Summary Document

Topic: Considerations for Within-platform Immuno-bridging for Monovalent, Modified SARS-CoV-2-Strain, COVID-19 Candidate Vaccines in primed individuals

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Disclaimer: This document provides a summary of key points from the literature, guidelines or other documents from experts on the subject matter, including from national and multilateral organizations and authorities. This document does not aim to be exhaustive. Due to the rapidly evolving situation, this summary document may not include latest evidence and updates are likely. New versions will be issued when significant new information becomes available. Its purpose is to support organizations and institutions involved in the development of COVID-19 vaccines. It is the responsibility of each vaccine developer to review available evidence, take into account relevant guidance and recommendations, and to seek scientific advice from regulatory agencies as appropriate.

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Overview:

Regulatory guidance (WHO, EMA, FDA, ACCESS) proposes immuno-bridging as an acceptable approach for licensure if the modified vaccine is manufactured using the same platform and process as the authorised prototype vaccine (hereafter referred to as "within-platform"). This Summary Document (SD) sets out core elements for consideration in the design of 'rapid-response' immuno-bridging trials of modified monovalent COVID-19 vaccine candidates (hereafter referred to as Omicron vaccine) to enhance efficacy against COVID-19 caused by a new variant of concern (VOC) (hereafter referred to as Omicron). We aim to apply the guidance to trial design considering the vaccine roll-out and high seroprevalence.

As per the guidance, Sponsors should ideally conduct the within-platform immuno-bridging booster study in 1) unvaccinated subjects with no history of COVID-19 disease, randomised to receive primary vaccination with the prototype or the Omicron vaccine using the approved dose schedule of the parent vaccine; and 2) individuals primed by vaccination, in which either a booster dose of the prototype vaccine or the Omicron vaccine is administered to individuals without a history of prior natural infection and who have previously received the prototype COVID-19 vaccine according to the authorised dose schedule.

For rapid-response clinical trials, the naïve trial population envisaged in the guidance poses a challenge as a result of high seroprevalence rates in both high-income (HIC) and low-and middle-income countries (LMIC). In HIC, most willing individuals have been vaccinated. In many LMIC, seroprevalence is approaching that of HIC due to high rates of prior SARS-CoV-2 infection. This renders assessment of primary vaccination regimens for immune-naïve individuals less practical.

This SD therefore considers key aspects for the design of immuno-bridging trials assessing single-dose boosters in seropositive individuals. The dosing schedule of prototype vaccines in national vaccination programs may have been modified complicating the assessment of booster doses. This includes implementation of longer dosing intervals, heterologous mix-and-match regimens, and additional booster doses. Furthermore, the numbers of individuals with breakthrough infection and those with a history of infection and vaccination are rapidly increasing. The assumptions underlying this SD are that Omicron will replace Delta as the prevailing strain within weeks, and that the clinical development of an Omicron vaccine is designed with a view of potentially replacing the prototype vaccine for boosting pre-existing immune responses.

Introduction: This SD discusses immuno-bridging of adapted strain COVID-19 vaccines in primed individuals. Priming can occur through vaccination or infection. Regulatory guidance (WHO, EMA, FDA, ACCESS) has proposed immuno-bridging as an acceptable approach for licensure of a modified, strain-adapted, monovalent COVID-19 vaccine to enhance efficacy against COVID-19 caused by a VOC if the modified vaccine is otherwise identical and manufactured using the same platform and process as the authorised prototype vaccine (i.e., 'within-platform'). This also applies to development of Omicron-strain adapted vaccines (hereafter referred to as Omicron vaccine).

Immuno-bridging aims to infer vaccine efficacy by demonstrating either non-inferior or superior immune responses between the candidate vaccine and a comparator vaccine for which efficacy or effectiveness in preventing a specific disease outcome has been demonstrated. The use of neutralising, and potentially binding, antibody levels as immunological markers for immuno-bridging of new COVID-19 vaccines is supported by the association between vaccine-induced antibody levels and efficacy in preventing symptomatic COVID-19, and the definition of specific, yet vaccine-dependent, thresholds associated with protection.

At present, approximately 80-95% of individuals in most HIC settings are primed, either by vaccination or prior SARS-CoV-2 infection. The equivalent in many LMIC is 60-90%. In high seroprevalence settings, the naïve trial population envisaged in current guidance for rapid-response immuno-bridging (e.g., for monovalent Omicron-strain adapted vaccines) poses a challenge, and primary vaccination regimens for un-primed, seronegative individuals may be of limited use.

The randomised comparison of a single booster dose of the prototype and Omicron vaccine in a primed population provides an alternative rapid-response approach for consideration. The administration of a single vaccine dose is effective in individuals primed by both vaccination and infection, and the randomised comparison is ethical as the provision of a prototype booster dose in primed individuals is the (current) standard-of-care response to Omicron and supported by preliminary effectiveness data.

Neutralising and binding antibody responses directed to the SARS-CoV-2 spike protein have been established as immune markers and are acceptable for key immunogenicity endpoints. Geometric mean titres (GMTs) and sero-response rates (SRRs) may serve as co-primary endpoints to compare the range and distribution of responses, where GMTs provides a measure for the upper end of the range and SRR provides information for the lower end of the range (non-responders).

The fold-increase that constitutes a clinically meaningful SRR in a primed population has yet to be established. A four-fold increase is often considered the default for SRRs. Alternatively, Sponsors could consider defining the optimum fold-increase by a target SRR of 95%, facilitating a meaningful and viable non-inferiority (NI) comparison when considering the sample size of the trial. The approach used in some Tdap trials, where the definition of SRR (i.e., fold-increase in antibodies) depended on baseline titre, could also be considered. Reverse cumulative distribution curves (RCDC) curves may provide additional supportive data regarding the whole range of sero-responses.

The study should be adequately powered for the primary immunogenicity analyses. The demonstration of statistical NI of the Omicron vaccine may be appropriate for classic immuno-bridging comparisons. Demonstration of superiority for an additional comparison to assess the suitability of the Omicron vaccine as an alternative or replacement to the prototype vaccine may also be of interest.

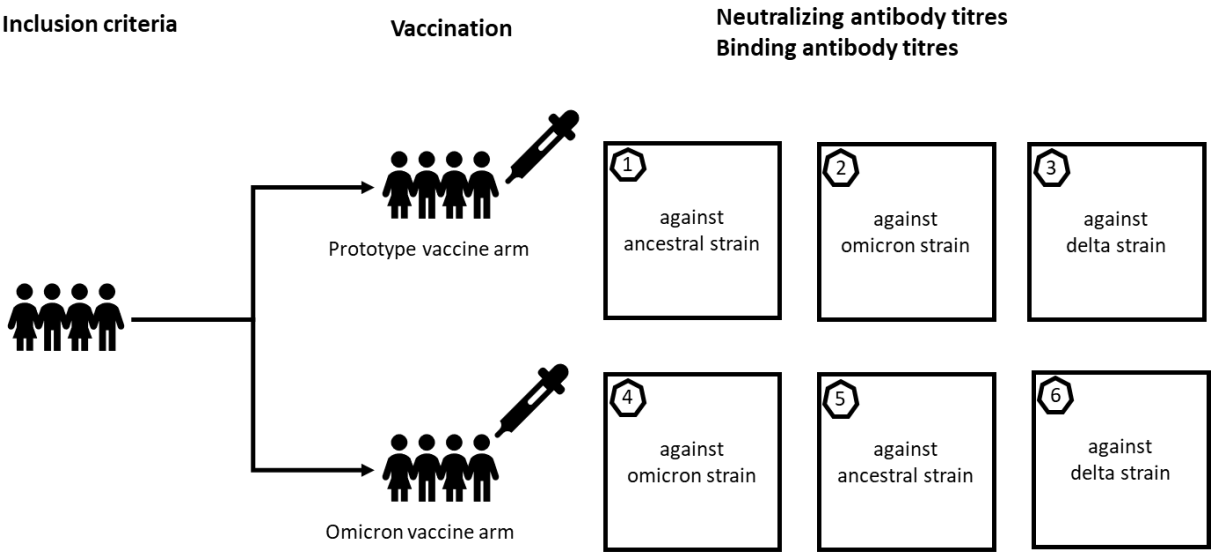
Given the rapid emergence of new COVID-19 waves with successive VOC, the totality of the immune data and specifically the assessment of cross-reactivity (including neutralising antibodies and cell-mediated immune responses) against a panel of VOC (e.g, Delta, Beta, others) will provide important additional information.

Key inclusion criteria

- **Single age group; e.g., adults aged 18-49 years**. Within-platform immuno-bridging trials may be conducted in a single age group with extrapolation of results to other age groups for which the prototype vaccine has been authorised. Younger adults are easier to recruit, have the potential for more homogeneous immune responses, and provide for a rigorous tolerability assessment as they are at risk of higher reactogenicity than older adults.

- **Baseline sero-status**. Subjects can be enrolled irrespective of baseline serostatus as long as the primary analysis is restricted to subjects that are sero-positive at baseline. The sample size should be adjusted for the estimated proportion of sero-negative individuals non-evaluable for the primary analysis.
- **Baseline COVID-19 vaccination status**. Ideally, Sponsors should conduct the within-platform immuno-bridging booster study in individuals primed by vaccination, in which the Omicron vaccine is administered to individuals who previously received the prototype COVID-19 vaccine according to the authorised dose and dosing regimen. If this is impractical, Sponsors could consider enrolling irrespective of baseline COVID-19 vaccination status and randomise stratified by COVID-19 vaccination status. The order of vaccines administered in heterologous prime boost combinations must be considered (see prime-boost studies under additional resources). We suggest, arbitrarily, a minimum three-month interval between the study vaccine and last COVID-19 vaccine dose.
- **Prior COVID-19 diagnosis.** Single dose vaccination in individuals with prior COVID-19 is more immunogenic than two doses administered to seronegative individuals and justifies single-dose 'booster' comparisons in this population. Upon modified-strain-vaccine licensure, especially in LMIC, a majority of individuals will have had one or more prior SARS-CoV-2 infections. If subjects are enrolled irrespective of prior COVID-19 history, consider stratified randomisation by prior COVID-19 status. We suggest, arbitrarily, a minimum three-month interval between the study vaccine and most recent PCR-confirmed COVID-19 episode.

Figure 1: Trial Schematic. Immuno-bridging of a Single Booster Dose in Primed Individuals



Primary Immunogenicity Objectives and Endpoints

- **The immuno-bridging comparison**: In Figure 1, the 'classic' immuno-bridging comparison (i.e., inferring [demonstrated] clinical vaccine efficacy of the prototype vaccine to the Omicron vaccine) is represented by demonstrating NI of immune responses of the Omicron vaccine to the Omicron strain (Box 4) compared to the immune responses of the prototype vaccine to ancestral strain(s) (Box 1). The co-primary endpoints are the GMT and SRR of anti-SARS-CoV-2 specific neutralising antibodies as measured by the validated live-virus assays against Omicron and ancestral strain, respectively. Alternatively, an Omicron-specific pseudovirus assay can be considered, if validated.
- **Key comparison of public health interest**: In Figure 1, the comparison of immune responses in Box 4 to Box 2 represents the current most relevant public health comparison. As the Omicron vaccine is designed for enhanced efficacy against COVID-19 caused by the Omicron VOC and developed with a view to potentially replace the prototype vaccine, a co-primary or dual primary objective demonstrating superiority of immune responses of the Omicron vaccine to the Omicron strain (Box 4) compared to the immune responses of the prototype vaccine to the Omicron strain (Box 2) may be considered. If considered applicable for a primary immune analysis, the corresponding primary endpoints would be the GMT and SRR of anti-SARS-CoV-2 specific neutralising antibodies as measured by a validated assay.

- **Virus neutralising titres against Delta**: It seems intuitive to consider a second key public health comparison represented by Boxes 6 and 3. If Omicron; however, rapidly outcompetes Delta in all settings, such comparison would primarily be of interest for assessing cross-reactivity. Cross-reactivity against a panel of VOC will be of interest and could be considered a secondary or exploratory objective (see below)
- **Timeframe**: For rapid-response clinical development, Day 15 (post trial vaccine administration) could be considered for the primary immunogenicity analysis. Alternatively, Day 29 can be considered if there are concerns regarding variability of immune responses on Day 15.
- **NI margins**: In line with regulatory guidance, the conventional NI margins of 0.67/1.5 and 10% for GMT ratios and SRR, respectively, should be considered as the default. Alternative margins may be considered in case of unrealistic sample size estimations (e.g., 0.5/2.0; 20%) or near-universal (>97%) SRRs (e.g., 5%).

Key secondary Immunogenicity Objectives and Endpoints

- **Binding antibodies**: The immune analyses for neutralising antibodies as described above can also be conducted (descriptively) for IgG binding antibodies. The corresponding endpoints are GMTs and SRRs of anti-SARS-CoV-2 binding (IgG) antibodies as measured by validated Omicron and ancestral-strain specific ELISA.
- **Reverse cumulative distribution curves**: RCDC are useful for comparing distribution of the whole range of immune responses by means of simple rank tests. RCDC tests are especially useful if there is no established correlate of protection or antibody level that correlates with protection against which the immune responses can be measured and if the SRR can be defined. RCDC allow all possible fold-rises in a single comparison by means of rank-tests.
- **Measuring cross-reactivity**: It is expected that a heterologous booster by an Omicron vaccine will increase the breadth of immune responses enhancing cross-reactivity. The assessment of GMTs of neutralising antibodies against a panel of VOC (e.g., Delta, Beta, others) will provide useful additional information. Measurement of cross-reactivity against SARS-CoV-1 could be a first indication of such an approach for pan Sarbeco protection.

Additional Resources:

US Emergency Use Authorization for Vaccines to Prevent COVID-19 APPENDIX 2: EVALUATION OF VACCINES TO ADDRESS EMERGING SARS-COV-2 VARIANTS ver 22 February 2021, revised 25 May 2021

EU Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2 ver 25 February 2021

ACCESS (UK, Australia, Canada, Singapore and Switzerland), Guidance on strain changes in authorised COVID-19 vaccines ver 4 March 2021

WHO ADDENDUM to Considerations for Evaluation of COVID-19 Vaccines for Prequalification or Emergency Use Listing. Considerations for evaluation of modified COVID-19 vaccines ver 12 March 2021

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Munro APS MN et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet 2021;S0140-6736(21)02717-3.

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