Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 3)
Evaluation of the vaccines based on Immunogenicity

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1. Background

Vaccination against the Novel Coronavirus SARS-CoV-2 has been advancing remarkably in many countries, and this trend is expected to continue. Clinical trials designed to assess the efficacy in preventing the onset of SARS-CoV-2 infectious disease (COVID-19) using placebo as a control arm, as shown in the notification "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" (Office of Vaccines and Blood Products, PMDA, September 2, 2020), can generate highly reliable evidence. However, in regions where public vaccination programs are implemented actively, it is becoming difficult to conduct new placebo-controlled clinical trials of SARS-CoV-2 vaccines because a chance of receiving SARS-CoV-2 vaccination has been assured for the inhabitants in these regions. To enable development of novel SARS-CoV-2 vaccines in the future, it is therefore necessary to establish a new methodology to assess risk-benefit balance using already approved SARS-CoV-2 vaccines as the active control in confirmatory clinical trials.

When clinical studies to assess novel SARS-CoV-2 vaccines candidates using active control are planned, there are two possible primary efficacy endpoints are considerable: (1) clinical events such as onset of symptomatic or severe COVID-19 and death after COVID-19, or (2) immunogenic markers as mentioned later. However, when the clinical events are used as primary efficacy endpoint in clinical trials to verify non-inferiority of the disease preventing effect comparing novel SARS-CoV-2 vaccine candidates to active comparators, such studies may require approximately two to three times as many person-years follow-up as conducting a placebo-controlled clinical trial.[1)] Such clinical trials have difficulties on feasibility.

Under such circumstances, the international community has been actively discussing the possibility of utilizing the immunogenic markers to assess newly developing SARS-CoV-2 vaccine candidates. At the International Coalition of Medicines Regulatory Authorities (ICMRA), consensus has been reached over implementation of immunogenicity bridging studies of novel SARS-CoV-2 vaccines may be needed if evaluation based on clinical endpoints is no longer feasible.[2)] The background to this discussion is that it has gradually revealed that neutralizing antibody titer measured after SARS-CoV-2 vaccination correlate with effectiveness of vaccines in preventing COVID-19 onset.[3), 4)] In practice, immunogenicity bridging strategy has been already utilized assessing effectiveness of SARS-CoV-2

vaccines for children and to assess efficacy of modified vaccines for variants. However, it should be noted that further pieces of evidence such as the threshold levels of immunogenic markers to indicate protection for COVID-19, the contribution of cellular immunity for protection, and the influence of SARS-CoV-2 variants in protection for COVID-19 induced by vaccines are needed to utilize immunogenic markers to assess all aspects of efficacy of vaccines.

Understanding these limitations, this appendix will present the principle for confirmatory clinical studies without setting the placebo arm, in particular, issues to be considered when evaluating efficacy based on immunogenic markers, to develop new SARS-CoV-2 vaccines for primary immunization, on the basis of the latest scientific knowledge.

Evaluation of vaccines for booster immunization needs to be conducted separately, the notification "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1); Evaluation of vaccines against variants" (Office of Vaccines and Blood Products, PMDA, April 5, 2021) can be one of referring guidances.

Although the basic principles presented in this document are based on the social conditions in Japan as of September 2021 and have been developed after discussion with external experts, the principles may change depending on the prevalence of COVID-19, accumulation of scientific evidence, advances in SARS-CoV-2 vaccines development, progress of the Official Vaccination Program in Japan.

2. Design of Confirmatory Clinical Trials

(1) Study Design

Randomized active comparator-controlled non-inferiority study or superiority study, using socially distributed SARS-CoV-2 vaccine as an active comparator, are requested.

(2) Study Subjects

In view of the evaluation of SARS-CoV-2 vaccine candidates for primary immunization, the subjects are requested without a history of both SARS-CoV-2 infection and administration of SARS-CoV-2 vaccines. Usually, healthy adults are enrolled in the studies; in some cases, individuals with underlying diseases can be acceptable when their diseases are stable.

As stated later, it is recommended to assess efficacy of to prevent symptomatic COVID-19 as a secondary endpoint. So, it is desirable to carry out the confirmatory clinical trials in countries/regions where COVID-19 is prevailing. Regarding the ages of subjects, it is required that the trial should covers all age groups anticipated to receive vaccination after its approval. When some age groups are difficult to enroll in the trials, a separate study for the age groups to bridge immunogenicity may be required.

If some particular age groups need to be excluded from the randomized active comparator-controlled clinical trials based on the range of age for the active comparator can be used in countries/regions trials carrying on, it is necessary to devise a plan to assess the efficacy and safety in the excluded age groups.

(3) Selection of an Active Comparator

In principle, it is required to select an already approved SARS-CoV-2 vaccine having the same kind of ingredients and mode of action (hereinafter referred to "the same modality") (e.g. if the vaccine candidate is mRNA vaccine, the comparator should be mRNA vaccine and if the vaccine candidate is virus vector vaccine, the comparator should be virus vector vaccine) and a similar immunogenicity profile to the vaccine candidate and having been confirmed to have a symptomatic COVID-19 preventive effect by comparative study in clinical events. If the vaccine candidate contains adjuvants, they are desirable to select the comparator while taking into consideration also the influence from the adjuvant on the vaccine's immunogenicity. From the viewpoint of ensuring appropriate blinding of the study, active comparator selection should be given to those vaccines whose dosing frequency and interval are identical to those of the vaccine candidate, whenever possible.

However, if it is impossible to select any active comparator with the same modality of the vaccine candidate, because the active comparator is not approved in the country or region where the clinical trial is to be conducted, or there is no vaccine with the same modality having been practically used in the world, an approved vaccine with a different modality may be selected. In such a case, it is required for the developer to explain the appropriateness of the selected vaccine as a comparator (similarities of immunogenicity profile between the vaccine candidate and the active comparator, etc.) on the basis of nonclinical and clinical data.

In addition, ICMRA report shows the principle that the immunogenicity bridging study for assessment of effectiveness could be designed as non-inferiority immunogenicity studies if the comparator vaccine has demonstrated high efficacy in clinical diseases endpoint efficacy trials and/or superiority designs if the comparator vaccine has demonstrated modest efficacy.[2)] Taking that into consideration, from the viewpoint of assuring demonstration of the efficacy required of a SARS-CoV-2 vaccine, when the developer assess the vaccine efficacy in non-inferior studies, it is appropriate to select an active comparator having 60% or higher symptomatic COVID-19 preventive effect. In addition to this basic principle, when deciding study design, it is necessary to take into account factors which may affect efficacy of active comparator such as dosing interval of initial immunization. Result of subgroup analysis conducted in clinical trials of the active comparator can be references to consider that factors.

(4) Blinding

In principle, SARS-CoV-2 vaccine candidates should be assessed in double-blind trial. However, in some cases, to conduct double-blind trials can be difficult because of differences in the optimum dosing interval or frequency between the vaccine candidates and the active comparators. In such cases, those trials need to be carried out while taking measures minimizing the biases as far as possible. If blinding is difficult, it is required to consider the impact of the factor that prevented blinding on the evaluation, especially on safety issue.

(5) Endpoints

[1] Primary endpoints

When developers of vaccine candidates decide to use indicators of immunogenicity to assess efficacy of the candidates, the primary endpoints in the confirmatory clinical trial should be the geometric mean of the neutralizing antibody titer (hereinafter referred to GMT) against the origin of each SARS-CoV-2 strain. The neutralizing antibody titer needs to be measured by a reliable system which has validated analytical capacity of precision and linearity, and has calibrated using the international standard for anti-SARS-CoV-2 antibody provided by the World Health Organization (WHO).

An appropriate timing for immunogenicity evaluation can be considered on the basis of the information yielded from exploratory clinical trials of the vaccine candidate. However, the timing should be set to avoid unfavorable effect on efficacy of active comparator. To confirm long-term efficacy, followed up evaluation on immunogenicity needs to be conducted for at least one year.

If a non-inferiority study is carried out with GMT serving as a primary endpoint, non-inferiority to the active comparator needs to be verified as primary endpoint also in terms of the seroconversion rate for neutralizing antibody (defined as proportion of subjects whose neutralizing antibody titer is increased by more than 4 times after vaccination).

[2] Secondary Endpoints

Evaluation of immunogenicity against SARS-CoV-2 variants should be conducted by measuring neutralizing antibody titer against not only SARS-CoV-2 strain which is measured as primary endpoint but also Variants of Interest; VOI and Variants of Concern; VOC identified by WHO as secondary endpoints. It is desirable that the status of clinical event onset related to the COVID-19 in the vaccine candidate group and the active comparator group is observed continuously after confirmation of the primary endpoint to endorse the validity of immunogenicity-based effectiveness assessment.

If a superiority study is carried out with GMT serving as a primary endpoint, it is required to also evaluate the non-inferiority of seroconversion rate for neutralizing antibody to the active comparator.

(6) Non-inferiority Margin

Taking into consideration about the level adopted as standard for assessment of variant vaccine effectiveness in former guidance[5], when non-inferiority studies on immunogenicity are conducted, the lower bound of the 95% confidence interval for the neutralizing antibody titer GMT ratio should not fall below 0.67 and that for difference in seroconversion rate for neutralizing antibody should not fall below -10%.

If any alternative criteria of the non-inferiority margin need to be selected for reasons such as the situation forcing selection of a vaccine with different modality from the test vaccine as the active comparator, sponsor need to explain validity of such a selection. In such cases, an appropriate non-inferiority margin needs to be set, taking into consideration also the viewpoint that the vaccine candidate should have the minimal efficacy (the efficacy on disease prevention should be 50% or higher and the lower bound of its 95% confidence interval should exceed 30% in accordance with the WHO and U.S. Food and Drug Administration(FDA) guidance document on evaluation of SARS-CoV-2 vaccines[6), 7)].) , and will be demonstrated through verification of non-inferiority to the active comparator.

(7) Sample Size

Sponsor of the non-inferiority study need to ensure the sample size (number of subjects) of the clinical trial large enough to allow assessment for safety and primary endpoint, thereby taking care also of the number of subjects included in the secondary endpoint evaluation. From the viewpoint of safety evaluation, the sample size should be at least 3,000, considering the statement of the WHO and FDA guidance document [3) 8)] that during development of vaccines for prevention of general infections, in principle, safety data are collected and evaluated on at least 3,000 subjects having received the vaccine candidate during clinical development at its proposed dosage and administration before the product is approved for marketing. This sample size allows 95% probability of detecting at least one adverse events arising at 0.1% probability. It is acceptable to allocate a larger number of subjects to the vaccine candidate group if the allocation allows sufficient assessment of effectiveness in the trial. As an approximate criterion, the ratio of the number of subjects in the vaccine candidate group to the active comparator group should be 3:1 at maximum.

However, when any serious safety concerns have arisen during development and further safety evaluation is needed, it may be necessary to take appropriate approach for safety evaluation such as allocating additional subjects or conducting additional clinical trials involving a specific vulnerable population for safety evaluation.

Measurement of antibody titer as a primary endpoint does not always need to be carried out on all subjects. The number of subjects requiring to evaluate immunogenicity can be considered from the information about immunogenicity of the vaccine candidate collected as a result of the exploratory

clinical trials and the published information about the immunogenicity of the active comparator. If the study is carried out in multiple regions where the prevailing strain of SARS-CoV-2 differs from each other (e.g., in a global cooperative clinical trial), it is desirable to set the sample size separately for each region to enable evaluation of the influence of the locally prevailing strain and to take measures to consider about regions as a stratification factor in randomization.

(8) Considerations in Clinical Trial Design for Rapid Assessment of Effectiveness

To enable rapid assessment of effectiveness with clinical studies, it is considerable to conduct a clinical trial with seamless design. Such kind of clinical trial should have predetermined criteria for transitioning from exploratory phase for determination of the vaccine candidate's dosage to confirmatory phase. When a sponsor decided to use a clinical trial with seamless design, the appropriate market authorized SARS-CoV-2 vaccine should be selected as the active comparator on the basis of the information of vaccine candidate from nonclinical studies and early clinical trials for collection of safety information, and the criteria for transitioning to a confirmatory phase (e.g., criteria for selecting the optimum dosage/administration of the vaccine candidate and how to evaluate the safety) should be pre-specified in the trial protocol.

The evaluation method and timing of primary and secondary endpoints need to be planned well in advance, and it is desirable for the sponsor to reach an agreement with the regulatory authorities about evaluation method and timing before the start of the study. If the sponsor conducts clinical trials which clinical events is statistically compared between the vaccine candidate group and the active comparator group as a secondary endpoint, the trials may take a long time to reach the point to evaluate. In such a case, to plan interim analyses in protocol of the clinical trial before starting the trial may be a choice. To achieve such analyses, it is required to set the criteria of early stopping for efficacy clearly in advance, in addition to implementation of statistical analysis to consider multiplicity of the statistical tests related to the interim analysis. Even when the trial is terminated early for a reason of confirmation of efficacy, follow-up examinations about immunogenicity and safety observations described Section 2. (5) and 2. (7) are required for at least one year from the last administration of the trial.

In the confirmatory clinical trial based on evaluation of immunogenicity, it is desirable to observe occurrence of clinical events (e.g., COVID-19 disease preventive effect) between the vaccine candidate group and the active comparator group, to continue observation even after marketing, and to evaluate occurrence of clinical events.

If efficacy of the vaccine candidate is estimated to be quite low on the basis of clinical event occurrence on which information is collected as a secondary endpoint, the efficacy of the vaccine candidate may be questionable even after the efficacy has been confirmed by the evaluation of immunogenicity as the primary endpoint. For that reason, interim analysis of the confirmatory clinical trial is desirable to take into consideration also the possibility that the disease preventive effect is lower

than expectations, by setting also the criteria for futility.

(9) Evaluation of Safety

On each clinical trial conducted, it is required to collect information about solicited local reactions and solicited systemic reactions observed during the at least 7-day period after administration of the vaccine candidate and active comparator as well as serious and other adverse events that have arisen during the immunogenicity assessment period. Follow-up observation needs to be made for at least one year after the last administration, referring to 3.1.4 Evaluation of Safety of "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" issued by Office of Vaccines and Blood Products, PMDA on 2 September 2020.

If any safety-related signal has been detected from the clinical trials or any other information, a larger-scale clinical trial for collecting safety data may be needed depending on the circumstances.

3. Utilization of Platform Trial

(1) Basic Concept

If multiple SARS-CoV-2 vaccines are developed concurrently during a relatively short period of time, conducting efficacy evaluation using a platform trial (i.e., evaluation of multiple vaccine candidates using a single common study protocol), particularly with using common active control, may be one option to facilitate efficient evaluation of their efficacy. For example in the U.S., guidance document[9)] for conducting evaluation of SARS-CoV-2 vaccine and therapeutics with the clinical trials conducted according to the master protocol was published, and it can be referenced in development of study design when conducting such study.

If a platform trial is carried out, it should be noted that management of substudy through the platform will be needed, such as organizing the common data monitoring committee (DMC)/Drug and Safety Monitoring Board (DSMB), etc. independent from the sponsor for the clinical trial on each vaccine candidate.

(2) Points to Consider for Utilization of the Platform trial

An appropriate active control vaccine for comparison with the vaccine candidate planned for evaluation in the platform trial needs to be selected before the start of the platform trial or before the addition of the vaccine candidate to the trial. If multiple vaccine candidates planned to be compared with the same active control vaccine concurrently, it is acceptable that the subjects allocated to the active control group are partially shared among the multiple vaccine candidates. Because SARS-CoV-2 is anticipated to be affected by time (e.g., the prevailing strain being likely to change over a short period of time), it is desirable to compare the subjects given the vaccine candidate with the subjects concurrently allocated to the active control vaccine group. If the data of subjects collected at different

time period are utilized, it is necessary to collect information about the viral genome analysis of patients having developed COVID-19 and the trend of prevailing strains in a given region during the study and to discuss also the influence of differences in the prevailing strain among regions or periods on the immunogenicity.

Concerning the possibility for early stopping for efficacy about the substudy of each vaccine candidate, see the description about secondary evaluation in Section 2. (8).

4. Collection of Supplementary Information for Efficacy Evaluation in Clinical Studies

(1) Nonclinical Study

If sponsors are trying to assess efficacy of vaccine candidates based on immunogenic markers, it is recommended to conduct challenge studies in appropriate model animals considering the dosage and administration planned to be used in the application of drug approval, because those challenge study can provide supplementary information about the disease preventive effect of the vaccine candidates.

(2) Assessment of Efficacy against Variant Strains

The efficacy against variant strains should be evaluated through challenge study in nonclinical study mentioned above or concurrently measuring the neutralizing antibody titer against variant strains during measurement of the neutralizing antibody titer for evaluation of the primary endpoint described in Section 2.(5)[2]. It should be considered that identification of SARS-CoV-2 strain among subjects who infected with COVID-19 in the continuous observation described in 2.(5)[2].

(3) Post-marketing Surveillance, etc.

If the sponsor of a SARS-CoV-2 vaccine candidate acquired marketing authorization on the basis of the data from clinical trials which primary endpoint is immunogenicity comparison between vaccine candidate and active comparator, it is required that prospective and/or retrospective surveys are carried out to evaluate the effectiveness of the vaccine on the basis of clinical events after marketing in Post-marketing Surveillance. This kind of survey does not need to be carried out within Japan. As a method for such surveys, it may be valid, for example, to establish evidence through implementation of a retrospective cohort study with the use of big data based on clinical practice (real world data: RWD) in regions equipped with an electronic health record (EHR) system. Other possible methods include implementation of a case control study with a design minimizing the confounding factors and implementation of a prospective cohort study.

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