <https://beta.regulations.gov/document/FDA-2020-P-1601-0028> (last visited August 11, 2020).

and “serious adverse events” for only 6 months after each dose.⁷ Limiting the review of safety in this manner is unethical and concerning given that the trial could easily and simply capture all adverse events for the entire duration of the trial.

5. The current study design is also underpowered as it will not be able to validate that the adverse event rate from this product is less than the adverse events caused by SARS-CoV-2 in each age group in which it seeks licensure. It also fails to test for T-cell reactivity pre-and-post vaccination which will call any resulting efficacy conclusion into question.

6. Petitioner will suffer irreparable harm if the stay requested herein is not granted because once the FDA licenses this COVID-19 vaccine, states are expected to make this product mandatory, and hence without the FDA assuring proper safety trials of the vaccine *now*, the Petitioner will not have the opportunity to object to receiving the vaccine based on deficient clinical trials *later*. Furthermore, if the vaccine is licensed without an appropriate safety review, ethical considerations prevent conducting another placebo-controlled study post-licensure, thereby preventing any properly designed clinical trial from ever occurring.

7. The request here is also not frivolous and is being pursued in good faith as it seeks to increase the scientific integrity and reliability of the trials of this potential COVID-19 vaccine. Requiring that all adverse events during the entire clinical trial be cataloged is simply common sense and supported by the sound public policy of assuring the safety of this product, to the greatest extent possible, before being injected into hundreds of millions of Americans.

8. The public interest also weighs strongly in favor of the requested relief because having adequate safety review protocols will comport with the best interests of all Americans slated to receive this product and will increase public confidence in the safety and efficacy of this product.

a. Tracking All Adverse Events

9. To increase assurance that potential adverse events from BNT162b are captured, all adverse events and reactions should be documented for each subject post-vaccination, whether or not they are considered vaccine-related by the investigator or sponsor, for the entire duration of the clinical trial.⁸ All adverse events and reactions include, but are not limited to: all systemic adverse reactions, adverse events, non-serious adverse events, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue of any degree or type arising or exacerbated post-vaccination, whether suspected, unexpected, expected or otherwise, and whether or not considered related to the vaccine.

⁷ <https://www.clinicaltrials.gov/ct2/show/NCT04368728> (last visited August 11, 2020).

⁸ See <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32> (defining “Adverse event” as “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related”) (last visited August 11, 2020); see also <https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event> (last visited August 11, 2020).

10. As noted above, the current study design for the Phase III clinical trial for BNT162b provides that, despite reviewing efficacy for at least 2 years, it will only capture “adverse events” for 1 month and “serious adverse events” for only 6 months after each dose.⁹

11. The adverse events captured beyond a month of injection should not be limited to “serious adverse events,” since there are many autoimmune, neurological, and chronic health disorders which have a major impact on the quality of life, yet are categorized by the FDA as “adverse reactions” and not categorized as “serious adverse reactions.”¹⁰ To wit, there are a myriad of post-licensure adverse reactions reported by consumers and physicians and are also listed in the package inserts for one or more vaccines that any individual living with would categorize as “serious”; yet the FDA, under its current guidelines, may not. These include, but are not limited to: alopecia, autoimmune disease, lupus erythematosus, vasculitis, Bell’s Palsy, hypotonia, migraine, myelitis, neuropathy, seizures, mental disorders, rhinitis, and vertigo.¹¹

12. The study design for BNT162b nonetheless provides that these adverse events should be captured for only one month after vaccination while “serious adverse events” should continue but be limited to 6 months.¹² These artificial limitations are unethical and render any claim of safety for this product based on this trial vacuous.

13. Given that efficiency will be tracked for two years in this trial, it is foolhardy to not capture all adverse events during this period. If BNT162b causes a systemic autoimmune issue to arise two months after vaccination, it would be irresponsible and unethical not to capture that reaction just because an autoimmune issue falls into the artificially defined zone of being an “adverse event” or “non-serious adverse event,” rather than what the FDA has decided to label a “serious adverse event.”

⁹ <https://www.clinicaltrials.gov/ct2/show/NCT04368728> (last visited August 11, 2020).

¹⁰ The FDA defines an adverse event to be “serious” if it results in one of the following specific outcomes: “death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.” FDA Guidance for Industry and Investigators, <https://www.fda.gov/media/79394/download> (last visited August 11, 2020).

¹¹ See <https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm> (last visited August 11, 2020). Also, the determination of whether an adverse reaction is a “serious adverse event” is typically left to the discretion of the sponsor of the clinical trial or the clinical investigators, who are paid by the sponsor, and therefore subject to bias. See 21 C.F.R. § 312.32, explaining that an adverse event may be categorized as “serious” if “in the view of either the investigator or sponsor, it results in any of the” listed outcomes.

¹² As the Principal Deputy Commissioner of the FDA, along with her colleagues at the FDA, wrote with regard to monitoring safety during a clinical trial: “sponsors are expected to monitor all adverse events, including nonserious ones, during drug development.” <https://www.nejm.org/doi/pdf/10.1056/NEJMp1103464> (last visited August 11, 2020).

c. Minimum Period to Track Adverse Events

14. At a minimum, all adverse events and reactions should be documented for each subject post-vaccination for at least: (i) twelve months for adults, (ii) thirty-six months for children, and (iii) sixty months for infants and toddlers. These minimal timeframes provide an opportunity to capture adverse and non-specific health issues that BNT162b may cause.

15. The importance of capturing all potential health issues for a material duration can be seen in the designs of the clinical trials of numerous drugs, including for example, Enbrel¹³, Lipitor¹⁴, and Botox,¹⁵ which had safety review periods of 6.6 years, 4.8 years, and 51 weeks respectively. As another example, the weight loss drug Belviq was safety tested for two years before being licensed by the FDA in 2012.¹⁶ Nevertheless, despite this two year period, in February 2020 the drug was voluntarily removed from the US market due to emerging data that clinical trial participants had an increased occurrence of cancer five years later.¹⁷

16. The FDA states that the length of study for phase III clinical trials is typically “1 to 4 years”¹⁸ and that the duration of a clinical trial should “reflect the product and target condition.”¹⁹ In accord with this guidance, and the fact that a COVID-19 vaccine will be an entirely novel product, the safety review period for adults should be at least 1 year. The need for this minimum safety review period following injection is further supported by the indications that the immunity conferred by a COVID-19 vaccine is expected to last approximately one year or maybe a few years, requiring repeated injections of the product during a person’s life.²⁰

¹³ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s55031bl.pdf (last visited August 11, 2020).

¹⁴ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s0561bl.pdf (last visited August 11, 2020).

¹⁵ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s53021bl.pdf (last visited August 11, 2020).

¹⁶ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/0225291bl.pdf (last visited August 11, 2020).

¹⁷ See <https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market> (last visited August 11, 2020); see also <https://www.health.harvard.edu/blog/weight-loss-drug-belviq-recalled-2020040919439> (last visited August 11, 2020).

¹⁸ <https://www.fda.gov/patients/drug-development-process/step-3-clinical-research> (last visited July 12, 2020).

¹⁹ <https://www.fda.gov/media/102332/download> (last visited August 11, 2020).

²⁰ The importance of the typical duration of a clinical trial was underscored by an AstraZeneca senior executive team member when he acknowledged the very real potential of side effects being discovered years down the line. In explaining why AstraZeneca needs protection from future product liability claims against its COVID-19 vaccine, Ruud Dobber stated: “This is a unique situation where we as a company simply cannot take the risk if in ... four years the vaccine is showing side effects.” <https://in.reuters.com/article/us-astrazeneca-results-vaccine-liability/astrazeneca-to-be-exempt-from-coronavirus-vaccine-liability-claims-in-most-countries-idINKCN24V2EN> (last visited August 11, 2020).

17. Moreover, taking into account the FDA’s guidance that clinical trials should “reflect the product and target condition,”²¹ the time frame for the safety review should be longer for minors, and in particular for infants and toddlers, since autoimmune, neurological, and developmental disorders will often not be diagnosed until after children are at least a few years old.²² Indeed, a 2019 review, authored by researchers at the FDA and Duke University, reviewed 306 pediatric clinical trials and found that short-term

pediatric studies may not provide complete safety data across all critical periods of growth and development. This observation may be important because multiple periods of critical pediatric growth and development exist... Although the first 3 years of life are often considered more critical than older ages for brain development, biochemical studies of brain metabolism suggest that high brain metabolic rates characteristic of early childhood may not decline to adult levels until ages 16 to 18 years, suggesting that the school-age and adolescent periods are equally critical periods of brain development. Given this information, even the longest trial duration identified in our study (364 weeks/7 years) does not completely evaluate potential critical stages of all pediatric growth and development periods.²³

The FDA and Duke authors explained that, compared to licensing a drug for adults, “data on drug efficacy and safety in children may require an additional 6 years.”²⁴ Since children have not been seriously affected by this virus, the risk of any vaccine must be fully understood in order to weigh it against any potential benefit.

²¹ <https://www.fda.gov/media/102332/download> (last visited August 11, 2020).

²² For example, according to the CDC, even for a common neurological disorder such as ADHD, “5 years of age was the average age of diagnosis for children reported as having severe ADHD.” <https://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html> (last visited August 11, 2020). As another example, learning disabilities, a group of common developmental issues, are often “identified once a child is in school.” <https://www.nichd.nih.gov/health/topics/learning/conditioninfo/diagnosed> (last visited August 11, 2020). Even for asthma, a very common autoimmune condition, whose symptoms are obvious, diagnosis can be difficult for children under 5 years of age because lung function tests aren’t accurate before 5 years of age and “[s]ometimes a diagnosis can’t be made until later, after months or even years of observing symptoms.” <https://www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/drc-20351513> (last visited August 11, 2020).

²³ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6526087/> (last visited August 11, 2020)

²⁴ *Id.*

d. Adequately Powered Sample Size

18. The study design for BNT162b provides for only 29,481 individual study subjects, which presumably means less than 15,000 individuals will be in the study group that will receive BNT162b and less than 15,000 individuals will be in the control group that will receive a placebo.²⁵

19. A Phase III trial of this size for BNT162b cannot produce an adequate safety profile for this product. SARS-CoV-2 poses a statistically insignificant risk of harm to children and young healthy adults. For this enormous cohort of the American population, the threshold for establishing that this vaccine is safer than the infection is exceedingly high and requires a highly powered trial. Even within so-called higher risk groups, the percent of individuals suffering serious health issues from SARS-CoV-2 is statistically small on a population level, which again demands a well-powered trial to assess the safety of the vaccine versus natural infection, since it is anticipated that this vaccine will be mandatory for most Americans.

20. Reflecting the foregoing, even Dr. Paul Offit, a member of VRBPAC and a staunch advocate for removing hurdles to the licensure of vaccines, has said that to determine whether a COVID-19 vaccine is safe and effective, “we are waiting for the big trial ... the large prospective placebo controlled trial, we have 20,000 people who get a vaccine, 10,000 people who get a placebo, then and only then will you know whether a vaccine is safe and effective.”²⁶ But even 20,000 subjects in the group receiving the experimental vaccine may not be sufficient according to a report from the Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, FDA, with regard to assessing the safety of BNT162b for anyone other than the groups with the highest risk of complications from SARS-CoV-2.²⁷

21. The study, then, must use an adequate sample size, appropriately powered, in order to (i) detect an increase in rare adverse events or, any untoward medical occurrence, whether or not considered vaccine related and (ii) determine that the rate of adverse events from the vaccine will not exceed the rate of adverse events known to occur from SARS-CoV-2 in the group under review.

e. T-cell Reactivity and Response

22. Clinical trial participants should be tested for T-cell reactivity to SARS-CoV-2 prior to vaccination and then again after vaccination.

23. This is necessary because, as recently explained in the journal *Nature Reviews Immunology* by researchers from the Center for Infectious Disease and Vaccine Research at La Jolla Institute for Immunology, “if subjects with pre-existing reactivity were sorted unevenly in

²⁵ See <https://www.clinicaltrials.gov/ct2/show/NCT04368728> (last visited August 11, 2020).

²⁶ <https://www.cnn.com/videos/health/2020/05/24/coronavirus-covid-19-vaccine-trials-vaccinologist-concern-ip-vpx.cnn> (emphasis added) (last visited August 11, 2020).

²⁷ See <https://pubmed.ncbi.nlm.nih.gov/11802587/> (last visited August 11, 2020).

different vaccine dose groups, this might lead to erroneous conclusions. Obviously, this could be avoided by considering pre-existing immunity as a variable to be considered in trial design.”²⁸

24. Dr. Sette, a member of this group, further explained that “if you have 10 people that have reactivity and 10 people that don't have the pre-existing reactivity and you vaccinate them with a SARS CoV-2 vaccine, the ones that have the pre-existing immunity will respond faster or better to a vaccine. ... So, we have been suggesting to anybody that is running vaccine trials to also measure T-cell response.”²⁹

g. Stay Urgently Required

25. Petitioner will suffer irreparable harm because once the FDA licenses this COVID-19 vaccine, states are expected to make this product mandatory, and hence without the FDA assuring proper safety trials of the vaccine *now*, the Petitioner will not have the opportunity to object to receiving the vaccine based on deficient clinical trials *later*. For example, the New York State Bar Association recently issued a report on COVID-19 recommending that “[w]hen the efficacy of a COVID-19 vaccine has been confirmed, enact legislation requiring vaccination of each person unless the person’s physician deems vaccination for his or her patient to be clinically inappropriate.”³⁰ Mandating administration of the vaccine, thereby eliminating the right to informed consent, makes acute the need to assure that the safety and efficacy of any COVID-19 vaccine is robustly studied in an adequate clinical trial monitoring for any potential adverse events.

26. Furthermore, as noted, ethical considerations prevent a placebo-controlled study post-licensure; thus, if the vaccine is licensed without an appropriate safety review, there will be no opportunity for any such study to ever occur. This is especially troubling because when parents assert that a licensed vaccine injured their child, the CDC regularly denies these assertions by stating that no cause and effect has been established between vaccination and the alleged injury. But as the FDA and CDC are well aware, *without* a placebo control trial, cause and effect is very difficult and often impossible to establish.³¹ Therefore, no matter how many or what type of vaccine injuries are reported post licensure, the FDA, CDC and manufacturers retort is that “a

²⁸ <https://www.nature.com/articles/s41577-020-0389-z> (last visited August 11, 2020).

²⁹ <https://amp.cnn.com/cnn/2020/08/02/health/gupta-coronavirus-t-cell-cross-reactivity-immunity-wellness/index.html> (last visited August 11, 2020).

³⁰ https://nysba.org/app/uploads/2020/05/HealthLawSectionTaskForceCOVID-19Report_5.13.20-1.pdf (last visited August 11, 2020).

³¹ See <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/adverse-reactions.html> (“establishing evidence for cause and effect on the basis of case reports and case series alone is usually not possible,” rather, researchers need “to compare the incidence of the event among vaccinees with the incidence among unvaccinated persons”) (last visited August 11, 2020); see also <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3505292/> (The entire advantage of a randomized placebo-controlled trial “is the ability to demonstrate causality i.e., cause-effect relationship.”) (last visited August 11, 2020); <https://www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html> (The Vaccine Adverse Events Reporting System (VAERS) is unable “to determine causation” because “there is a lack of an unvaccinated group for comparison in VAERS.”) (last visited August 11, 2020).

cause and effect relationship with the vaccine has not been established.”³² The FDA can avoid this ethical and conflict ridden quagmire now by issuing the stay and requiring the basic amendments to the trial design requested in this petition.

27. This request is also not frivolous and is being pursued in good faith as it seeks to increase the scientific integrity and reliability of the trials of this potential COVID-19 vaccine. Requiring that safety actually be reviewed during the study period is well supported by sound public policy. It is also supported by the fact that the Secretary of the United States Department of Health & Human Services has already granted those developing and selling any COVID-19 product broad immunity from liability for injuries thereby eliminating the potential liability which drives companies to assure the safety of their products.³³

28. The good faith nature of this request is further supported by the fact that (i) according to the most recent CDC estimates, COVID-19 rarely injures children and younger healthy adults; (ii) overall, over 99% of those infected with COVID-19 recover;³⁴ and (iii) the vaccine will likely be administered to at least hundreds of millions of individuals. If the vaccine, for example, causes .3% of children to develop a chronic health condition a year after injection, that could cause lifelong health issues for millions of children. This is why international scientists have declared that “inadequately powered studies should themselves be considered a breach of ethical standards.”³⁵ Without a clinical trial of sufficient size that reviews all potential adverse events for a sufficient duration, this potentially catastrophic result will not be identified prior to licensure.

29. Finally, the public interest also weighs strongly in favor of the requested relief because having adequate safety review protocols will comport with the best interests of all Americans slated to receive this product and will increase public confidence in the safety and efficacy of this product.

30. The changes requested herein can also be implemented rapidly and with minimal disruption to the trial of BNT162b. Extending the duration that adverse events are captured would require no disruption, merely a change in the study protocol. The addition of more subjects similarly will not disrupt the ongoing trial – just increase its size – and will also provide an opportunity to test the T-cell reactivity to SARS-CoV-2 in this group pre-and-post vaccination. Hence, the request in this petition can be fulfilled with little, if any, disruption to the trial of BNT162b. And any minimal disruption will be far outweighed by the benefits of conducting a trial that actually assess safety.

³² *Id.*

³³ See <https://www.phe.gov/Preparedness/legal/prepact/Pages/default.aspx> (last visited August 11, 2020).

³⁴ See <https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html#box> (last visited August 11, 2020).

³⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2504487/> (last visited August 11, 2020).

31. The Petitioner therefore respectfully urges that this request be granted forthwith.

Respectfully submitted,

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