Appendix 3

Grant-in Aid for Health, Labor, and Welfare Administration Promotion Survey Project
(Special Research Project for Health and Labor Sciences)
Research Report

Biostatistical Perspective on Accelerating the Planning of Clinical Trials for Vaccine Development

Shared research: Assessment and performance evaluation of potential clinical trial designs/plans
Co-investigator: Yuki Ando
Affiliation: Senior Scientist for Biostatistics, Office of New Drug I, Pharmaceuticals and Medical Devices Agency

Abstract:

The novel coronavirus infection has impacted the entire world in a number of ways. Based on prior experience and current vaccine development conditions, this study examined potential situations that may affect vaccine development for future novel infectious diseases, investigated situationally specific factors that should be considered, and assessed clinical trial designs that may be considered useful. We also conducted a simulation study to evaluate the operating characteristics of possible designs that could be applied in situations where an early decision on vaccine efficacy is required.

In the early stages of vaccine development, the available information on infectious diseases is limited; moreover, the environment of infectious diseases may change substantially over time. The use of trial designs that allow for decision-making and modifications to the design during trial implementation is considered helpful, and innovative and recent trial designs and analysis methods may be utilized based on specific circumstances. In addition, to accelerate vaccine development, an implementation system capable of planning and conducting large-scale clinical trials should be constructed that can also incorporate multi-regional conditions and multi-vaccines. To provide evidence confirming vaccine efficacy, it is essential to design clinical trials that consider various factors that lead to potential changes as early as possible. Considering that an early decision on efficacy is needed to supply vaccines based on the infectious disease circumstances, it is crucial to understand decision-making uncertainties during clinical trials in advance to ensure that these issues can be discussed at the earliest. Discussing and considering such expectations during normal nonepidemic periods will facilitate appropriate action by both vaccine developers and regulatory

reviewers when an actual outbreak of infectious disease occurs.

A. Objective

The coronavirus disease pandemic has had a great impact worldwide, and due to the magnitude of the impact of this novel infection, the development of new vaccines in many countries has proceeded at an extremely rapid speed compared to that under normal situations because of the support from industry, government, academia, and society. Rapid implementation of vaccines is required in Japan, and regulatory approval applications and procedures for vaccines developed abroad have been accelerated. However, by the end of March 2022, domestic vaccines developed in Japan had not reached the practical application stage, thus highlighting various issues in the development system in Japan. Some of these issues include the lack of a system for prompt clinical trial design and planning under unexpected circumstances and the need to consider appropriate designs and planning of clinical trials for the development of new vaccines in situations where established vaccines already exist.

In this shared research, we examined the factors that should be considered for the rapid development of vaccines for future outbreaks of emerging infectious diseases and possible clinical trial designs that could be used. Our work references the situation since the outbreak of the novel coronavirus infection and the development of approved novel coronavirus vaccines. In addition, assuming that rapid decisions regarding vaccine efficacy or approval will be required in the early stages of emerging infectious disease outbreaks, we evaluated the performance of designs for early decision-making in response to potential scenarios.

B. Methods

1. Factors to be considered and possible trial designs for developing vaccines for emerging infectious diseases

Based on public information on approved vaccines in Japan, international regulations and recommendations by various regions, including Japan and the WHO, and the content of discussions during relevant international workshops regarding vaccine development since the outbreak of new coronavirus infectious diseases, we reviewed the factors to be considered and possible clinical trial designs for developing vaccines against emerging infectious diseases.

2. Evaluation of the design performance for early decisions on efficacy

The findings in 1 indicated that a rapid decision on the efficacy of the developed vaccine is expected, even with limited relevant information during the early stage of development. Therefore, we conducted a simulation study on the performance of such designs in a possible emerging infectious disease scenario. Specifically, we considered a situation in which a pre-planned interim analysis for early efficacy determinations is conducted and early termination of the study (which is not necessarily pre-planned) is required based on public health needs according to the infection situation.

Based on the results of interviews with infectious disease specialists to identify the types of infectious diseases that have high potential for vaccine development, we considered scenarios for respiratory infections, including novel influenza and novel coronavirus infections, with the aim of developing a vaccine for emerging infectious diseases. Specifically, a scenario for a novel coronavirus infection with high infectivity but relatively low mortality and a scenario with limited infections but relatively high mortality using Middle East Respiratory Syndrome (MERS) as an example were considered. The simulation study was designed under the assumption that an appropriate dose with efficacy and acceptable safety has been established based on prior clinical trials and that the study was designed as a confirmatory study for regulatory approval. A placebo-controlled study with the onset of symptomatic infection as the primary endpoint, which required a relatively long study duration, was planned. Assuming that the spread of infectious disease would require early decisions regarding efficacy and vaccine approval, the operating characteristics for both the planned interim analysis and unplanned early termination of the study were evaluated using a simulation study. In addition, for the scenario with the new coronavirus infection as an example, we also examined the design of a clinical trial in which the conclusion can be obtained in a short period from the start (3 months using the 100 Days mission proposed in Carbis Bay G7 Summit[1)] as a reference).

Details on the assumed parameters and simulation conditions for each scenario are provided in Appendix 1.

C. Results

1. Factors to be considered and possible trial designs for developing vaccines for emerging infectious diseases

The following points should be assumed and considered in advance, and the possible trial designs should be considered when planning a clinical trial for vaccine development in the context of an emerging infectious disease epidemic.

- Amount of information on infectious diseases

From the outbreak of an emerging infectious disease to the early stages of an epidemic, insufficient information is available on the infectiousness, pathogenesis, severity, and fatality rate of the disease. Therefore, vaccines developed in the early stages of an epidemic require randomized placebo-controlled trials to evaluate efficacy and safety, with the primary endpoint represented by prevention of clinical events, such as the onset of symptomatic infection[2)]. In this case, a relatively large clinical trial would be planned, and it would have little information on the actual infectiousness and incidence of the infectious disease. Therefore, it would be helpful to consider a group sequential design (interim analysis) and an adaptive design to enable decision-making on efficacy/futility and/or sample size re-estimations during the course of the clinical trial. It is important to pre-

plan the details of such interim evaluations and modifications along with the criteria for decision-making.

In situations where little information is available on both infectious diseases and vaccines, multiple doses may be evaluated in several small trials and multiple target populations (cohorts) with different ages and background factors may be studied in clinical trials in specific regions. In such cases, by designing each trial with specific objectives and a certain degree of commonality, a pre-planned integrated analysis can be conducted to evaluate preventive effects that require a larger number of subjects. To consider such an integrated analysis as a confirmatory result, it is important that the design of each trial consider the possibility of integration, especially in the planning of each trial. Additionally, integrated analyses should be planned and defined prior to obtaining any of the results of the trials. To evaluate the results, the adequacy of the integration based on the results of each trial should be explained.

With the progress of vaccine development and research on the mechanisms to prevent disease onset, information on the correlations between post-vaccination neutralizing antibody titers and efficacy in preventing disease onset is expected to accumulate, which facilitate evaluations of vaccine efficacy using an indicator of immunogenicity as the primary endpoint of efficacy. However, certain information is needed on the threshold for immunogenicity indicators of vaccine preventive efficacy and the contribution of cell-mediated immunity to preventive efficacy. In addition, the sufficiency of safety information should also be considered.

Accumulated information on immunogenicity indicators associated with prophylaxis and certain epidemiological information on infectious diseases may allow for certain assessments of specific considerations, such as the effects of additional doses, by comparison with non-randomized external controls.

- Changes in infection rates due to infectious disease countermeasures, variants, etc.

Infection and incidence rates may decrease due to the implementation of countermeasures against infectious diseases or the spread of variants with different infection rates. Such factors may lead to changes in the expected incidence rate from the values assumed at the time of planning, which may be the primary endpoint of clinical trials for vaccines, particularly in the early stages of an infectious disease epidemic. To compensate for such changes, the sample size may be changed in a blinded manner based on information collected on incidence and other factors. For confirmatory trials, possible changes in the design should be planned in advance, including the decision-making process and criteria for determining whether changes are necessary.

Differences or changes in incidence rates associated with infectious disease countermeasures, variants, and other factors may occur when evaluating the efficacy and safety of a particular vaccine based on multiple clinical trials conducted in different regions and at different times, assessing integrated analyses, and using external information from clinical

trials.

- Increase in the vaccination rate of approved vaccines

Increased vaccination with approved vaccines developed early in the course of an infectious disease outbreak may result in a decrease in the number of subjects who may be eligible to participate in clinical trials for subsequent vaccines and may reduce the recruitment rate of subjects in ongoing clinical trials. In addition, the presence of an approved vaccine may require careful consideration in the design of ongoing placebo-controlled trials[4] and may make it difficult to design and conduct new placebo-controlled clinical trials. After a certain time, trials of subsequent vaccines may be realistically planned and conducted as non-inferiority trials, using approved vaccines as controls[3]. For clinical trials planned at this point, it is necessary to establish efficacy measures available at the planning stage according to the "amount of information available on infectious diseases" and set a clinically appropriate margin of non-inferiority.

- Increasing number of concurrently developed vaccines

In the development phase of a subsequent vaccine, in addition to the potential decrease of subjects due to the increased immunization with approved vaccines, the simultaneous development of multiple subsequent vaccines may make it even more difficult to enroll subjects.

In situations where multiple vaccines are developed simultaneously in a relatively short period of time, they could be evaluated using a common platform under a single common protocol (master protocol) for more efficient efficacy evaluations (platform studies[3),5)]). This platform study design may be particularly beneficial when using approved vaccines as common active control vaccines. In a platform study, vaccines developed by multiple companies are evaluated, and in some cases, large-scale and long-term management of the platform is required. Therefore, a clinical trial implementation system should be established to ensure that a clinical trial is appropriately managed through the platform. Moreover, considering the effect of changes in infection rates due to infectious disease countermeasures and variants, as previously described, the results of a study vaccine group should be compared with those of control vaccine group subjects enrolled at the same time period, even when using the results of the common control vaccine group for multiple study vaccines.

- Other factors

In the context of a global epidemic of emerging infectious diseases, the use of available worldwide data on vaccines under development and the evaluation of such data from global clinical trials[6], including those conducted in Japan, are also important elements for regulatory approval. In such evaluations, it is necessary to address regional differences in infection status, distribution of variants, and differences in vaccination rates. It is also important to consider other ethnic factors[7] in

advance.

Some vaccine trials for new coronavirus infections have used the Bayesian approach for statistical analysis[8] rather than statistical hypothesis testing, which is traditionally used for the primary analysis of confirmatory trials. The Bayesian approach may be potentially useful in making flexible decisions regarding efficacy in vaccine trials. In addition, this approach has been used for the analyses of trials using adaptive design and platform studies. In the Bayesian approach, it is important to evaluate the appropriateness of the prior information used and the operational characteristics of the analysis. Prior consultations with regulatory agencies are recommended before Bayesian approach is used for statistical analyses.

2. Evaluation of design performance for early decisions on efficacy

In a randomized controlled trial of a novel coronavirus infection scenario with an allocation ratio of 1:1 between the vaccine and placebo groups and assuming an incidence rate of 1% at 6 months for the placebo group and an expected VE of 60%, we investigated the situation to confirm that the lower limit of the 95% confidence interval for VE based on the hazard ratio exceeded 30%[9]. Assuming an enrollment period of 3 months and a maximum observation period of 6 months for each subject, 19350 subjects were required to evaluate the efficacy at 9 months from the start of the study[10]. When the VE varied from 50% to 70% and the incidence rate of the placebo group at 6 months varied from 0.50% to 1.50%, the number of required subjects varied from 99959 to 6058 and exceeded 10000 for most combinations (Appendix 1, Table 1). When interim analyses for early discontinuation due to efficacy were conducted at 50% and 75% of the total number of events, the time period from study start to analysis was reduced to 5 and 6 months, respectively; however, the power at each time point was 20% and 60%, respectively. The O'Brien-Fleming type α-spending function based on the Lan-DeMets method was used for the multiplicity adjustment for the interim analysis. However, when early termination was conducted at 40%, 60%, and 80% of the total number of events without multiplicity adjustment for reasons due to public health, the time required for analysis was reduced to 4, 5, and 6 months from the start of the study, respectively, and the power at each time point was 46%, 65%, and 76%, respectively (Appendix 1, Table 2). In the simulation results, the Type I error rate for early termination 2 (at 60%, 81 events) was 5.38%, which exceeded 5%; however, this finding could be explained by an insufficient number of simulations, as confirmed by the increasing number of simulations (Appendix 1, Table 3).

Assuming the completion of the study within 3 months under similar conditions (1 month for enrollment and 2 months for the maximum duration of observation for each subject), the number of required subjects was 57388 for a required number of 135 events. The duration from study start to analysis was reduced from 2.0 to 3.0 months for the interim to final analysis

and from 1.8 to 2.6 months for early termination for public health reasons, and the power and other results did not change relative to the aforementioned results (Appendix 1, Table 4). Analysis based on the risk ratio using Poisson regression[11] with robust variance was also performed, but the results did not change (Appendix 1, Table 5).

For the MERS scenario, events were considered deaths, with a 35% mortality rate at 1 month in the placebo group, and other settings were the same as for the novel coronavirus infection scenario. The required number of events was 135, resulting in 534 subjects in the two groups. The time from study start to analysis was shortened from 1.0 to 1.5 months for the interim and final analysis and from 0.9 to 1.3 months for early termination for public health reasons, and the power at each time point did not differ substantially compared to the other conditions (Appendix 1, Table 6).

D. Discussion

1. Factors to be considered and possible trial designs for developing vaccines for emerging infectious diseases

When planning a clinical trial, many factors should be considered, especially those that change over time, such as the amount of information on infectious diseases, changes in infection rates due to infectious disease countermeasures and variants, increases in immunization rates of approved vaccines, and increases in the number of vaccines to be developed. Especially in the early stages of vaccine development, when a large-scale, long-term clinical trial is required, rapid initiation of the clinical trial plan with adequate infrastructure is critical and the possibility of time variability, as described above, should be recognized and considered.

In vaccine development in the early stages of an infectious disease outbreak, interim analysis for early decision-making on vaccine efficacy and adaptive designs for design modification during the course of clinical trials are considered useful for addressing the issues of the spread of the infectious disease and other factors. In addition, an integrated analysis of clinical trials initiated in the early stages of development may be used to evaluate disease-preventive effects. In particular, for these designs, it is important that the details of the analysis methods, modifications, and criteria be planned in advance and specified in the study protocol and statistical analysis plan to avoid an increase in the probability of Type I errors due to multiplicity and avoid bias resulting from design changes based on the results. Even for changes that do not involve unblinding, it is important to consider the possibility of such changes a priori, whenever possible. Although an increase in the number of approved vaccines and vaccines to be developed may affect the efficacy to be confirmed, it is important to select an appropriate design when planning a clinical trial, recognize the impact of these changes on the plan during implementation, and prepare in advance for any necessary actions.

Under circumstances in which multiple

clinical trials are integrated or multiple vaccines are evaluated in a platform study using a master protocol, it is important to establish a clinical trial management system for appropriate implementation. Such a system includes the development of the clinical trial protocol and standardization of data collection, which improves the consistency of clinical trial management. In addition, when conducting a global clinical trial or using foreign data and then applying for regulatory approval in multiple regions, it is necessary to have a framework that considers the planning of the clinical trial and the usage of the results based on the conditions in each region corresponding to the factors to be considered.

Even when early decision-making regarding vaccine efficacy is required, safety evaluations of the vaccine and assessments of the benefit-risk balance are also important. When making decisions early in the course of a clinical trial, careful review of the contents of the safety database at that point in time is necessary to confirm that there is an acceptable benefit-risk balance. Particular attention should be given when efficacy is evaluated based on immunogenicity indicators, where the balance needs to be considered based on the assumed efficacy of the disease-preventive effect.

Furthermore, in the development of vaccines against emerging infectious diseases, consultation with regulatory authorities is important, and the planned modification of the trial design during the trial, need for other anticipated changes, and use of relatively new methods, such as master protocols and statistical methods utilizing the Bayesian approach, should be discussed in detail in such consultations.

2. Performance evaluation by simulation

Under the pandemic coronavirus infection scenario, which had a VE of 50% to 70% and a placebo incidence of 0.50% to 1.50% at 6 months, more than 10,000 subjects were required in most cases. In early vaccine development, the number of subjects may be conservatively estimated because of the small amount of information at the time of study planning. Therefore, a large-scale clinical trial is expected to take a long time until the final results are obtained, and it may be useful to consider how to respond to any changes in circumstances in advance, such as modification of the design and early discontinuation based on efficacy.

In this study, early termination from the viewpoint of public health, which is not planned in advance, was examined based on the assumption that early termination could occur at any stage depending on the spread of infectious diseases, and the efficacy evaluation was based on the results at that point in time. For example, an analysis of 40% of the overall number of events showed a low power of 46%. Although unplanned design changes and termination should be avoided in general, in circumstances when it is necessary to consider these, the uncertainty of the efficacy results at the time should be fully considered. In addition, the infection status at that time as well as safety information and information expected to be available after approval should be considered.

For scenarios using MERS as an example, which is considered to have a high mortality rate, the estimated power was similar to that of the novel coronavirus infection scenario when the proportion of events at the time of early termination was similar. In this scenario, because of the high event rate, the number of subjects of trials required for the efficacy evaluation was relatively small and the expected time to completion of the planned trial was relatively short. However, given the severity of the infection, a more rapid decision may be required. Points on the uncertainty of outcomes as a result of changes in circumstances should be assumed beforehand so that studies and decision-making can be conducted quickly as needed.

In this study, the simulations conducted are based on the experiences of recent cases and do not reflect every possible condition. However, during actual outbreaks of advanced infectious diseases, especially in the early stages of vaccine development, it is necessary to consider various aspects of the clinical trial to be conducted; moreover, the uncertainty of information on infectious diseases available at that time should be considered. Discussions with regulatory agencies on clinical trial design should include the results of simulations under various settings for the planned clinical trial.

E. Conclusion

In this study, the novel coronavirus infection that has affected the entire world and experience and current conditions of vaccine development were considered to examine the possible situations that could be assumed when developing a vaccine against future emerging infectious diseases, evaluate factors that should considered depending on the situation, and assess clinical trial designs that may be useful. In addition, assuming a situation in which an early decision on efficacy is necessary, we conducted a performance evaluation using simulations of possible scenarios for designs that could be employed in such a situation.

In early vaccine development, the amount of information on infectious diseases is limited and the environment surrounding infectious diseases is expected to change significantly over time. It is important to recognize in advance the points to assume and consider when planning a clinical trial for vaccine development, and the possible trial designs should also be considered to facilitate the development of an implementation system for conducting trials when necessary. For situations in which an early decision on efficacy is required to supply vaccines rapidly depending on the status of infectious diseases, it is important to recognize in advance the uncertainties associated with decision-making during the course of a clinical trial to facilitate actual discussions. We believe that discussing and considering such expectations during normal times will facilitate the implementation of necessary actions by both vaccine developers and regulatory authorities when an actual outbreak of infectious disease occurs.

Acknowledgments: The authors acknowledge Junichi Asano, principal reviewer for biostatistics of the Office of New Drug IV, and

Ryosuke Kato, biostatistics reviewer of the Office of New Drug V of the Pharmaceuticals and Medical Devices Agency, for their contributions as research collaborators in this shared research.

F. Research presentation

Not applicable

G. Status of acquisition of intellectual property rights

Not applicable

<References>

1) G7 Summit 2021, 100 Days mission to respond to future pandemic threats. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/992762/100_Days_Mission_to_respond_to_future_pandemic_threats__3_.pdf (Accessed 23, May 2022).
2) Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency, Principles for the evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2. September 2, 2020.
3) Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency, Principles for the evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 3) Evaluation of the Vaccines Based on Immunogenicity. October 22, 2021.
4) Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency. Principles for the evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 2) Ethical Considerations for Subjects in Placebo-Controlled Studies. June 11, 2021.
5) International Council for Harmonization of Technical Requirement for Pharmaceuticals for Human Use, E8(R1) General Considerations for Clinical Studies. October 6, 2021.
6) MHLW, General Principles for Planning and Design of Multi-Regional Clinical Trials. PMSB/ELD Notification No. 612 No. 1, June 12, 2018.
7) MHLW, Ethnic factors in the acceptability of foreign clinical data. PMSB/ELD Notification No. 672, August 11, 1998
8) Pharmaceuticals and Medical Devices Agency, Review report on COMIRNATY intramuscular injection. Feb 8, 2021.
9) World Health Organization, CONSIDERATIONS FOR EVALUATION OF COVID19 VACCINES – Points to consider for manufacturers of COVID 19 vaccines. November 25, 2020.
10) Schoenfeld D, The Asymptotic Properties of Nonparametric Tests for Comparing Survival Distributions. Biometrika, 68, 316-319, 1981.
11) Zou G, A Modified Poisson Regression Approach to Prospective Studies with Binary Data. Am J Epidemiol, 159:702–706, 2004.

[Appendix 1] Details of the simulations performed

For the novel coronavirus infection scenario, we set the study design, primary endpoints, and criteria for efficacy as follows:

- We conducted a placebo-controlled randomized controlled trial comparing a previously established vaccine dose with a placebo.
- The primary endpoint was the time to onset of symptomatic infectious disease based on phase 3 trials of approved novel coronavirus SARS-CoV-2 vaccines.
- Hazard ratios, $HR = \lambda_E/\lambda_P$, were estimated using the Cox proportional hazards model to ascertain whether the lower bound of the 95% CIs of the hazard ratio-based vaccine efficacy ($VE = (1 - HR) \times 100$) was more than 30%.
    - t_E: Time to event for subjects in the vaccine group
    - t_P: Time to event for subjects in the placebo group
    - λ_E: Hazard in the vaccine group $t_E \sim Exponential(\lambda_E)$
    - λ_P: Hazards in the placebo group, $t_P \sim Exponential(\lambda_P)$
    - Null hypotheses $H_0: VE \leq 30\%$
    - Null hypothesis for the hazard ratio $H_0: HR \geq 0.7$
- An interim analysis aimed at the early discontinuation of efficacy is planned. We use the alpha spending function of the O'Brien-Fleming type based on the Lan-DeMets method for the multiplicity adjustment for the interim analyses. In this plan, it is assumed that no sample size re-estimation based on events is planned and the required sample size is conservatively estimated prior to the trial.
- Apart from the planned interim analysis, early termination of the trial for public health reasons that have not been pre-planned is assumed to be implemented. In this case, the trial will always be terminated, regardless of the results. For example, an interim analysis for efficacy is conducted for 50% of the events, the trial continues because the results do not meet the efficacy criteria, and early termination for public health reasons can be performed at 60% of the events.

Simulation conditions were as follows:

- The allocation ratio of the vaccine and placebo groups was 1:1.
- The incidence rate at six months for the placebo group was 1%. The λ_P calculated from the incidence rate in the placebo group was 0.02.
- Assumed the expected VE of 60% then the λ_E was 0.008.
- The enrollment period was set to three months, and the maximum observation period for each subject was set to six months (i.e., the final analysis was conducted at nine months from the start of the study).

- The dropout rate at six months was set to 2%, assuming an exponential distribution for the rate ($\lambda_{Censor} = 0.04$).
- For the enrollment period, a uniform distribution of enrollment was assumed from the start of the study ($Uniform(0,3)$).
- The two-sided significance level was set at 5%. In this case, the required number of events to ensure 90% power for the hypothesis test was 135 and the required number of subjects was 19350 in the two groups (Schoenfeld's method, Table1).
- The interim analysis for efficacy was performed at 50% (68 events) and 75% (102 events) of the total number of events. The two-sided significance levels were 0.0042 for the first interim analysis, 0.0194 for the second interim analysis, and 0.043 for the final analysis.
- The early termination not prespecified due to public health reasons was performed at 40% (at 54 events), 60% (at 81 events), and 80% (at 108 events) of the total number of events. The significance level for early termination consumed all remaining alphas. The two-sided significance levels were 0.05, 0.048, and 0.043 for the 40%, 60%, and 80% time-points, respectively.
- The final analysis was performed for 135 events. To obtain 135 events in the simulation, the maximum observation period for each subject was set at 1 year.
- The number of simulations was set at 10,000.

Simulations were also conducted based on the following conditions under the assumption that the study would be completed within three months, which referenced the 100 Days mission proposed at the Carbis Bay G7 Summit:

- The final analysis was conducted at 3 months from the start of the study, with an enrollment period of 1 month and a maximum observation period of 2 months for each subject.
- The two-sided significance level was set at 5%. In this case, the number of subjects required was 57388 for the vaccine and placebo groups to obtain 135 events to ensure that the hypothesis test achieved 90% power.
- An analysis based on the risk ratio by Poisson regression with robust variance (Zou G, 2004) was also performed. The vaccine was effective if the upper limit of the confidence interval for the risk ratio was lower than 0.7.

Other simulation settings were the same as those used in the previous simulations.

Table 1 shows the number of subjects required to ensure a two-sided significance level of 5% and a power level of 90% for the combination of event rates and the expected value of VE at 6 months in the placebo group.

The simulation results for the interim and final analyses as well as for each early termination are shown in Table 2. These results indicate the Type I error rate, power, point estimate of the hazard ratio (calculated from the case with statistical significance; true value of hazard ratio is 0.4), and duration

from the start of the study until each analysis. Note that the power for each interim analysis was not calculated based on the results of the other interim analyses. In addition, because the Type I error rate at the 60% point of early termination (81 events) was 5.38%, which exceeded the significance level at 4.8%, the number of simulations was increased from 10,000 to 20,000 and 100,000 to investigate the accuracy of the Type I error rate. The results are presented in Table 3. We found that the discrepancy in the values occurred because of an insufficient number of simulations.

Table 4 shows the results of the simulation, which assumed that the study was closed within three months. Table 5 shows the power using the Poisson regression with robust variance and Cox proportional hazards model. We found that the power of the analysis methods was very similar.

For the scenario assuming MERS, which has limited infectiousness but relatively high mortality, although the study design was the same as that for the scenario assuming novel coronavirus infection, the settings differed as follows:

- The primary endpoint was time to death.
- The mortality rate at one month in the placebo group was assumed to be 35%. The λ_P calculated from the mortality rate in the placebo group was 0.43.
- An expected VE of 60% was assumed; thus, λ_E was 0.17.
- The enrollment period was set to one month, and the maximum observation period for each subject was set to one month (i.e., the final analysis was conducted at two months from the start of the study).
- The dropout rate at six months was set to 4%, which assumed an exponential distribution for the rate ($\lambda_{Censor} = 0.04$).
- For the enrollment period, a uniform distribution of enrollment was assumed from the start of the study ($Uniform(0,1)$).
- The two-sided significance level was set at 5%. In this case, the required number of events to ensure 90% power for hypothesis testing was 135 events and 534 subjects in the two groups (Schoenfeld's method).

The simulation results are shown in Table 6, including the Type I error rate, power, point estimate of hazard ratio calculated from the simulation with statistical significance (true value of the hazard ratio is 0.4), and the time period from the start of the study until the analysis.

Table 1. Study design assumptions and required sample size

Incidence rate at 6 months for placebo group	Expected value of VE		
	50%	60%	70%
0.50%	99959	38717	18189
0.75%	66626	25806	12124
1.00%	49959	19350	9091
1.25%	39958	15477	7271
1.50%	33292	12895	6058

Table 2. Simulation results under the new coronavirus infection scenario

Objective of the analysis	Time point Number of events	Type I error rate (Significance level at each time point)	Power	Point estimate of HR[a),b)]	Duration from the start of the study until analysis
Interim Analysis 1	50% time point 68	0.034% (0.420%)	20%	0.26	5 months
Interim Analysis 2	75% time point 102	1.94% (1.94%)	60%	0.35	6 months
Final analysis	100% time point 135	4.30% (4.30%)	84%	0.38	8 months
Early termination 1	40% time point 54	4.80% (5.00%)	46%	0.30	4 months
Early termination 2	60% time point 81	5.38% (4.80%)	65%	0.35	5 months
Early termination 3	80% time point 108	4.30% (4.30%)	76%	0.37	6 months

HR: hazard ratio

a) Point estimate of the hazard ratio calculated from the simulation with statistical significance

b) True value of HR is 0.4.

Table 3. Relationship between the number of simulations and Type I error rate (the bottom row represents the level of significance used at each analysis time point).

Objective of the analysis	Time point Number of events	10000 times	20000 times	100000 times
Interim Analysis 1	50% time point 68	0.03% (0.42%)	0.25% (0.42%)	0.24% (0.42%)
Interim Analysis 2	75% time point 102	1.94% (1.94%)	1.79% (1.94%)	1.62% (1.94%)
Final analysis	100% time point 135	4.30% (4.30%)	4.19% (4.30%)	3.84% (4.30%)
Early termination 1	40% time point 54	4.80% (5.00%)	4.69% (5.00%)	4.35% (5.00%)
Early termination 2	60% time point 81	5.38% (4.80%)	4.91% (4.80%)	4.56% (4.80%)
Early termination 3	80% time point 108	4.30% (4.30%)	3.97% (4.30%)	3.74% (4.30%)

Table 4. Simulation results under the new coronavirus infection scenario, in which the study was completed within 3 months

Objective of the analysis	Time point Number of events	Type I error rate (Significance level at each time point)	Power	Point estimate of HR[a),b)]	Duration from the start of the study until analysis
Interim Analysis 1	50% time point 68	0.22% (0.420%)	19%	0.26	2.0 months
Interim Analysis 2	75% time point 102	1.46% (1.94%)	60%	0.35	2.5 months
Final analysis	100% time point 135	3.94% (4.30%)	85%	0.38	3.0 months
Early termination 1	40% time point 54	4.18% (5.00%)	46%	0.31	1.8 months
Early termination 2	60% time point 81	4.84% (4.80%)	66%	0.35	2.2 months
Early termination 3	80% time point 108	4.24% (4.30%)	76%	0.37	2.6 months

HR: hazard ratio

a) Point estimate of the hazard ratio calculated from the simulation with statistical significance

b) True value of HR is 0.4.

Tabular 5. Power for the Cox proportional hazards and Poisson regression models with robust variance under the new coronavirus infection scenario

Objective of analysis	Timepoint Number of events	Power	
		Cox proportional hazards models	Poisson regression model with robust variance
Interim Analysis 1	50% time point 68	18%	18%
Interim Analysis 2	75% time point 102	60%	60%
Final analysis	100% time point 135	84%	84%
Early termination 1	40% time point 54	46%	46%
Early termination 2	60% time point 81	65%	65%
Early termination 3	80% time point 108	75%	75%

Table 6. Simulated results under the MERS scenario

Objective of the analysis	Time point Number of events	Type I error rate (Significance level at each time point)	Power	Point estimate of HR[a),b)]	Duration from the start of the study until analysis
Interim Analysis 1	50% time point 68	0.2% (0.420%)	19%	0.27	1.0 months
Interim Analysis 2	75% time point 102	1.58% (1.94%)	62%	0.35	1.2 months
Final analysis	100% time point 135	3.76% (4.30%)	86%	0.38	1.5 months
Early termination 1	40% time point 54	3.92% (5.00%)	47%	0.31	0.9 months
Early	60% time point	4.26%	65%	0.35	1.1 months

termination 2	81	(4.80%)			
Early termination 3	80% time point 108	4.08% (4.30%)	77%	0.37	1.3 months

HR: hazard ratio

a) Point estimate of the hazard ratio calculated from the simulation with statistical significance

b) True value of HR is 0.4.