



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CONFIDENTIAL

Scientific advice Joint report

<COVID-19 vaccine (recombinant, adjuvanted)>

As this report may contain confidential information relating to other products (please highlight), it will not be released to the Applicant.

Invented name:	{COVID-19 vaccine (recombinant, adjuvanted)}
Active substance:	{Recombinant protein derived from the SARS CoV2 prefusion Spike delta TM protein}
Pharmaco-therapeutic group:	{ATC Code: J}
Indication(s):	{Active immunization for the prevention of SARS-CoV-2 infection and/or associated disease}
Applicant:	{Sanofi Pasteur}
Coordinators, <Country>:	{Mario Miguel Rosa, PT and Walter Janssens, BE}
Peer Reviewer:	{}
Experts (origin, CoI):	Felix Carvalho (NonClinical): FFUP, Infarmed

Expected Plenary discussion: Choose an item.

DM proposed: Choose an item.

A. Advice profile

- Product and target indication

This product is intended for the active immunisation to prevent SARS-CoV-2 infection and/or associated disease.

The candidate antigen is a stabilized prefusion trimer of the SARS-CoV-2 S protein. The S protein precursor is cleaved to form non-covalently associated subunits, S1 and S2. The S protein appears on the surface of the virus as a mushroom-like structure, containing a cap of three S1 subunits and a stem of three S2 subunits.

- Regulatory status (existing licensure, prev SAs, etc)

Presently there is no approved vaccine for SARS-CoV-2 infection or associated disease.

Previous CHMP-SAWP interaction consisted of: 1) An initial rapid Scientific Advice: Final Advice Letter was issued on 05 June 2020 (Procedure No.: EMEA/H/SA/4562/1/2020/III); 2) A paediatric rapid Scientific Advice: Final Advice Letter was issued on 23 October 2020 (Procedure No.: EMEA/H/SA/4688/1/2020/PED/II); and A Follow Up rapid Scientific Advice (clinical): Final Advice Letter was issued on 10 November 2020 (Procedure No.: EMEA/H/SA/4562/1/FU/1/2020/II).

- Scope of questions < Quality/Non-clinical/clinical>

There are two Non-clinical questions.

B. Advice content

- High Level Overview of the Advice Setting

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

An agency of the European Union



The proposed strategy for the nonclinical program regarding both safety for clinical phase + the immunogenicity and efficacy evaluation can be agreed with some comments and advices. Data is yet to be provided. If any safety signal emerges from both clinical or preclinical studies, other preclinical dedicated studies may be required.

- Key Messages of Answers to All Questions

Q1: Agreement on the preclinical safety program

A1: CHMP agrees with the proposed non clinical safety program, pending an evaluation of the data that will be available. If new safety concerns would arise during the proposed studies or during clinical trials these may need to be addressed by dedicated animal studies. Given the absence of alert on reproductive organs in the initial repeated dose toxicity study (Study No 5003471), the Applicant intends to conduct the DART study in parallel of Phase III using a Phase III batch. This position is endorsed, conditional to inclusion of appropriate birth control methods for women of childbearing potential in clinical trials, and the recommendation on contraception and pregnancy testing published by CTFG.

Q2: Agreement with the proposed strategy for the immunogenicity and efficacy evaluation

A2: The proposed strategy is in line with recommendations on the data that should be available before initiation of phase III clinical trials. Both Syrian hamsters and Rhesus macaques show relevant features of infection with SARS-CoV-2. In addition to showing protection by the vaccine against the consequences of infection with the virus, the studies should also allow to gain a preliminary insight into the potential to cause vaccine induced enhancement of respiratory disease. The analysis of the ratio between binding and virus neutralising titres, assessing Th1 and Th2 associated cytokines upon challenge in vaccinated versus control groups, as well as the analysis of pathology in target organs via gross pathology in the lungs and histopathological analyses of the target organs (i.e. lungs, nasal turbinates and gastrointestinal tract) are considered of importance for the detection of enhanced disease. The analysis of binding versus neutralising antibodies, the ratio of IgG1 and IgG2a antibodies and identification of Th1/Th2 responses may be more sensitive than the observation of lung pathology. Non clinical data will be of use to estimate potential risks before exposure of large numbers of study participants but ultimately clinical data will be prevailing in this regard. Immunogenicity data from early clinical trials (neutralizing antibodies, Th1/Th2 balance) should also supplement the available information. No information was provided on the similarity of the immune response to the adjuvant in hamsters relatively to humans. Ideally, the response of the immune system to the antigen should be enhanced by the adjuvant through a similar mechanism as expected in humans, not only from the efficacy point of view, but also concerning the potential adjuvant-induced immuno-toxicity.

C. Coordinator's critical topics for SAWP plenary discussion

N/A

D. Draft questions for discussion meeting list of issues

N/A

E. Need for consultation and/or information from previous advices/licensures

N/A

F. Additional comments for SAWP plenary presentation

Background information as submitted by the Applicant

Background information on the disease to be treated

<An outbreak of severe respiratory illnesses in Wuhan City, Hubei Province, China in December 2019 heralded the appearance of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in the human population. The rapid escalation of the outbreak led to a declaration by the World Health Organization on 20 January 2020 of a Public Health Emergency of International Concern, followed by declaration on 11 March 2020 of a pandemic. As of 06 October 2020, the virus has been detected in over 188 countries/regions and infected over 35 million individuals.

The clinical profile of COVID-19, the illness caused by SARS-CoV-2, is variable. In the majority of cases, the manifestations are mild, or individuals may be asymptomatic. Among those with symptoms, typical presentations include fever, cough, and shortness of breath. More severe manifestations include acute hypoxemic respiratory failure requiring intubation and mechanical ventilation, in some cases resulting in death. Based on early data, adults over 50 years of age and individuals with chronic medical conditions are at a higher risk of severe outcomes and death. At present, there is no licensed vaccine for the prevention of this virus nor any other human coronaviruses.>

Background information on the product

<Vaccination is the most effective way to prevent disease and severe outcomes.

As with most vaccines for active immunization, the mechanism of action of COVID-19 vaccines consists of the induction of immune responses against the antigens contained in the vaccine. As common for vaccines, the pharmacodynamic (PD) profile of inactivated influenza vaccine is defined by its immunogenicity profile.

The candidate antigen is a stabilized prefusion trimer of the SARS-CoV-2 S protein. The coronavirus Spike (S) protein is the major viral envelope glycoprotein and mediates attachment and entry into host cells. The S protein precursor is cleaved to form non-covalently associated subunits, S1 and S2. The S protein appears on the surface of the virus as a mushroom-like structure, containing a cap of three S1 subunits and a stem of three S2 subunits. The S1 subunit contains the receptor binding domain (RBD), which attaches to the host cellular receptor. In the case of SARS-CoV-2, the receptor is Angiotensin Converting Enzyme-Related Peptidase 2, a membrane-bound carboxypeptidase localized to vascular endothelial as well as epithelial surfaces. The RBD is a major antigenic target for immune responses. The S2 domain contains the fusion peptide and transmembrane regions. Upon binding to the cellular receptor, S1 is cleaved from the virus and the S2 subunit undergoes a conformational change to mediate viral membrane fusion with the host cell membrane.

Sanofi Pasteur will apply the manufacturing technology that is used to produce commercialized recombinant hemagglutinin vaccine, FluBlok, also known as Supemtek in EU. It is anticipated that the recombinant protein vaccine will require an adjuvant to optimize the immune response.

The vaccine antigen consists of a prefusion-stabilized trimer of the SARS-CoV-2 Spike (S) protein (CoV2 preS dTM). The CoV2 preS dTM Drug Product consists of recombinant protein corresponding to the extra domain of S protein of SARS-CoV2 stabilized on its prefusion conformation. The coronavirus stabilized prefusion S protein purified from the baculovirus expression system platform is the vaccine antigen. This protein is produced in Protein Science Corporation's patented expresSF (Lepidopteran) insect cells, using a baculovirus expression vector, later formulated with a buffer solution.

CoV2 preS dTM Drug Product consists of recombinant protein (CoV2 preS dTM) formulated into a sterile liquid and supplied in a 2.5 mL glass vial. The CoV2 preS dTM Drug Product will be mixed at bedside with adjuvant AS03, supplied by GlaxoSmithKline to prepare an intramuscular injection.

AS03 adjuvant is a squalene oil/water emulsion performed by micro-fluidization containing α -tocopherol and Tween 80. AS03 is provided as a vial container of 2.5 mL.

1. Quality development

Please refer to the Briefing Document provided to support the initial rapid Scientific Advice (Procedure No.: EMEA/H/SA/4562/1/2020/III), which is summarized in Appendix 3 of this document.

2. Nonclinical development

To support Phase I/II clinical study (VAT00001) dedicated to the prophylactic application of CoV2 preS dTM plus AS03, or CoV2 preS dTM plus AF03, a comprehensive pharmacology and toxicology program has been developed to evaluate the immunogenicity and nonclinical safety profiles of the SARS-CoV-2 Recombinant Protein Vaccine Formulations. The study details and results are reported in the Section 2.4 of the submitted in August 2020 to support the Phase I/II initiation (attached in Appendix 2 of this document).

After two injections, the vaccine immune responses were demonstrated in several species (mice, rhesus and hamsters).

To support the first administration to human with the adjuvanted CoV-2 preS dTM vaccine with AF03 or AS03, a repeated dose toxicity study was conducted in rabbits. The first step of the toxicity study tested one human dose of 15 µg preS dTM protein antigen per dose, which is considered to cover any lower dose of antigen that would be finally selected for licensure. The doses of AF03 or AS03 adjuvant tested correspond to the respective final dose of adjuvant that will be tested in humans.

After one or three injection(s), in life and histopathology data did not show any unexpected effects. The observations were consistent with those usually observed following intramuscular injection of a recombinant protein vaccine with or without an adjuvant, with no safety concerns that would preclude dosing in humans.

Based on available data, the results of the nonclinical studies demonstrated the good immunogenicity and safety profile of the CoV-2 preS dTM AF03- or AS03-adjuvanted formulations and supported their evaluation in the Phase I/II clinical trials.

To support Phase III clinical efficacy study (VAT00002) dedicated to the prophylactic application of CoV-2 preS dTM plus AS03, the vaccine efficacy is currently assessed in NHP and in hamster challenge models. In addition to the pharmaceutical parameters measured on both Phase I/II and Phase III batches, the potential impact of the process changes will be assessed in an immuno-bridging study in NHPs comparing Phase I/II and Phase III vaccine batches.

Additionally, a second repeated dose toxicity study (Study No. 5003591) will be conducted with two IM injections (i.e., same number as in human), two weeks apart, in NZW rabbits, using a Phase III batch to support the bridging study between formulations tested in Phase I/II trial and those to be tested in Phase III clinical trials. The objective of this toxicology study will be to evaluate the local tolerance and systemic toxicity CoV-2 preS dTM (at the dose selected to progress further in clinical development) adjuvanted with AS03 adjuvant, and to evaluate the reversibility and/or delayed occurrence of any findings following a 2-week recovery period. The parameters evaluated will be similar to that of the initial toxicology study, and the study will also be conducted in compliance to GLP. Only the treatment phase (i.e. until the first post Dose 2 necropsy timepoint) will be completed, and non-audited results submitted before the initiation of the Phase III.

3. Clinical development

Please refer to the Briefing Document provided to support the Follow Up rapid Scientific Advice (clinical) (Procedure No.: EMEA/H/SA/4562/1/FU/1/2020/II).

Justified by the pandemic setting and urgent need for effective prevention approaches, Sanofi Pasteur proposed to accelerate development by advancing from the Phase I/II trial in adults directly to the pivotal

Phase III efficacy trial. Formulation and schedule will be selected based on data from the Phase I/II and results from nonclinical studies completed in parallel to the Phase I/II.

4. Regulatory status

The Scientific Advice Working Party (SAWP) was consulted for:

- An initial rapid Scientific Advice: Final Advice Letter was issued on 05 June 2020 (Procedure No.: EMEA/H/SA/4562/1/2020/III),
- A paediatric rapid Scientific Advice: Final Advice Letter was issued on 23 October 2020 (Procedure No.: EMEA/H/SA/4688/1/2020/PED/II),
- A Follow Up rapid Scientific Advice (clinical): Final Advice Letter was issued on 10 November 2020 (Procedure No.: EMEA/H/SA/4562/1/FU/1/2020/II).

Similar advices were and are conducted with the CBER.

The eligibility for evaluation under the Centralised Procedure has been granted on 04 September (Product reference: H0005754). The CHMP Rapporteur and Co-Rapporteur, as well as the Peer Reviewer have been appointed on 13 October. The PRAC Rapporteur and Co-Rapporteur have been appointed on 26 October.

5. Rationale for seeking advice

The aim of this Follow-up Scientific Advice is to share the protocol of the Developmental and Reproductive Toxicity Study for information (attached in Appendix 1 of this document) and to answer questions raised in the initial Scientific Advice by showing the progress of the nonclinical strategy and sharing the data already available (as part of the IND 2.4, attached in Appendix 2 of this document). The applicant seeks advice on the proposed strategy for the nonclinical program.

>

Questions from the Applicant

General Remark

It is not within the remit of CHMP to Approve clinical trials. Advice is given as consideration to prepare clinical trial applications and in view of any future application for marketing authorisation. Clinical trial applications are within the remit of National Competent Authorities in Member States where the trial is conducted and of Ethics Committees involved.

Questions on Toxicopharmacological development

Question <1>

<Does EMA agree with the proposed nonclinical safety program?>

Applicant's position

<An initial SARS-CoV-2 repeated dose toxicology study was performed (Study No 5003471) to support Phase I/II study initiation. Furthermore, a second toxicology study with two administrations 14-day apart using Phase III batches will be conducted (Study No 5003591) to support the bridging between Phase I/II and Phase III product batches.

Finally, considering the target age range for this new vaccine candidate, and to support vaccination of Women of Child-Bearing Potential (WOCBP), a Developmental and Reproductive Toxicity study (DART) study will be conducted. Given the absence of alert on reproductive organs in the initial repeated dose toxicity study (Study No 5003471), the DART study will be conducted in parallel of Phase III using a Phase III batch.>

CHMP answer

<CHMP agrees with the proposed non clinical safety program, pending an evaluation of the data that will be available. If new safety concerns would arise during the proposed studies or during clinical trials these may need to be addressed by dedicated animal studies. Given the absence of alert on reproductive organs in the initial repeated dose toxicity study (Study No 5003471), the Applicant intends to conduct the DART study in parallel of Phase III using a Phase III batch. This position is endorsed, conditional to inclusion of appropriate birth control methods for women of childbearing potential in clinical trials, according to "Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2)" and the recommendation on contraception and pregnancy testing published by CTFG https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf .>

Question <2>

<Does EMA agree with the proposed strategy for the immunogenicity and efficacy evaluation in the nonclinical program?>

Applicant's position

<The nonclinical efficacy of CoV-2 PreS dTM vaccine with AS03 will be assessed in two animal species, hamsters and rhesus macaques. Both species have been shown to be susceptible to a challenge with SARS-CoV-2 virus. Protection against viral replication in the lungs, and reduction of the viral loads in the upper respiratory tract will be measured in both models, three to four weeks after immunization performed according to the schedule used in Humans (I.M, 2-dose injections 3-weeks apart). An additional immunogenicity study in rhesus macaques will be performed to document the impact of the process changes between Phase I/II and Phase III vaccine batches.>

CHMP answer

<The proposed strategy to assess immunogenicity and efficacy in animals and the choice of the two species is considered in line with recommendations on the data that should be available before initiation of phase III clinical trials. Both Syrian hamsters and Rhesus macaques show relevant features of infection with SARS-CoV-2. In addition to showing protection by the vaccine against the consequences of infection with the virus, the studies should also allow to gain a preliminary insight into the potential to cause vaccine induced enhancement of respiratory disease. The analysis of the ratio between binding and virus neutralising titres, assessing Th1 and Th2 associated cytokines upon challenge in vaccinated versus control groups, as well as the analysis of pathology in target organs via gross pathology in the lungs and histopathological analyses of the target organs (i.e. lungs, nasal turbinates and gastrointestinal tract) are considered of importance for the detection of enhanced disease. The analysis of binding versus neutralising antibodies, the ratio of IgG1 and IgG2a antibodies and identification of Th1/Th2 responses may be more sensitive than the observation of lung pathology. Non clinical data will be of use to estimate potential risks before exposure of large numbers of study participants but ultimately clinical data will be prevailing in this regard. Immunogenicity data from early clinical trials (neutralizing antibodies, Th1/Th2 balance) should also supplement the available information.

No information was provided on the similarity of the immune response to the adjuvant in hamsters relatively to humans. Ideally, the response of the immune system to the antigen should be enhanced by

the adjuvant through a similar mechanism as expected in humans, not only from the efficacy point of view, but also concerning the potential adjuvant-induced immuno-toxicity.

<Other comments not directly related to the questions>