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EMA/140520/2021
Stakeholders and Communication Division

Dear Dr Frost,

Many thanks for your letter dated 28 February 2021 regarding the COVID-19 vaccines.

Please allow us to address your questions point by point:

1. **Following intramuscular injection, it must be expected that the gene-based vaccines will reach the bloodstream and disseminate throughout the body [1]. We request evidence that this possibility was excluded in pre-clinical animal models with all three vaccines prior to their approval for use in humans by the EMA.**

   The uptake of the mRNA in the vaccine occurs mainly in macrophages and dendritic cells of the immune system at the site of injection and draining lymph nodes. In addition, the mRNA is detected in the plasma and other tissues for up to 9 days, and this has been studied for existing COVID-19 mRNA vaccines using animal models receiving much higher vaccine doses compared to doses used in humans in order to identify any potential safety issues. It was found that the vaccine's mRNA, formulated inside lipid nanoparticles, remains mainly at the injection site and only small amounts can reach other tissues, such as the liver.

   Regarding the COVID-19 AstraZeneca vaccine, upon administration of the same vector carrying another virus protein, it was found that most of the injected viral vector remained at the injection site, and only low amounts were detected in other tissues.

   The non-clinical studies performed with the 3 COVID_19 vaccines did not identify any safety concerns linked to their tissue distribution in the animal model under the experimental conditions used.

2. **If such evidence is not available, it must be expected that the vaccines will remain entrapped in the circulation and be taken up by endothelial cells. There is reason to assume that this will happen particularly at sites of slow blood flow, i.e. in small vessels and capillaries [2]. We request evidence that this probability was excluded in pre-clinical animal models with all three vaccines prior to their approval for use in humans by the EMA.**

   The cited reference relates to an in vitro system used to investigate the interplay between gold nanoparticles and flow rate versus uptake by endothelial cells also facilitated by specific ligands. This is a hypothesis-generating study for improving novel nanoparticles technologies for medical applications and is not considered relevant to the vaccines in question. Non-clinical studies with COVID-19 mRNA vaccines do not indicate any detectable uptake of lipid nanoparticles by endothelial cells. Similarly, there is no evidence that the AstraZeneca vaccine vector is able to enter endothelial cells in vivo. It is known that the receptor for this vector is not expressed or

Safety findings from clinical and non-clinical studies with the COVID-19 mRNA vaccines and with the AstraZeneca vaccine showed an expected immune reaction to vaccine administration, with clinically manageable and acceptable risks in the intended population. The safety database from clinical studies studied was 43,448 people for Comirnaty, 30,351 people for Moderna and over 12,000 for Astra Zeneca vaccine.

3. **If such evidence is not available, it must be expected that during expression of the vaccines' nucleic acids, peptides derived from the spike protein will be presented via the MHC I - pathway at the luminal surface of the cells. Many healthy individuals have CD8-lymphocytes that recognize such peptides, which may be due to prior COVID infection, but also to cross-reactions with other types of Coronavirus [3; 4] [5]. We must assume that these lymphocytes will mount an attack on the respective cells. We request evidence that this probability was excluded in pre-clinical animal models with all three vaccines prior to their approval for use in humans by the EMA.**

   It is rare for cytotoxic lymphocytes to attack cells exposing an antigen on their surface to the extent of hampering the immune response to reinfection or vaccination. Optimal cytotoxic T lymphocytes activation requires recognition of multiple virus epitopes as well as the presence of additional co-stimulatory signals.

   Regarding COVID-19 vaccines, there is no evidence of immunotoxicity or autoimmunity in any of the studies conducted either in animal models or in humans so far.

   In line with these observations, there is growing evidence from clinical trials with COVID-19 vaccines that efficacy and safety is similar in individuals pre-exposed to COVID-19 vs. unexposed individuals.

   There is a theoretical risk of original antigenic sin, whereby an immune system already imprinted by natural infection to respond to a certain virus is not able to effectively respond to a subsequent reinfection or vaccination by a slightly different virus or epitope. This phenomenon could potentially lead to ineffective vaccination or to vaccine-induced enhancement of disease (VAED)–VAED has been extensively investigated for COVID-19 vaccines and so far there is no evidence from either animal or human studies indicating that this can be an issue for COVID-19 vaccines.

4. **If such evidence is not available, it must be expected that endothelial damage with subsequent triggering of blood coagulation via platelet activation will ensue at countless sites throughout the body. We request evidence that this probability was excluded in pre-clinical animal models with all three vaccines prior to their approval for use in humans by the EMA.**

   Minor effects on coagulation have been seen in non-clinical studies for Moderna COVID-19 vaccine but not for Comirnaty, including slight increases in fibrinogen and activated partial thromboplastin time. For Comirnaty, decreased platelet counts were noted after repeat administration in some hamster studies, but were small in magnitude, likely related to inflammation-related platelet activation and 'platelet consumption', and unassociated with other alterations in haemostasis.

   All these changes are compatible with an inflammatory/immune response induced by the vaccines given at very high doses in animals, and were reversed after a few days. They are unlikely to have any relevance for humans due to their small magnitude.

   No changes related to coagulation or platelets have been detected in animals with the AstraZeneca vaccine.

   Clinical haematology and chemistry evaluations (WBCs, Hgb, PLTs, ALT, AST, ALP, T. Bili, Cr, and Lipase) are normally conducted in human phase 1 and 2 trials for any vaccines including COVID-19 vaccines. Blood samples were collected immediately prior to the first vaccination to serve as the baseline (Day 1), and were repeated at three subsequent time points.

   Regarding Moderna COVID-19 vaccine, other than minor reversible changes in liver enzymes in few

Regarding Comirnaty, except for minor transient decrease in lymphocyte count for some of the subjects, no abnormal laboratory results were reported from the Phase 1 studies.

The clinical laboratory results for the AstraZeneca vaccine were within normal clinical range and did not raise any safety concerns.

Although no safety signal linked to coagulation disorders was seen in the large clinical trials, which included several thousands of individuals, more data were provided during the enhanced safety monitoring that is in place for all COVID-19 vaccines.

It is in this context that cases of thrombocytopenia were reported which led to an investigation for Comirnaty, Moderna and Astra Zeneca COVID-19 vaccines which is currently ongoing. For further information please see here:

https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-8-11-march-2021

The continuous safety monitoring also found reports of a combination of thrombocytopenia and thromboembolism with the COVID-19 Vaccine AstraZeneca which led to an urgent investigation which concluded on 18 March. EMA's safety committee, PRAC, concluded that the vaccine may be associated with very rare cases thromboembolism associated with thrombocytopenia, including cerebral venous sinus thrombosis. There were 18 reports of CVST and 7 reports of disseminated intravascular coagulation, out of around 20 million people vaccinated with the vaccine as of March 16.

A causal link with the vaccine is not proven but deserves further analysis. Overall, the benefits of the vaccine in combating the still widespread threat of COVID-19 (which itself results in clotting problems and may be fatal) continue to outweigh the risk of side effects.

For further information please refer to the press release: COVID-19 Vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets | European Medicines Agency (europa.eu)

See also responses to question 6.

5. **If such evidence is not available, it must be expected that this will lead to a drop in platelet counts, appearance of D-dimers in the blood, and to myriad ischaemic lesions throughout the body including in the brain, spinal cord and heart. Bleeding disorders might occur in the wake of this novel type of DIC-syndrome including, amongst other possibilities, profuse bleedings and haemorrhagic stroke. We request evidence that all these possibilities were excluded in pre-clinical animal models with all three vaccines prior to their approval for use in humans by the EMA.**

   None of the mentioned unwanted effects have been detected in non-clinical or clinical studies. See also responses to questions 4 and 6.

6. **The SARS-CoV-2 spike protein binds to the ACE2 receptor on platelets, which results in their activation [6]. Thrombocytopenia has been reported in severe cases of SARS-CoV-2 infection [7]. Thrombocytopenia has also been reported in vaccinated individuals [8]. We request evidence that the potential danger of platelet activation that would also lead to disseminated intravascular coagulation (DIC) was excluded with all three vaccines prior to their approval for use in humans by the EMA.**

   No evidence of thrombocytopenia or coagulation disorders was detected in clinical trials for any of the COVID-19 vaccines so far authorised.

   Cases of thrombocytopenia and thromboembolic events have recently been reported for the 3 vaccines from real-life use. The PRAC is currently investigating cases thrombocytopenia reported with the three vaccines and more information will be shared once the assessment is concluded.

https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-prac-investigating-cases-thromboembolic-events-vaccines-benefits

For the cases of thromboembolic events please refer to question 4 and to EMA's press release:

COVID-19 Vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets | European Medicines Agency (europa.eu)

See also response to question 4.

After authorisation these vaccines are closely monitored like all medicines so that prompt regulatory action can be taken in the event of any identified safety issue. Such safety monitoring takes place more frequently and includes activities that apply specifically to COVID-19 vaccines. Companies for example provide monthly safety reports in addition to the regular updates required by the legislation and conduct studies to monitor the safety and effectiveness of COVID-19 vaccines after their authorisation as requested by the Regulatory Authorities.

For further information we invite you to refer to EMA's detailed assessment report as well as the risk assessment for the individual vaccines:

- **for Comirnaty**

Assessment report:

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

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

Assessment report:

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

- **for COVID-19 Astra Zeneca**

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

Assessment report:

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

7. **The sweeping across the globe of SARS-CoV-2 created a pandemic of illness associated with many deaths. However, by the time of consideration for approval of the vaccines, the health systems of most countries were no longer under imminent threat of being overwhelmed because a growing proportion of the world had already been infected and the worst of the pandemic had already abated. Consequently, we demand conclusive evidence that an actual emergency existed at the time of the EMA granting Conditional Marketing Authorisation to the manufacturers of all three vaccines, to justify their approval for use in humans by the EMA, purportedly because of such an emergency.**

In the EU, COVID-19 vaccines received a conditional marketing authorisation (CMA). CMAs are

possible. Of note, even though there is evidence of increased immunity in the population to SARS-CoV-2 (up to 10% in certain countries), this may not prevent reinfection.

In addition, high numbers of hospitalisation and death from COVID-19 continue to be reported and novel virus variants are emerging and slowly taking over, some of which are showing worrying features of enhanced transmissibility and potentially morbidity/mortality.

In this context, CMA is the most appropriate regulatory mechanism for use among the portfolio of emergency tools that the EMA has available.

Please note that a conditional marketing authorisation is not exclusively reserved for public health emergencies. They are also granted to medicines for orphan diseases or for seriously debilitating or life-threatening diseases on the basis of less comprehensive clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required.

We hope that the above reassures you that the COVID-19 vaccines have been evaluated following the same stringent scientific requirements for quality, safety and efficacy as for all other vaccines. Authorisation has been made after a positive benefit-risk balance has been established on all available data. In addition, we would like to reiterate that enhanced and stringent safety monitoring is in place for all COVID-19 vaccines, to ensure that the benefits always outweigh the risks.

Kind regards,

Juan Garcia Burgos

Juan Garcia Burgos

Head of Public and Stakeholders Engagement Department