



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3 December 2021
EMA/689868/2021

Subject: Integrity of clinical data, additional clinical trials and studies, pharmacovigilance and mRNA COVID-19 vaccine safety

Dear Honourable Members of the European Parliament, Ms Michèle Rivasi, Mr Piernicola Pedicini and Ms Tilly Metz,

Thank you for your letter of 16 November 2021, in which you asked about the data underpinning EMA's recommendations for Comirnaty (from BioNTech/Pfizer) and Spikevax (from Moderna) and the review of data on the risk of myocarditis and pericarditis.

I understand from your questions and accompanying text that you would like more information about the data that EMA relies upon to make recommendations on the use of COVID-19 vaccines.

Please find below my reply to the questions and issues you raised:

A. Additional, booster or extra, doses

1. What are the additional data and studies on which the EMA has based its recommendations for additional, booster or extra doses, applications to extend the use made by manufacturers Pfizer and Moderna for their respective mRNA vaccines?

EMA's Committee for Medicinal Products for Human Use (CHMP) based its recommendation for extra doses of Comirnaty and Spikevax for immunocompromised people on data from studies carried out by independent researchers, which we cited in our communication of 4 October 2021.^{1,2,3} The studies showed that an extra dose of these vaccines increased the ability to produce antibodies against SARS-CoV-2 in immunocompromised organ transplant patients. EMA has published its assessment reports on extra doses for both vaccines.^{4,5}

The studies on boosters in people with healthy immune systems were carried out by the respective marketing authorisation holders. EMA's assessment reports on boosters for Comirnaty⁶ and

¹ <https://www.ema.europa.eu/en/news/comirnaty-spikevax-ema-recommendations-extra-doses-boosters>

² Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med* 2021;385:661-662.

³ Hall VG, Ferreira VH, Ku T, et al. Randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients. *N Engl J Med* 2021;385:1244-1246

⁴ https://www.ema.europa.eu/en/documents/variation-report/comirnaty-h-c-5735-ii-0062-epar-assessment-report-variation_en.pdf

⁵ https://www.ema.europa.eu/en/documents/variation-report/spikevax-previously-covid-19-vaccine-moderna-h-c-5791-ii-31-epar-assessment-report-variation_en.pdf

⁶ https://www.ema.europa.eu/en/documents/variation-report/comirnaty-h-c-5735-ii-0067-epar-assessment-report-variation_en.pdf



Spikevax⁷ are available on EMA's website. The data on booster doses are also described in sections 5.1 of the publicly available product information for both vaccines.^{8,9} These data show the extent to which levels of antibodies against SARS-CoV-2 rise after a booster dose.

In addition to the above, EMA will publish the clinical data contained in the application packages submitted by the companies. These consist of the clinical overviews, clinical summaries and the clinical study reports along with the study protocols, case report forms and statistical analyses plans. We aim to publish these on EMA's clinical data website¹⁰ by the first quarter of next year after anonymising files containing personal data, particularly sensitive patient health data in accordance with the General Data Protection Regulation (GDPR) and redacting commercially confidential information.

I would also like to highlight that, in line with our transparency measures, EMA publishes assessment reports on all marketing authorisation applications for COVID-19 medicines and vaccines, as well as applications to extend their use, for example, in children.¹¹ The Agency also publishes the relevant data from the companies' application packages on EMA's clinical data website.

2. How to access these studies and data? When will they be publicly available?

Please see our reply to question 1.

B. Flawed clinical data for Comirnaty vaccine, exposed by the BMJ

3. Has the EMA been given access to adequate, complete raw data from Pfizer's Comirnaty clinical trials? Are those data publicly available?

EMA receives extensive data, including full clinical study reports with individual patient-level data, in marketing authorisation applications. Although EMA does not request raw data sets or re-analyse such data, studies supporting the marketing authorisation of a medicine must comply with strict rules and are highly regulated. International standards, called Good Clinical Practice (GCP), apply to the study design and the recording and reporting of results to ensure that studies are scientifically sound, robust and conducted in an ethical manner. Regulators conduct inspections routinely to verify compliance with these standards.

In addition, EMA scrutinizes the designs of studies to ensure that they provide meaningful data. In the case of the main study for Comirnaty, the primary endpoint was an important measure, namely protection against confirmed COVID-19. EMA continues to evaluate data from this and other studies as they become available.

As discussed in the reply to question 1, EMA publishes clinical data in the application packages submitted by the companies.

4. Has this raw data been analysed by experts independent of Pfizer?

Please see our reply to question 3.

5. How has the EMA ensured that the data provided by the company is verified?

⁷ https://www.ema.europa.eu/en/documents/variation-report/spikevax-previously-covid-19-vaccine-moderna-h-c-5791-ii-34-epar-assessment-report-variation_en.pdf

⁸ https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

⁹ https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf

¹⁰ <https://clinicaldata.ema.europa.eu/web/cdp/home>

¹¹ <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/transparency-exceptional-measures-covid-19-medicines>

During the evaluation of the marketing authorisation application for Comirnaty, EMA sought reassurance that the applicant's studies were GCP compliant. EMA considered a report of a GCP inspection of a site in Germany by Regierungspräsidium Karlsruhe and the Paul Ehrlich-Institut; reports from a GCP inspection by US Food and Drug Administration (FDA) of six investigator sites in the United States; and reports and the summaries of the outcome from two GCP inspections by the National Administration of Drugs, Foods and Medical Devices (the Argentinian medicines authority) conducted at the single site located in Argentina.

After reviewing the available clinical data and the above-mentioned reports, there were no concerns warranting an EMA inspection. This information is included in the published assessment report.¹²

As noted above, companies conducting trials for EU medicines must comply with GCP, which covers the design and conduct of clinical trials and the reporting of data from these trials. National authorities regulate clinical trials to ensure that companies meet their obligations. In addition, during the evaluation of an application, EMA can request a GCP inspection if there are concerns about the way the studies were conducted.

6. Has the EMA been informed of any irregularities reported during the Phase 3 clinical trial coordinated by Ventavia?

EMA is aware of the reported irregularities. See our reply to question 7 below.

7. Will the EMA review its assessment of Comirnaty in the light of these new data and the comments made by the BMJ?

EMA, in close collaboration with the US FDA, has looked into the issues reported in the BMJ. EMA concluded that the deficiencies identified do not jeopardize the quality and integrity of the data from the main Comirnaty trial and have no impact on the benefit-risk assessment or on the conclusions on the safety, effectiveness and quality of the vaccine.

The main trial that supported the authorisation of Comirnaty included around 44,000 people and was conducted in about 150 sites around the world.

Ventavia enrolled around 1,000 subjects in 3 sites in the United States, representing less than 3% of the total study population. The issues affected one of those 3 sites and mainly concerned a lack of trained staff which resulted in deficiencies such as delays in data entry and queries resolution. The marketing authorisation holder audited the company at the end of 2020, and corrective actions were taken, including oversight visits and hiring of additional staff. These actions were deemed appropriate.

Ventavia also recruited participants in studies on the use of Comirnaty in children and as a booster (representing about 1.6% and 3.5% of the total study populations respectively). As with the main study, EMA considered that the issues reported at the concerned site have no impact on the assessments of the benefits and risks of the vaccine for these uses. The corrective actions taken by the company were put in place before these later trials started enrolling participants.

C. Suspension of the use of Moderna's Spikevax for males under the age of 30 in October 2021 by Finland, Sweden, Norway and Denmark

8. To date, how many cases of myocarditis and pericarditis were reported after injections in under 30s of Moderna's vaccine, and to a lesser extent Pfizer's? How many cases and

¹² https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

studies will be needed before the EMA revises its position and follows the precautionary recommendations already made in 4 EU countries?

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed recent data on the risk of myocarditis and pericarditis following vaccination with the COVID-19 vaccines Comirnaty and Spikevax.¹³ The PRAC's review looked at two large European epidemiological studies, one that used data from the French national health system (EPI-PHARE) and the other which was based on Nordic registry data.

The review found that these conditions occur very rarely after vaccination with Comirnaty and Spikevax, meaning that up to a maximum of 1 in 10,000 vaccinated people may be affected. Additionally, the data show that the increased risk of myocarditis after vaccination is highest in younger males. The PRAC has recommended updating the product information accordingly

With regard to the data, for Comirnaty, the French study shows that in a period of 7 days after the second dose there were about 0.26 extra cases of myocarditis in 12-29 year old males per 10,000 compared to unexposed persons. In the Nordic study, in a period of 28 days after the second dose there were 0.57 extra cases of myocarditis in 16-24 year old males per 10,000 compared to unexposed persons.

In the case of Spikevax, the French study showed that in a period of 7 days after the second dose there were about 1.3 extra cases of myocarditis in 12-29 year old males per 10,000 compared to unexposed persons. The Nordic study shows that in a period of 28 days after the second dose of Spikevax there were around 1.9 extra cases of myocarditis in 16-24 year old males per 10,000 compared to unexposed persons.

I would like point out that myocarditis and pericarditis are generally mild and respond to treatment. It is important when discussing risks to also take into account the benefits of vaccination, including reduced hospitalisation and deaths due to COVID-19.

With respect to national vaccination campaigns, Member States decide on the use of approved vaccines in their countries and consider many factors, including the local availability of vaccines, the spread of the virus (especially any variants of concern), and the capacities of national health systems.

9. Why did the EMA not take the initiative of an emergency plan, including active pharmacovigilance, on the under 30s vaccinated with Comirnaty or Spikevax, in order to have reinforced data? And why, instead of entrusting this analysis to Pfizer or Moderna, does the EMA not carry out its own in-depth analysis of the data already published or collected by the laboratories or the national authorities?

The EU regulatory network is fully implementing its pharmacovigilance plan¹⁴ established prior to the start of the vaccination campaigns and continues to closely monitor the safety of COVID-19 vaccines, and that includes identifying new risks and further characterising known ones such as the risk of myocarditis and pericarditis with mRNA vaccines.

EMA's review of the myocarditis and pericarditis risks was comprehensive, covering all available information, including data from EudraVigilance (EU's adverse events database), information from independent EMA-funded studies, published studies such as the recent study by France's EPI-

¹³ <https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-29-november-2-december-2021>

¹⁴ https://www.ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf

PHARE, and the as yet unpublished Nordic study carried out by academics. EMA is also working closely with international partners.

In addition to the above and in line with EU legislation, marketing authorisation holders were required to collate and analyse all publicly available safety data for their products. EMA's Pharmacovigilance Risk Assessment Committee (PRAC) scrutinizes all analyses and data from marketing authorisation holders, and the marketing authorisation holders are required to address any questions raised.

10. Does the EMA realize that by asking Pfizer and Moderna to carry out this in-depth analysis, the EMA is placing these companies in a conflict of interest situation?

Please see our reply to question 9.

11. How can we take into account the fact that the two companies Pfizer and Moderna, which have filed applications in the United States and the European Union to extend the authorisation of their vaccines for 5-11 year old, have a direct commercial and financial interest in minimising the risks of myocarditis and pericarditis that can occur in these youngest populations?

Please see our reply to question 9.

12. How can this in-depth analysis be complete and objective when the post vaccination surveillance data from the Scandinavian study which were sent to the EMA at the beginning of October have not yet been made public?

EMA has reviewed the data from the Nordic study and will publish a full assessment report containing data from that study.

13. How, in these circumstances, does the EMA plan to verify and ensure the quality and integrity of the extensive data analysis requested from Pfizer and Moderna? What are the EMA's safeguards to ensure the data are legitimate and accurate? Does the EMA request any additional independent studies on this issue?

Please see our reply to question 9.

14. Will these in depth analyses be provided to the EMA before its decision on the extension of the use of BioNTech/Pfizer's Comirnaty and Moderna's Spikevax COVID- 19 vaccines for children aged 5 - 11 years?

The review of the application for the use of Comirnaty in children aged 5 to 11 years has recently concluded¹⁵ and took account of the data that had already been assessed about the risk in adolescents and adults. The review for Spikevax is currently underway and will also take into account all data available during the review. There are currently no reports of myocarditis or pericarditis from clinical trials in this lower age group, although given the rarity of those side effects such reports are unlikely. EMA will continue to closely monitor data from this age group.

The PRAC assessment of the risk of myocarditis and pericarditis, which has now concluded, further characterised this risk in adolescents and adults. It should be recalled that myocarditis and pericarditis in adolescents and adults are very rare side effects, which are generally mild and respond to treatment (see reply to question 8). The product information for both vaccines will soon be updated.

Vaccinating children can help protect them from COVID-19 and related possible severe complications, including multi-organ inflammatory syndrome (MIS) and even death. This benefit

¹⁵ <https://www.ema.europa.eu/en/news/comirnaty-covid-19-vaccine-ema-recommends-approval-children-aged-5-11>

far outweighs the risks of very rare side effects, such as myocarditis and pericarditis, that have been seen so far with mRNA COVID-19 vaccines.

15. Will these in-depth studies and their data be publicly available?

In line with EMA exceptional transparency measures for COVID-19 products, EMA will publish its assessment report, which will contain details of the studies and data submitted by the marketing authorisation holders as well as publicly available data.

I hope that the above reassures you that the assessment of COVID-19 vaccines and any extension of their use is robust and follows stringent scientific requirements for quality, safety and efficacy. I will be happy to address any follow-up questions you may have about the work EMA is doing to ensure that EU citizens continue to benefit from safe and effective COVID-19 vaccines and therapeutics during this pandemic.

Yours sincerely,

Emer Cooke
Executive Director