25 February 2021
EMA/117973/2021
Committee for Human Medicinal Products (CHMP)

Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2

Draft agreed by COVID-ETF[1]	18 February 2021
Adopted by CHMP	25 February 2021

Keywords	COVID-19, SARS-CoV-2, vaccine, regulatory requirements, variant strain, variant vaccine, parent vaccine, immunogenicity, quality, nonclinical, multivalent

[1] COVID-19 - EMA Pandemic Task Force (COVID-ETF); https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/emas-governance-during-covid-19-pandemic#covid-19-ema-pandemic-task-force-section

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

Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2

Table of contents

1. Introduction

This reflection paper should be read in conjunction with the following:

Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1)

Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases (EMA/488220/2012 Corr)

In this paper:

- The original licensed vaccines against SARS-CoV-2 are referred to as parent vaccines and the SARS-CoV-2 strain from which they were derived is designated as the parent strain.
- Vaccines that are intended to protect against one or more SARS-CoV-2 variants that have emerged are referred to as variant vaccines and the SARS-CoV-2 strain(s) from which they are derived is/are designated as the variant strain(s).

There must be a justification for the relevance of the variant(s) included in a variant vaccine intended for use in the EU based on disease surveillance and characterisation of strains circulating at the time of selecting the variant(s). As soon as there is a global forum established to support SARS-CoV-2 strain selection for vaccines (e.g. by the WHO), the recommendations made should be consulted when selecting the variant strain(s).

It is recommended that sponsors obtain scientific advice on the details of the development programmes for variant vaccines.

The concepts hereby expressed may be subject to further revision as additional evidence is generated and based on the evolving situation.

Scope

This reflection paper outlines the quality, nonclinical and clinical data that would be required to support approval of a variant vaccine, whether monovalent or multivalent.

The requirements apply only when both of the following criteria are met:

- The parent vaccine has been granted marketing authorisation in the EU;
- Except for the SARS-CoV-2 antigen(s) to be presented to the human immune system following vaccination, the manufacturing process and controls and the facilities for vaccine production of the variant vaccine, are the same or very similar to those for the parent vaccine.

2. Discussion

2.1. Quality - Module 3

The requirements for authorisation of a variant vaccine will largely depend on the technology underlying the parent vaccine construct (e.g. mRNA vaccine, viral vector, purified protein produced by recombinant DNA technology, inactivated viral vaccine). The updated Module 3 should address the following:

- There should be an update of the starting materials (e.g. DNA template, virus seed);
- Reliance on the parent vaccine control strategy should be possible with some adaptations to accommodate the new strain-specific requirements;

- Testing of critical quality attributes (e.g. purity, content) should be performed to demonstrate compliance with the registered specifications. Any deviation from or change to the registered specifications (e.g. identity, potency) would require adequate scientific and/or clinical justification;
- Manufacturing consistency should be demonstrated (e.g. by active substance and finished product characterisation, in-process control results, batch analyses);
- In principle, the registered shelf life conditions/period would be applicable. However, confirmation of the suitability of the active substance and finished product registered shelf life needs to be demonstrated (e.g. by available real-time stability data, predictive stability models, early stability data under accelerated storage conditions). Confirmatory real-time stability data need to be provided post-approval.

If the variant vaccine is to be multivalent, there may be further considerations to assure the quality of the individual active substances at release and up to the end of shelf life.

These considerations would primarily relate to the manufacturing and control of the finished product (e.g. the control of total level of impurities and the validity of the analytical procedures to test vaccines containing different variant strains). The specifications would need to be adapted due to the additional variants. Pharmaceutical development studies and a change to the finished product control strategy in terms of formulation would be required. The requirements for batch analysis data and process validation data are also considered to be higher when moving from a monovalent parent vaccine to a multivalent variant vaccine.

2.2. Nonclinical - Module 4

There is no requirement to conduct any further in-vitro or in-vivo nonclinical testing to support the development of variant vaccines. If MAHs choose to conduct such studies they will be viewed as supportive of the clinical data.

2.3. Clinical – Module 5

2.3.1. Efficacy of the variant vaccine

The efficacy of a monovalent or a multivalent variant vaccine against the variant strain(s) may be inferred from provision of immunogenicity data:

- After primary vaccination with the variant vaccine; and
- After a single dose of the variant vaccine when given to subjects who previously received primary vaccination with the parent vaccine.

The subsections that follow outline recommendations for clinical trials in which the variant vaccine is given for primary vaccination or following primary vaccination with the parent vaccine.

In the following instances:

- The variant vaccine is intended to replace the parent vaccine as the sole marketed vaccine; and/or
- The variant vaccine will include the parent strain, i.e. it will consist of one or more variant strains plus the parent strain;

and

- The parent strain is still in circulation in the EU

there would be an additional requirement to demonstrate that the variant vaccine elicits an immune response to the parent strain after primary vaccination that is non-inferior to that elicited by the parent vaccine against the parent strain after primary vaccination.

SARS-CoV-2-naïve subjects (i.e. unvaccinated and with no evidence of prior infection)

It is currently recommended that at least one trial should be conducted in a SARS-Cov-2-naïve population.

In the absence of an immune correlate of protection (ICP)

It is recommended that unvaccinated subjects with no history of COVID-19 disease are randomised to receive primary vaccination with the parent vaccine or with the variant vaccine using the dose schedule approved for the parent vaccine. Trial population may be confined to adults who are not in priority groups for vaccination. The timing of the post-vaccination blood samples for the primary analysis should be based on what is known from data generated with the parent vaccine.

The primary analysis should be conducted in the subset with no serological evidence of prior infection with SARS-CoV-2 found in baseline samples. To immunobridge from the efficacy previously documented with the parent vaccine to the variant vaccine, neutralizing antibody titres should be measured against the corresponding vaccine strain(s), i.e. in the parent vaccine group against the parent strain and in the variant group against the variant strain(s). The following criteria should be met when comparing the immune response elicited by the variant vaccine against the variant strain to the immune response elicited by the parent vaccine against the parent strain:

- The lower bound of the 95% confidence interval around the difference in seroconversion rates for the (or each) variant vs. the parent strain should not exceed -10%. Seroconversion should be defined as at least a 4-fold increase in titre from pre-vaccination to post-vaccination; since the primary analysis will be in seronegative subjects, a nominal value should be applied to the pre-vaccination samples to calculate the seroconversion rate.
- The lower bound of the 95% confidence interval around the GMT ratio should be at least 0.67.

Among the secondary endpoints:

- The immune response elicited by the parent vaccine against the variant strain(s) and by the variant vaccine against the parent strain should be determined;
- For vaccines with 2-dose primary schedules, the immune responses after the first dose should be compared along the same lines as for the primary analysis.

The reverse cumulative distribution curves should be provided.

If the epidemiology of SARS-CoV-2 indicates that it is no longer in the best interest of subjects to receive primary vaccination with the parent vaccine, an alternative approach to immunobridge from the efficacy previously documented with the parent vaccine to the variant vaccine could be a comparison between immune responses elicited by primary vaccination with the variant vaccine against the variant strain and prior data on the immune response elicited by primary vaccination with the parent vaccine against the parent strain. The primary analysis would then proceed as described above.

To support this alternative approach:

- The assay conditions applied at the time or generating the prior data should not have changed and/or the post-primary samples should be re-assayed for neutralizing antibody against the parent strain;

- The historical data should be obtained from subjects that are matched to the group enrolled into the prospective trial to receive the variant vaccine at least based on age, gender and presence of important underlying comorbidities;
- Residual sera should be available from the matched historical controls so that the immune response elicited by parent vaccine against the variant strain(s) can be determined.

In the presence of an immune correlate of protection (ICP)

If there is an ICP which CHMP agrees is applicable to the vaccine construct in question, SARS-CoV-2-naïve subjects should receive primary vaccination with the variant vaccine respecting the dose schedule as per the SmPC for the parent vaccine. The percentage of subjects that achieve titres at or above the ICP (i.e. the seroprotection rate) against the variant strain(s) should be determined. The precision of the point estimate for the seroprotection rate should be estimated by calculating the 95% confidence interval. The lower bound of the confidence interval for concluding that the seroprotection rate is acceptable should be agreed with CHMP.

Subjects previously vaccinated against SARS-CoV-2

In the absence of an immune correlate of protection (ICP)

The efficacy of the variant vaccine against the variant strain(s) when administered to subjects who received primary vaccination with the parent vaccine may be inferred by conducting a trial in subjects with fully documented prior vaccination with the parent vaccine.

It is recommended that trial subjects should have participated in previous trials with the parent vaccine so that their post-primary neutralizing antibody titres are available. If this is not possible, the post-primary neutralizing antibody titres used in the primary analysis should be drawn from a population that is matched at least based on age, gender and presence of important underlying comorbidities to the population enrolled into the prospective trial to receive a dose of variant vaccine.

The interval between completion of the primary series with the parent vaccine and administration of a dose of the variant vaccine and the window allowed around the interval require consideration and justification.

For the purposes of obtaining the data required to conduct the primary analysis, it would suffice that all subjects enrolled into the trial receive a dose of the variant vaccine.

The primary analysis should be conducted in subjects with no serological evidence of SARS-CoV-2 infection. It should compare the neutralizing antibody GMT elicited by a dose of variant vaccine against the variant strain(s) with the post-primary neutralizing antibody GMT elicited by the parent vaccine against the parent strain. The lower bound of the 95% confidence interval around the GMT ratio should be at least 0.67.

A secondary analysis should compare the neutralizing antibody GMT elicited by the variant vaccine against the variant strain(s) with the post-primary neutralizing antibody GMT elicited by the parent vaccine against the variant strain(s).

Other secondary analyses should compare the seroconversion rates elicited by parent and variant vaccines against each of the parent and variant strains.

It is optional that this trial involves randomisation of subjects who completed primary vaccination with the parent vaccine to receive a dose of parent vaccine or variant vaccine. If this design is adopted, the primary analysis to support use of the variant vaccine in subjects who received primary vaccination with the parent vaccine would proceed exactly as outlined above.

In addition to the primary analysis, this optional trial design would allow for a secondary analysis that compares the neutralizing antibody titres against the variant strain(s) elicited by one dose of variant or parent vaccine in subjects who received primary vaccination with parent vaccine. This comparison is of interest since it is possible that the immune response to a further dose of parent vaccine could give substantially higher neutralizing antibody titres against the variant strain(s) compared to the titres against the variant strain(s) obtained after primary vaccination.

If the GMT against a variant strain after a dose of variant vaccine is superior to the GMT against the variant strain after a dose of parent vaccine (lower bound of the 95% confidence interval around the GMT ratio >1) the result would give support to the potential value of administering the variant vaccine rather than the parent vaccine to subjects who received primary vaccination with parent vaccine.

In the presence of an immune correlate of protection (ICP)

If there is an ICP which CHMP agrees is applicable to the vaccine construct in question, all subjects may receive a dose of variant vaccine as described above. The primary analysis should be based on the seroprotection rate elicited by the variant vaccine against the variant strain(s). The precision of the point estimate for the seroprotection rate should be estimated by calculating the 95% confidence interval. The lower bound of the confidence interval for concluding that the seroprotection rate is acceptable should be agreed with CHMP.

2.3.2. Safety of the variant vaccine

Unless there were safety concerns for the parent vaccine and/or safety concerns emerge from trials with the variant vaccine, the safety data collected during immunogenicity trials with the variant vaccine as outlined above should suffice for approval.