



SUBMISSION FROM THE AFRICAN CENTRE OF BIODIVERSITY TO THE REGISTRAR:

**GENETICALLY MODIFIED ORGANISMS  
REGARDING THE APPLICATIONS FOR  
IMPORT AND TRIAL RELEASES OF  
AZD1222 (CHADOX1 NCO-V-19) VACCINE  
CLINICAL TRIALS FOR COVID-19**

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HAVE PREPARED THIS SUBMISSION.

9 JUNE 2020

The African Centre for Biodiversity (ACB) is a research and advocacy organisation working towards food sovereignty and agroecology in Africa, with a focus on biosafety, seed systems and agricultural biodiversity. The organisation is committed to dismantling inequalities and resisting corporate-industrial expansion in Africa's food and agriculture systems. The ACB was established in 2004, and has since, consistently submitted objections to the Registrar: GMOs in South Africa on numerous GM applications for various uses, in respect to various food and fibre crops. It has also made submissions concerning GM HIV vaccines in 2009.

We thank the Registrar for bringing the notice, which was published in the Sunday Times on 10 May, 2020, to our attention by email on 26 May, 2020. But for this email, we would not have known about these trials. The ACB shared this notice immediately with social movements in South Africa as well as on social media. We further thank the Department of Agriculture for expediting our access to information to the application for import and trial release.

In this submission, we deal principally with the application for approval for release of ChAdOx1 nCoV-19 vaccine for clinical phase I/II trials on 2 800 both healthy and HIV-positive adults over 12 months.

As a global community, we are unified in our shared sense of urgency to find long-term life-saving solutions to the current pandemic. While the world works on effective treatments to be developed as rapidly as possible, we wish to emphasise that this must not come at the cost of the highest standards of safety, efficacy, transparency, and ethics in clinical research. With any treatment, whether it is a drug or non-therapeutic intervention, such treatments must be designed as a public good, with full access to information underpinning any project and its progress through the stages of research to clinical approval.

Scientific integrity at the time of a pandemic is needed more than ever to ensure trust in the safety and efficacy of future treatments going forward. The necessary urgency in solving the coronavirus crisis has already put pressure on research integrity standards<sup>1</sup>, with the flood of pre-printed, non-peer-reviewed 'research' papers. This has had direct implications for policy decisions, with the World Health Organisation's trials being terminated and then reinstated following the retraction of substandard publications on trial drugs<sup>2</sup>. Lack of transparency has also diminished trust in government responses in nations such as the UK<sup>1</sup>, where the vaccine under discussion was developed, threatening public adherence to coronavirus advice and health and safety policy. With the Oxford program described as undergoing a 'very aggressive clinical

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1 <https://blogs.bmj.com/bmj/2020/06/08/assuring-research-integrity-during-a-pandemic/>

2 <https://www.sciencemag.org/news/2020/06/two-elite-medical-journals-retract-coronavirus-papers-over-data-integrity-questions>

development program'<sup>3</sup>, we urge that full public participation in the decision-making process, as defined in the South Africa's Genetically Modified Organisms Act in particular and its legal regime governing fair administrative procedures in general, are not sacrificed.

### CONCERNS REGARDING THE REDACTION OF CRUCIAL BACKGROUND AND SAFETY INFORMATION IN THE APPLICATION

With such a context in mind, we raise several concerns regarding the application to trial Oxford University's vaccine in South Africa. We note that key information pertaining to safety has been redacted as 'confidential business information', making it impossible for the public to assess the risks of trialling a treatment that should indeed be of service to the public. This is particularly concerning given that the proposed vaccine is assumed to be a global public good.

In several sections of the application for trial release, important information is not given at all, or a very brief input with doubtful informational value is followed by a standard insertion – "[Confidential Information Deleted in accordance with section 68 of The Promotions of Access to Information Act, 2000]".

In most cases, it is more than difficult to understand why this is practised. A good example of this is presented in PART I, 2 "Brief description of the GMO", because: The full protocol for construction and production of ChAdOx1 nCoV-19 is given in several open sources and articles, among them the key article by van Doremalen et al. (2020), where the vaccine was first tested on laboratory monkeys (see Van Doremalen, N, Munster VJ et al. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. bioRxiv preprint doi: <https://doi.org/10.1101/2020.05.13.093195>. This version was posted May 13, 2020).

Redaction of information is repeated for sections on human health, where information on toxicity (Section 8.1.2 (a)) and allergenicity (Section 8.1.2 (b)) to humans and animals; as well as other sections on survivability in the environment (Section 4.5); reproductive capacity (Section 4.4); and trial design (Section 7.5) has been redacted.

The application also has a regrettable lack of literature references throughout to substantiate health and ecosystem safety claims. This makes it very difficult to evaluate some of the claims being made as to safety, as is more fully dealt with below.

Finally, we were unable to find any written account of the results from the UK's phase I/II single-blinded, randomised, placebo-controlled trial to investigate the safety, efficacy, and

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<sup>3</sup> <https://blogs.sciencemag.org/pipeline/archives/2020/04/23/a-close-look-at-the-frontrunning-coronavirus-vaccines-as-of-april-23>

immunogenicity of the vaccine, which began in March 2020, with an expected completion date of May 2021. Such information is key to determining the progress to the next phases of clinical investigation, and it remains unclear why such information would not be presented in the application that is being made available for public scrutiny.

#### WHAT IS THE VACCINE BEING TRIALLED?

The vaccine being developed is termed AZD1222 (previously known as ChAdOx1 nCoV-19). It was developed at the University of Oxford and is produced in partnership between the University of Oxford's Jenner Institute and Italian pharmaceutical manufacturer Advent Srl. Oxford University has formed a partnership with AstraZeneca, a British-Swedish multinational pharmaceutical and biopharmaceutical company, headquartered in England, for further development, large-scale manufacture and potential distribution of the vaccine.

The vaccine involves the use of a chimpanzee adenovirus that has been genetically engineered to remove the genetic elements required for it to replicate inside people. It has then been further modified to produce the coronavirus spike (S) protein into it as the antigen that is designed to invoke a protective antibody response against the virus upon being infected.

ChAdOx1 viral vectors have been used to develop investigational vaccines against several pathogens, including a closely related coronavirus that causes Middle East respiratory syndrome (MERS). The scientists quickly adapted the platform to SARS-CoV-2 when the first cases of COVID-19 emerged. Trials have thus far been conducted in the UK, and more are planned for Kenya (as set out in the application), as well as Brazil and the United States<sup>4</sup>.

#### COMMENTS ON THE EVIDENCE OF EFFICACY

Preliminary studies were conducted to provide data for clinical testing to commence. A single dose of AZD1222 protected six rhesus macaques from pneumonia caused by the virus, according to National Institutes of Health scientists and University of Oxford collaborators. The researchers posted their data to the preprint server bioRxiv. The findings are not yet peer-reviewed but are being shared to assist the public health response to COVID-19. Based on these data, a Phase 1 trial of the candidate vaccine began on April 23 in healthy volunteers in the United Kingdom (see van Doremalen, N, Munster VJ et al. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. bioRxiv preprint doi: <https://doi.org/10.1101/2020.05.13.093195>. This version posted May 13, 2020).

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<sup>4</sup> <http://www.ox.ac.uk/news/2020-06-04-brazilian-health-regulatory-agency-approves-trial-oxford-covid-19-vaccine>

The van Doremalen study claims to show “that the adenovirus-vectored vaccine ChAdOx1 nCoV-19, encoding the spike protein of SARSCoV-2, is immunogenic in mice, eliciting a robust humoral and cell-mediated response.”

However, numerous expert reactions<sup>5</sup> to the monkey study express doubts and concerns about the potential efficacy of the vaccine that, while preventing pneumonia in all the monkeys, did not prevent all from developing symptoms. Most crucially, it did not reduce viral load in the noses of the animals, suggesting that vaccinated individuals would still be contagious.

Jonathan Ball, Professor of Molecular Virology at University of Nottingham, recently stated:

“If this represents infectious virus and a similar thing occurs in humans, then vaccinated people can still be infected, shed large amounts of virus which could potentially spread to others in the community. If the most vulnerable people aren’t protected by the vaccine to the same degree, then this will put them at risk. Therefore, vaccine efficacy in vulnerable populations and the potential for virus shedding in vaccinated people needs very careful monitoring.”

Prof Eleanor Riley, Professor of Immunology and Infectious Disease at the University of Edinburgh, also stated<sup>5</sup>:

“Whilst the vaccine induced neutralising antibodies and vaccinated animals experienced less severe clinical symptoms than unvaccinated animals (good), the neutralising antibody titres were low and insufficient to prevent infection and – importantly – insufficient to prevent viral shedding in nasal secretions (worrying). If similar results were obtained in humans, the vaccine would likely provide partial protection against disease in the vaccine recipient but would be unlikely to reduce transmission in the wider community.”

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#### COMMENTS ON THE CHOICE OF TEST PROCEDURES

Unfortunately, there appears to be a lack of protocols to address the potential shedding of infectious virus, and protocols to distinguish between infectious and non-infectious virus RNA. Patients will only be tested for the virus upon showing two or more symptoms. Does this mean that we will not know if they are contagious or not?

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<sup>5</sup> <https://www.sciencemediacentre.org/expert-reaction-to-preprint-on-the-chadox1-ncov-19-vaccine-and-sars-cov-2-pneumonia-in-rhesus-macaques/>

Further, the most critical first line of defence against SARS-CoV-2 infection is the local immunity on the respiratory tract mucous membranes. This fact is not reflected in this application, nor the article published on the monkey experiments. With regards to safety concerns, there also appears to be no methods included in the trial to assess the threat of Antibody Dependent Enhancement (ADE). It is therefore surprising that methods to assess whether this appears in trial participants are not included in the application.

Finally, the vaccine virus expresses the full-length S protein. It would be interesting to hear the applicant's reaction to the statement by Yong et al:

"Vaccine candidates against SARS-CoV were initially developed based on the full-length S protein. However, these vaccines were later demonstrated to induce non-neutralizing antibodies which did not prevent infection, and the immunized animals were not protected from the viral challenge, instead they experienced adverse effects like enhanced hepatitis, increased morbidity, and stronger inflammatory responses. (Yong et al. *Frontiers in Microbiology*, August 2019, volume 10, article 1781)

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#### COMMENTS ON SAFETY CLAIMS

As raised above, regrettably, some of the information on the safety of the vaccine has been deleted as confidential business information (CBI), leaving safety claims unsubstantiated.

Of foremost concern is the claim that the vaccine is safe because it is replication-defective. While some of the information provided regarding reproductive capacity has been CBI deleted, the available information states that:

"The ChAdOx1 (AdvY25) viral vector is replication-deficient as the essential E1 gene region – which is essential for viral replication – has been deleted. The virus is unable to replicate within vaccinated animals or humans."

However, this is not by any means proof of safety as evidenced by the vaccine production system itself. The defective vaccine virus can replicate in human HEK 293 cells because it is rescued by the human adenovirus 5 E1 locus being inserted into this cell line to replace the lost gene that was removed from the viral vaccine. The applicants are directed to several peer-reviewed articles where E1-deleted adenoviruses have been rescued by double infections with another, competent adenovirus. Since adenoviruses are commonly circulating in most animal species that have been investigated, this is a matter of concern for human as well as animal health. Hence, repeated claims that adverse effects are "none" are not justified. Interspecies transmission of adenoviruses is not an unknown phenomenon (see for instance, Wevers et al. *Journal of Virology* 85: 10774-10784, 2011).

Finally, we seek further attention to the claims in Section 4 that, “Simian adenoviruses are not known to cause pathological illness in humans...” without any reference to work that demonstrates this being provided. Furthermore, there are peer-reviewed articles showing higher antibody prevalence of cross-reactive antibodies to adenoviruses from chimpanzees and other nonhuman primates than those thrown in here (see, for instance, McCoy et al. Journal of Virology 81: 6594-6604, 2007).

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#### THE ROLE OF PUBLIC PARTICIPATION IN THE DECISION-MAKING PROCESS

Considering the involvement of South African citizens in this trial, we urge that the Executive Council: GMO Act, require that the applicant address the concerns and comments raised above to ensure the integrity of this trial and the protection of the trial participants, some of whom will also be HIV positive. It is unclear from the application of how health complications will be addressed after the 12-month study period.

We call upon the EC to ensure that the applicant ensures full disclosure of the safety data and information to the public to enable us to exercise our rights to administrative justice.

Further, the public has the right to fair administrative decision-making and the right to democratic participation. We are of the respectful view that these rights of the public cannot be said to be upheld unless there is full and meaning public participation and that decision making is done in a procedurally fair, open and transparent manner. In this regard, we strongly urge the EC to set up an independent panel comprised of multi-disciplinary experts to conduct an open and transparent process to assist the EC in reviewing this application and to conduct public hearings in an open and transparent way, on the concerns being raised in this submission and that may be raised by other sections of the South African society, online still in June 2020.