

24 November 2020

EMA/634278/2020

Biological Health Threats and Vaccines strategy Office (HTV)

Summary of the ETF meeting on vaccines against COVID-19

26th November 2020 @ 11:00 CET time – ROOM 07/A at EMA

Chair: Marco Cavaleri

1. Declarations of Interest

The Chairperson opened the 26th November 2020 meeting by welcoming all participants.

Based on the declarations of interest submitted by the ETF members and experts and based on the topics in the agenda of the current meeting, the ETF Secretariat announced the restricted involvement of some members and experts in upcoming discussions; in accordance with the Agency's policy on the handling of conflicts of interests, participants in this meeting were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion (see Annex I – List of participants). No new or additional conflicts were declared.

Discussions took place in full respect of the restricted involvement of ETF members and experts in line with the relevant provisions of the [Rules of Procedure](#).

2. Summary

Ad26.COVS.2 Janssen Vaccine – assessment of the evidence required for the Start of the Rolling Review

Demonstration of the proof of principle (non-clinical studies including results from challenge studies in hamsters and NHPs), and proof of concept (clinical immunogenicity preliminary results from phase 1/2a study COV1001, neutralising antibodies and tolerability acceptable) justify the start of the rolling review. Additional data with the same platform carrying different antigens is considered supportive.

The ETF agrees with the (co)Rapporteurs.

COVID-19 vaccine (recombinant, adjuvanted) (Sanofi) - EMA/SA/0000047681 - recombinant protein derived from the SARS-CoV-2 prefusion Spike delta TM protein for the prevention of COVID-19 disease

The Sanofi COVID-19 vaccine is a recombinant, AS03 adjuvanted vaccine containing the Spike delta TM protein derived from the SARS CoV2 in a stabilized prefusion trimer conformation. The CoV2 preS dTM Drug Product will be mixed at bedside with adjuvant AS03, supplied by GlaxoSmithKline to prepare an intramuscular injection. The applicant posed 2 non-clinical questions.

To support the 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. 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 showing no unexpected effects.

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.

Question 1 - Does EMA agree with the proposed nonclinical safety program?

The presented non-clinical programme is considered acceptable by both coordinators as well as the ETF. The tox study in rabbits conducted in parallel to the phase 3 study is agreed but the authority responsible for the clinical trial authorisation will ask for contraception and pregnancy screening in order to enrol women of child-bearing potential.

Question 2 - Does EMA agree with the proposed strategy for the immunogenicity and efficacy evaluation in the nonclinical program?

The immunogenicity and challenge studies measure immune responses, protection against disease and signs of VAERD in hamsters and macaque, in line with previous advices. Importantly these studies assess neutralising antibody titres, Th1/Th2 cytokines responses and lung (hysto)pathology upon challenge to identify signs of immune toxicity that could be indicative of VAERD. Such data are considered necessary to reassure on lack of undue immunotoxicity signs before testing large number of individuals, but the most relevant data will come from the clinical trials.

BNT162 (mRNA1273 vaccine) Biontech/Pfizer -Rolling Review (CMC wave 1)

Only one wave so far has assessed data from the quality dossier, which however is not yet completed. Three major objections (MOs) have been raised By (co)Rapporteurs and endorsed by BWP: on the GMP status for DS and DP manufacturing sites, on the comparability between clinical and commercial material, and on the omission of data on DP manufactured at the commercial site. The ETF discussion focused on the MOs, which are justified due to the identified problems with comparability and lack of product characterisation data.

The main point for concern is the GMP inspection that is being conducted this week. Informal feedback is envisaged from the inspector early next week and will be useful to understand if critical deficiencies will be found that could prevent issuing GMP certification on time.

Regarding the other 2 MOs, the expectation is that they can be resolved upon submission of further data. The main concern remains the issues of the mRNA integrity which is raised to 50% in the commercial batches vs. 20% in the clinical batches.

On this aspect a teleconference was held yesterday with EMA/FDA/HC and MHRA. FDA have received more data, hence the company can be asked to align submissions. RNA integrity seemed overall a theoretical problem for FDA and HC, which nevertheless needs to be clarified.

Lack of efficacy due to lower potency could be a concern. The ETF considered that immunogenicity studies looking at responses after 2 doses of batches from different processes, which may deliver data in January or February 2021, as well as early clinical studies with different doses, could help shed more light, but results may be difficult to interpret without a correlate of protection. Therefore it remains essential that the product is well characterised and specifications for potency and integrity may need to be kept more conservative for the time being. The company will send more data from 2 additional drug substance batches that appears to be more similar to clinical batches in terms of amount of intact mRNA. Interestingly MHRA approach for emergency use is going to be providing a batch-specific authorisation.

Safety is not seen as of major concern by ETF, at least for fragmented RNA that is not capped and polyA (resulting in potential transcription), but in absence of data it is difficult to be conclusive. Therefore the ETF agreed with the request to generate more data as much as possible as mentioned in MO2a. MO2 could be resolved by the new data asked. Further discussion will have to take place based on new data assessment.

BNT162 (mRNA1273 vaccine) – (002861-PIP02-20) - Biontech – update on the PIP discussion

The ETF was given an overview of the PIP for the Biontech/Pfizer vaccine, which will be adopted by PDCO next week.

ETF questioned whether the company's proposed number of participants to the immunogenicity and safety trials are justified from a safety perspective (approximately 3000 per age strata). Although it is difficult to discourage a company from proposing a sample size larger than what would be a minimum requirement, they should be reminded to include an adequate justification of any proposed sample size in terms of outcome, and to seek further scientific advice from CHMP on safety requirements for paediatric studies once more data will become available.

Of note, Moderna proposed in their PIP 250 subjects per age strata, which sounds more reasonable.

Although it is difficult to provide clear cut numbers as it depends on the sought outcome, as a general principle the ETF agreed that for reactogenicity it would be sufficient to test around 300 subjects per age stratum. Serious rare events could be disproportionately represented in children vs. adults e.g. narcolepsy or other autoimmune disorders that are more likely to occur in adolescents than adults. However, such events would require sample sizes larger than 30,000 individuals to be able to detect anything. As this would be unfeasible, especially for a paediatric study, we need to rely on post-authorisation surveillance.

3. A.O.B.

- Update on AZD1222 vaccine top line efficacy data from the UK and Brazil phase 3 trials and difference between the LD/SD vs. SD/SD regimens. The company's presentation will be shared with the ETF.
- EMA is part of the OPEN experts project for vaccines, which means that 2 assessors from respectively HC, Swiss Medics, Japan and WHO (plus 4 assessors through WHO from other Countries i.e. TGA, Korea, Brazil) will attend the ETF discussions on the vaccines RR as additional experts (no role in the decision making process).

Annex I – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the ETF meeting on 26th November 2020.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Harald Enzmann	Member	CHMP - chair	No interests declared	Full involvement
Bruno Sepodes	Member	CHMP – vice-chair	No interests declared	Full involvement
Sabine Straus	Member	PRAC - chair	No interests declared	Full involvement
Koenraad Norga	Member	PDCO - chair	No restrictions applicable to this meeting	Full involvement
Anja Schiel	Member	SAWP - chair	No interests declared	Full involvement
Maria Cortizo	Member	IDWP - chair	No interests declared	Full involvement
Filip Josephson	Member	IDWP - member	No interests declared	Full involvement
Regine Lehnert	Member	IDWP - member	No interests declared	Full involvement
Nathalie Morgensztejn	Member	IDWP - member	No interests declared	Full involvement
Mair Powell	Member	VWP - chair	No interests declared	Full involvement
Mikael Andersson	Member	VWP - member	No interests declared	Full involvement
Sol Ruiz	Member	BWP - chair	No interests declared	Full involvement
Ralf Wagner	Member	BWP - assessor	No interests declared	Full involvement
Blanka Hirschlerova	Member	QWP - chair	No interests declared	Full involvement
Sven-Erik Hillver	Member	QWP - member	No interests declared	Full involvement
Jean-Michel Dogne	Member	PRAC, WHO GACVS - member	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ann Marie Janson Lang (MPA SE)	Member	CTFG	No interests declared	Full involvement
Eleonora Wijnans	Member	VWP - member	No interests declared	Full involvement
Jacqueline Kerr	Member	BPWP - member	No interests declared	Full involvement
Ita Walsh	Member	BPWP - member	No interests declared	Full involvement
Agustin Portela	Member	VWP - member	No interests declared	Full involvement
Isabelle Bekerredjian-Ding	Member	VWP - member	No interests declared	Full involvement
Ulla Wändel Liminga	Member	PRAC - member	No interests declared	Full involvement
Martin Huber	Member	PRAC – vice-chair	No interests declared	Full involvement
Daniel Morales	Member	PRAC - member	No interests declared	Full involvement
Kora Doorduyn - van der Stoep	Member	CMDh - chair	No interests declared	Full involvement
Rui Pedro da Costa Vilar	Member	CMDh - alternate	No interests declared	Full involvement
Jan Müller-Berghaus	Member	SAWP and CAT member	No interests declared	Full involvement
Sara Galluzzo	Member	PDCO - member	No interests declared	Full involvement
Sabine Mayrhofer	Member	CHMP - Expert	No interests declared	Full involvement
Ingrid Schellens	Member	SAWP Alternate	No interests declared	Full involvement
Charlotta Bergquist	Member	VWP - member	No interests declared	Full involvement
Dagmar Stara	Member	EC	No interests declared	Full involvement
Edit Szepessy	Expert	EC	No interests declared	Full involvement
Kristof Bonnarens	Expert	EC	No interests declared	Full involvement
Laurence O'Dwyer	Expert	EU IN	No interests declared	Full involvement
Kaisa Immonen	Observer	Civil society - observer	No restrictions applicable to this meeting	Full involvement
Leire Solis	Alternate	Civil society - observer alternate	No restrictions applicable to this meeting	Full involvement
Anita Simond	Observer	Civil society - observer	No restrictions applicable to this meeting	Full involvement
Tiago Villanueva	Alternate	Civil society - observer alternate	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marco Cavaleri	ETF - chair	EMA	No interests declared	Full involvement
Manuela Mura (or relevant back -up)	ETF Secretariat (vaccines)	EMA	No interests declared	Full involvement
Radu Botgros (or relevant back -up)	ETF Secretariat (therapeutics)	EMA	No interests declared	Full involvement
Katarzyna Turobos (or relevant back -up)	ETF Secretariat	EMA	No interests declared	Full involvement