



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doctors for COVID Ethics



25 May 2021
EMA/292405/2021
Stakeholders and Communication Division



We acknowledge receipt of your follow-up letters dated 1 and 20 April 2021 regarding the COVID-19 vaccines.

We strongly reject any accusations of complacency and concealing the truth. In fact, EMA is providing enhanced transparency of its regulatory activities on treatments and vaccines for COVID-19, beyond that provided for other medicines.¹ In this respect EMA is publishing clinical data submitted as part of regulatory procedures on COVID-19 medicines, which can be viewed on the following page:

<https://clinicaldata.ema.europa.eu/home>

In addition to being more transparent, EMA also routinely communicates to the public and to healthcare professionals on all outcomes of its assessments through dedicated press releases and direct healthcare professional communications (DHPC) (the DHPC of 24 March 2021 regarding thrombotic events with Vaxzevria can be found here:

<https://www.ema.europa.eu/en/medicines/dhpc/vaxzevria-previously-covid-19-vaccine-astrazeneca-risk-thrombocytopenia-coagulation-disorders>).

EMA is therefore providing comprehensive and invaluable information to support informed treatment decisions.

EMA is fully committed to following scientific evidence in all its decisions. It is mobilising extensive resources to closely monitor safety and assess any new information for all COVID-19 vaccines as outlined in their respective pharmacovigilance plans

(https://www.ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf).

For clarification, once a medicinal product is granted a marketing authorisation by a regulatory authority, it can no longer be considered as an investigational product. For a medicine to be authorised by the EU, the Agency's human medicines committee (CHMP), composed of scientific experts from all

¹ For more information on the exceptional measures for COVID-19 medicines please consult the dedicated EMA webpage <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/transparency-exceptional-measures-covid-19-medicines>.



EU Member States, must conclude that its quality, safety and efficacy are properly and sufficiently demonstrated.

The European Commission granted marketing authorisations to the COVID-19 vaccines based on favourable CHMP scientific opinions. These opinions confirmed that the COVID-19 vaccines are compliant with the technical requirements in Directive 2001/83/EC, applicable to all medicines, and the provisions in Regulation (EC) No 726/2004 which allow for a conditional marketing authorisation to be granted on less comprehensive data than normally required. A conditional marketing authorisation can be granted if all of the following criteria are met:

- the benefit-risk balance of the medicine is positive;
- it is likely that the applicant will be able to provide comprehensive data post-authorisation;
- the medicine fulfils an unmet medical need;
- the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.

Below you can find some additional clarifications to the points you raise in your letter of 1 April:

1. **“You concede that the “vaccines” enter the bloodstream but you can obviously provide no quantitative data.”**

In our previous response we provided a high-level summary of the results of biodistribution studies that were performed, based on information in the EPAR.

Please note that nonclinical pharmacokinetic studies such as biodistribution studies are not usually required to support the development and authorisation of vaccines for infectious diseases (only in the case of new formulations or novel excipients used). Any biodistribution studies that are submitted as part of the marketing authorisation application are referenced in the EPAR. To obtain the quantitative data, you would need to make a request for access to documents related to the individual study reports that you wish to see.

For further information please refer to the following webpage: <https://www.ema.europa.eu/en/about-us/how-we-work/access-documents#how-to-submit-a-request-section>

Please see EMA’s public “Guide on access to unpublished documents”, where you will also find information on the type of documents you can request (Q17 and Q18):

https://www.ema.europa.eu/en/documents/other/guide-access-unpublished-documents_en.pdf

For your information, biodistribution studies were carried out as follows:

- For COVID-19 Vaccine Moderna, a biodistribution study using a qualified multiplex branched DNA (bDNA) assay was used to determine mRNA in various tissues with the vaccine platform mRNA-1647, a cytomegalovirus using the same platform as COVID-19 Vaccine Moderna (mRNA-1273).
- For Comirnaty, a biodistribution study in mice and rats was carried out using a surrogate of a LNP-formulated nucleoside-modified messenger RNA (modRNA) luciferase.
- For Vaxzevria, a single-dose intramuscular biodistribution study with AZD1222 in mice (study 514559) was submitted post-authorisation.

A study with the same platform vector ChAdOx-1 (hepatitis B virus) and two studies with a similar viral vector (ChAd63) were also carried out and the results are summarised qualitatively in the EPAR.

- Similarly, for COVID-19 Vaccine Janssen (also referred to as Ad26.COV2.S), the biodistribution profile of its vector platform was evaluated in rabbits using two Ad26-based vaccines encoding other antigens than the SARS-CoV-2 S protein. Results show that the replication-incompetent Ad26 vector is not widely distributed following intramuscular administration.
2. **“Your statement that non-clinical studies do not indicate any detectable uptake of the vaccines into endothelial cells lacks credibility. We demand to see the scientific evidence.”**

No dedicated *in vitro* experiments on endothelial cells were performed or needed to be performed, because based on the results of the biodistribution studies and toxicology studies, there are no signs of toxicity at the level of the vascular system.

3. **“Auto-attack could not have been excluded in animals unless they had been immunologically primed beforehand. We demand evidence that such experiments had been performed.”**

No specific preclinical models of antibody-dependant enhancement were reported for any of the authorised vaccines. However, the risk of potential vaccine associated-enhanced disease (VAED) was assessed in animal challenge studies for all authorised COVID-19 vaccines. In these studies, animals were first vaccinated with 1 or 2 doses of vaccine (as per intended clinical use of the vaccine) and then inoculated experimentally with a dose of SARS-CoV-2 virus as reported in the corresponding EPARs (indicated in the links below).

For COVID-19 Vaccine Moderna, for example, the potential risk of vaccine-induced VAED was evaluated in vaccine immunised mice and non-human primates (NHP), as measured by IgG subclasses and/or T-cell cytokines upon ex vivo S1 or S2 peptide pool stimulation.

In each animal model, intramuscular administration of the vaccine at clinically relevant dose(s) showed induction of a Th1-directed T-cell response characterised by IFN- γ , IL-2 and TNF- α , and additionally IL-21-producing follicular helper T (Tfh) cells in NHPs. There was no evidence of a Th2-directed CD4+T cell response induced in the vaccinated NHPs and overall Th2 cytokine secreting cells (e.g. IL-4, IL-5, IL-13) were lower than Th1-directed T cells in vaccinated mice, which is thought to be beneficial to minimise potential risk of vaccine-associated enhanced disease (VAED).

Similarly, for COVID-19 Vaccine Janssen, nonclinical studies conducted in mice and in rhesus monkeys have shown the induction of a Th1 skewed immune response.

As mentioned above, the results of histopathology from the lower and upper respiratory tract samples taken from animals after SARS CoV-2 inoculation did not reveal any sign of increased pathology or immunotoxicity in vaccinated animals compared with the unvaccinated control group. Based on the non-clinical and clinical data available so far, there is no evidence indicative of an undue risk of VAED linked to COVID-19 vaccines. In addition, long term safety data from the ongoing clinical trials continue to be generated and will be assessed as soon as available.

These data are requested as obligations to the marketing authorisation holders.

Although relatively limited, the available data in individuals seropositive to SARS-COV-2 prior to vaccination did not show any signs of safety issues linked to a potential autoimmune reaction to the vaccines.

For further information please refer to the EPAR assessment reports for the relevant vaccines which can be found here:

- Comirnaty:
[Comirnaty, INN-COVID-19 mRNA Vaccine \(nucleoside-modified\) \(europa.eu\)](https://www.ema.europa.eu/en/medicines/humans/CTX/CTX001/CTX001-epar-assessment-report)

- Vaxzevria:

[h-5675-par-en \(europa.eu\)](https://www.ema.europa.eu/en/medicines/humans/CTX/h-5675-par-en)

- COVID-19 Vaccine Moderna:

[COVID-19 Vaccine Moderna, INN-COVID-19 mRNA Vaccine \(nucleoside modified\) \(europa.eu\)](https://www.ema.europa.eu/en/medicines/humans/CTX/covid-19-vaccine-moderna)

- COVID-19 Vaccine Janssen:

https://www.ema.europa.eu/en/documents/assessment-report/covid-19-vaccine-janssen-epar-public-assessment-report_en.pdf

4. “In view of the plausible connection between production of spike protein and the emergence of thromboembolic serious adverse events (SAEs), we demand to see the results of D-dimer determinations.”

At the time the marketing authorisations were granted for the COVID-19 vaccines, the non-clinical and clinical studies did not include analysis of D-dimers because no cardiovascular impairments were observed that would have justified such a test.

Given the recent developments, in order to assess the impact of the possible link between vaccination and coagulation, EMA has requested the four marketing authorisation holders to provide a series of additional analyses. For instance, for the Janssen COVID-19 vaccine, studies will require laboratory tests for the assessment of potential vaccine-induced antiphospholipid syndrome and vaccine-induced activation of coagulation (e.g. lupus anticoagulants, anti-beta 2 glycoprotein, anti-cardiolipin and D-dimers) pre and post vaccination in newly vaccinated subjects, i.e. to perform assessments of at least anti-cardiolipin IgG and IgM, and anti-β2 glycoprotein 1 IgA, IgG, IgM in frozen serum material pre- and post-first and second vaccination.

It is important to clarify that at the time our first set of responses was sent to you, a causal relationship between rare cases of unusual blood clots with low blood platelets and Vaxzevria had not yet been established. EMA’s safety committee, PRAC, concluded on 7 April that very rare cases thromboembolism associated with thrombocytopenia, including cerebral venous sinus thrombosis may occur very rarely with Vaxzevria. PRAC also concluded that the benefits of Vaxzevria still outweighed its risks in adults of all age groups.

In addition, CHMP is further analysing available data to put the risk of these very rare blood clots into context of the vaccine’s benefits for different age groups and different rates of infection. This is to support national authorities making decisions on how to best use the vaccine in their territories. For further information please refer to the published press release reflecting the ongoing work performed:

<https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-benefits-risks-context>

EMA’s benefit-risk assessments necessarily take into account the consensus view of the risks of the disease itself. The Agency disagrees strongly with the repeated denigration of these risks by Doctors for Covid Ethics, which is not supported by the outcomes previously or currently seen in those countries in which no vaccination is available to the bulk of the population.

Regarding the request for data in your letter of 20 April we would like to respond as follows:

1. the effects of gene-based vaccine on fertility in women of child bearing age, and in men:

Reproduction toxicity studies have been performed in animals for both mRNA vaccines as well as Vaxzevria and Janssen COVID-19 vaccine. These showed no harmful effects on fertility and gestation, nor on embryo-foetal or offspring development. Details can be found in the respective EPAR.

There is a limited amount of data from the use of the COVID-19 vaccines in pregnant and/or lactating women, or from women who became pregnant after receiving the vaccine. Even though the non-clinical safety findings have not indicated any concern to date, the risk for adverse pregnancy effects in humans is unknown, as data are currently insufficient to inform on any vaccine-associated risk.

Use in pregnancy and while breast-feeding are confirmed as missing information in the Risk Management Plans (RMP) of all COVID-19 vaccines. Therefore, the use of these vaccines in pregnant and breastfeeding women will be investigated in the planned post-authorisation safety studies. For further details, please see the RMPs listed below:

- **for Comirnaty**

Risk assessment report:

https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf

- **for COVID-19 Vaccine Moderna**

Risk management plan:

https://www.ema.europa.eu/en/documents/rmp-summary/covid-19-vaccine-moderna-epar-risk-management-plan_en.pdf

- **for Vaxzevria**

Risk management plan:

[vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-risk-management-plan_en.pdf](https://www.ema.europa.eu/en/documents/rmp-summary/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-risk-management-plan_en.pdf)
(europa.eu)

- **for COVID-19 Vaccine Janssen**

Risk management plan:

https://www.ema.europa.eu/en/documents/rmp-summary/covid-19-vaccine-janssen-epar-risk-management-plan_en.pdf

Please note that PRAC evaluates information on issues which are 'Missing information' in the RMP via the Monthly summary safety report submitted by the MAH for each vaccine. This includes pregnancy-related events and in particular reported pregnancies experiencing adverse outcomes.

We can inform you that, up to now, PRAC concluded there were no trends or new safety signals identified following evaluation of 'Missing Information' and the close monitoring is continuing.

If there are specific documents you would like to obtain please make a request for access to documents.

2. **number of cremations and burials of people recorded as having died of COVID-19**

This is outside EMA's remit; we therefore do not hold any document or information on this topic and cannot comment on it.

3. **medical justification for the interval between the two Pfizer injections being increased from 3 to 12 weeks**

For Comirnaty, Section 4.2 of the Summary of Product Characteristics says: "it is recommended to administer the second dose 3 weeks after the first dose (see sections 4.4 and 5.1)". In Section 5.1, reference is made to the fact that "the efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination".

At present the companies involved in the development of Comirnaty have provided no evidence to support extending the length of time between doses.

National vaccination schedules in the EU and decisions on how the vaccines will be allocated and given are outside the EMA's remit and are decided by the health authorities in each EU country. Member States are responsible for the roll-out of their own vaccination programmes and will have developed accompanying guidelines specific to the national situation, which may provide more advice about giving the second vaccination later.

4. mixing and matching different gene-based vaccines

At present the companies involved in the development of these vaccines have provided no evidence to support mixing vaccines in order to immunise more people against COVID-19.

5. Depriving recipients of the gene-based vaccines of knowledge of which vaccine they have received.

This concerns informed consent which is handled at national level. We would therefore recommend that you follow this up at national level.

We trust this addresses your latest correspondence.

Kind regards,



Head of Stakeholders and Public Engagement Department