Dear Dr Keil, dear Dr Spelsberg,

Thank you for contacting EMA with your questions regarding the safety of mRNA vaccines addressed to Marco Cavaleri, Fergus Sweeney and Georgy Genov.

Please allow us to make some general comments before answering your questions in more detail.

EMA fully recognises the need for safety data in pregnant women. As pregnant women are excluded from the initial clinical studies, monitoring vaccine safety in pregnant women is critical.

EMA's COVID-19 task force (ETF) recently reviewed the results of several studies involving over 65,000 pregnancies at different stages. You can find the EMA's relevant communication on the following link: https://www.ema.europa.eu/en/news/covid-19-latest-safety-data-provide-reassurance-about-use-mrna-vaccines-during-pregnancy

The review did not find any sign of an increased risk of pregnancy complications, miscarriages, preterm births or adverse effects in the unborn babies following mRNA COVID-19 vaccination. Despite some limitations in the data, the results appear consistent across studies looking at these outcomes. EMA echoes your call for transparency of clinical trial results. Observational research, including the collection of data in pregnancy is an important pillar of post-marketing surveillance of COVID-19 treatments and vaccines and a key priority of EMA; several initiatives are ongoing at the agency to optimise this. EMA recently called for transparency for protocols and results, as well as collaboration between researchers, to ensure high-quality, powerful studies.

In terms of transparency of regulatory output, the Agency applies the highest level of transparency to COVID-19 vaccines and treatments it ever provided for medicines. Exceptional transparency measures (https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/transparency-exceptional-measures-covid-19-medicines ) have been put in place to meet an unprecedented public demand for information, support and to make global research more efficient and allow public scrutiny and independent review. They include publication of clinical data submitted to EMA in initial marketing authorisation applications and extensions of indication for COVID-19 medicines, following conclusion of the scientific assessment by CHMP and once the European Commission has granted or refused a marketing authorisation, or in case the company withdraws the application. The clinical data can be accessed here:

https://clinicaldata.ema.europa.eu/web/cdp/home

In addition you can find information on the studies conducted in pregnant women in the vaccines' risk management plan, which provides further details on how information on pregnancy is collected through dedicated studies on pregnancy.

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

For Spikevax (Moderna's vaccine): https://www.ema.europa.eu/en/documents/rmp-summary/spikevax-previously-covid-19-vaccine-moderna-epar-risk-management-plan_en.pdf

Please see below more detailed answers to your questions:

1 protocol changes with NCT04754594

The study identifier is the identifier used by clinical trials.gov. We understand that study NCT04754594 corresponds to EudraCT number 2020-005444-35. This study is a post authorisation study that is currently ongoing to specifically monitor the safety in pregnant women who received the vaccine and is one of several ongoing studies.

As the supervision of clinical studies is within the remit of the national competent authorities EMA cannot comment on the reason behind any protocol changes for a study it has not yet assessed.

Please note that there are several studies that have been requested in Comirnaty's risk management plan (RMP) to gather more data in pregnant women including clinical (C4591015) and non-interventional studies (C4591009 and C4591011).

In addition to the specific studies detailed in the RMP there are a number of initiatives to improve the safety monitoring of data in pregnancy. EMA has set up infrastructure to support the monitoring of the safety of COVID-19 treatments and vaccines when used in day-to-day clinical practice. In particular EMA has funded studies on vaccines including pregnant women cohorts ("Early-Covid-Vaccine-Monitor" and the "Covid-Vaccine-Monitor").

More information is published here (details on each study can be viewed when clicking on the relevant drop down arrows): https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/monitoring-covid-19-medicines-0). EMA is working with international partners to align regulatory requirements and address the knowledge gaps regarding medicine safety and efficacy in pregnant and breastfeeding women. Since April 2020, EMA and Health Canada have organised a series of regulatory workshops, convened under the umbrella of International Coalition of Medicines Regulatory Authorities (ICMRA - https://www.icmra.info/drupal/en/covid-19), to identify priority areas for cooperation on COVID-19-related observational studies and real-world data, including pregnancy research.

EMA, US Food and Drug Administration (FDA) and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) also co-chaired an ICMRA regulatory workshop on pregnancy and lactation in February 2021 (https://www.icmra.info/drupal/covid-19/9february2021 ). Meeting participants stressed the need for international collaboration and harmonisation to develop a new global approach and obtain systematic data on medicine efficacy and safety in pregnant and breastfeeding women. In addition, the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) harmonised guideline "General Considerations for Clinical Studies E8(R1)" has been extensively revised and the final version adopted at ICH and EU level in October 2021 which emphasises the importance of the investigation of medicines that may be used during pregnancy.

2. To inform the public what EMA has done in terms of oversight, in response to specific reports of data integrity problems at clinical trial sites operated by Ventavia, as well as provide a report similar to the FDA BIMO report, [8] indicating which clinical trial sites from trial NCT04754594 and NCT04368728 EMA has inspected, and the outcome of the inspections.

The integrity problems that were reported in November 2021 for one of the 3 Ventavia's sites were mainly due to lack of trained staff which resulted in deficiencies such as delays in data entry and queries resolution.

EMA carried out a review of the implications of these issues and the corrective actions taken and concluded that these deficiencies did not jeopardize the quality and integrity of the data from the sites concerned, and have no impact on the benefit-risk assessment nor on the conclusions on the

safety, effectiveness and quality of the vaccine itself. In addition it considered the actions taken by the company, including oversight visits and hiring of additional staff, as appropriate.

EMA did not inspect any of the 3 Ventavia sites. None of the inspections carried out in other sites involved in the main study raised serious concerns.

The determination of the need for inspections will depend on a number of factors, such as the number, nature and size of the trials, the number of countries and investigating centres involved, the complexity of the data set, and any issues of concern that are raised during the evaluation and it is considered on a case by case basis. Factors taken into account are described in the points to consider document at the following link: https://www.ema.europa.eu/en/documents/other/points-consider-assessors-inspectors-european-medicines-agency-inspection-coordinators_en.pdf. EMA works closely with EU and international regulatory authorities and partners to collect all available inspection information and share the outcome of the inspections performed by those authorities with EMA's human medicines committee (CHMP), in order for this information to be considered in the assessment. At any time during the evaluation of an application CHMP may signal that in their opinion a GCP inspection is necessary (for more details, see: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ins-gcp-1-procedure-coordinating-good-clinical-practice-inspections-requested-chmp_en.pdf).

Regarding a report similar to the FDA BIMO report please note that since EMA did not inspect the Ventavia sites this is not available.

Regarding trials NCT04754594 and NCT04368728 (which seems to correspond to EudraCT 2020-002641-42), EMA has also not inspected these. Please note that inspections are not routinely carried out but can be requested to verify compliance with standards. EMA's CHMP has also not requested a GCP inspection for any of the trial sites included in the Comirnaty application, however it took into account the outcome of the GCP inspections performed by Germany (Laender and PEI), US FDA and Argentinian authorities, as stated in the AR on p.57 (https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf)

No serious concerns related to GCP compliance were raised during these inspections.

3. Did you receive severe adverse events (SAE) reports and if so, how many reports about miscarriages, fetal or maternal deaths, fetal malformation, intrauterine disease, growth anomalies, premature births, complicated pregnancies or any other severe adverse events from NCT04754594 or Pfizer's pivotal trial NCT04368728 among vaccinated pregnant women (including information on week of pregnancy)?

As part of regular safety monitoring activities EMA collects unsolicited reports from patients and healthcare professionals received after authorisation of a medicine. It also collects reports of Suspected Unexpected Serious Adverse Reactions that occur during interventional clinical trials. These SUSAR reports are not publicly available. Your request for numbers of reports will therefore be handled according to the agency's access to document policy (https://www.ema.europa.eu/en/about-us/how-we-work/access-documents) and you will receive an answer as a follow-up to this letter (the reference for this request is ASK-106924).

Any safety issues related to clinical trials are analysed within the dedicated study reports once the study has concluded. Specifically, SAEs are collected by the sponsor and compiled in the final study report. EMA publishes clinical data submitted by pharmaceutical companies to support their regulatory applications for human medicines under the centralised procedure:

https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication.

Information on the studies, including any safety issues, that have been evaluated or have been requested by EMA can be found in the relevant assessment report or risk management plan of the vaccine.

In addition as part of the intense safety monitoring activities in place for COVID-19 vaccines, the companies have to submit regular safety reports. These include an analysis of pregnancy reports following vaccination and their outcomes. The review of the cases by EMA's safety committee, PRAC, did not reveal any new safety issues.

Reports of suspected side effects, including adverse outcomes of pregnancy that have been received in the postmarketing period, can be viewed in the adverse reactions database: https://www.adrreports.eu/en/ The suspected side effects reports describe medical events observed following the use of a vaccine. The fact that someone has had a medical issue or died after vaccination does not necessarily mean that this was caused by the vaccine. This may have been caused, for example, by health problems not related to the vaccination.

4. Have you been informed about problems with recruitment of study participants which obviously persisted even after doubling recruitment sites from originally 44 sites in the U.S. to roughly 100 sites also abroad (South Africa, Spain, UK) by June 2021?

EMA has not been informed of any problems with recruitment with the trials.

5.In the context of Moderna mRNA vaccine: Did you receive any SAE reports from this study (NCT04958304)?

Your request for numbers of reports will be handled according to the agency's access to document policy (https://www.ema.europa.eu/en/about-us/how-we-work/access-documents) and you will receive an answer as a follow-up to this letter (with reference ASK-106924).

We hope that the above reassures you that safe use of mRNA vaccines in pregnancy is a key priority and EMA together with the EU network and international partners is putting unprecedented efforts into collecting data on safety of COVID-19 vaccines in pregnancy in order to guide decision-making about vaccine indications, vaccination policies and treatment options for COVID-19 in pregnant women.

Kind regards,

Juan Garcia Burgos on behalf of Marco Cavaleri, Fergus Sweeney and Georgy Genov

Head of Public and Stakeholders Engagement Department

European Medicines Agency