Supplemental Online Content

Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults. *JAMA.* Published online May 26, 2021. doi:10.1001/jama.2021.8565

Supplement 2. Statistical analysis plan

This supplemental material has been provided by the authors to give readers additional information about their work.

To evaluate the protective efficacy, safety and immunogenicity of inactivated SARS-CoV-2 Vaccine (Vero cells) after vaccination in healthy people aged 18 and above.
International Multicenter, Randomized, Double Blind, Placebo Parallel Controlled Phase III Clinical Trial

Sponsor: China National Biotec Group Company Limited

Wuhan Institute of Biological Products Co., Ltd.

Beijing Institute of Biological Products Co., Ltd.

Interim Analysis Statistical Analysis Plan

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Content

1 Description of Abbreviations and Statistics Used

AE	Adverse Event
CI	Confidence Interval
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
IAP	Interim Analysis Plan
Max	Maximum
Mean	Average
Median	Median
MedDRA	International Medical Dictionary for Regulatory Activities)
Min	Minimum value
PPS	Compliance with the Scenario Data Set (Per Protocol Set)
PT	Preferred Term
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event

2 Preface

This document is the Interim Analysis Plan (IAP) for the interim analysis of the International Multicenter, Randomized, Double Blind, Placebo Parallel Control Phase III Clinical Trial to Evaluate the Protection Efficacy, Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccine (Vero Cells) in Healthy Population Aged 18 and above, This paper mainly explains the specific statistical analysis methods used for mid-term analysis and reporting of baseline characteristics of subjects, vaccine efficacy evaluation and safety evaluation. The relevant statistical analysis results of this study may be used for the regulatory submission of this product.

This statistical analysis plan will be finalized and approved before the database is locked, and the corresponding statistical analysis programming work will be gradually improved with the accumulation of research data until the database is locked.

This IAP statistical analysis sample table will be provided separately in the form of attachments.

2.1 Purpose of Analysis

The purpose of this IAP is to evaluate the protective efficacy of an inactivated SAR-CoV-2 vaccine (Vero cell) developed by Wuhan Institute of Biological Products and Beijing Institute of Biological Products on the prevention of COVID-19 in healthy people aged 18 years old and above. The corresponding statistical analysis results will be presented in the final clinical summary report, and will also be used for the regulatory submission, article publication and other clinical needs of this product.

Post hoc exploratory analysis can further mine the study data, but it is not described in this IAP because it cannot be predicted. If it will occur subsequently, the corresponding statistical analysis methods for post hoc exploratory analysis

will be detailed in the final statistical analysis report and clinical summary report.

Additional analysis for other purposes, such as article publication, regulatory authorities or sponsor requirements, is also not described in this IAP due to unpredictability. If it occurs subsequently, the corresponding statistical analysis method for the additional analysis may not be detailed in the final clinical summary report, but will be detailed in the document presenting the additional results.

2.2 Changes in Statistical Analysis compared to protocol

The statistical analysis planned in this IAP is consistent with the protocol.

3 Trial Objective

To evaluate the efficacy, safety and immunogenicity of the inactivated SARS-CoV-2 vaccines (Vero cell) developed by Beijing and Wuhan Institute of Biological Products Co., Ltd against COVID-19 in healthy people aged 18 years old and above.

3.1 Primary Objective

To evaluate the efficacy against COVID-19 of inactivated SARS-CoV-2 Vaccines (Vero Cell) after 2 doses of immunization in healthy subjects aged 18 years old and above.

3.2 Secondary Objectives

✓ To evaluate the safety of inactivated SARS-CoV-2 vaccines in healthy subjects aged 18 years old and above;

✓ To evaluate the immunogenicity of inactivated SARS-CoV-2 vaccines in healthy subjects aged 18 years old and above;

✓ To evaluate the vaccine efficacy against severe COVID-19 and deaths associated with COVID-19 after 14 days following 2-dose immunization.

3.3 Exploratory Objectives

✓ Explore the anti-SARS-CoV-2 neutralizing antibody protective level after 14 days following 2 doses of immunization (immunological surrogate endpoint).

✓ Explore the occurrence of ADE/VED after immunization of inactivated SARS-CoV-2 Vaccine.

4 Study Design

This phase III trial is an international multicenter, randomized, double-blind, placebo-controlled trial involving 45,000 healthy subjects. This study includes the following two periods:

➢ Vaccination period up to 6 weeks.

After signing the informed consent form voluntarily, the overall health status of the subjects will be evaluated. If it is determined that the conditions are met, 2 doses of investigational vaccine or placebo will be injected into the deltoid muscle of the upper arm according to the immunization schedule at 0, 21 days (+7 days).

➢ Safety follow-up period of 12 months after vaccination.

After completing the vaccination and the established safety assessment (until the 10th visit), the safety follow-up period started by regulator teleconsultation of the subjects.

Subjects will be randomly assigned at a ratio of 1: 1: 1 and receive 2 doses of inactivated SARS-CoV-2 WIV04 vaccine, inactivated SARS-CoV-2 HB02 vaccine or placebo respectively, with a maximum interval of 28 days.

Immunization procedure

All immunizations are performed by vaccinating with 2 doses of investigational vaccines or placebo on the deltoid muscle of the upper arm according to the immunization schedule at 0, 21 days (+7 days).

Safety observation

After each dose was vaccinated, the subjects are observed at the site for 30 minutes, and local and systemic adverse events were collected. Within 0-21 days (+7 days), the local and systemic reactions of the subjects were actively followed up and recorded on the vaccination diary card/contact card. Serious adverse events (SAE) need to be monitored within 12 months after vaccination and followed up, recorded and reported as required.

Immunogenicity observation

Subjects will enter the immunogenic subgroup to evaluate the antibody response of the subjects to the inactivated SARS-CoV-2 Vaccine/placebo.

Observation of vaccine efficacy

Monitoring of the cases of SARS-CoV-2 infection will be started after the first dose of inoculation. It's necessary to follow up the subjects on a planned and active basis, and to establish monitoring networks in local health institutions, to enable timely identify the subjects suspected of SARS-CoV-2 infection who developed symptoms and signs of fever, dry cough, fatigue, nasal obstruction or runny nose, sore throat, myalgia or diarrhea caused by unknown reasons, Nasopharyngeal swabs, sputum, other lower respiratory secretions and venous blood were collected, and the nucleic acid of the SARS-CoV-2 Vaccine was detected by nucleic acid PCR method, and the SARS-CoV-2 specific antibody was detected at the same time. The incidence of COVID-19 in two groups of study samples was calculated and the epidemiological protection efficacy and confidence interval of inactivated SARS-CoV-2 Vaccine against COVID-19 was analyzed.

5 Evaluation endpoint

5.1 Endpoint of vaccine efficacy evaluation

5.1.1 Primary Vaccine efficacy Evaluation Endpoint

(1) Vaccine efficacy against COVID-19 after 14 days following 2 doses of vaccination in healthy subjects aged 18 years old and above.

- Calculate the vaccine efficacy based on person-year incidence by using the following formula:

$$\text{Vaccine efficacy} = \left(1 - \frac{\text{person-year incidence of vaccine group}}{\text{person-year incidence of placebo group}}\right) \times 100\%$$

Of which, the person-year incidence rate= (number of confirmed cases /number of person-years exposed) ×100%. The start date for calculating the number of person-years exposed is after 14 days following the 2nd dose of vaccination (15th day after vaccination). For the confirmed COVID-19 cases collected before the database cutoff date, the end date is the first onset date of COVID-19. For dropout subjects without COVID-19 before the data analysis cutoff date, the end date is the data analysis cutoff date or the last follow-up date.

The vaccine efficacy is calculated based on incidence by following formula:

$$\text{Vaccine efficacy} = \left(1 - \frac{\text{incidence of vaccine group}}{\text{incidence of placebo group}}\right) \times 100\%$$

Among which, incidence = (number of cases/number of subjects) × 100%

5.1.2 Endpoint of Secondary Vaccine Efficacy Evaluation

(1) Vaccine efficacy of inactivated SARS-CoV-2 vaccine (Vero cells) against severe cases of COVID-19 after 14 days following 2 doses of vaccination.

(2) Vaccine efficacy of inactivated SARS-CoV-2 vaccine (Vero cells) against death cases of COVID-19 after 14 days following 2 doses of vaccination.

5.1.3 Endpoint of Exploratory Vaccine efficacy Evaluation

(1) The protective efficacy of inactivated SARS-CoV-2 Vaccine (Vero cells) on preventing COVID-19 after 1 dose of vaccination.

(2) The protective efficacy of inactivated SARS-CoV-2 Vaccine (Vero cells) on preventing severe cases of COVID-19 after 1 dose of vaccination.

(3) The protective efficacy of inactivated SARS-CoV-2 Vaccine (Vero cells) on preventing death cases accompanied by COVID-19 after 1 dose of vaccination.

5.2 Safety Endpoint

(1) **Adverse events**: In this study, adverse events within 30 days after inoculation of each dose were collected, including local adverse events at the injection site, systemic adverse events at non-injection site and other adverse events. Among them,

(1.1) **Adverse events at the injection site (local):** including pain, induration, swelling, rash, redness and pruritus.

(1.2) **Adverse events at non-injection site (systemic)**: including fever, diarrhea, constipation, dysphagia, anorexia, vomiting, nausea, muscle pain (non-vaccination sites), arthralgia, headache, cough, dyspnea, pruritus at non-injection sites (no skin damage), skin mucosal abnormalities, acute allergic reactions, fatigue/fatigue.

(1.3) **Other adverse events**: Any adverse events and medical events other than the above occur during clinical trials.

(2) **Serious adverse events**: including all serious adverse events from the first dose of vaccination to the end of the study, especially those occurring within 6 months after the full immunization (from the first dose

of vaccination to 6 months after the full immunization).

6 Analysis Set

6.1 Vaccine efficacy Analysis Set

(1) Full Analysis Set-1 (FAS1, Full Analysis Set-1)

Includes all subjects who follow intent to treat (ITT) principle, undertake randomization, received at least one dose of vaccine, PCR test is negative during screening and have ≥1 follow up for case surveillance.

(2) Full Analysis Set-2 (FAS2, Full Analysis Set-2)

Includes all subjects who follow intent to treat (ITT) principle, undertake randomization, received at least one dose of vaccine, and have ≥1 follow up for case surveillance.

COVID-19 cases included in FAS1 (or FAS2) analysis: all the COVID-19 cases and deaths accompanied by COVID-19 with initial occurrence post first-dose vaccination, included in efficacy assessment in FAS-1 (or FAS-2) analysis and confirmed by etiological and serological evidence.

(3) Modified Full Analysis Set-1 (mFAS1)

Includes all subjects who take two doses of vaccinations, PCR test is negative during screening and have at least 1 follow-up for efficacy after whole course of immunizations.

(4) Modified Full Analysis Set-2 (mFAS2, modified Full Analysis Set-2)

Includes all subjects who take two doses of vaccinations and have at least 1 follow-up for efficacy after whole course of immunizations. mFAS-1 and mFAS-2 are used to complete evaluation of VE after 14 days following 2 doses of vaccinations, the endpoint case is calculated after 14 days following 2nd dose vaccination.

mFAS1 and mFAS2 were used to evaluate the vaccine efficacy of patients who completed the full immunization after 14 days of 2 doses of immunization. Endpoint cases were calculated from 14 days after the second dose of vaccination. Among them, mFAS1 is the main analysis set for vaccine efficacy evaluation, and mFAS2 is sensitivity analysis set for mFAS1.

(5) Vaccine efficacy Per protocol Set Analysis Set-1 (PPS1, Per Protocol Set-1)

As a subset of mFAS1, the subjects in PPS-1 are more compliant to the protocol, including all subjects who meet the inclusion/exclusion criteria, participate in randomization, receive 2 doses of vaccination according to the protocol requirements, PCR test is negative during screening and have ≥1 follow up after 14 days following the 2nd vaccination for case surveillance. Among them, subjects who meet the following conditions should be excluded from PPS-1:

- ✓ those do not meet the inclusion criteria;
- ✓ The subjects received the wrong vaccination or incorrect dose of vaccine;
- ✓ For those whose vaccination time exceeds the window, the investigator, the sponsor and the statistician shall jointly agree on the time exceeding the window before unblinding;
- ✓ any other conditions which potentially affect the evaluation of vaccine efficacy

(6) Vaccine efficacy Per Protocol Set-2 (PPS2, Per Protocol Set-2)

As a subset of mFAS, the subjects in PPS-2 are more compliant to the protocol, including all subjects who meet the inclusion/exclusion criteria, participate in randomization, receive 2 doses of vaccinations according to the protocol requirements, and have ≥1 follow up after 14 days following the 2nd vaccination for case surveillance. Among them, subjects who meet the following conditions should be excluded from PPS-2:

- ✓ those do not meet the inclusion criteria;
- ✓ The subjects received the wrong vaccination or incorrect dosage of vaccine;
- ✓ For those whose vaccination time exceeds the window, the investigator, the sponsor and the statistician shall jointly agree on the time exceeding the window before unblinding;
- ✓ any other conditions which potentially affect the evaluation of vaccine efficacy.

All confirmed COVID-19 cases and deaths accompanied by COVID-19 with the first occurrence 14 days after 2 doses of inoculation, and included in efficacy assessment in PPS-1 (or PPS-2) dataset and confirmed by etiological and serological evidence.

6.2 Safety Analysis Set

(1) Safety Set (SS)

Includes all subjects who receive at least one dose of vaccine. Among which, subjects with wrong vaccination will be conducted safety analysis according to the actual treatment group as per All Subjects as Treated (ASaT) principle.

The safety analysis set defines the total safety analysis set, the first dose safety analysis set and the second dose safety analysis set respectively. Among them, the total safety analysis set includes all subjects vaccinated with at least one dose of vaccine, which is used for analysis of all adverse events and is recorded as SS; The safety analysis set of the first dose includes the subjects who have completed the first dose of vaccine, and is used for the analysis of adverse events after the first dose of vaccine, which is recorded as SS1; The safety analysis set of the second dose includes the subjects who have completed the second dose of vaccine, and is used for the analysis of adverse events after the second dose of vaccine, which is recorded as SS2.

The above analysis data set will be discussed and decided before the database is locked by the principal investigator, the sponsor, the statistician and the data manager at the data blinded review meeting.

7 Statistical Analysis Method

7.1 General considerations

7.1.1 General analysis method

➢ **Descriptive statistics**

Unless otherwise specified, the following descriptive statistical summaries will be given by variable type:

- ✓ Continuous variables are summarized by means, standard deviation, median, minimum and

maximum.

✓ Classified or ordered variables will be summarized by frequency and percentage. 95% confidence intervals would be estimated by Clopper-Pearson method.

➢ **Decimal Places**

Unless otherwise specified, the number of decimal points in the analysis report shall be implemented according to the following rules:

✓ The minimum, maximum, median, 25% and 75% quantiles are consistent with the maximum digits of the original data.

✓ The number of decimal points in mean, geometric mean, standard deviation and 95% confidence interval is one more than the maximum number of digits in the original data.

✓ The percentage is kept to 2 decimal places;

✓ The coefficient of variation and geometric coefficient of variation shall be kept to 2 decimal places.

✓ If the P value is ≥ 0.0001, it will be kept to 4 decimal places. If the P value is < 0.0001, it is reported as < 0.0001.

✓ The test statistics of all statistical tests shall be kept to 3 decimal places.

✓ Derivative data shall be kept to 2 decimal places.

7.1.2 Relevant Definitions and Derivative Rules

➢ **Baseline**

Unless otherwise specified, the "baseline" in this study is defined as the last non-empty test value before the first vaccination.

➢ **Year, Month and Day Conversion**

Month = Days/30.4375, Year = Days/365.25, rounded to one decimal place.

➢ **Adverse Events**

Adverse Event Occurrence Time (Days) = Adverse Event Occurrence Date-Inoculation Date of Adverse Event Occurrence Date. Duration (days) = Adverse Event End Date-Adverse Event Start Date + 1.

➢ **Treatment-Emergent Adverse Event (TEAE)**

TEAE is defined as an adverse event that occurs after the first vaccination (including the day of the first vaccination) or is aggravated after the first vaccination. Programming is carried out according to the following rules: if the occurrence time of the adverse event is after the time of the first vaccination (including the same time), it is calculated as TEAE; If the occurrence time of adverse events is before the time of the first vaccination, it is counted as non-TEAE. If the absence of the occurrence time of adverse events or the time of the first vaccination makes it impossible to clearly judge whether the adverse events occurred after the first vaccination, the adverse events shall be counted as TEAE.

Adverse events with severity level 0 are not included in the analysis. Adverse events with missing severity and correlation are treated as missing, and are not included in the analysis when the corresponding severity and correlation analysis are carried out.

7.1.3 Analysis Window

For visits after the baseline, statistical scores will be made according to the visit time points in the protocol when analyzing by visit.

Analysis, unplanned time points will not be considered. The results of unplanned inspections will be listed in the list.

7.1.4 Analysis software

All statistical analyses will be performed using the statistical software SAS 9.4 or above.

7.1.5 Tables and Lists

➢ **Table**

Data are generally aggregated by group (WIV04 group, HB02 group and placebo group). Groups will generally be displayed in columns.

➢ **List**

Unless otherwise specified, all lists will include group and subject numbers, and will give priority to the original data in EDC. The list is generally sorted by group, subject number, visit time or other relevant time (such as AE occurrence time).

7.2 Subject Distribution

Summarize the number of subjects who failed to screen, randomly enrolled and completed each dose of inoculation in each site, summarize the number of subjects who failed to screen, randomly enrolled in each group and completed each dose of inoculation according to the total number of centers, and the number of subjects who completed each dose of inoculation in each group, as well as the number of subjects in each analysis set.

The list of subjects who failed in screening, the list of subjects who did not complete all vaccinations and the list of subjects who did not enter each analysis set were listed respectively.

7.3 Demographic data and baseline characteristics

The following demographic data, baseline characteristics and other indicators are statistically described:

✓ Demographic data (including age, gender and nationality);

✓ Clinical features (including height, weight, body temperature before vaccination, skin, throat, nutritional development, systolic and diastolic blood pressure);

According to the total and each dose, the use cases, number of cases and utilization rate of all kinds of combined drugs in each group were calculated respectively, and the method was adopted.

Fisher's exact probability test was used to statistically compare the differences between groups. Make a list of combined medication.

7.4 Vaccine efficacy evaluation

7.4.1 Hypothesis test

The Primary hypothesis of this study: In the healthy population aged 18 years and above, lower boundary of 95% confidence interval (CI) of vaccine efficacy (VE) after 14 days following two doses of vaccination is greater than 30% in vaccine groups compared with placebo.

Null hypothesis H_0: VE ≤ 30%,

Alternative hypothesis H_1: VE > 30%.

The total type I error in this study is α= 0.05 (two-sided). When the lower boundary of two-sided 95% confidence interval of vaccine efficacy (VE) is > 30%, the study is considered successful.

7.4.2 Primary Vaccine efficacy Evaluation Endpoint

The efficacy of the inactivated SARS-CoV-2 Vaccine (Vero cells) against COVID-19 in healthy people aged 18 and above 14 days after 2 doses of immunization

The person-year incidence and 95% confidence interval of confirmed COVID-19 14 days after 2 doses of vaccine were calculated respectively in the trial vaccine-1 group, the trial vaccine-2 group and the placebo group. Poisson regression model was used to statistically compare the differences between groups. According to the model, the vaccine efficacy and its confidence interval based on person-year incidence of trial vaccine-1 group and placebo group, trial vaccine-2 group and placebo group were estimated. The model takes the number of patients as the dependent variable, groups as the fixed effect, the number of years of exposure as the offset, and uses the log link function. If the person-year incidence of the vaccine group or placebo group is close to zero, the exact method is used to calculate the 95% confidence interval of vaccine efficacy based on person-year incidence. The calculation method of protection rate based on person-year incidence is the primary analysis method of vaccine protection efficacy. mFAS1 is the primary analysis set for interim analysis.

In addition, the following methods will be used to carry out sensitivity analysis on the primary vaccine efficacy.

(1) Sensitivity analysis 1 (protection rate analysis based on incidence rate): Calculate the confirmed incidence rate and Clopper-Person 95% confidence interval of infection with COVID-19 in investigational vaccine-1 group, investigational vaccine-2 group and placebo group 14 days after vaccination with 2 doses of vaccine respectively, and statistically test the difference between the groups by CMH-χ2 test; According to the protection rate = 1－(vaccine group incidence rate/control group incidence rate), the vaccine efficacy and 95% confidence interval in the investigational vaccine-1 group and the placebo group, the investigational vaccine-2 group and the placebo group were calculated.

7.4.3 Endpoint of Secondary Vaccine efficacy Evaluation

In the healthy population aged 18 and above, the following secondary vaccine efficacy evaluation endpoints were statistically analyzed respectively:

(l) The efficacy of the inactivated SARS-CoV-2 vaccine (Vero cell) against severe cases of COVID-19 after 14 days following 2 doses of immunization.

(2) The efficacy of the inactivated SARS-CoV-2 vaccine (Vero cell) against deaths accompanied by COVID-19 after 14 days following 2 doses of immunization.

The statistical analysis method of all secondary vaccine efficacy endpoints is the same as that of primary vaccine efficacy evaluation endpoints.

7.4.4 Endpoint of Exploratory Vaccine efficacy Evaluation

In the healthy population aged 18 and above, the following secondary vaccine efficacy evaluation endpoints were statistically analyzed respectively:

(1) After inoculating one dose of vaccine, the vaccine efficacy of the inactivated SARS-CoV-2 Vaccine (Vero cell) against the COVID-19.

(2) After inoculating one dose of vaccine, the vaccine efficacy of the inactivated SARS-CoV-2 Vaccine (Vero cell) against severe cases of COVID-19.

(3) After inoculating one dose of vaccine, the efficacy of the inactivated SARS-CoV-2 vaccine (Vero cell) against death cases accompanied by COVID-19.

The statistical analysis of all exploratory vaccine efficacy endpoints is based on FAS, and the method is the same as that of the primary vaccine efficacy evaluation endpoints.

7.5 Safety evaluation

7.5.1 Adverse Events

Adverse events and serious adverse events were coded by MedDRA and classified according to system organs (System of Class, SOC) and Preferred Term (PT). In addition, the collected adverse events (including vaccination site (local) and non-vaccination site (systemic) adverse events) will be classified and counted according to the plan. In this experiment, the adverse events (TEAE) occurred after inoculation were statistically analyzed, and the adverse events occurred before inoculation were listed in the form of a list. Unless otherwise specified, the following adverse events are TEAE.

The times, cases and incidence of the following adverse events in each group were calculated respectively:

✓ All adverse events,

✓ Adverse events related to investigational vaccine, adverse events unrelated to investigational vaccine,

✓ Adverse events with an incidence of ≥ 1% in any group and adverse events related to investigational vaccines with an incidence of ≥ 1% in any group.

✓ Any group of adverse events with an incidence rate of ≥ 10%, any group of adverse events related to vaccine research with an incidence rate of ≥ 10%

Fisher's exact probability method was used to statistically compare the differences between groups in the incidence of the above adverse events. Descriptive statistics are carried out on the severity, dosage and time of adverse events respectively, and descriptive statistics are carried out on the severity and time of adverse events after each dose of inoculation respectively.

The severity composition ratios of adverse events and adverse events related to investigational vaccines in

each group were calculated respectively, and the differences between groups were statistically tested by rank sum test.

List the adverse events related to the investigational vaccine and the adverse events unrelated to the investigational vaccine.

The times, cases and incidence of all serious adverse events, serious adverse events related to the investigational vaccine and serious adverse events unrelated to the investigational vaccine in each group were calculated respectively, and the differences between groups were statistically compared by Fisher exact probability method. Serious adverse events were listed.

7.6 Subgroup analysis

Subgroup analysis is not planned for this interim analysis, and will be evaluated later when necessary.

7.7 Interim analysis

Two interim analyses are planned in this trial when 1/3 and 2/3 of expected COVID-19 cases are observed. Early stopping for efficacy is considered in the interim analysis. Lan DeMets O'Brien-Fleming spending function is employed to control the family-wise type I error within 5% of two-sided. When the number of COVID-19 cases in any one vaccine (vaccine-1 or vaccine-2) and placebo groups achieves 50, the first interim analysis will be performed and the corresponding nominal significance level is $\alpha\_1=0.0001$ (one-sided). When 100 COVID-19 cases in any one vaccine (vaccine-1 or vaccine-2) and placebo groups are observed, the second interim analysis will be conducted and the corresponding nominal significance level is $\alpha\_2=0.0060$ (one-sided). If the null hypothesis is not rejected in the two interim analyses, the nominal significance level of final analysis is $\alpha\_3=0.0231$ (one-sided). In the practical clinical trial, the nominal significance level will be calculated based on the number of COVID-19 cases observed at the interim analysis from pre-specified Lan DeMets O'Brien-Fleming spending function.

Brien-Fleming consumption function determines the nominal test level of interim analysis.

In order to ensure the implementation of blind method, the following measures will be taken in this experiment: ① Set up a controlled firewall team to process serological data that may cause accidental blind breaking. (2) Establishing an Independent Data Monitoring Committee Monitoring Committee (IDMC). During the interim analysis, IDMC was responsible for completing blindness, primary efficacy endpoints and safety assessment, while the sponsors, researchers and biostatisticians of this trial remained blind.

7.8 Multiplicity problem

Two interim analyses are planned in this trial when 1/3 and 2/3 of expected COVID-19 cases are observed. Early stopping for efficacy is considered in the interim analysis. Lan DeMets O'Brien-Fleming spending function is employed to control the family-wise type I error within 5% of two-sided. See the interim analysis section for details.

In the safety evaluation results, the calculated P value is only the nominal P value, which is mainly used to describe the strength of the correlation between the evaluation endpoint and the processing packet, and is not used as the basis for formal statistical inference.

7.9 Processing of Missing Data

After 14 days of 2 doses of vaccination in healthy people aged 18 and above, In the evaluation of the protective efficacy of the inactivated SARS-CoV-2 Vaccine (Vero cell) against the COVID-19, The actual exposure time of the subject is taken as the denominator, and the incidence observed during the exposure time is taken as the numerator to calculate the incidence and vaccine protection rate. If the subject has not undergone a certain follow-up, the follow-up will evaluate the vaccine efficacy based on not-a-case.

This study does not process missing data in the safety endpoint.

Version History

Version	Version Date	Written by	Update
V1.0	2020-10-09	Zhao Guoqing	Original