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VIA ELECTRONIC FILING

October 16, 2020

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
Commissioner Stephen M. Hahn, M.D.
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Dear Commissioner Hahn,

Enclosed is an Amended Citizen Petition filed by Del Bigtree and the Informed Consent Action Network ("ICAN") regarding the Phase III clinical trial of Astra Zeneca's ChAdOx1 nCoV-19 vaccine for SARS-CoV-2 which raises exigent concerns that demand your immediate attention. This amended petition relates to ICAN's original Citizen Petition filed on August 17, 2020 at Docket No. FDA-2020-P-1768.

ICAN looks forward to receiving a timely decision and we, as counsel to the petitioners, remain available to answer questions and provide any relevant additional information.

Very truly yours,

/s/ Aaron Siri

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UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES AND THE FOOD AND DRUG ADMINISTRATION

PETITION FOR ADMINISTRATIVE ACTION REGARDING PHASE III CLINICAL TRIAL OF ChAdOx1 nCoV-19 - NCT04400838	**:**	**Docket No. 2020-P-1768**

AMENDED CITIZEN PETITION

The original petition in this matter was submitted on August 17, 2020. In that petition, the Petitioner requested that the Food and Drug Administration (the "**FDA**") require that the Phase III clinical trial of Astra Zeneca's ChAdOx1 nCoV-19 vaccine meet certain enumerated conditions regarding safety and efficacy.

In light of the clinical trial protocol dated September 17, 2020 and titled "A Phase III Randomized, Double-blind, Placebo-controlled Multicenter Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19"[1] made public by Astra Zeneca following Petitioner's submission, it appears that some of Petitioner's conditions have been met and Petitioner therefore submits this amended petition to address the outstanding conditions.

[1] "A Phase III Randomized, Double-blind, Placebo-controlled Multicenter Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19", September 17, 2020, available at https://s3.amazonaws.com/ctr-med-7111/D8110C00001/52bec400-80f6-4c1b-8791-0483923d0867/c8070a4e-6a9d-46f9-8c32-cece903592b9/D8110C00001_CSP-v2.pdf (last visited October 15, 2020).

This amended petition for administrative action is submitted on behalf of Informed Consent Action Network[2] ("**Petitioner**") pursuant to 21 C.F.R. § 10.35 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act to request that the Commissioner of Food and Drugs (the "**Commissioner**") require that the Phase III trial of ChAdOx1 nCoV-19 (NCT04400838) conforms with the amended requests in the "Actions Requested" section below before licensure.

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 and related petition for stay of action by October 30, 2020.[3]**

A. ACTION REQUESTED

1. It is hereby requested that the study design for the Phase III trial of ChAdOx1 nCoV-19 (NCT04400838)[4] be amended to provide that:

a. any and all adverse events and reactions[5] will be documented for the entire duration of the trial;

b. such documenting of adverse events and reactions shall last *at least* twenty-four months for adults, thirty-six months for children and sixty months for infants and toddlers or such longer duration as appropriate, and in no event end prior to the subject reaching eight years of age;

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[6];

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

[3] Petitioner also submitted a separate Citizen Petition, located at https://beta.regulations.gov/search?filter=FDA-2020-P-1871, addressing critically needed HIV incident monitoring during Astra Zeneca's Phase III trial. Those requests are now included within this amended petition.

[4] NCT04400838 available at https://www.clinicaltrials.gov/ct2/show/NCT04400838 (last visited October 14, 2020).

[5] 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.

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

d. participants are tested for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination;

e. germline transmission tests are conducted for male participants; and

f. HIV incidence will be "monitored at the end of the study and for an appropriate follow-up period"[7] and the trial will "evaluate the levels and distribution of both vector and insert responses in target tissues where HIV acquisition is known to occur."[8]

B. STATEMENT OF GROUNDS[9]

2. The current study design for the Phase II/III clinical trial for ChAdOx1 nCoV-19 ("**nCOV-19 Vaccine**") is inadequate to assess safety.

3. Petitioner will suffer irreparable harm if the action requested herein is not granted because once the FDA licenses this COVID-19 vaccine, states are expected to make this product mandatory. 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."[10] 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*.

4. Furthermore, if the vaccine is licensed without an appropriate safety review, ethical considerations prevent a placebo-controlled study post-licensure, thereby preventing any such study from ever occurring. This is especially troubling because when parents assert that when a licensed vaccine injured their child, the FDA and CDC regularly deny these assertions by stating that no cause and effect has been established between vaccination and the alleged injury. But as

[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4414116/ (April 29, 2015 article by Dr. Anthony Fauci, *Immune Activation with HIV Vaccines: Implications of the Adenovirus Vector Experience*) (last visited Sept. 3, 2020).

[8] *Id*.

[9] 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).

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

the FDA and CDC are well aware, without a placebo control trial, cause and effect is very difficult and often impossible to establish.[11]

5. The public interest also weighs strongly in favor of the requested relief because using adequate safety review protocols, T-cell testing, germline transmission testing, and HIV monitoring (i) will comport with the best scientific practices, (ii) increase public confidence in the safety and efficacy of a product expected to be mandated, and (iii) not doing so will have the opposite result in that it will create uncertainties regarding the safety of this COVID-19 vaccine.

a. Tracking All Adverse Events

6. To increase assurance that potential adverse events from the nCoV-19 Vaccine 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 full duration of the clinical trial.[12] 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. The current study design for nCoV-19 Vaccine provides that "adverse events" should be captured for only 28 days post-vaccination while "serious adverse events" ("**SAEs**"), "medically attended adverse events" ("**MAAEs**"), and "adverse events of special interest" ("**AESIs**") should continue to be captured through the last participant contact.[13] MAAEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Thus, any adverse event to arise at a scheduled visit to a doctor would be excluded.

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[11] *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).

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

[13] 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).

8. The adverse events captured beyond a short duration should not be limited to SAEs, MAAEs leading to unscheduled medical visits, and AESIs since there are many autoimmune, neurological, and chronic health disorders which have a major impact on the quality of life, yet may evade falling into one of these categories and which would therefore be ignored simply because they were attended to during a scheduled medical visit.[14] To wit, there are a myriad of post-licensure adverse reactions reported by consumers that are also listed in the package inserts for one or more vaccines that have a serious impact on quality of life but which would not fall into one of these categories. For example: alopecia, vasculitis, Bell's Palsy, hypotonia, migraine, myelitis, neuropathy, mental disorders, rhinitis, and vertigo. There are also many life altering reactions or conditions that may be missed in the event that a participant did not have an unscheduled visit with a medical doctor. Creating artificial lines which exclude potential adverse events is both reckless and avoidable.

9. Given that SAEs, MAAEs leading to unscheduled medical visits, and AESIs are already being captured through the last participant contact, it appears foolhardy to not also capture *all* adverse events. If nCoV-19 Vaccine causes a progressive neurological or systemic autoimmune issue to arise two months after vaccination that, for example, causes mild life issues in the near term but serious issues in the long term, it would be irresponsible and unethical not to capture that reaction just because it falls into the artificially defined zone of being an "adverse event" or "non-serious adverse event," rather than what the FDA labels as a "serious adverse event" or because a participant may have only raised this with a doctor at a scheduled visit, taking it outside the definition of a MAAE.

b. Minimum Period to Track Adverse Events

10. At a minimum, all adverse events and reactions should be documented for each subject post-vaccination for *at least* twenty-four months for adults, thirty-six months for children and sixty months for infants and toddlers or such longer duration as appropriate, and in no event end prior to the subject reaching eight years of age. These minimal timeframes provide an opportunity to capture adverse and non-specific health issues that nCoV-19 Vaccine may cause.

11. The importance of capturing all potential health issues for the duration of the clinical trial can be seen in the designs of the clinical trials of numerous drugs, including for

[14] 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).

example, Enbrel[15], Lipitor[16], and Botox,[17] which had safety review periods of 6.6 years, 4.8 years, and 51 weeks respectively, with a placebo control group. As another example, the weight loss drug Belviq was safety tested in a placebo-controlled trial for two years before being licensed by the FDA in 2012.[18] Nevertheless, despite this two year period, in February 2020 the drug was voluntarily removed from the US market due to emerging data showing that people who had taken the drug as part of a large clinical trial had an increased occurrence of cancer five years later.[19]

12. The FDA states that the length of study for phase III clinical trials is typically "1 to 4 years"[20] and that the duration of a clinical trial should "reflect the product and target condition."[21] In accord with this guidance, and the fact that a COVID-19 vaccine will be an entirely novel product, the safety review period should be at least twenty-four months for adults, thirty-six months for children, and sixty months for infants and toddlers, or such longer duration as appropriate, and in no event end prior to the subject reaching eight years of age. The need for these minimum safety review periods 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.

13. 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."[22]

14. Moreover, taking into account the FDA's guidance that clinical trials should "reflect the product and target condition,"[23] the time frame for the safety review must be long for

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[15] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503lbl.pdf (last visited August 11, 2020).

[16] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf (last visited August 11, 2020).

[17] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf (last visited August 11, 2020).

[18] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022529lbl.pdf (last visited August 11, 2020).

[19] *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).

[20] https://www.fda.gov/patients/drug-development-process/step-3-clinical-research (last visited August 11, 2020).

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

[22] 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).

[23] *See* n. 21, *supra*.

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 and for many conditions, not until reaching seven years of age.[24] 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.[25]

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."[26] Since children have not been seriously affected by COVID-19, the risk of any vaccine for SARS-CoV-2 must be fully understood in order to weigh it against any potential benefit.

c. Adequately Powered Sample Size

15. The study design for nCoV-19 Vaccine provides for only 30,000 individual study subjects, with presumably only 20,000 individuals in the study group that will receive the nCoV-19 Vaccine and 10,000 individuals in the control group that will receive the placebo.

16. A Phase III trial for nCoV-19 Vaccine with 30,000 subjects cannot produce an adequate safety profile for this product. SARS-CoV-2 poses a statistically insignificant risk of

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[24] 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).

[25] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6526087/ (last visited August 11, 2020).

[26] *Id*.

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.

17. A total of 20,000 subjects in the group receiving the experimental vaccine will only be potentially sufficient for populations severely affected by COVID-19 and will be insufficient for all other populations. This is plain from a report from the Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research at the FDA, with regard to assessing its safety of the nCoV-19 Vaccine for anything other than the groups with the highest risk of complications from SARS-CoV-2.[27]

18. The trial should have 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.

d. T-cell Reactivity and Response

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

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

21. 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]

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

e. Germline Transmission Tests

22. According to the European Medicines Agency, viral or non-viral vectors may be associated with a risk of vertical germline transmission of vector DNA.[30] While "currently there are no non-invasive means to monitor women for germline transmission," male participants in the clinical trials can and should be monitored.[31]

23. "Since one cycle of spermatogenesis takes approximately 64-74 days in man, the timing of the appearance of transduced progenitor daughter cells in the semen is predictable. This can be taken into account in the planning of germline transmission tests as part of clinical trial protocols."[32] Further, "this can be accomplished by investigating sperm at different time points taking into account the duration of spermatogenesis…The earlier the differentiation stage at which germline transmission takes place in the spermatogenesis process, the greater the risk that the germline alteration is permanent and the greater will be the fraction of transduced sperm cells."[33]

24. Requiring this simple test will not delay the study, would add very little burden to the sponsor, and will provide comfort that the vaccine is not having deleterious effects on the male germline.

f. HIV Incidence Monitoring and Evaluating Target Tissues Where HIV Acquisition is Known to Occur

25. The NZD1222 and ChAdOx1 nCoV-19 ("**nCOV-19 Vaccine**") is a recombinant viral vector vaccine. In past viral vector vaccine clinical trials, HIV incidence was higher in vacinees than in placebo recipients.[34]

26. The Step Study, opened in 2004, was a multicenter, double-blind, randomized, placebo-controlled phase II test of concept study of a trial HIV vaccine. The vaccine consisted of a 1:1:1 mixture of 3 separate replication-defective Ad5 vectors. In that trial, study participants were seen at Day 1 and Weeks 2, 4, 8, 12, 26, 30, 52, and every 26 weeks thereafter through week 208. As pre-specified in the protocol, an interim analysis of HIV incidence and early HIV-1 viral load was conducted. This analysis showed that HIV incidence was higher in the vaccine group than in the placebo group. All additional vaccinations in the study were immediately halted. HIV rates appeared to be more than twice as high in vaccinees compared with placebo recipients in Ad5 seropositive men.[35]

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[30] *See* https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-testing-inadvertent-germline-transmission-gene-transfer-vectors_en.pdf (last visited August 11, 2020).

[31] *Id.*

[32] *Id.*

[33] *Id.*

[34] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2721012/ (November 29, 2008 article titled *Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial*) (last visited Sept. 3, 2020).

[35] *Id.*

27. In April 2014, Dr. Fauci co-authored the article *Immune Activation with HIV Vaccines: Implications of the Adenovirus Vector Experience*. This article reviewed the Step Study data and in its "Considerations for the future" section stated:

> **For non-HIV vaccine trials using vectors that induce strong T-cell immunity… it may be important to monitor for HIV acquisition**, depending on the target population. **In such studies where the population may be at risk of HIV exposure, HIV incidence should be monitored at the end of the study and for an appropriate follow-up period**."

The article co-authored by Dr. Fauci further states: "**Future clinical testing of Ad-based vaccines should evaluate the levels and distribution of both vector and insert responses in target tissues where HIV acquisition is known to occur**."[36] Although the nCOV-19 Vaccine is not specifically an Ad-5 vector vaccine, the principle still stands: an adenovirus-based vaccine that may potentially "induce strong T-cell immunity" must be evaluated in order to determine whether or not it makes vacinees more susceptible to contracting HIV.

28. Other studies evidence that the appropriate target tissues to be evaluated are mucosal tissues. An October 29, 2010 a peer-reviewed article titled *Immunologic Basis of Vaccine Vectors* by Margaret A. Liu explores "insights obtained from preclinical and clinical studies of" vaccines, including the vaccine in the Step Study.[37] The article, discussing the increased incidence of HIV in the Step Study, states:

> One possible explanation for these [Step Study] results [higher incidence of HIV in vaccines than placebo group], aside from it being stochastic, is that in patients with high anti-Ad5 titers, (i.e., presumably indicative of prior infection with adenovirus 5, and hence also with pre-existing Ad5 T helper cell responses) activated Ad5-specific T cells were more susceptible to infection by HIV… a further study showed that when T cells from individuals who had pre-existing antibodies against adenovirus were stimulated with adenovirus, an increase in memory CD4+T cells occurred, and these T cells were more easily infected with HIV. In addition, **these T cells homed to mucosa, which could provide an explanation for the results of the two prior studies that had sampled peripheral blood lymphocytes rather than mucosal lymphocytes.** These studies highlighted, among other issues, that many of the read-outs of immunologic parameters have utilized **peripheral blood**

[36] *See* n. 3, *supra* (emphasis added) (last visited Sept. 3, 2020).

[37] https://reader.elsevier.com/reader/sd/pii/S107476131000364X?token=61C565C0A6959F11E5D5973F8A3349325B842CC01BE4D3374810526447BA211AA6498A721777BEF965CC606096B4A0F4 (October 29, 2010 article, *Immunologic Basis of Vaccine Vectors*) (last visited Sept. 3, 2020).

lymphocytes, which may not reflect cells or immune conditions in organs or at the sites of infection.[38]

Therefore, in evaluating the HIV incidence in trial participants, mucosal lymphocytes are the appropriate target tissues to test.

29. In July 2015, Dr. Fauci authored an article titled *Toward an HIV vaccine: A scientific journey*, again discussing the Step data, and stated: "Unfortunately, two phase IIb trials (STEP and Phambili) testing a candidate that expressed HIV *gag*, *pol*, and *nef* were halted after interim Data and Safety Monitoring Board reviews revealed poor efficacy. In fact, **the trials demonstrated evidence of increased risk of viral acquisition among vaccine recipients as compared with placebo**. A scientific symposium reviewing those data concluded that **vaccine-related immune activation might have led to increased susceptibility to infection.**"[39]

30. Recognizing Dr. Fauci's future considerations for viral vector vaccines, Petitioner therefore requests that the incidence of HIV be assessed in trial participants at the end of the trial, and for an appropriate follow-up period after the trial, and also that the evaluations are completed in appropriate mucosal target tissues.

C. ENVIRONMENTAL IMPACT

31. The undersigned hereby states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. §§ 25.30 and 25.31.

D. ECONOMIC IMPACT

32. Economic impact information will be submitted upon request of the commissioner.

E. CERTIFICATION

33. The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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

Respectfully submitted,

/s/ Aaron Siri
Aaron Siri
Elizabeth Brehm

[38] *Id*. (emphasis added).

[39] https://science.sciencemag.org/content/349/6246/386.long (July 24, 2015 article titled *Toward an HIV vaccine: A scientific journey*) (emphasis added) (last visited Sept. 3, 2020).

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