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VIA ELECTRONIC FILING

September 10, 2020

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

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 AND HIV INCIDENCE	**:**	**Docket No. _____**

CITIZEN PETITION

This petition for administrative action is submitted on behalf of the Informed Consent Action Network[1] ("**Petitioner**") pursuant to 21 C.F.R. § 10.30 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 AZD1222 and ChAdOx1 nCoV-19 (NCT04400838 and NCT04516746) conforms with the requests in the "Actions Requested" section below prior to 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 the FDA act on the instant Petition by September 25, 2020.**

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

A. ACTION REQUESTED

1. It is hereby requested that the study design for the Phase III trials of AZD1222 and ChAdOx1 nCoV-19 (NCT04400838 and NCT04516746)[2] be amended to provide that:

a. HIV incidence will be "monitored at the end of the study and for an appropriate follow-up period;"[3] and

b. the trial will "evaluate the levels and distribution of both vector and insert responses in target tissues where HIV acquisition is known to occur."[4]

B. STATEMENT OF GROUNDS[5]

2. 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.[6]

3. 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.[7]

4. 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**

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[2] NCT04400838 available at https://www.clinicaltrials.gov/ct2/show/NCT04400838 (last visited Sept. 3, 2020); NCT04516746 available at https://www.clinicaltrials.gov/ct2/show/NCT04516746 (last visited Sept. 3, 2020).

[3] 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).

[4] *Id*.

[5] 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 Sept. 3, 2020).

[6] 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).

[7] *Id*.

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**."[8] 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.

5. 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.[9] 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 lymphocytes, which may not reflect cells or immune conditions in organs or at the sites of infection.**[10]

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

6. 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

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

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

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

(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.**"[11]

7. 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."[12] 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*.

8. 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

9. 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. Sections 25.30 and 25.31.

D. ECONOMIC IMPACT

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

E. CERTIFICATION

11. 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.

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[11] 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).

[12] https://nysba.org/app/uploads/2020/05/HealthLawSectionTaskForceCOVID-19Report_5.13.20-1.pdf (last visited Sept. 3, 2020).

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

Respectfully submitted,

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