Clinical Study Protocol

NCT Number: NCT05299359

Title: A Phase 3, Single Arm, Open-Label Trial to Evaluate the Immunogenicity and Safety of a Single Heterologous Booster Vaccination of TAK-019 in Healthy Japanese Male and Female Adults Aged 20 Years and Older

Study Number: TAK-019-3001

Document Version and Date: Amendment 1 / 29-Jul-2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

(English for reference purpose)

<Title>

A Phase 3, Single Arm, Open-Label Trial to Evaluate the Immunogenicity and Safety of a Single Heterologous Booster Vaccination of TAK-019 in Healthy Japanese Male and Female Adults Aged 20 Years and Older

<Short Title>

A Phase 3 Single Heterologous Booster Vaccination Study of TAK-019 in Healthy Japanese Adults

Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka Japan
Trial Identifier:	TAK-019-3001
IND Number:	022430 **EudraCT Number:** 2020-004042-11
Investigational Medicinal Product (s):	TAK-019
Takeda Approval Date:	29 July 2022
Version:	Version 2.0 (amendment 1)

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the annexes.

1.2 Principles of Clinical Studies

This trial will be conducted with the highest respect for the individual subjects in accordance with the requirements of this clinical trial protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki [1].
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (R2) Good Clinical Practice: Consolidated Guideline [2].
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.

1.3 Protocol Version Summary of Changes

This section describes the changes in the protocol version 2.0.

The primary purpose of this amendment is to update the protocol to include the **Extension Part**. Minor grammatical and editorial changes are included for clarification purposes only. Summary of the changes is given in Section 1.3.2.

1.3.1 Version History

Date	Version	Change Type	Region
21 February 2022 (English for reference purpose: 02 March 2022)	1.0	Not applicable	All trial sites in Japan
29 July 2022 (English for reference purpose: 29 July 2022)	2.0 (amendment 1)	Substantial	All trial sites in Japan

1.3.2 Summary of Changes

Section	Description of Change	Rationale for Change
Cover page	Added “English for reference purpose”.	To clarify the protocol in English has been prepared for reference purpose.
2.0, 2.1, 5.1.1, 5.1.2, 5.1.3, 5.2.1, 5.2.2, 5.2.3, 6.1, 6.2, 6.3, 7.1, and 7.2.	Added the **Extension Part** and set existing part as the **Main Part**.	To add study part for the second booster vaccination.
2.1, 9.1.2, 9.1.7, 9.1.12, 9.3, 9.3.1, and 9.3.4.	Added description to confirm concomitant therapies.	To clarify procedures.
3.0	Added and deleted abbreviations.	To correspond to modification of other sections.
4.1, 4.1.2, 4.1.2.1, 4.1.2.2, 4.1.3, 4.1.4, 4.2, 6.2, and 16.0.	Added justification of the **Extension Part**.	To justify the addition of the **Extension Part**.

Section	Description of Change	Rationale for Change
7.0, 7.3, 7.4, 7.5, 8.1.3, 8.2, 8.2.1, 9.1.1, 9.1.2, 9.1.3, 9.1.4, 9.1.5, 9.1.6, 9.1.7, 9.1.12, 9.1.13, 9.1.14, 9.1.15, 9.1.16, 9.2, 9.3, 9.3.1, 9.3.2, 9.3.3, 9.3.4, 9.3.5, 9.3.6, 9.3.7, 9.3.8, 9.3.9, 9.3.10, 10.1.3, 10.1.4, 10.3, 10.4.1.1, 10.4.2, 10.4.3, and 10.4.4.	Modified procedures according to the addition of the **Extension Part**.	To correspond to the addition of the **Extension Part**.
8.1, 8.1.1.1, and 8.1.1.2.	Added description of the commercial product.	Due to the market approval in Japan.
13.1, 13.1.1, 13.1.3, 13.1.4, 13.2, and 13.3.	Added statistical method for the **Extension Part**.	To correspond to the addition of the **Extension Part**.

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2.0 TRIAL SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited		**Product Name:** TAK-019
Trial Title: A phase 3, single arm, open-label trial to evaluate the immunogenicity and safety of a single heterologous booster vaccination of TAK-019 in healthy Japanese male and female adults aged 20 years and older		
IND No.: 022430		**EudraCT No.:** 2020-004042-11
Trial Identifier: TAK-019-3001	**Phase:** 3	**Blinding Schema:** Open-label
Indication: Prevention of infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).		

Trial Design:

Main Part

This is a phase 3, single arm, open-label trial to evaluate the immunogenicity and safety of a single heterologous booster vaccination of TAK-019 by intramuscular (IM) injection in healthy Japanese male and female adults who completed 2 doses primary vaccinations with Comirnaty Intramuscular Injection from 6 to 12 months before the trial vaccination.

The trial is planned to enroll 150 subjects (all in the TAK-019 arm). They will be stratified by age; 100 subjects as ≥20 years to <65 years, and 50 subjects as ≥65 years of age.

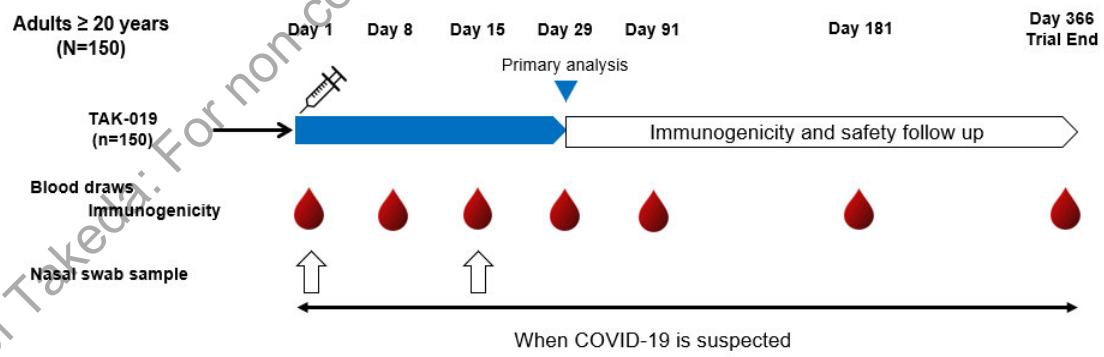
Once all screening assessments following informed consent are completed and eligibility is confirmed, the subject will receive a single booster vaccination of TAK-019, by IM injection. All subjects will be followed up for immunogenicity and safety for 12 months after the trial vaccination.

Each subject will be provided with an electronic diary (eDiary). Oral body temperature and solicited local and systemic adverse events (AEs) will be recorded in the eDiary by the subjects for 7 days after booster vaccination (including the day of vaccination). All subjects will be followed for unsolicited AEs for 28 days following booster vaccination (day of vaccination + 27 subsequent days).

All subjects will be followed for serious AEs (SAEs), AEs of special interest (AESIs), medically-attended AEs (MAAEs), and AEs leading to trial withdrawal during their entire participation in the trial. All subjects will also be tested for SARS-CoV-2 infection at prespecified visits (Day 1 and Day 15) or, in case of clinical symptoms suspected for coronavirus disease 2019 (COVID-19) throughout the trial.

The primary analysis will be performed for immunogenicity and safety after all subjects have completed the Day 29 visit.

Schematic of Phase 3 Trial Design (Main Part)



Abbreviations: COVID-19: coronavirus disease 2019; N/n: number of subjects.

Extension Part

Extension Part is designed to offer a second single booster vaccination of TAK-019 to participants who received the first single booster vaccination of TAK-019 in the **Main Part** and remained in study follow-up at least 5 months. The end of the **Main Part** is defined as the earlier of the completion of the final visit on Day 366 or the

initiation of the **Extension Part**. Therefore, data of the **Main Part** will consist data of all subjects in the **Main Part**, data of the **Extension Part** will consist only data of subjects after the initiation of the **Extension Part**. The end of **Extension Part** is defined as the completion of the final visit on **Extension Part** Day 366. All analyses will be performed descriptively in the **Extension Part**.

All subjects who are willing to proceed to the **Extension Part** and to receive a second booster vaccination of TAK-019 will be asked to schedule a Participant Decision Visit about 5 months after the first single booster vaccination.

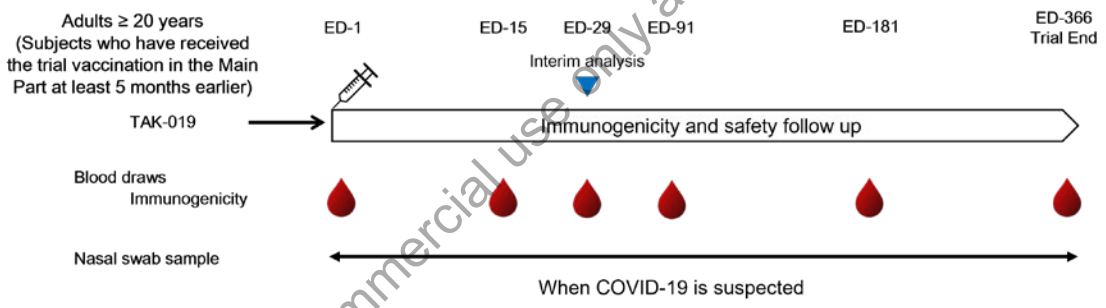
All subjects who provide additional informed consent for the **Extension Part** at the Participant Decision Visit and are eligible for enrollment in the **Extension Part** will receive a second single booster vaccination of TAK-019, by IM injection (**Extension Part** Day 1). All subjects in the **Extension Part** will be followed up for immunogenicity and safety for 12 months after the **Extension Part** Day 1.

Each subject will be provided an eDiary. Oral body temperature and solicited local and systemic AEs will be recorded in the eDiary by the subjects for 7 days after the second booster vaccination (including the **Extension Part** Day 1). All subjects will be followed-up for unsolicited AEs for 28 days following the second booster vaccination (**Extension Part** Day 1 + 27 subsequent days).

All subjects will be followed-up for SAEs, AESIs, MAAEs, and AEs leading to trial withdrawal in the **Extension Part**. All subjects will also be tested for SARS-CoV-2 infection in case of clinical symptoms suspected for COVID-19 in the **Extension Part**.

An interim analysis will be performed for immunogenicity and safety after all subjects have completed the **Extension Part** Day 29 visit.

Schematic of Trial Design (Extension Part)



Abbreviations: COVID-19: coronavirus disease 2019; ED: Extension Part Day.

Primary Objectives:

Main Part

To evaluate the immunogenicity and safety of a single heterologous booster vaccination of TAK-019 by IM injection in healthy Japanese male and female adults aged ≥20 years.

Immunogenicity:

To assess the immunogenicity of TAK-019 in terms of:

- Non-inferiority of geometric mean titers (GMTs) of neutralizing antibody titers to wild-type virus 14 days after a single booster vaccination (Day 15) compared with that observed 14 days after the second vaccination (Day 36) in Study TAK-019-1501.

Safety:

To assess the safety of TAK-019 in terms of:

- Solicited local and systemic AEs for 7 days following booster vaccination (day of vaccination + 6 subsequent days).
- Unsolicited AEs for 28 days following booster vaccination (day of vaccination + 27 subsequent days).
- SAEs, AESIs, MAAEs, AEs leading to trial withdrawal, and SARS-CoV-2 infection until Day 29.

Secondary Objectives:

Main Part

Immunogenicity:

To assess the immunogenicity of TAK-019 in terms of:

- Serum immunoglobulin G (IgG) antibody levels to SARS-CoV-2 recombinant spike (rS) protein.
- Serum neutralizing antibody titers to the ancestral strain (wild-type virus).

Safety:

To assess the safety of TAK-019 in terms of:

- SAEs, AESIs, MAAEs, AEs leading to trial withdrawal, and SARS-CoV-2 infection throughout the trial.

Extension Part

To evaluate the immunogenicity and safety of a second single booster vaccination of TAK-019 by IM injection in healthy Japanese male and female adults aged ≥20 years.

Immunogenicity:

To assess the immunogenicity of TAK-019 in terms of:

- Serum IgG antibody levels to SARS-CoV-2 rS protein.
- Serum neutralizing antibody titers to the ancestral strain (wild-type virus).

Safety:

To assess the safety of TAK-019 in terms of:

- Solicited local and systemic AEs for 7 days following the second single booster vaccination (day of vaccination + 6 subsequent days).
- Unsolicited AEs for 28 days following the second single booster vaccination (day of vaccination + 27 subsequent days).
- SAEs, AESIs, MAAEs, AEs leading to trial withdrawal, and SARS-CoV-2 infection until **Extension Part** Day 29.
- SAEs, AESIs, MAAEs, AEs leading to trial withdrawal, and SARS-CoV-2 infection throughout the trial.

[redacted]

Subject Population:

Main Part

Healthy Subjects: Yes.

Age Range: ≥20 years (Two age strata: ≥20 years to <65 years and ≥65 years).

Planned Number of Subjects: 150 subjects stratified by age as ≥20 years to <65 years (100 subjects), and ≥65 years (50 subjects).

Planned Number of Trial Arms: 1 arm

- Arm 1: (n=150 subjects), Investigational product (TAK-019).

Planned Number of Trial Sites: 2 sites

Extension Part

Subjects who received a first single booster vaccination of TAK-019 in the **Main Part** at least 5 months earlier.

Key Inclusion Criteria:

Main Part

- Healthy Japanese male and female adult subjects aged ≥20 years of age at the time of signing of informed consent.
- Subjects who understand and are willing to comply with the trial procedures and are available for the duration of follow‐up.
- Subjects who completed 2 doses primary vaccinations with Comirnaty Intramuscular Injection 6 to 12 months prior to the trial vaccination (with showing their vaccination certificate issued by Japanese municipality).
- A male subject or a female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use acceptable contraceptive methods from 28 days prior to the first single booster vaccination until 3 months after the first single booster vaccination.

Extension Part

- Subjects who received the first trial vaccination at least 5 months earlier and are currently enrolled in the **Main Part** (ie, not have withdrawn or discontinued early).
- Subjects who signed an additional informed consent form for the **Extension Part**, understand and are willing to comply with trial procedures and are available for the duration of follow-up.
- A male subject or a female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use acceptable contraceptive methods from 28 days prior to the second single booster vaccination until 3 months after the second single booster vaccination.

Key Exclusion Criteria:

Main Part

- Subjects who received any other SARS-CoV-2 vaccine (except for Comirnaty Intramuscular Injection) or other experimental novel coronavirus vaccine prior to the trial.
- Subjects who received a booster vaccination (ie, 3rd dose) with Comirnaty Intramuscular Injection or Spikevax Intramuscular Injection (previously COVID-19 Vaccine Moderna Intramuscular Injection).
- Subjects who have close contact of anyone known to have COVID-19 within 14 days prior to the first trial vaccination.
- Subjects who were tested positive for SARS-CoV-2 prior to the trial.
- Subjects who have traveled outside of Japan in the 30 days prior to the trial participation.
- Subjects with a clinically significant active infection (as assessed by the Investigator) or oral temperature ≥38°C within 3 days of the intended date of the first single booster vaccination.
- Subjects with known hypersensitivity or allergy to any of the investigational vaccine components and/or Comirnaty Intramuscular Injection.
- Subjects with history or any illness that, in the opinion of the Investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial.
- Subjects with known or suspected impairment/alteration of immune function, including history of any autoimmune disease or neuro-inflammatory disease.
- Abnormalities of splenic or thymic function.
- Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
- Subjects with any serious chronic or progressive disease (eg, neoplasm, insulin dependent diabetes, cardiac, renal or hepatic disease).
- Subjects with body mass index (BMI) greater than or equal to 30 kg/m^2 (BMI= weight in kg/ height in $meters^2$).
- Subjects participating in any clinical trial with another investigational product within 30 days prior to the

first trial vaccination or intend to participate in another clinical trial at any time during the conduct of this trial.

- Subjects who received or plan to receive any other licensed vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to the first trial dose administration.
- Subjects with acute or chronic clinically significant disease including pulmonary, cardiovascular, hepatic or renal abnormality evaluated by physical examination.
- Subjects involved in the trial conduct or their first-degree relatives.
- Subjects who have history or infection of hepatitis B, hepatitis C, and HIV.
- Female subjects who are pregnant or breastfeeding.

Extension Part

- Subjects with a clinically significant active infection (as assessed by the Investigator) or oral temperature ≥38°C within 3 days of the intended date of the second single booster vaccination.
- Subjects with known hypersensitivity or allergy to any of the investigational vaccine components and/or Comirnaty Intramuscular Injection.
- Subjects with history or any illness that, in the opinion of the Investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial.
- Subjects with known or suspected impairment/alteration of immune function, including history of any autoimmune disease or neuro-inflammatory disease.
- Abnormalities of splenic or thymic function.
- Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
- Subjects with any serious chronic or progressive disease (eg, neoplasm, insulin dependent diabetes, cardiac, renal or hepatic disease).
- Subjects participating in any clinical trial with another investigational product within 30 days prior to the second single booter vaccination or intend to participate in another clinical trial at any time during the conduct of this trial.
- Subjects who received or plan to receive any other licensed vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to the second single booter dose administration.
- Subjects with acute or chronic clinically significant disease including pulmonary, cardiovascular, hepatic or renal abnormality evaluated by physical examination.
- Subjects who have history or infection of hepatitis B, hepatitis C, and HIV.
- Subjects with a history of myocarditis or pericarditis.
- Female subjects who are pregnant or breastfeeding.

Trial Vaccine and Placebo:

Trial Vaccine

Investigational vaccine: TAK-019 for injection as a 0.5 mL volume will be used. The investigational vaccine contains 5 µg of SARS-CoV-2 rS plus 0.05 mg of Matrix-M adjuvant.

Route of Administration: IM injection in the mid deltoid, preferable in the non-dominant upper arm.

Placebo

Placebo is not used in this trial.

Duration of the Trial and Subject Participation:

Subjects Participating Only in the Main Part

The trial participation for each subject is for 12 months following the first single booster vaccination.

Subjects Entering the Extension Part

The trial participation for each subject is for at least 17 months in total (at least 5 months following the first single

booster vaccination in the **Main Part** and 12 months following the second single booster vaccination in the **Extension Part**).

Criteria for Evaluation and Analyses:

Primary Endpoints:

Main Part

Immunogenicity:

- GMT ratio of neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 15 after a single booster vaccination (14 days after the booster vaccination) compared with that observed on Day 36 (14 days after the second vaccination) in subjects from Study TAK-019-1501.

Safety:

- Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following the first single booster vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with solicited systemic AEs: fever, fatigue, malaise, myalgia, arthralgia, nausea/vomiting, and headache for 7 days following the first single booster vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with unsolicited AEs for 28 days following the first single booster vaccination (day of vaccination + 27 subsequent days).
- Percentage of subjects with SAEs until Day 29.
- Percentage of subjects with AESIs until Day 29.
- Percentage of subjects with MAAEs until Day 29.
- Percentage of subjects with any AEs leading to subject's withdrawal from the trial until Day 29.
- Percentage of subjects with SARS-CoV-2 infection until Day 29.

Secondary Endpoints:

Main Part

Immunogenicity:

- GMT, geometric mean fold rise (GMFR), and seroconversion rate (SCR; defined at proportion of subjects with ≥4-fold rises from baseline [Day 1]) of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 8, Day 15, Day 29, Day 91, Day 181, and Day 366.
- GMT, GMFR, and SCR of serum neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 8, Day 15, Day 29, Day 91, Day 181, and Day 366.

Safety:

- Percentage of subjects with SAEs throughout the trial.
- Percentage of subjects with AESIs throughout the trial.
- Percentage of subjects with MAAEs throughout the trial.
- Percentage of subjects with any AEs leading to subject's withdrawal from the trial from the day of the first single booster vaccination throughout the trial.
- Percentage of subjects with SARS-CoV-2 infection throughout the trial.

Extension Part

Immunogenicity:

- GMT, GMFR, and SCR (defined at proportion of subjects with ≥4-fold rises from baseline [**Extension Part** Day 1]) of serum IgG antibody levels to SARS-CoV-2 rS protein on **Extension Part** Day 15, Day 29, Day 91, Day 181, and Day 366.
- GMT, GMFR, and SCR of serum neutralizing antibody titers to the ancestral strain (wild-type virus) on **Extension Part** Day 15, Day 29, Day 91, Day 181, and Day 366.

Safety:

- Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following the second single booster vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with solicited systemic AEs: fever, fatigue, malaise, myalgia, arthralgia, nausea/vomiting, and headache for 7 days following the second single booster vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with unsolicited AEs for 28 days following the second single booster vaccination (day of vaccination + 27 subsequent days).
- Percentage of subjects with SAEs until **Extension Part** Day 29.
- Percentage of subjects with AESIs until **Extension Part** Day 29.
- Percentage of subjects with MAAEs until **Extension Part** Day 29.
- Percentage of subjects with any AEs leading to subject's withdrawal from the trial until **Extension Part** Day 29.
- Percentage of subjects with SARS-CoV-2 infection until **Extension Part** Day 29.
- Percentage of subjects with SAEs throughout the trial.
- Percentage of subjects with AESIs throughout the trial.
- Percentage of subjects with MAAEs throughout the trial.
- Percentage of subjects with any AEs leading to subject's withdrawal from the trial from the day of the second single booster vaccination throughout the trial.
- Percentage of subjects with SARS-CoV-2 infection throughout the trial.

[redacted]

Statistical Considerations:

Main Part

The primary analysis will be performed for immunogenicity and safety after all subjects have completed the Day 29 visit.

Immunogenicity Analysis:

For immunogenicity endpoints, analyses will be conducted using the Per-protocol Set (PPS).

For neutralizing antibody titer values to the ancestral strain (wild-type virus), summary statistics, GMT, and the two-sided 95% CIs will be calculated.

For GMT ratio of serum neutralizing antibody titers to the ancestral strain (wild-type virus) between booster vaccination group in the proposed study and the 2 doses primary vaccinations group in Study TAK-019-1501 (called study group), point estimate and the two-sided 95% CIs will be provided using a 2-way analysis of variance (ANOVA) model. The 2-way ANOVA model will include log-transformed (common log) serum

neutralizing antibody titers to the ancestral strain (wild-type virus) 14 days after vaccination as dependent variable, and categorized age (20<= - <65, 65<=) and study group as independent variable. Each estimate by the model will be back transformed to the original scale. The lower limit of two-sided 95% CI of the GMT ratio will be compared with non-inferiority margin of 0.67 to assess the non-inferiority of neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 15 after a single booster vaccination compared with that observed on Day 36 (14 days after 2nd vaccination) in subjects from Study TAK-019-1501. If the lower limit of the 95% CI will be ≥0.67, the immune response to a single heterologous booster vaccination of TAK-019 will be considered to be non-inferior of that to the primary series of TAK-019.

SCR of each immunogenicity endpoint at each time point will be calculated along with its 95% CI. For antibody titer values and GMFR from baseline, summary statistics, GMT, and the two-sided 95% CIs of each endpoint at each time point will be calculated.

Safety analysis:

For safety endpoints, analyses will be performed using the Safety Analysis Set (SAS).

Solicited local and systemic AEs will be summarized for each day post the first single vaccination and the total duration (day of vaccination + 6 subsequent days).

Unsolicited AEs for 28 days following the first single booster vaccination will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and tabulated by the System Organ Class (SOC) and the Preferred Term (PT).

The percentage of subjects with SARS-CoV-2 infection will be summarized.

For continuous variables of vital signs, the observed values and the changes from baseline will be summarized for each scheduled time point using descriptive statistics. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled time point will be provided.

Extension Part

Immunogenicity Analysis:

For immunogenicity endpoints, analyses will be conducted using the PPS in **Extension Part**.

SCR of each immunogenicity endpoint at each time point will be calculated along with its 95% CI. For antibody titer values, summary statistics, GMT and GMFR from baseline, and 95% CIs of each endpoint at each time point will be calculated.

Safety analysis:

For safety endpoints, analyses will be performed using the SAS in **Extension Part**.

Solicited local and systemic AEs will be summarized for each day post the second single booster vaccination and the total duration (day of vaccination + 6 subsequent days).

Unsolicited AEs for 28 days following the second single booster vaccination will be coded using the MedDRA dictionary and tabulated by the SOC and the PT.

The percentage of subjects with SARS-CoV-2 infection will be summarized.

For continuous variables of vital signs, the observed values and the changes from baseline (**Extension Part** Day 1) will be summarized for each scheduled time point using descriptive statistics. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled time point will be provided.

Sample Size Justification:

Main Part

In Study TAK-019-1501, GMT and geometric SD of serum neutralizing antibody titers to wild-type virus after the primary vaccinations on Day 36 (14 days after the 2nd vaccination) were 884.4 and 2.80 respectively in the vaccine group.

There is no immunogenicity data of serum neutralizing antibody titers to the ancestral strain (wild-type virus) after a booster vaccination of TAK-019 in Japanese subjects available. However, an estimate has been made on the results of the primary vaccination in Study TAK-019-1501 and the homoeologous booster vaccination in Study 2019nCoV-101 (Part 2). The assumption was made that neutralizing antibody titers on Day 15 in the proposed study would be equivalent to titers on Day 36 in Study TAK-019-1501 (ie, assuming GMT ratio to be 1 and geometric SD to be 2.80). With the guidance document, Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1) Evaluation of Vaccines Against Variants, issued by the Pharmaceuticals and Medical Devices Agency of Japan, in mind, the non-inferiority margin of GMT ratio between booster vaccination group in the proposed study and the primary vaccination group in Study TAK-019-1501 is set as 0.67 fold. This results in 132 subjects be required as the number of evaluable subjects in PPS to ensure 90% power with the lower limit of 2-sided 95% CI of the GMT ratio exceeding the non-inferiority margin. Considering around 10% non-evaluable subjects, 150 subjects will be required into the proposed study.

Extension Part

The number of subjects in this part is not based on statistical power considerations as this is an **Extension Part** of Study TAK-019-3001 following the **Main Part**.

Interim Analysis:

No interim analysis is planned for the **Main Part**.

An interim analysis of immunogenicity and safety is planned for the **Extension Part** after all subjects have completed **Extension Part** Day 29 (immunogenicity data through **Extension Part** Day 15 and safety data through **Extension Part** Day 29).

Data Monitoring Committee:

No independent data monitoring committee will be used for this trial.

2.1 Schedule of Trial Procedures

MAIN PART

Procedure	Day 1 [a]		Day 8	Day 15	Day 29	Day 91	Day 181	Day 366 or Early Termination / Trial End [b]
	Before Vaccination	After Vaccination						
Visits number	1		2	3	4	5	6	7
Days Post Dose	0		7	14	28	90	180	365
Visit window (Days)	-		+3	+3	+3	+7	±7	±14
Signed informed consent [c]	X							
Assessment of eligibility criteria [d]	X							
Demographics	X [e]							
Medical history [f]	X							
Medication history [f]	X							
Physical examination [g]	X		X	X		X		X
Vital signs	X	X [h]	X	X		X		X
Pregnancy test [i]	X				X	X		
Oral body temperature [j]	X	X [h]	X	X		X		X
Vaccine administration		X						
Dispensing eDiary		X						
Assessment of eDiary			X					
Solicited AEs [k]		X	X					
Unsolicited AEs [l]		X	X	X	X			
Concomitant medications [m]	X		X	X	X			
SAEs [n]		X	X	X	X	X	X	X
AEs leading to withdrawal from trial		X	X	X	X	X	X	X
AESIs and MAAEs		X	X	X	X	X	X	X
Blood draw for immunogenicity tests	X		X	X	X	X	X	X
Nasal swab sample collection [o]	X			X				
[redacted]			X					

Abbreviations: AE: adverse event; AESI: adverse event of special interest; BMI: body mass index; COVID-19: coronavirus disease 2019; eDiary: electronic diary; MAAE: medically-attended adverse event; PCR: polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2.

[a] The day before booster vaccination is designated as "Day -1", and the day of booster vaccination (visit number 1) is designated as "Day 1".

[b] For the subjects who withdraw from the trial, efforts should be made to retain the subjects in the safety observation period, whenever possible. Blood sample for immunogenicity data will not be collected at the early termination visit. The observation items of Early Termination / Trial End should be carried out as much as possible.

[c] To be obtained from the subject prior to initiation of any trial procedure. Signed informed consent obtained between Day -28 to Day 1 is valid.

[d] Assessment of eligibility by review of all inclusion and exclusion criteria or contraindications will be documented before the booster vaccination on Day 1.

[e] The data within 14 days before Day 1 (Day -14 to Day 1) can be used for the trial.

[f] Medical and medication history will be collected at the time of informed consent.

[g] Height and weight will be measured on Day 1 before vaccination only and BMI will be calculated. On the day of vaccinations ie, Day 1 the Investigator will monitor for any findings such as acute hypersensitivity reactions for 30 minutes after each vaccination. Review of systems will be performed as explained in Section 9.1.4.

[h] On the day of vaccination, oral body temperature, blood pressure (systolic and diastolic, resting more than 5 minutes), pulse rate, and respiratory rate should be measured before the vaccination as well as 30 minutes after the vaccination.

[i] Urine pregnancy test will be performed only in women of childbearing potential.

[j] For 7 days after booster vaccination (including the day of the vaccination) oral body temperature will be measured and recorded in the eDiary every day by the subjects.

[k] Solicited local and systemic AEs will be collected for 7 days after booster vaccination (day of vaccination + 6 subsequent days).

[l] Unsolicited AEs will be collected for 28 days following booster vaccination (day of vaccination + 27 subsequent days).

[m] All concomitant medications (including concomitant therapies) information will be collected for 28 days following booster vaccination until Day 29. Follow up for concomitant medications (including concomitant therapies) associated with SAEs, AEs leading to withdrawal from trial, and treatments for COVID-19 will be performed 365 days following booster vaccination.

[n] SAEs must be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event.

[o] Nasal swabs will be collected at prespecified time points (Day 1 and Day 15). In case of suspected for COVID-19 clinical symptoms, samples for COVID-19 diagnostic test will be collected throughout the trial. If subjects show a sign of SARS-CoV-2 infection during the trial (from Day 1 to Day 366), a sample will be collected from the subject by medically qualified staff within 72 hours or as soon as possible, at an ad hoc visit or home visit. If a sample for the trial is unavailable, COVID-19 diagnostic test results including PCR test performed at a local public health or hospital will be accepted.

EXTENSION PART

Procedure	ED-1 [a] Participant Decision Visit		ED-15	ED-29	ED-91	ED-181	ED-366 or Early Termination / Trial End [b]
	Before Vaccination	After Vaccination					
Visits number	1		2	3	4	5	6
Days Post Dose	0		14	28	90	180	365
Visit window (Days)	-		+3	+3	+7	±7	±14
Signed informed consent [c]	X						
Assessment of eligibility criteria [d]	X						
Physical examination [e]	X		X		X		X
Vital signs	X	X [f]	X		X		X
Pregnancy test [g]	X			X	X		
Oral body temperature [h]	X	X [h]	X		X		X
Vaccine administration		X					
Dispensing eDiary		X					
Assessment of eDiary			X				
Solicited AEs [i]		X	X				
Unsolicited AEs [j]		X	X	X			
Concomitant medications [k]	X		X	X			
SAEs [l]		X	X	X	X	X	X
AEs leading to withdrawal from trial		X	X	X	X	X	X
AESIs and MAAEs		X	X	X	X	X	X
Blood draw for immunogenicity tests	X		X	X	X	X	X
Nasal swab sample collection [m]	(Collected throughout the **Extension Part** for suspected COVID-19 cases)						
[redacted]			X				

Abbreviations: AE: adverse event; AESI: adverse event of special interest; COVID-19: coronavirus disease 2019; ED: Extension Part Day; eDiary: electronic diary; IMP: investigational medicinal product; MAAE: medically-attended adverse event; PCR: polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2.

[a] The day before the booster vaccination in the **Extension Part** is designated as "**Extension Part** Day -1", and the day of booster vaccination (visit number 1) in the **Extension Part** is designated as "**Extension Part** Day 1".

[b] For the subjects who withdraw from the trial, efforts should be made to retain the subjects in the safety observation period, whenever possible. Blood sample for immunogenicity data will not be collected at the early termination visit. The observation items of Early Termination/Trial End should be carried out as much as possible.

[c] To be obtained from the subject prior to initiation of any trial procedure in the **Extension Part**. Signed informed consent obtained between **Extension Part** Day -28 to **Extension Part** Day 1 is valid.

[d] Assessment of eligibility by review of all inclusion and exclusion criteria or contraindications, including prior medications of the 2nd booster vaccination, will be documented before the booster vaccination at **Extension Part** Day 1.

[e] On the day of vaccination (ie, **Extension Part** Day 1), the Investigator will monitor for any findings such as acute hypersensitivity reactions for 30 minutes after vaccination. Review of systems will be performed as explained in

[f] On the day of vaccination, body temperature, blood pressure (systolic and diastolic, resting more than 5 minutes), pulse rate, and respiratory rate should be measured before the vaccination as well as 30 minutes after the vaccination.

[g] Urine pregnancy test will be performed only in women of childbearing potential.

[h] For 7 days after booster vaccination (including the day of the vaccination), oral body temperature will be measured and recorded in the eDiary every day by the subjects.

[i] Solicited local and systemic AEs will be collected for 7 days after the booster vaccination in the **Extension Part** (day of vaccination in the **Extension Part** + 6 subsequent days).

[j] Unsolicited AEs will be collected for 28 days following the booster vaccination in the **Extension Part** (day of vaccination in the **Extension Part** + 27 subsequent days).

[k] All concomitant medications (including concomitant therapies) information will be collected for 28 days following the booster vaccination in the **Extension Part** until **Extension Part** Day 29. Follow up for concomitant medications (including concomitant therapies) associated with SAEs, AEs leading to withdrawal from trial, and treatments for COVID-19 will be performed 365 days following the booster vaccination in the **Extension Part**.

[l] SAEs must be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event.

[m] Nasal swabs will be collected in case of suspected for COVID-19 clinical symptoms throughout the trial. If subjects show a sign of SARS-CoV-2 infection during the trial (from **Extension Part** Day 1 to **Extension Part** Day 366), a nasal swab sample will be collected from the subject by medically qualified staff within 72 hours or as soon as possible, at an ad hoc visit or home visit. If a nasal swab sample for the trial is unavailable, PCR test results performed at a local public health or hospital will be accepted.

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
BMI	body mass index
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EUA	emergency use authorization
FAS	Full Analysis Set
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	geometric mean fold rise
GMT	geometric mean titer
GP	glycoprotein
GPSP	Good Post-Marketing Study Practice
GVP	Good Vigilance Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IM	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
ISF	Investigator Site File
jRCT	Japan Registry of Clinical Trials
MAAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MHLW	Ministry of Health, Labour, and Welfare
mRNA	messenger RNA
NDA	new drug application
OTC	over-the-counter
PCR	polymerase chain reaction
PIMMC	Potential Immune Mediated Medical Conditions
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per-protocol Set

PT	Preferred Term
PTE	pretreatment event
QTL	quality tolerance limit
rS	recombinant spike
S	spike
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SAS	Safety Analysis Set
SCR	seroconversion rate
Sf9	*Spodoptera frugiperda*
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
VE	vaccine efficacy
VOC	variant of concern
VOI	variant of interest
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Coronaviruses are a large family of viruses that cause illness for human ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).

Coronaviruses are enveloped, positive-stranded RNA viruses, with a characteristic crown-like appearance in electron micrographs due to circumferential studding of the viral envelope with projections comprising the spike (S) protein. There are 4 different strains (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) which are ubiquitous in humans and generally result in mild upper respiratory illnesses and other common cold symptoms including malaise, headache, nasal discharge, sore throat, fever, and cough [3].

In December 2019, a respiratory disease caused by novel coronavirus (2019-nCoV) was confirmed in Wuhan Hubei Province, China [4]. The 'virus' discerned genetic relationship with the 2002-2003 severe acute respiratory syndrome coronavirus (SARS-CoV) and resulted in adoption of name "SARS-CoV-2" (severe acute respiratory syndrome coronavirus-2) with the disease being referred as coronavirus disease 2019/"COVID-19" [5].

On 11 March 2020, the World Health Organization (WHO) officially declared COVID-19 a pandemic [6]. As of 5 June 2022, the WHO reported over 520 million confirmed cases and over 6 million deaths globally [7]. In Japan, as of 12 June 2022, the Ministry of Health, Labour, and Welfare (MHLW) reported over 9 million confirmed cases with a positive polymerase chain reaction (PCR) test result for COVID-19, with over 30,000 deaths in Japan [8]. The MHLW has reported that the highest risk of disease burden is in older adults (≥65 years old) and people who have serious underlying medical conditions, such as chronic obstructive pulmonary disease, chronic renal disease, diabetes, hypertension, cardiovascular disease, and obesity (body mass index [BMI] of 30 kg/m^2 or higher) [9].

Multiple vaccines for SARS-CoV-2 are currently under development including inactivated vaccines, recombinant protein vaccines, messenger RNA (mRNA) vaccines, DNA vaccines, and viral vector vaccines. When this study was planned, as of 18 January 2022, Comirnaty Intramuscular Injection and Spikevax Intramuscular Injection (mRNA vaccines), and Vaxzevria Intramuscular Injection (a viral vector vaccine) were available in Japan [10]. Thereafter, Nuvaxovid Intramuscular Injection (discussed below for Nuvaxovid) has become also available, and Jcovden Intramuscular Injection (a viral vector vaccine) has been approved in Japan by June 2022.

Novavax, Inc. is developing Nuvaxovid (development code: NVX-CoV2373) as a novel vaccine option for SARS-CoV-2. Nuvaxovid is a SARS-CoV-2 recombinant spike (rS) protein nanoparticle vaccine (SARS-CoV-2 rS), constructed from the full-length wild-type SARS-CoV-2 S glycoprotein (GP) based on nucleotides 21563 to 25384 of GenBank gene sequence MN908947, derived from 2019 SARS-CoV-2 genome. The S protein is a Type 1 trimeric GP of 1,273 amino

acids that is produced as an inactive S0 precursor. To produce the SARS-CoV-2 rS vaccine candidate, the S-gene was codon optimized for expression in *Spodoptera frugiperda* (Sf9) insect cells. Nuvaxovid also contains saponin-based adjuvant, Matrix-M, which has previously shown to enhance the immunogenicity of other nanoparticle vaccines in nonclinical and clinical studies. In Japan, Nuvaxovid is developed by Takeda Pharmaceutical Company Limited (development code: TAK-019).

Nuvaxovid was firstly approved for emergency use authorization (EUA) in Indonesia in November 2021. By 1 May 2022, Nuvaxovid have obtained approval, conditional approval, or EUA in more than 40 countries. In Japan, before this study was initiated, new drug application (NDA) was submitted on 16 December 2021. And after this study was initiated, on 19 April 2022, Nuvaxovid was approved in Japan for adults over 18 years of age. Approved regimen in Japan is the following: "*Primary immunization: Administer 2 doses of 0.5 mL each typically 3 weeks apart intramuscularly. Booster immunization: Administer 0.5 mL per dose intramuscularly.*" Also, intervals were defined as the following: "*Primary immunization: If more than 3 weeks have passed since the first dose, administer the second dose as soon as possible. Booster immunization: The third dose of this product can typically be given at least 6 months after the second dose.*"

4.1.1 Nonclinical Studies

As nonclinical pharmacological evaluations, immunogenicity evaluation using animal models of mice, hamsters, cynomolgus macaques, and baboons, and protective efficacy evaluation using mice, hamsters, cynomolgus macaques, and rhesus macaques were conducted. These nonclinical studies showed that NVX-CoV2373 has highly immunogenic to induce neutralizing antibody production at safe and tolerated doses, and induce reduction in lung inflammation and viral replication with one or two doses. In addition, NVX-CoV2373 also appeared to induce strong Th1 type CD4+ T-cell responses to SARS-CoV-2 S protein without exacerbation of the inflammatory response due to viral attack.

A Good Laboratory Practice (GLP)-compliant toxicity study in rabbit was performed to evaluate 50 µg of the SARS-CoV-2 rS with and without 50 µg Matrix-M adjuvant by intramuscular (IM) injection. SARS-CoV-2 rS with or without 50 µg Matrix-M adjuvant was well tolerated and had no effects on mortality, cageside observations, body weight, food consumption, or physical examination findings. Serum chemical markers of acute reaction (including fibrinogen and C-reactive protein) were transient and recovered. In autopsy and pathology examination, there was no vaccine-related change, aside from subacute local injection site reactions.

A GLP-compliant reproductive toxicity study was performed in rat. The administration of SARS-CoV-2 rS with Matrix-M adjuvant or Matrix-M adjuvant alone had no effect on fertility, pregnancy and lactation, growth and development of the embryos/fetuses, and development of pups through post-natal 21 days. And given that GLP in vitro genotoxicity studies with Ames test and mammalian cell micronucleus assay in Chinese hamster ovary cells showed that Matrix-M adjuvant was non-mutagenic in these assays.

4.1.2 Clinical Studies

Following overseas and Japan clinical studies evaluating NVX-CoV2373/TAK-019 in adult subjects are ongoing or completed, with accumulating safety data from approximately 30,000 subjects exposed to NVX-CoV2373/TAK-019. Refer to the latest investigator's brochure (IB) of NVX-CoV2373/TAK-019 and the latest package insert of Nuvaxovid for further details.

4.1.2.1 Primary Vaccination

Efficacy, immunogenicity, and safety of NVX-CoV2373/TAK-019 as 2-dose primary series are evaluated in the following clinical studies:

- **Study 2019nCoV-101 (oversea phase 1/2 study, conducted in Australia and the United States):** in this first-in-human study in healthy adults (18 to 59 years of age), 2-dose regimens of 5 µg and 25 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant generated robust immune responses (anti-S protein immunoglobulin G [IgG] and neutralizing antibody) including a relative skew toward CD4+ T-cell responses of the Th1 phenotype, supporting the dose sparing effect of Matrix-M adjuvant. In the phase 2 part of this study, the 2-dose regimen of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant was better tolerated than the 2-dose regimen of 25 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant with generally comparable immune responses between the 2 antigen doses, and thus the lower dose was selected for use in later stage efficacy studies (later became the approved dosage as primary series in Japan and oversea countries).
- **Study 2019nCoV-301 (oversea phase 3 study, conducted in the United States and Mexico when multiple variant of concern [VOC]/variant of interest [VOI] were predominant):** in this study, primary series of NVX-CoV2373 at the later approved dosage was evaluated in 29,582 healthy or medically stable adult subjects (18 years of age or order). Overall vaccine efficacy (VE) against symptomatic COVID-19 and VE against severe cases of COVID-19 were 90.40% (95% CI: 82.88, 94.62) and 100%, respectively. NVX-CoV2373 was well-tolerated and showed acceptable safety profile.
- **Study 2019nCoV-302 (oversea phase 3 study, conducted in the United Kingdom when alpha variant was predominant):** in this study, primary series of NVX-CoV2373 at the later approved dosage was evaluated in 15,139 healthy or medically stable adult subjects (18 years of age or order). Overall VE against symptomatic COVID-19 and VE against severe cases of COVID-19 were 89.7% (95% CI: 80.2, 94.6) and 100%, respectively. NVX-CoV2373 was well-tolerated and showed acceptable safety profile.
- **Study 2019nCoV-501 (oversea phase 2a/b study, conducted in South Africa when beta variant was predominant):** in this study, primary series of NVX-CoV2373 at the later approved dosage was evaluated in 4,164 HIV-negative subjects (18 to 84 years of age) and 244 HIV-positive subjects (18 to 64 years of age). Overall VE against symptomatic COVID-19 were 48.6% (95% CI: 28.4, 63.1) in the whole study population and 55.4% (95% CI: 35.9, 68.9) in the HIV-negative subgroup. VE against severe cases of COVID-19 was

100% in the HIV-negative subgroup. NVX-CoV2373 was well-tolerated and showed acceptable safety profile.

- **Study TAK-019-1501 (phase 1/2 study, conducted in Japan):** in this study, primary series of TAK-019 at the later approved dosage was evaluated in 200 healthy adult subjects (20 years of age or order). TAK-019 was well tolerated, and safety and immunogenicity profile of TAK-019 were generally comparable to those shown in the oversea studies.

4.1.2.2 Booster Vaccination

Immunogenicity and safety of NVX-CoV2373/TAK-019 as booster vaccination are evaluated in the following clinical studies:

- **Study 2019nCoV-101 (oversea phase 1/2 study, homologous booster, third and fourth shot):** in this study, safety and immunogenicity of NVX-CoV2373 as the third shot at approximately 6 months after the primary series (Day 189) at the same dosage (later became the approved dosage for the booster shot in Japan and oversea countries) were evaluated in the subjects enrolled in the Part 2 and received primary series at the later approved dosage. Prior to administration of the third shot at Day 189, geometric mean titers (GMTs) of anti-S protein IgG and neutralizing antibody to ancestral SARS-CoV-2 were markedly lower than those titers at 2 weeks after the second shot (Day 35). However, GMT of anti-S protein IgG and neutralizing antibody showed robust increase at 4 weeks after the third shot (Day 217) and substantially outweighed those of Day 35. Non-inferiority of Day 217 immunogenic response compared to Day 35 was demonstrated, and the safety profile of the third shot was acceptable. In addition, safety and immunogenicity of NVX-CoV2373 as the fourth shot at approximately 12 months after the primary series (Day 357) at the same dosage are being evaluated in the subjects who received the third shot.
- **Study 2019nCoV-301 (oversea phase 3 study, homologous booster, third shot):** in this study, safety and immunogenicity of NVX-CoV2373 as the third shot at 8 months after the second shot of primary series at the approved dosage are being evaluated.
- **Study 2019nCoV-501 (oversea phase 2a/b study, homologous booster, third shot):** in this study, Blinded Crossover part that administer the third shot of NVX-CoV2373 and one placebo shot to the original NVX-CoV2373 arm and two NVX-CoV2373 shots (primary series) to the original placebo arm was commenced at 6 months after the second shot of the primary series, and safety and immunogenicity of NVX-CoV2373 as the third shot at the approved dosage were evaluated in this part. Immune response after the third shot overweighed those induced by the primary series. Also, the third shot was well-tolerated and showed acceptable safety profile.
- **Study COV-BOOST (oversea phase 2 study, heterologous booster, third shot):** as a part of this study designed to evaluate multiple combinations of heterologous booster shot using multiple SARS-CoV-2 vaccines, NVX-CoV2373 as the third shot at the approved dosage was evaluated in 115 adult subjects who received 2 primary shots of Vaxzevria at least 70 days

before and 114 adult subjects who received 2 primary shots of Comirnaty at least 84 days before. Compared to the meningococcal conjugate vaccine arm (control vaccine arm), NVX-CoV2373 as the third shot at the approved dosage induced meaningful response of anti-S protein IgG and neutralizing antibody. Also, the third shot was well-tolerated and showed acceptable safety profile [11].

- **Study 2019nCoV-311 (oversea phase 3 study, heterologous booster, third and fourth shot):** in this study, safety and immunogenicity of 2 booster shots of NVX-CoV2373 (ancestral-type SARS-CoV-2 rS 5 µg + Matrix-M adjuvant 50 µg), BA.1 vaccine (BA.1 SARS-CoV-2 rS 5 µg + Matrix-M adjuvant 50 µg), and a bivalent vaccine of these 2 vaccines are being evaluated in adult subjects who received 2 shots of mRNA vaccine at least 180 days before and adult subjects who received 3 shots of mRNA vaccine at least 90 days before (NCT05372588).

4.1.3 Post-Marketing Data

Based on the post-marketing surveillance, more than 740,000 doses have been administered among Australia, Canada, the European Union, New Zealand, and South Korea by 30 April 2022. Based on the cumulative safety data, the benefit-risk balance of Nuvaxovid remains positive.

4.1.4 Benefit-Risk Assessment

Refer to the latest IB of NVX-CoV2373/TAK-019 and the latest package insert of Nuvaxovid for overall benefit-risk profile of NVX-CoV2373/TAK-019.

4.2 Rationale for the Proposed Trial

While SARS-CoV-2 vaccination is being promoted worldwide, the respread of SARS-CoV-2 infection has been observed in many parts of the world since the summer of 2021. As factors of respread of the infection, the mainstream of the epidemic has become variants with high infectious and transmissible power, and some cases of breakthrough infection have been observed in previously fully vaccinated people [12], raising concerns that the preventive effect of the SARS-CoV-2 vaccine may weaken over time. In light of these circumstances, booster vaccination for people after primary vaccinations with the SARS-CoV-2 vaccine has been implemented as a public health measure to control the respreading of the infection in each country or region. In Japan as of 31 January 2022, about 80% of the population has completed their 2 doses primary vaccinations; those were mostly by mRNA vaccines, and Comirnaty Intramuscular Injection was predominantly used [13].

The primary objective of this trial is to evaluate immunogenicity and safety of a single heterologous booster vaccination (third dose) of TAK-019 by IM injection in the **Main Part** in Japanese healthy adults who completed 2 doses primary vaccinations with Comirnaty Intramuscular Injection 6 to 12 months prior to the trial booster vaccination. As of February 2022, 2 overseas clinical trials evaluating NVX-CoV2373 as booster are ongoing (phase 2 part of Study

2019nCoV-101 and Study COV-BOOST) with no new safety concern observed, which supports initiation of this trial in Japan.

In addition, there is rising importance of evaluating the safety and immunogenicity of TAK-019 as the fourth-dose booster shot based on that Japan government is currently recommending the fourth-dose booster of mRNA vaccines to high-risk populations (ie, elderlies and those who have high-risk underlying diseases) as of June 2022 [14]. Therefore, protocol amendment 1.0 (version 2.0) added an **Extension Part** to evaluate the safety and immunogenicity of TAK-019 as the fourth-dose booster shot in subjects who have completed the third-dose booster shot of TAK-019 in the **Main Part** at least 5 months earlier. This amendment is also supported by robust immunogenicity response and acceptable safety profile shown in preceding overseas clinical trials evaluating NVX-CoV2373 as booster shots.

The trial will be conducted in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki [1], International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) Guidelines E6 (R2) [2], and applicable regulatory requirements.

If TAK-019 will be approved in Japan prior to completion of the trial, the trial will be continued as a post-marketing clinical trial in accordance with the applicable regulations such as Good Vigilance Practice (GVP) and Good Post-Marketing Study Practice (GPSP).

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

MAIN PART

The primary objective is to evaluate the immunogenicity and safety of a single heterologous booster vaccination of TAK-019 by IM injection in healthy Japanese male and female adults aged ≥20 years.

Immunogenicity:

To assess the immunogenicity of TAK-019 in terms of:

- Non-inferiority of GMTs of neutralizing antibody titers to wild-type virus 14 days after a single booster vaccination (Day 15) compared with that observed 14 days after the second vaccination (Day 36) in Study TAK-019-1501.

Safety:

To assess the safety of TAK-019 in terms of:

- Solicited local and systemic adverse events (AEs) for 7 days following booster vaccination (day of vaccination + 6 subsequent days).
- Unsolicited AEs for 28 days following booster vaccination (day of vaccination + 27 subsequent days).
- Serious AEs (SAEs), AEs of special interest (AESIs), medically-attended AEs (MAAEs), AEs leading to trial withdrawal, and SARS-CoV-2 infection until Day 29.

EXTENSION PART

Not applicable.

5.1.2 Secondary Objectives

MAIN PART

Immunogenicity:

To assess the immunogenicity of TAK-019 in terms of:

- Serum IgG antibody levels to SARS-CoV-2 rS protein.
- Serum neutralizing antibody titers to the ancestral strain (wild-type virus).

Safety:

To assess the safety of TAK-019 in terms of:

- SAEs, AESIs, MAAEs, AEs leading to trial withdrawal, and SARS-CoV-2 infection throughout the trial.

EXTENSION PART

To evaluate the immunogenicity and safety of a second single booster vaccination of TAK-019 by IM injection in healthy Japanese male and female adults aged ≥20 years.

Immunogenicity:

To assess the immunogenicity of TAK-019 in terms of:

- Serum IgG antibody levels to SARS-CoV-2 rS protein.
- Serum neutralizing antibody titers to the ancestral strain (wild-type virus).

Safety:

To assess the safety of TAK-019 in terms of:

- Solicited local and systemic AEs for 7 days following the second single booster vaccination (day of vaccination + 6 subsequent days).
- Unsolicited AEs for 28 days following the second single booster vaccination (day of vaccination + 27 subsequent days).
- SAEs, AESIs, MAAEs, AEs leading to trial withdrawal, and SARS-CoV-2 infection until **Extension Part** Day 29.
- SAEs, AESIs, MAAEs, AEs leading to trial withdrawal, and SARS-CoV-2 infection throughout the trial.

5.1.3 [redacted]

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

MAIN PART

Immunogenicity:

- GMT ratio of neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 15 after a single booster vaccination (14 days after the booster vaccination) compared with that observed on Day 36 (14 days after the second vaccination) in subjects from Study TAK-019-1501.

Safety:

- Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following the first single booster vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with solicited systemic AEs: fever, fatigue, malaise, myalgia, arthralgia, nausea/vomiting, and headache for 7 days following the first single booster vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with unsolicited AEs for 28 days following the first single booster vaccination (day of vaccination + 27 subsequent days).
- Percentage of subjects with SAEs until Day 29.
- Percentage of subjects with AESIs until Day 29.
- Percentage of subjects with MAAEs until Day 29.
- Percentage of subjects with any AEs leading to subject's withdrawal from the trial until Day 29.
- Percentage of subjects with SARS-CoV-2 infection until Day 29.

EXTENSION PART

Not applicable.

5.2.2 Secondary Endpoints

MAIN PART

Immunogenicity:

- GMT, geometric mean fold rise (GMFR), and seroconversion rate (SCR; defined at proportion of subjects with ≥4-fold rises from baseline [Day 1]) of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 8, Day 15, Day 29, Day 91, Day 181, and Day 366.
- GMT, GMFR, and SCR of serum neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 8, Day 15, Day 29, Day 91, Day 181, and Day 366.

Safety:

- Percentage of subjects with SAEs throughout the trial.
- Percentage of subjects with AESIs throughout the trial.
- Percentage of subjects with MAAEs throughout the trial.
- Percentage of subjects with any AEs leading to subject's withdrawal from the trial from the day of the first single booster vaccination throughout the trial.
- Percentage of subjects with SARS-CoV-2 infection throughout the trial.

EXTENSION PART

Immunogenicity:

- GMT, GMFR, and SCR (defined at proportion of subjects with ≥4-fold rises from baseline [**Extension Part** Day 1]) of serum IgG antibody levels to SARS-CoV-2 rS protein on **Extension Part** Day 15, Day 29, Day 91, Day 181, and Day 366.
- GMT, GMFR, and SCR of serum neutralizing antibody titers to the ancestral strain (wild-type virus) on **Extension Part** Day 15, Day 29, Day 91, Day 181, and Day 366.

Safety:

- Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following the second single booster vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with solicited systemic AEs: fever, fatigue, malaise, myalgia, arthralgia, nausea/vomiting, and headache for 7 days following the second single booster vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with unsolicited AEs for 28 days following the second single booster vaccination (day of vaccination + 27 subsequent days).

- Percentage of subjects with SAEs until **Extension Part** Day 29.
- Percentage of subjects with AESIs until **Extension Part** Day 29.
- Percentage of subjects with MAAEs until **Extension Part** Day 29.
- Percentage of subjects with any AEs leading to subject's withdrawal from the trial until **Extension Part** Day 29.
- Percentage of subjects with SARS-CoV-2 infection until **Extension Part** Day 29.
- Percentage of subjects with SAEs throughout the trial.
- Percentage of subjects with AESIs throughout the trial.
- Percentage of subjects with MAAEs throughout the trial.
- Percentage of subjects with any AEs leading to subject's withdrawal from the trial from the day of the second single booster vaccination throughout the trial.
- Percentage of subjects with SARS-CoV-2 infection throughout the trial.

[redacted]

MAIN PART

- Percentage of subjects who not to perform normal daily activities on the level of leaving school/work due to solicited AEs for 7 days following the first single booster vaccination (day of vaccination + 6 subsequent days).

EXTENSION PART

- Percentage of subjects who not to perform normal daily activities on the level of leaving school/work due to solicited AEs for 7 days following the second single booster vaccination (day of vaccination + 6 subsequent days).

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

MAIN PART

This is a phase 3, single arm, open-label trial to evaluate the immunogenicity and safety of a single heterologous booster vaccination of TAK-019 by IM injection in healthy Japanese male and female adults who completed 2 doses primary vaccinations with Comirnaty Intramuscular Injection from 6 to 12 months before the trial vaccination.

The trial is planned to enroll 150 subjects (all in the TAK-019 arm). They will be stratified by age; 100 subjects as ≥20 years to <65 years, and 50 subjects as ≥65 years of age.

Once all screening assessments following informed consent are completed and eligibility is confirmed, the subject will receive a single booster vaccination of TAK-019 by IM injection. All subjects will be followed up for immunogenicity and safety for 12 months after the trial vaccination.

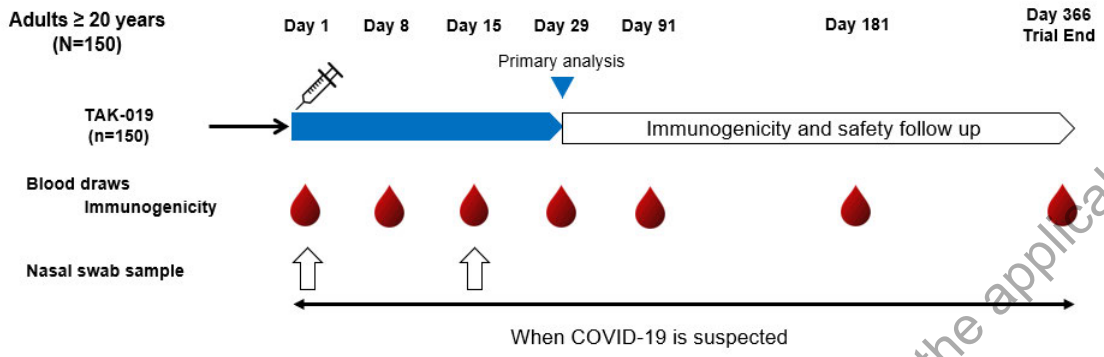
Each subject will be provided with an electronic diary (eDiary). Oral body temperature and solicited local and systemic AEs will be recorded in the eDiary by the subjects for 7 days after booster vaccination (including the day of vaccination). All subjects will be followed for unsolicited AEs for 28 days following booster vaccination (day of vaccination + 27 subsequent days).

All subjects will be followed for SAEs, AESIs, MAAEs, and AEs leading to trial withdrawal during their entire participation in the trial. All subjects will also be tested for SARS-CoV-2 infection at prespecified visits (Day 1 and Day 15) or, in case of clinical symptoms suspected for COVID-19 throughout the trial.

The primary analysis will be performed for immunogenicity and safety after all subjects have completed the Day 29 visit.

A schematic of the trial design is included as Figure 6.a.

Figure 6.a Schematic of Phase 3 Trial Design (Main Part)



Abbreviations: COVID-19: coronavirus disease 2019; N/n: number of subjects.

EXTENSION PART

Extension Part is designed to offer a second single booster vaccination of TAK-019 to participants who received the first single booster vaccination of TAK-019 in the **Main Part** and remained in study follow-up at least 5 months. The end of the **Main Part** is defined as the earlier of the completion of the final visit on Day 366 or the initiation of the **Extension Part**. Therefore, data of the **Main Part** will consist data of all subjects in the **Main Part**, data of the **Extension Part** will consist only data of subjects after the initiation of the **Extension Part**. The end of **Extension Part** is defined as the completion of the final visit on **Extension Part** Day 366. All analyses will be performed descriptively in the **Extension Part**.

All subjects who are willing to proceed to the **Extension Part** and to receive a second booster vaccination of TAK-019 will be asked to schedule a Participant Decision Visit about 5 months after the first single booster vaccination.

All subjects who provide additional informed consent for the **Extension Part** at the Participant Decision Visit and are eligible for enrollment in the **Extension Part** will receive a second single booster vaccination of TAK-019, by IM injection (**Extension Part** Day 1). All subjects in the **Extension Part** will be followed up for immunogenicity and safety for 12 months after the **Extension Part** Day 1**.**

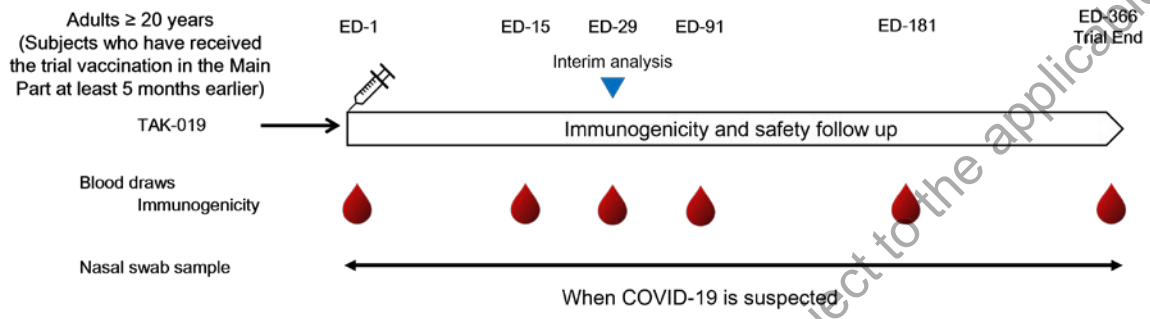
Each subject will be provided an eDiary. Oral body temperature and solicited local and systemic AEs will be recorded in the eDiary by the subjects for 7 days after the second booster vaccination (including the **Extension Part** Day 1). All subjects will be followed-up for unsolicited AEs for 28 days following the second booster vaccination (**Extension Part** Day 1 + 27 subsequent days).

All subjects will be followed-up for SAEs, AESIs, MAAEs, and AEs leading to trial withdrawal in the **Extension Part**. All subjects will also be tested for SARS-CoV-2 infection in case of clinical symptoms suspected for COVID-19 in the **Extension Part**.

An interim analysis will be performed for immunogenicity and safety after all subjects have completed the **Extension Part** Day 29 visit.

A schematic of the trial design for the **Extension Part** is included as Figure 6.b.

Figure 6.b Schematic of Trial Design (Extension Part)



Abbreviations: COVID-19: coronavirus disease 2019; ED: Extension Part Day.

6.2 Justification for Trial Design, Dose, and Endpoints

MAIN PART

The **Main Part** is to evaluate immunogenicity and safety of a single heterologous booster vaccination of TAK-019 by IM injection in the Japanese healthy adults who completed 2 doses primary vaccinations with Comirnaty Intramuscular Injection, approved in Japan as a SARS-CoV-2 vaccine, 6 to 12 months prior to the trial booster vaccination. The trial design (assessment timing and period of immunogenicity and safety endpoints and the trial follow-up periods) has been developed according to the guidance document, Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2, issued by the Pharmaceuticals and Medical Devices Agency of Japan (PMDA) [15].The booster dose of TAK-019 (5 µg of SARS-CoV-2 rS and 50 µg of Matrix-M) and the administration route (IM injection) for the trial have been selected based on assessment of available safety data from Studies 2019nCoV-101 and COV-BOOST outside Japan.

As the data for 2 doses primary vaccinations, the immunogenicity and safety data in healthy Japanese adults of Study TAK-019-1501 were comparable to overseas pivotal studies that showed efficacy against COVID-19. The trial design of evaluate effectiveness of booster vaccination has been developed according to the guidance document, Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1) Evaluation of Vaccines Against Variants, issued by the PMDA [16], to assess non-inferiority of GMTs of neutralizing antibody titers to wild-type virus 14 days after a single booster vaccination (Day 15) compared with that observed 14 days after the second vaccination (Day 36) in Study TAK-019-1501. In order to

improve comparability with the data of neutralizing antibody titers at the time of 2 doses primary vaccinations in Study TAK-019-1501, which served as a comparison control, healthy Japanese adult males and females (including the elderly) matching the subject population of Study TAK-019-1501 will be included, and the measurement facility and assay method used for the study of neutralizing antibody titer are the same.

EXTENSION PART

Study design, dosage, and endpoints of the **Extension Part** were defined according to those of the **Main Part**. Of note, safety assessments conducted on Day 8 in the **Main Part** are to be conducted on **Extension Part** Day 15 because no site visit is not scheduled on **Extension Part** Day 8.

Based on the approved intervals of the fourth doses of Comirnaty Intramuscular Injection and Spikevax Intramuscular Injection (defined as followings in their package inserts: "*the fourth dose can be determined at least 5 months later than the third dose in elderlies and other populations; the determination should be made on their benefits and risks*"), vaccination interval from the third shot of the **Main Part** was defined as at least 5 months.

Also, based on the primary analysis of the **Main Part**, an interim analysis for immunogenicity (until **Extension Part** Day 15) and safety (until **Extension Part** Day 29) is planned in the **Extension Part** when all subjects completed **Extension Part** Day 29 visit.

6.3 Planned Duration of Subject's Participation in the Trial

SUBJECTS PARTICIPATING ONLY IN THE MAIN PART

The trial participation for each subject is for 12 months following the first single booster vaccination.

SUBJECTS ENTERING THE EXTENSION PART

The trial participation for each subject is for at least 17 months in total (at least 5 months following the first single booster vaccination in the **Main Part** and 12 months following the second single booster vaccination in the **Extension Part**).

6.4 Premature Termination or Suspension of Trial or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Trial

The trial will be completed as planned unless one or more of the following criteria that require temporary suspension or early termination of the trial are satisfied.

- New information or other evaluation regarding the safety or efficacy of the investigational vaccine that indicates a change in the known risk/benefit profile, such that the risk/benefit is no longer acceptable for subjects participating in the trial.

- Significant deviation from GCP that compromises the ability to achieve the primary trial objectives or compromises subject safety.
- The Sponsor decides to terminate or suspend the trial.

6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

A trial site may be terminated prematurely or suspended if the site (including the Investigator) is found in significant deviation from GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the trial, or as otherwise permitted by the contractual agreement.

6.4.3 Procedures for Premature Termination or Suspension of the Trial or the Participation of Investigational Site(s)

In the event that the Sponsor, an Institutional Review Board (IRB) or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or trial suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

Subject eligibility is determined according to all criteria for applicable part including laboratory test results before each of the trial vaccination.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

MAIN PART

1. Subjects aged ≥20 years of age at the time of signing of informed consent.
2. Healthy Japanese male and female subjects.
3. Subjects who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs), and clinical judgment of the Investigator.
4. Subjects who have signed and dated a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained.
5. Subjects who understand and are willing to comply with the trial procedures and are available for the duration of follow-up.
6. Subjects who completed 2 doses primary vaccinations with Comirnaty Intramuscular Injection 6 to 12 months prior to the trial vaccination.
   - Subjects who can show their vaccination certificate issued by Japanese municipality of 2 doses primary vaccinations with Comirnaty Intramuscular Injection.
7. A male subject or a female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use "Acceptable contraceptive methods" from 28 days prior to the first single booster vaccination until 3 months after the first single booster vaccination.

*Definitions of childbearing potential female, nonsterilized male and "Acceptable contraceptive methods" are defined in Section 7.2 and reporting responsibilities on pregnancy are defined in Section 9.1.15.

EXTENSION PART

8. Subjects who received the first trial vaccination at least 5 months earlier and are currently enrolled in the **Main Part** (ie, not have withdrawn or discontinued early).
9. Subjects who signed an additional ICF for the **Extension Part**, understand and are willing to comply with trial procedures and are available for the duration of follow-up.
10. A male subject or a female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use "Acceptable contraceptive methods" from 28 days

prior to the second single booster vaccination until 3 months after the second single booster vaccination.

*Definitions of childbearing potential female, nonsterilized male and "Acceptable contraceptive methods" are defined in Section 7.2 and reporting responsibilities on pregnancy are defined in Section 9.1.15.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the trial:

MAIN PART

1. Subjects who received any other SARS-CoV-2 vaccine (except for Comirnaty Intramuscular Injection) or other experimental novel coronavirus vaccine prior to the trial.
2. Subjects who received a booster vaccination (ie, 3rd dose) with Comirnaty Intramuscular Injection or Spikevax Intramuscular Injection (previously COVID-19 Vaccine Moderna Intramuscular Injection).
3. Subjects who have close contact of anyone known to have COVID-19 within 14 days prior to the first trial vaccination.
   "Subjects who have close contact of anyone known to have COVID-19" are defined as subjects who have contact of COVID-19 diagnosed patients within possible infectious period (from 2 days prior to the onset) and who meet any of the following criteria:
   - Subjects who live together or have contact for a long period of time (including contacts in a car or airplane) with COVID-19 diagnosed patients.
   - Subjects who performed physical examination, nursing or caregiving for COVID-19 diagnosed patients without appropriate protective measurements against infection.
   - Subjects most likely who directly touched the contaminants of respiratory secretions or body fluids from COVID-19 diagnosed patients.
   - Others: subjects who have contact with COVID-19 diagnosed patients for ≥15 minutes within a distance that can be touched by hand (roughly, 1 m) without necessary preventive measurements against infection (the patient's infectiveness will be judged for each situation by taking consideration with surrounding circumstances or contacting situation).
4. Subjects who were tested positive for SARS-CoV-2 prior to the trial.
5. Subjects who have traveled outside of Japan in the 30 days prior to the trial participation.
6. Subjects with a clinically significant active infection (as assessed by the Investigator) or oral temperature ≥38°C within 3 days of the intended date of the first single booster vaccination.

7. Subjects with known hypersensitivity or allergy to any of the investigational vaccine components and/or Comirnaty Intramuscular Injection (including excipients as summarized in Section 8.1.1.1).
8. Subjects with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the Investigator, may interfere with the subject's ability to participate in the trial.
9. Subjects with any history of progressive or severe neurologic disorder, seizure disorder or neuro-inflammatory disease (eg, Guillain-Barré syndrome).
10. Subjects with history or any illness that, in the opinion of the Investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial.
11. Subjects with known or suspected impairment/alteration of immune function, including:
    a. History of any autoimmune disease or neuro-inflammatory disease.
    b. Chronic use of oral steroids (20 mg/day prednisolone ≥12 weeks or ≥2 mg/kg body weight/day prednisolone ≥2 weeks continuously) within 60 days preceding the booster administration of investigational medicinal product (IMP) (use of inhaled, intranasal, or topical corticosteroids is allowed).
    c. Receipt of parenteral steroids (20 mg/day prednisolone ≥12 weeks or ≥2 mg/kg body weight/day prednisolone ≥2 weeks continuously) within 60 days preceding the booster administration of IMP.
    d. Receipt of immunoglobulins and/or any blood products within the 3 months preceding the booster administration of IMP, or planned administration during the trial
    e. Receipt of immunostimulants within 60 days preceding the booster administration of IMP.
    f. Receipt of parenteral, epidural or intra-articular Ig preparation, blood products, and/or plasma derived products within 3 months preceding the booster administration of IMP or planned administration during the trial.
    g. Known HIV infection or HIV-related disease.
    h. Genetic immunodeficiency.
12. Abnormalities of splenic or thymic function.
13. Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
14. Subjects with any serious chronic or progressive disease (eg, neoplasm, insulin dependent diabetes, cardiac, renal or hepatic disease).
15. Subjects with BMI greater than or equal to 30 kg/m^2 (BMI= weight in kg/ height in $meters^2$).
16. Subjects participating in any clinical trial with another investigational product within 30 days prior to the first trial vaccination or intend to participate in another clinical trial at any time during the conduct of this trial.
17. Subjects who have received blood, blood products and/or plasma derivatives or any parenteral Ig preparation in the past 3 months (prior to the first trial dose).

18. Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to the first trial vaccination.
19. Subjects who received or plan to receive any other licensed vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to the first trial dose administration.
20. Subjects with acute or chronic clinically significant disease including pulmonary, cardiovascular, hepatic or renal abnormality evaluated by physical examination.
21. Subjects involved in the trial conduct or their first-degree relatives.
22. Subjects who have history or infection of hepatitis B and hepatitis C.
23. Subjects with history of substance or alcohol abuse within 2 years prior to the first trial vaccination.
24. Female subjects who are pregnant or breastfeeding.
25. A male subject who is non-sterilized and sexually active with a female partner of childbearing potential or a female subject of childbearing potential who is sexually active with men and those have not used any of the "Acceptable contraceptive methods" for at least 28 days prior to the first trial vaccination.
    a) "Childbearing potential" is defined as status post-onset of menarche and not meeting any of the following conditions: menopausal for at least 2 years, status after bilateral tubal ligation for at least 1 year, status after bilateral oophorectomy, or status after hysterectomy.
    b) "Acceptable contraceptive methods" are defined as follows:
    A male subject who is non-sterilized and sexually active with a female partner of childbearing potential must use male condom with or without spermicide. A female subject of childbearing potential who is sexually active with a nonsterilized male partner must use the method of contraception below:
        - Intrauterine device.
        - Bilateral tubal interruption tubal ligation.
        - A Male partner who is the only partner of the subject and was postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.
        - Progestin/estrogen mixed preparation for inhibition of ovulation.
26. A male subject who is non-sterilized and sexually active with a female partner of childbearing potential, or a female subject of childbearing potential who is sexually active with men and those refuse to use an "Acceptable contraceptive method" through to 3 months after the first booster dose of IMP.
27. Any positive or indeterminate pregnancy test (Section 9.1.15).

EXTENSION PART

28. Subjects with a clinically significant active infection (as assessed by the Investigator) or oral temperature ≥38°C within 3 days of the intended date of the second single booster vaccination.
29. Subjects with known hypersensitivity or allergy to any of the investigational vaccine components and/or Comirnaty Intramuscular Injection (including excipients as summarized in Section 8.1.1.1).
30. Subjects with history or any illness that, in the opinion of the Investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial.
31. Subjects with known or suspected impairment/alteration of immune function, including history of any autoimmune disease or neuro-inflammatory disease. Refer to exclusion criterion #11 for details.
32. Abnormalities of splenic or thymic function.
33. Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
34. Subjects with any serious chronic or progressive disease (eg, neoplasm, insulin dependent diabetes, cardiac, renal or hepatic disease).
35. Subjects participating in any clinical trial with another investigational product within 30 days prior to the second single booter vaccination or intend to participate in another clinical trial at any time during the conduct of this trial.
36. Subjects who have received blood, blood products and/or plasma derivatives or any parenteral Ig preparation in the past 3 months (prior to the second trial dose).
37. Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to the second single booster vaccination.
38. Subjects who received or plan to receive any other licensed vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to the second trial dose administration.
39. Subjects with acute or chronic clinically significant disease including pulmonary, cardiovascular, hepatic or renal abnormality evaluated by physical examination.
40. Subjects who have history or infection of hepatitis B and hepatitis C.
41. Subjects with a history of myocarditis or pericarditis.
42. Female subjects who are pregnant or breastfeeding.
43. A male subject who is non-sterilized and sexually active with a female partner of childbearing potential or a female subject of childbearing potential who is sexually active with men and those have not used any of the “Acceptable contraceptive methods” for at least 28 days prior to the second trial vaccination. Refer to exclusion criterion #25 for details.

44. A male subject who is non-sterilized and sexually active with a female partner of childbearing potential, or a female subject of childbearing potential who is sexually active with men and those refuse to use an "Acceptable contraceptive method" through to 3 months after the second booster dose of IMP.
45. Any positive or indeterminate pregnancy test (Section 9.1.15).

There may be instances when individuals meet all entry criteria except one that relates to transient clinical circumstances (eg, body temperature elevation or recent use of prohibited medication[s] or vaccine[s]). Under these circumstances, eligibility for trial enrollment may be considered if the appropriate window for delay has passed, inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible (Section 7.4).

7.3 Prohibited Medications

Any other SARS-CoV-2 or other experimental novel coronavirus vaccine are prohibited throughout the trial. Other licensed vaccines not for SARS-CoV-2 should be administrated before/after 14 days for inactivated vaccines or 28 days for live vaccines prior to each trial dose administration.

7.4 Criteria for Delay of Investigational Medicinal Product Administration

After enrollment, subjects may encounter clinical circumstances that warrant a delay in the any booster administration of IMP. These situations are listed below. In the event that a subject meets a criterion for delay of any IMP administration, the subject may receive the IMP for applicable part once the window for delay has passed within 7 days as long as the subject is otherwise eligible for trial participation.

- Subjects with a clinically significant active infection (as assessed by the Investigator) or body temperature >37.5°C, within 3 days of planned IMP administration. Consider whether applicable as a criterion for delay or as an exclusion criterion, see Section 7.2.
- Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to vaccination. The reason for their use (prophylaxis versus treatment) must be documented. IMP administration should be delayed to allow for a full 24 hours to have passed between having used antipyretics and/or analgesic medications and IMP administration.

7.5 Criteria for Early Termination of a Subject's Trial Participation

Under some circumstances, a subject's trial participation may be terminated early. Even if the subject early terminates trial participation, all efforts should be made to continue the collection of safety data according to protocol. The primary reason for early termination of the subject's trial participation should be documented in the electronic case report form (eCRF) using the following categories.

The subjects who receive approved SARS-CoV-2 vaccine except for TAK-019 in the **Extension Part** during the trial will be terminated from the trial.

1. Adverse Event: The subject has experienced an AE (irrespective of being related/unrelated to the IMP or trial-related procedures) that requires early termination because continued participation imposes an unacceptable risk to the subject's health and/or the subject is unwilling to continue participation because of the AE. If the subject is unwilling to continue because of the AE, the primary reason for early termination of trial participation in this case will be 'withdrawal due to AE' and not 'withdrawal of consent', see below.
2. Lost to follow-up: The subject did not return to the site and at least 3 attempts to contact the subject were unsuccessful.
3. Withdrawal of consent: The subject wishes to withdraw from the trial. The primary reason for early termination will be 'withdrawal of consent' if the subject withdraws from participation due to a non-medical reason (ie, reason other than AE). While the subject has no obligation to provide a reason for withdrawing consent, attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be documented.
4. Premature trial termination by the Sponsor, a regulatory agency, the IRB, or any other authority.

   If the clinical trial is prematurely terminated by the Sponsor, the Investigator is to promptly inform the trial subjects and local IRB and should assure appropriate follow-up for the subjects. The primary reason for early termination in this case will be 'trial termination'.
5. Subject's death during trial participation.
6. Other.

For screen failure subjects, refer to Section 9.1.16.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

8.1 Investigational Medicinal Product(s)

TAK-019 will be supplied to the trial sites by the Sponsor or its designee. TAK-019 used for **Extension Part** is a commercial product (Nuvaxovid Intramuscular Injection).

Details regarding the dosage form description and strengths, or composition for the extemporaneous preparation, of the IMP can be found in the pharmacy manual.

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Dosage Form and Contents

Code of IMP: TAK-019

Generic name: Recombinant Coronavirus (SARS-CoV-2) Vaccine

Dosage form: Colorless and milky white liquid available in glass vial for injection.

[redacted]

8.1.1.2 Package and Labeling

TAK-019 for **Main Part** will be labeled and packaged in each carton with 1 vial which include storage conditions of the IMP. TAK-019 for **Extension Part** will be packaged labeled vials as the commercial product.

Refer to the pharmacy manual for details.

8.1.2 Inventory and Storage

TAK-019 investigational vaccine should be refrigerated at 2°C to 8°C and should not be frozen.

The investigational product storage manager should store the IMP in a secure, environmentally controlled and monitored area until it is used or returned to the Sponsor or designee. All sponsor-supplied IMP must be stored under the conditions specified on the label. A daily temperature log of the vaccine storage area must be maintained every working day.

8.1.3 Dose and Regimen

The IMP TAK-019 will be administered as an IM injection (0.5 mL) in the mid deltoid, preferable in the non-dominant upper arm on Day 1 in the **Main Part** and **Extension Part** Day 1 as explained in the pharmacy manual.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.4.4.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Investigational Medicinal Product Dispensing Procedures

Subjects will receive treatment according to the study schedule. The subject number will be entered onto the eCRF.

Where a subject does not meet all the eligibility criteria for the applicable part but incorrectly receives the IMP, the Investigator should inform the Sponsor immediately, and a decision regarding whether to continue or discontinue the subject should be taken based on discussion with the Sponsor.

The Investigator will administer the IMP.

If sponsor-supplied IMP is lost or damaged, the site uses a replacement of IMP. Expired IMP must not be administered.

8.2.1 Precautions to Be Observed When Administering the Investigational Medicinal Product

Prior to each IMP booster administration, a subject must be determined to be eligible to receive IMP (Sections 7.1 and 7.2), and it must be clinically appropriate in the judgment of the Investigator to administer each of the IMP.

Standard immunization practices are to be observed and care should be taken when booster administering an IMP intramuscularly. In addition, WHO recommendations to reduce anxiety and pain at the time of vaccination should be followed [17]. Before each booster administration of IMP, the vaccination site must be disinfected with a skin disinfectant (eg, 70% alcohol) and the skin allowed to dry. Refer to the pharmacy manual for details on preparation and administration of IMP.

As with all injectable vaccines, the Investigator and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccination. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

8.3 Randomization Code Creation and Storage

Not applicable.

8.4 Investigational Medicinal Product Blind Maintenance

This is an open-label trial.

8.5 Unblinding Procedure

This is an open-label trial.

8.6 Accountability and Destruction of Sponsor-Supplied Investigational Medicinal Products, and Other Clinical Trial Materials

The Investigator or designee must ensure that the sponsor-supplied IMP are used in accordance with the approved protocol and are administered only to subjects enrolled in the trial. To document appropriate use of sponsor-supplied IMP, the Investigator must maintain records of all sponsor-supplied IMP delivery to the site, site inventory, administration and use by each subject, and return to the Sponsor or designee.

Upon receipt of sponsor-supplied IMP, the Investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the IMP is received within the labeled storage conditions (ie, no cold chain break has occurred during transit), and is in good condition. If quantity and conditions are acceptable, Investigator or designee will acknowledge receipt of the shipment to the Sponsor per instructions provided on the form.

If there are any discrepancies between the packing list versus the actual product received, the Sponsor or designee must be contacted to resolve the issue. The packing list should be filed in the Investigator Site File (ISF).

The Investigator must maintain 100% accountability for all sponsor-supplied IMPs, and other clinical trial material received and administered during their entire participation in the trial. Accountability includes, but is not limited to:

- Verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the vaccine lot used to prepare each dose.
- Verifying that all IMP kits used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

The Investigator must record the current inventory of all sponsor-supplied IMP on a sponsor-approved IMP accountability log. The following information will be recorded at a minimum: protocol number and title, name of the Investigator, site identifier and number, description of sponsor-supplied IMPs, expiry date, date and amount. The IMP log should include all required information as a separate entry for each subject to whom sponsor-supplied IMP is administered.

The Investigator will be notified of any expiry date or retest date extension of IMP during the trial conduct. On expiry date notification from the Sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical trial material for return to the Sponsor or designee for destruction.

The on-site pharmacist (site designee) will receive the pharmacy manual created by the Sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The Investigator will also receive those procedures from the Sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, and dispensation of the sponsor-supplied drug as well as return of them to the Sponsor or destruction of them. The on-site pharmacist (site designee) will immediately return unused study drugs to the Sponsor after the study is closed at the study site.

All clinical trial materials will be provided by the trial site, Sponsor or designee, depending upon availability. The list of clinical trial materials and source information can be found in the pharmacy manual. Prior to site closure or at appropriate intervals throughout the trial, before any IMP or clinical trial materials are returned to the Sponsor or designee for destruction, a representative from the Sponsor will perform clinical trial material accountability and reconciliation. The Investigator will retain a copy of the documentation regarding clinical trial material accountability, return, and/or destruction, and originals will be sent to the Sponsor or designee.

9.0 TRIAL PLAN

9.1 Trial Procedures

The following sections describe the trial procedures and data to be collected. For each procedure, subjects are to be assessed by the same Investigator or site personnel whenever possible. The schedule of trial procedures is located in Section 2.1. All procedures must be performed by qualified and trained staff.

9.1.1 Informed Consent

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained before any protocol-directed procedures are performed. Signed ICF should be obtained from Day -28 to Day 1 in the **Main Part** ,the same for the **Extension Part**.

A unique subject number will be assigned to each subject by the appropriate coding after informed consent is obtained for the **Main Part**. If all eligibility criteria for the **Main Part** are fulfilled, this subject number will be used throughout the trial. Subject numbers assigned to subjects who do not receive vaccination should not be reused (Section 9.1.16).

The subjects who receive approved SARS-CoV-2 vaccine except for TAK-019 in the **Extension Part** during the trial will be terminated from the trial.

9.1.2 Demographics, Medical History and Prior Medications

Demographic information to be obtained will include age/date of birth, sex, and race.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for trial participation such as prior vaccinations, concomitant medications (including concomitant therapies), and previous and ongoing illnesses and/or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during trial participation, if it represents an exacerbation of an underlying disease/pre-existing problem.

Medical history (including corresponding medication) to be obtained will include any significant conditions or diseases that have disappeared or resolved at or prior 5 years to signing of ICF for the **Main Part**.

Adverse medical occurrences emerging during the time between signing of ICF and the first booster administration of IMP will be recorded in the medical history eCRF page. If such an adverse medical occurrence is assessed as related to a screening procedure this should be recorded as an AE related to trial procedure in the eCRF.

All medications, vaccines, and blood products taken by the subjects are to be collected as prior (if the start and stop dates are before Day 1 in the **Main Part**, the same for **Extension Part**) and concomitant medications (if the stop date is on or after Day 1 in the **Main Part**, irrespective of the start date).

<Periods to collect medical and medications information>

a) Medications: 2 months prior to Day 1 in the **Main Part** (day of the first booster vaccination).

b) Primary SARS-CoV-2 vaccinations: Dates of 2 doses primary vaccinations with Comirnaty Intramuscular Injection on their certificate issued by Japanese municipality (prior to the first booster vaccination on Day 1 in the **Main Part**) .

c) Other vaccines: 2 weeks (for inactivated vaccines) and 4 weeks (for live vaccines) each prior to Day 1 (day of the first booster vaccination) and **Extension Part** Day 1 (day of the second booster vaccination).

d) Blood products: 3 months prior to Day 1 in the **Main Part** (day of the first booster vaccination) and **Extension Part** Day 1 (day of the second booster vaccination).

e) Therapies: 30 days prior to Day 1 in the **Main Part** (day of the first booster vaccination).

The use of antipyretics and/or analgesic medications within 24 hours prior to each of the booster vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be documented. Booster administration of the IMP should be delayed if subjects have used antipyretics and/or analgesics within 24 hours prior to each booster vaccine administration.

Assess and record concomitant therapies (prescription medications ONLY) and vaccine history from 30 days prior to Day 1 in the **Main Part** in the subject's source document.

Any other SARS-CoV-2 or other experimental novel coronavirus vaccines including TAK-019 out of the study are prohibited throughout the trial. Other licensed vaccines not for SARS-CoV-2 should be administrated before/after 14 days for inactivated vaccines or 28 days for live vaccines prior to each trial dose administration.

These data must be written in the source documents.

9.1.3 Documentation of Trial Entry

For each part of the study, only subjects who have a signed ICF, and meet all of the inclusion criteria and none of the exclusion criteria are eligible for entry and receiving the booster vaccination.

If the subject is ineligible for receiving any of the booster vaccination, the Investigator should record the primary reason for failure on the eCRF.

9.1.4 Physical Examination

Physical examinations must be performed by a qualified health professional in accordance with local regulations and as listed within the site responsibility delegation log. A complete physical examination will be performed according to the schedule of procedures (Section 2.1). The date and time of the physical examinations and any findings should be documented in the subject's source document and the eCRF.

The physical examination will be performed in accordance with standards at the site. The physical examination will include, at a minimum, assessments of the body systems listed below:

- General appearance.
- Ears, nose, and throat.
- Head and Neck.
- Ophthalmological.
- Respiratory.
- Cardiovascular.
- Abdomen.
- Neurological.
- Extremities.
- Dermatological.
- Lymphatic.

In addition, height and weight will be measured at the Day 1 in the **Main Part** before the first booster vaccination visit only in accordance with standards of the site and BMI will be calculated.

Symptom-directed physical examination may be performed if deemed necessary.

9.1.5 Vital Signs

Vital signs will be assessed according to the schedule of procedures (Section 2.1). Vital signs will include body temperature (oral body temperature), blood pressure (systolic and diastolic, resting more than 5 minutes), pulse rate, and respiratory rate.

Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest. Blood pressure should be determined using the same arm and the same equipment, and the same body position for each assessment throughout the trial. Blood pressure should not be taken on the trial vaccination arm. The Investigator will make a reasonable effort to using the same equipment and not taken on the trial vaccination arm to measure the blood pressure.

During the trial, additional vital signs measurements will be performed if clinically indicated.

Every effort should be made to measure and record vital signs prior to any blood sample collection.

The Investigator will assess whether a change from baseline (ie, the booster predose measurement on Day 1 in the **Main Part** or **Extension Part** Day 1) in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE.

9.1.6 Immunogenicity Assessments

All subjects will undergo blood sampling for immunogenicity testing at visit time points listed below:

- Day 1, Day 8, Day 15, Day 29, Day 91, Day 181, and Day 366 in the **Main Part.**
- **Extension Part** Day 1, Day 15, Day 29, Day 91, Day 181, and Day 366.

The handling and transport of the samples will be described in the handling manual of samples for immunogenicity assessment, separately prepared.

The maximum volume of blood taken at any single visit for immunogenicity assessment is approximately 20 mL, and the approximate total volume of blood for the trial is maximum 220 mL for subjects if they enter the **Extension Part** between Day 91 and Day 181 in the **Main Part** (Table 9.a).

Table 9.a Volume and Numbers of Sampling

Laboratory tests	Volume/sampling	Number of sampling	Total volume
Subjects participating only in the **Main Part**			
Immunogenicity	20 mL	7	140 mL
Subjects entering the **Extension Part** between Day 91 and Day 181 in the **Main Part**			
Immunogenicity	20 mL	11 (5 in the **Main Part**, 6 in the **Extension Part**)	220 mL

[redacted]

9.1.7 Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over-the-counter (OTC). Concomitant medication is not provided by the Sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent until Day 29 in the **Main Part** or **Extension Part** Day 29), and all medication including vitamin supplements, OTC medications, and oral herbal preparations must be recorded in the eCRF by the Investigator. Medications used for treatment of SAEs, AEs leading to withdrawal from trial, and COVID-19 must be recorded in the eCRF during the trial. When subjects receive approved SARS-CoV-2 vaccine except for TAK-019 in the study, it must be recorded in the eCRF as well. Concomitant therapies given to subjects will be confirmed and recorded in the eCRF similarly.

9.1.8 Processing, Labeling and Storage of Biological Samples

All biological samples will be processed, labeled, and stored according to the laboratory manual or other appropriate guideline provided to the site.

9.1.9 Safety Assessments

Safety assessments will include collection and recording of solicited local (injection site) reaction and solicited systemic AEs, unsolicited AEs, AEs (serious and non-serious), and pregnancies. For timing and details refer to Section 2.1. Refer to Section 10.1 for definitions of AEs. Details on collection and reporting of AEs are in Sections 10.4 and 10.5.

9.1.10 Clinical Safety Laboratory Variables

Not applicable.

9.1.11 Hematology and Blood Chemistry

Not applicable.

9.1.12 Nasal Swab Sample

Nasal swab samples will be collected for PCR testing of SARS-CoV-2 infection on Day 1 and Day 15 in the **Main Part** in all subjects.

Also, subjects will consult with the Investigator about the necessity of a COVID-19 diagnostic test including PCR test throughout the trial (Day 1 to Day 366 in the **Main Part** or the **Extension Part** Day 366), if the subject shows the following symptoms of potential SARS-CoV-2 infection and/or have/had exposure to an individual confirmed to be infected with SARS-CoV-2. The Investigator judges if a COVID-19 diagnostic test is necessary by the information obtained from the subject according to the guidance for COVID-19 medical treatment [9]. When the Investigator judges the necessity of a COVID-19 diagnostic test, an ad hoc trial visit or home visit by medically qualified staff will be arranged as soon as possible (at least within 72 hours) to collect a sample from the subject. In the **Extension Part**, nasal swab sample will be collected, and PCR test results performed at a local laboratory will be accepted.

Subjects may be asked to submit follow-up samples after consultation with the Investigator. If a sample is unavailable in the trial for some reason (eg, emergency admission to the hospital or COVID-19 intensive care ward), COVID-19 diagnostic test results performed at a local public health or hospital will be taken as a valid result for this trial.

If COVID-19 is confirmed by the diagnostic test, all clinical findings will be recorded in the eCRF including relevant concomitant medications (including concomitant therapies) and details about severity, seriousness, and outcome.

<Symptoms of COVID-19 suspected>

If subject shows the following symptoms, consult with the Investigator about the necessity of collection of COVID-19 diagnostic test samples:

- Fever (temperature ≥37.5°C) or chills.
- Cough.
- Shortness of breath or difficulty breathing.
- Fatigue.
- Muscle or body aches.
- Headache.
- New loss of taste or smell.
- Sore throat.
- Congestion or runny nose.
- Nausea or vomiting.
- Diarrhea.

<In case where a subject possibly has close contact of COVID-19 patients>

The Investigator confirms if the subject meets the definition of "Subjects who have close contact of anyone known to have COVID-19" in exclusion criterion #3 of Section 7.2, by the information from the subject.

9.1.13 [redacted]

[redacted]

9.1.14 Contraception and Pregnancy Avoidance Procedure

All subjects must use "Acceptable contraceptive methods" through to 3 months after each of the trial dose of IMP.

For female subjects of childbearing potential, pregnancy testing (urine pregnancy test with measuring human chorionic gonadotropin) will be performed on Day 1 in the **Main Part** prior to trial vaccination, on Day 29 and Day 91 in the **Main Part**, **Extension Part** Day 1 prior to trial vaccination, and **Extension Part** Day 29 and Day 91. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be

asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova. During the course of the trial, regular pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the trial procedures (Section 2.1). Subjects must have a negative pregnancy test prior to receiving each trial vaccination on Day 1 in the **Main Part** and **Extension Part** Day 1. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is strongly recommended.

Refer to Section 7.2 (Exclusion Criteria) for contraception.

9.1.15 Pregnancy

To ensure the safety of a female subject and the unborn child or the safety of the unborn child of the partner of a male subject, each pregnancy in the female subject having received any booster IMP or in the partner of the male subject having received any trial IMP must be reported to the Sponsor promptly. The follow-up procedures for her according to the protocol should be performed, if possible. The Investigator should report the pregnancy to the Sponsor promptly with a pregnancy notification form, by taking her course of pregnancy continuously. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The pregnancy for the partner of the male subject, if the partner becomes pregnant, will also be followed as much as possible. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended.

Any pregnancy occurring following any IMP administration should be reported immediately, using a pregnancy notification form, to the contact listed in the ISF.

Any SAE occurred during pregnancy should be reported throughout the trial as per timelines and procedures described in Section 10.4.4.

9.1.16 Documentation of Subjects Who Discontinue Prior to the Trial Vaccination

Investigators must account for all subjects who sign an informed consent. If the subject is found to be not eligible at this visit, the Investigator should still complete the eCRF.

The primary reason for discontinuation prior to the first trial vaccination would be recorded in the eCRF using the following categories:

- Screen failure (did not meet one or more inclusion criteria or did meet one or more exclusion criteria).
- Withdrawal by subject.
- Trial terminated by the Sponsor.
- Others (eg, as decided by the Investigator).

Subject identifier assigned to subjects who discontinue prior to the first trial vaccination should not be reused.

9.2 Monitoring Subject Compliance

The doses of trial vaccination should be administered at the site under direct observation of the Investigator. The trained site staff injecting the vaccine will confirm that the subject has received the entire dose. The location (right or left arm), date and timing of all doses of the trial vaccine will be reported in the eCRF. If a subject is not administered the trial vaccine, the reason for missed dose will be recorded.

9.3 Schedule of Observations and Procedures

The schedule for all trial-related procedures for all evaluations is shown in Section 2.1.

The trial visits should be performed on the planned dates and subject should be asked to adhere to the trial visit within the visit window. The results of the evaluation will be recorded on the appropriate eCRF pages.

For a subject who withdraws early from the trial, all assessments planned on Day 366 (Visit 7) in the **Main Part** (for withdrawals from the **Main Part**) or **Extension Part** Day 366 (for withdrawals from the **Extension Part**) should be performed as possible.

The screening procedures (Day 1 in the **Main Part** before the trial vaccination) will be carried out within 14 days prior to the first IMP administration. The subjects will receive information on the trial objective(s) and procedures from the Investigator. Prior to all screening assessments, the written consent form should be signed and dated. The screening assessments for this trial are grouped under the heading of a single visit in this protocol. However, it is possible for the screening assessments to be performed over more than 1 site visit if necessary, as long as the screening visit window prior to Day 1 (Visit 1) in the **Main Part** is maintained. The following will be checked and recorded by the Investigator or designee:

- Assess eligibility by review of inclusion/exclusion criteria.
- Demographics.
- Medical history.
- Prior and concomitant medications (including prior and concomitant therapies).
- Complete physical examination and other vital signs as listed in Sections 9.1.4 and 9.1.5.
- Review of systems: Review of systems is a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
- Height, weight, and BMI calculation.
- Pregnancy testing: women of childbearing age will be tested.

- Nasal swab sample collection.

All subjects who are willing to proceed to the **Extension Part** and to receive the second booster vaccination of TAK-019 will be asked to schedule a Participant Decision Visit about 5 months after the first single booster vaccination. In case of the subjects entering the **Extension Part** between Day 91 and Day 181 in the **Main Part**, the Participant Decision Visit will be performed after Day 91 in the **Main Part**, and from then trial visits for the **Extension Part** will be performed for the subjects.

If a subject is not eligible to enter the **Extension Part**, the subject will be followed in the **Main Part**.

9.3.1 Pre Booster Vaccination Procedures (Day 1 in the Main Part)

The following will be checked and recorded by the Investigator or designee prior to the trial vaccination on Day 1 in the **Main Part**. Please refer to Section 2.1 for further details.

1. Assess eligibility by review of inclusion/exclusion criteria for the **Main Part**.
2. Prior and concomitant medications (including prior and concomitant therapies).
3. Complete physical examination and other vital signs as listed in Sections 9.1.4 and 9.1.5.
4. Review of systems: Review of systems is a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
5. Pregnancy test in women of childbearing potential.
6. Blood sampling for immunogenicity.
7. Nasal swab sample collection.

9.3.2 Booster Vaccination Procedures (Day 1 in the Main Part)

After confirming eligibility of the subject, perform IMP administration according to the procedures described in Section 8.2.1.

9.3.3 Post Booster Vaccination Procedures (Day 1 in the Main Part)

After the trial vaccination, the subject will be observed in the trial site by the Investigator for at least 30 minutes including confirmation of acute hypersensitivity reactions, measurement of vital sign (oral body temperature, blood pressure, pulse rate, and respiratory rate), and observation for solicited local (injection site) reactions.

The Investigator or delegate should confirm that the subject receives training on how and how often to record in the eDiary and can perform the recording appropriately. The following procedures will be explained:

- Solicited local and systemic AEs and the severity, and oral body temperature will be recorded in the eDiary for 7 days following booster vaccine administration (day of vaccination + 6 subsequent days).
- The assessment of solicited AEs and measurement of oral body temperature will preferably be taken place in the evening or at the same time of day. Oral body temperature is to be measured using the thermometer provided by the site. If the subject has a fever, the highest body temperature observed that day should be recorded on the eDiary.

9.3.4 Site Visits After Booster Vaccination (Day 8, Day 15, Day 29, Day 91, and Day 181 in the Main Part)

Site visits that do NOT include a booster vaccination prior to the final visit will be performed on Day 8, Day 15, Day 29, Day 91, and Day 181 in the **Main Part**. At these site visits, the Investigator will record unsolicited AEs and concomitant medications (including concomitant therapies) by confirming to the subject with review of the eDiary.

The following will be conducted at each visit. Refer to Section 2.1 in detail.

- Physical examination and vital sign: Day 8, Day 15, and Day 91 in the **Main Part**.
- Pregnancy test in women of childbearing potential: Day 29 and Day 91 in the **Main Part**.
- Confirmation of solicited AEs by the eDiary: Day 8 in the **Main Part**.
- Confirmation of unsolicited AEs and concomitant medications (including concomitant therapies): Day 8, Day 15, and Day 29 in the **Main Part**.
- Confirmation of SAEs, AEs leading to withdrawal from trial, AESIs, and MAAEs: Day 8, Day 15, Day 29, Day 91, and Day 181 in the **Main Part**.
- Blood sampling for immunogenicity: Day 8, Day 15, Day 29, Day 91, and Day 181 in the **Main Part**.
- Nasal swab sample collection: Day 15 in the **Main Part**.
- [redacted]

9.3.5 Final (End of Trial) Visit in the Main Part

The final (end of trial) visit for the **Main Part** will be performed on Day 366 in the **Main Part**. If a subject terminates earlier in the **Main Part**, the final (end of trial) visit procedures should be performed at their last trial visit in the **Main Part**, if possible. The Investigator must complete the End of Trial eCRF page for all subjects who received IMP.

The following will be conducted at the visit. Refer to Section 2.1 in detail.

- Physical examination and vital sign.

- Confirmation of SAEs, AEs leading to withdrawal from trial, AESIs, and MAAEs.
- Blood sampling for immunogenicity (except for the early termination visit).

9.3.6 Pre Booster Vaccination Procedures (Extension Part Day 1, Participant Decision Visit)

The following will be checked and recorded by the Investigator or designee prior to the trial vaccination on **Extension Part** Day 1. Please refer to Section 2.1 for further details.

1. Assess eligibility by review of inclusion/exclusion criteria for the **Extension Part**.
2. Prior and concomitant medications (including concomitant therapies).
3. Complete physical examination and other vital signs as listed in Sections 9.1.4 and 9.1.5.
4. Review of systems: Review of systems is a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
5. Pregnancy test in women of childbearing potential.
6. Blood sampling for immunogenicity.

9.3.7 Booster Vaccination Procedures (Extension Part Day 1, Participant Decision Visit)

After confirming eligibility of the subject for the **Extension Part**, perform the second single IMP administration according to the procedures described in Section 8.2.1.

9.3.8 Post Booster Vaccination Procedures (Extension Part Day 1, Participant Decision Visit)

After the second single booster vaccination, the subject will be observed in the trial site by the Investigator for at least 30 minutes including confirmation of acute hypersensitivity reactions, measurement of vital sign (oral body temperature, blood pressure, pulse rate, and respiratory rate), and observation for solicited local (injection site) reactions.

The Investigator or delegate should confirm that the subject receives training on how and how often to record in the eDiary and can perform the recording appropriately. The following procedures will be explained:

- Solicited local and systemic AEs and the severity, and oral body temperature will be recorded in the eDiary for 7 days following the second single booster vaccine administration (day of vaccination + 6 subsequent days).
- The assessment of solicited AEs and measurement of oral body temperature will preferably be taken place in the evening or at the same time of day. Oral body temperature is to be measured using the thermometer provided by the site. If the subject has a fever, the highest body temperature observed that day should be recorded on the eDiary.

9.3.9 Site Visits After Booster Vaccination (Extension Part Day 15, Day 29, Day 91, and Day 181)

Site visits that do NOT include a booster vaccination prior to the final visit in the **Extension Part** will be performed on **Extension Part** Day 15, Day 29, Day 91, and Day 181. At these site visits, the Investigator will record unsolicited AEs and concomitant medications (including concomitant therapies) by confirming to the subject with review of the eDiary.

The following will be conducted at each visit. Refer to Section 2.1 in detail.

- Physical examination and vital sign: **Extension Part** Day 15 and Day 91.
- Pregnancy test in women of childbearing potential: **Extension Part** Day 29 and Day 91.
- Confirmation of solicited AEs by the eDiary: **Extension Part** Day 15.
- Confirmation of unsolicited AEs and concomitant medications (including concomitant therapies): **Extension Part** Day 15 and Day 29.
- Confirmation of SAEs, AEs leading to withdrawal from trial, AESIs, and MAAEs: **Extension Part** Day 15, Day 29, Day 91, and Day 181.
- Blood sampling for immunogenicity: **Extension Part** Day 15, Day 29, Day 91, and Day 181.
- Nasal swab sample collection: throughout the **Extension Part** for suspected COVID-19 case.
- [redacted]

9.3.10 Final (End of Trial) Visit in the Extension Part

The final (end of trial) visit for the **Extension Part** will be performed on **Extension Part** Day 366. If a subject terminates earlier in the **Extension Part**, the final (end of trial) visit procedures should be performed at their last trial visit in the **Extension Part**, if possible. The Investigator must complete the End of Trial eCRF page for all subjects who received IMP.

The following will be conducted at the visit. Refer to Section 2.1 in detail.

- Physical examination and vital sign.
- Confirmation of SAEs, AEs leading to withdrawal from trial, AESIs, and MAAEs.
- Blood sampling for immunogenicity (except for the early termination visit).

9.3.11 Post−Trial Care

No post-trial care will be provided.

9.4 Biological Sample Retention and Destruction

In this trial, specimens for immune response testing will be collected as described in Section 9.1.6. After blood draw and serum processing, the serum samples will be preserved and retained at a

central laboratory that was contracted by the Sponsor for this purpose for up to but not longer than 20 years or as required by applicable law. The Sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered an IMP; it does not necessarily have to have a causal relationship with IMP administration.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the administration of an IMP whether or not it is considered related to the IMP.

AEs will be graded by the Investigator in the following manner. Solicited AEs (Section 10.1.3) will be graded by the criteria in Table 10.a.

Mild	Grade 1	Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities. Relieved with or without symptomatic treatment.
Moderate	Grade 2	Sufficient discomfort is present to cause interference with normal activity. Only partially relieved with symptomatic treatment.
Severe	Grade 3	Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities. Not relieved with symptomatic treatment.
Potentially Life-threatening	Grade 4	Only used for grading of solicited AEs. Refer to Table 10.a for the criteria of each event.

10.1.3 Solicited Adverse Events

Subjects will record solicited local and systemic AEs (Table 10.a), and oral body temperature, for 7 days following each booster vaccination (day of vaccination + 6 subsequent days) in the eDiary.

Severity grading of solicited AEs will occur automatically based on subject's entry into the eDiary according to the grading scales presented in Table 10.a modified from the Food and Drug Administration guidance (Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials) [18].

If a solicited local or systemic AE continues beyond 7 days after the first or second booster dosing (including the day of administration), the solicited AEs should be reviewed by the Investigator either via phone call or at the following trial visit.

Table 10.a Solicited Local (Injection Site) and Systemic AEs

Local Reaction to Injectable Product				
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Injection site pain	Does not interfere with activity	Repeated use of nonnarcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/ redness [a]	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration [a]	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis
Swelling [a]	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis
Systemic (General)				
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Fever [b]	38.0°C – 38.4°C	38.5°C – 38.9°C	39.0°C – 40.0°C	>40.0°C
Fatigue	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Malaise	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Arthralgia	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Nausea/ vomiting	No interference with activity or 1–2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, or requires outpatient intravenous hydration	Emergency room visit or hospitalization for hypotensive shock
Headache	No interference with activity	Repeated use of OTC pain reliever >24 hours or some interference with activity	Any use of prescription pain reliever or prevents daily activity	Emergency room visit or hospitalization

Abbreviations: AE: adverse event; OTC: over-the-counter.

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Oral temperature; no recent hot or cold beverages.

Any solicited AE that meets any of the following criteria must also be recorded in the eCRF:

- Medically-attended solicited AE (MAAE).
- Solicited AE leading to the subject withdrawing from the trial (AE leading to withdrawal).
- Solicited AE lasting beyond 7 days post any booster injection.
- Solicited AE that otherwise meets the definition of an SAE.

10.1.4 Adverse Events of Special Interest

AESIs are defined as AEs that will be specifically highlighted to the Investigator.

AESIs for the study include the Potential Immune Mediated Medical Conditions (PIMMC) listed below and AEs specific to COVID-19 including myocarditis and/or pericarditis [19,20]. The Investigators have to be especially vigilant to AESIs. Any AEs considered AESIs will be recorded on the AE page of the eCRF.

PIMMC is included as Table 10.b, and AEs specific to COVID-19 is included as Table 10.c.

Table 10.b Potential Immune-Mediated Medical Conditions (PIMMC)

Categories	Diagnoses (as MedDRA PT)
Neuroinflammatory Disorders	Acute disseminated encephalomyelitis (including site specific variants: eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), cranial nerve disorders including paralysis/paresis (eg, Bell's palsy), generalized convulsion, Guillain-Barre syndrome (including Miller Fischer and other variants), immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and polyneuropathies associated with monoclonal gammopathy), myasthenia gravis, multiple sclerosis, narcolepsy, optic neuritis, transverse myelitis, and uveitis.
Musculoskeletal and Connective Tissue Disorders:	Antisynthetase syndrome, dermatomyositis, juvenile chronic arthritis (including Still's disease), mixed connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome], and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, and Sjogren's syndrome.
Vasculitides	Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], necrotizing vasculitis and ANCA-positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis).
Gastrointestinal Disorders	Crohn's disease, celiac disease, ulcerative colitis, and ulcerative proctitis.

Categories	Diagnoses (as MedDRA PT)
Hepatic Disorders	Autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, and primary biliary cirrhosis.
Renal Disorders	Autoimmune glomerulonephritis (including IgA neuropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis).
Cardiac Disorders	Autoimmune myocarditis/cardiomyopathy. Myocarditis and/or pericarditis.
Skin Disorder	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome, and Sweet's syndrome.
Hematologic Disorders	Autoimmune hemolytic anemia, autoimmune thrombocytopenia, antiphospholipid syndrome, and thrombocytopenia.
Metabolic Disorders	Autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto's thyroiditis[a], diabetes mellitus type I, and Addison's disease.
Other Disorders	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anemia, and sarcoidosis.

Abbreviations: ANCA: anti-neutrophil cytoplasmic antibody; CREST: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; IgA: immunoglobulin A; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term.

[a] For Hashimoto thyroiditis: new onset only

Table 10.c Adverse Events Specific to COVID-19[a]

Categories	Diagnoses (as MedDRA SOC/PT)
Respiratory/Infectious Disorders	ARDS, pneumonitis, and septic shock-like syndrome
Cardiac Disorders	Acute cardiac injury, arrhythmia, and myocarditis and/or pericarditis.
Coagulopathy	Deep vein thrombosis, myocardial infarction, and stroke
Renal Disorder	Acute kidney injury
Hematologic Disorders	Thrombocytopenia, and septic shock-like syndrome.
Inflammatory Disorders	Cytokine Release Syndrome related to COVID-19 infection[b] and multisystem inflammatory syndrome in children.
Neurologic Disorder	Generalized convulsions.

Abbreviations: ARDS: acute respiratory distress syndrome; CEPI: Coalition for Epidemic Preparedness Innovations; COVID-19: coronavirus disease 2019; DAIDS: Division of AIDS; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SOC: System Organ Class.

[a] COVID-19 manifestations associated with more severe presentation and decompensation with consideration of enhanced disease potential. The current listing is based on CEPI/Brighton Collaborations Consensus Meeting (12/13 March 2020) and expected to evolve as evidence accumulates.

[b] Cytokines release syndrome related to COVID-19 infection is a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath [21].

10.1.5 Medically-Attended Adverse Events

MAAEs are defined as AEs leading to an unscheduled visit to or by a healthcare professional including visits to an emergency department, but not fulfilling seriousness criteria.

10.1.6 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT in the offspring of a subject.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.4.4 and 10.5).

10.2 Causality of Adverse Events

Relationship (causality) to the IMP will also be assessed by the Investigator. The relationship of each AE to the IMP, including solicited systemic AEs (solicited local AEs are considered as related by default) will be assessed using the following categories:

Related: There is suspicion that there is a relationship between the IMP and the AE (without determining the extent of probability); there is a reasonable possibility that the IMP contributed to the AE.

Not Related: There is no suspicion that there is a relationship between the IMP and the AE; there are other more likely causes and administration of the IMP is not suspected to have contributed to the AE.

10.2.1 Relationship to Trial Procedures

Relationship (causality) to trial procedures should be determined for all AEs.

The relationship should be assessed as "Yes" if the Investigator considers that there is a reasonable possibility that an event is due to a trial procedure. Otherwise, the relationship should be assessed as "No".

10.2.2 Outcome of Adverse Events

Resolved:	The subject has fully recovered from the event or the condition has returned to the level observed at baseline.
Resolving:	The event is improving but the subject is still not fully recovered.
Not resolved:	The event is ongoing at the time of reporting and the subject has still not recovered.
Resolved with sequelae:	As a result of the AE, the subject suffered persistent and significant disability/incapacity (eg, became blind, deaf or paralysed).
Fatal:	The subject died due to the event. If the subject died due to other circumstances than the event, the outcome of the event per se should be stated otherwise (eg, not resolved or resolving).
Unknown:	If outcome is not known or not reported.

10.2.3 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or investigator.

The start date of PTEs/AEs will be determined using the following criteria;

PTEs/AEs	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms/diseases were noted by the subject and/or the investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings or the onset time can be estimated.
Worsening or complication of concurrent medical conditions or any signs/symptoms/diseases before treatment	The date that a worsening or complication of the condition was noted first by the subject and/or the investigator should be recorded.
The examination after start of the study drug showed abnormal values/findings.	The date of examination when an abnormal value or findings that was judged to be clinically significant was noted should be recorded.
The examination at the start of the study drug showed abnormal values/findings and the subsequent examinations showed worsening of the symptoms.	The date of examination when apparent elevation, reduction, increase or decrease was confirmed in judgment according to the trends in those values or findings should be recorded.

10.2.4 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.2.5 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.3 Additional Points to Consider for Adverse Events

An untoward occurrence generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. Intermittent events for pre-existing conditions or underlying disease should not be considered as PTEs or AEs.
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require a change in concomitant medication.
- Be considered unfavorable by the Investigator for any reason.

PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, signs or symptoms should be recorded appropriately as an AE(s).

Laboratory values and electrocardiogram (ECG) findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG retest and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded

appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of ...").

- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of ...").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of ...").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after any booster administration of the IMP, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of …").
- If the subject experiences a worsening or complication of an AE, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of ...").

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of ICF are not considered as AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Trial procedures:

- Adverse occurrences related to trial procedures after signing of ICF are considered as AEs and should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.4 Procedures

10.4.1 Collection and Reporting of Adverse Events

10.4.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is booster administered study drug (Visit 1 in the **Main Part**) or until discontinuation prior to the first study drug booster administration. For subjects who discontinue prior to the first study drug booster administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is booster administered study drug (Visit 1 in the **Main Part**). Routine collection of AEs will continue until Day 366 (Visit 7) in the **Main Part** or **Extension Part** Day 366. The collection schedule of each AE is located in Section 2.1.

10.4.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed up for the purposes of the protocol.

All AEs, whether considered related to the use of the IMP or not, must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full autopsy report should be supplied, if possible. All findings must be reported on an AE eCRF and on the SAE form (see Section 10.4.4). All findings in subjects experiencing AEs must also be

documented in the subject's source documents. AEs leading to discontinuation from the trial are collected throughout the trial.

The following information will be documented for each event:

- Reported term for the AE.
- Start and end date, duration.
- Serious (Y/N).
- Severity.
- Investigator's opinion of the causality (relationship) between the event and administration of IMP ("related" or "not related").
- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure.
- Action taken with the IMP.
- Treatment for the AE.
- Outcome of event.

10.4.2 Collection and Reporting of Solicited Adverse Events

The occurrence of selected indicators of safety will be collected on eDiary by the subjects for 7 days following each administration of booster IMP dose (including the day of each administration). These will be summarized in the final report under the category "solicited AEs" to differentiate them from unsolicited AEs. Any solicited local (injection site) or systemic AE observed as continuing beyond 7 days after the first or second booster trial vaccination will be additionally recorded as an AE on the AE eCRF for follow-up. For these persistent/prolonged solicited AEs, the end date will be captured on the AE eCRF to permit a separate analysis from the unsolicited AEs.

Any solicited AE that meets any of the following criteria must be entered as an AE on the AE eCRF page.

- Solicited local (injection site) or systemic AEs that lead the subject to withdraw from the trial.
- Solicited local (injection site) or systemic AEs that lead to the subject being withdrawn from the trial by the Investigator.
- Solicited local (injection site) and systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.3).

10.4.3 Collection and Reporting of Adverse Events of Special Interest/ Medically-Attended Adverse Events

AESIs/MAAEs will be collected by close monitoring from Day 1 in the **Main Part** up to Day 366 in the **Main Part** or **Extension Part** Day 366. AESIs /MAAEs need to be reported to the Sponsor as soon as possible after the Investigator becoming aware of the event.

AESIs/MAAEs must be recorded as an AE on the AE eCRF page. AESIs/MAAEs will be summarized separately at the end of the trial.

10.4.4 Collection and Reporting of Serious Adverse Events

Collection of SAEs will commence from the time that the subject is administered the IMP (Day 1 in the **Main Part**). Routine collection of SAEs will continue until the end of the trial (Day 366 in the **Main Part** or **Extension Part** Day 366).

SAEs should be reported according to the following procedure:

An SAE should be reported by the Investigator to the Sponsor within 24 hours of the SAE occurrence, along with any relevant information. The Investigator should submit the detailed SAE form to the Sponsor within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Causality assessment.
- Protocol number.
- Subject identification number.
- Investigator's name.

The SAE form should be transmitted within 24 hours to for the attention of the contact(s) in the list provided to each site.

The Investigator should submit the original copy of the SAE form to the Sponsor.

Any SAE spontaneously reported to the Investigator following the AE collection period should be reported to the Sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.5 Follow-up Procedures

10.5.1 Adverse Events

All AEs will be monitored until resolution or a stable status is reached or until the satisfactory explanation for the changes observed can be found or until the end of the trial, whichever occurs first.

10.5.2 Serious Adverse Events

If information not available at the time of the first report becomes available later, the Investigator should complete a follow-up SAE form or provide other written documentation immediately. Copies of any relevant data from the hospital notes (eg, laboratory tests, discharge summary, postmortem results) should be sent to the Sponsor after redaction for privacy.

All SAEs should be followed up until resolution, permanent outcome of the event, or is otherwise explained. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.5.3 Safety Reporting to Investigators, Investigational Review Boards, and Regulatory Authorities

The Sponsor or designee will be responsible for the reporting of all suspected unexpected serious adverse reactions (SUSARs) and any other SAEs to regulatory authorities, Investigators and IRB, as applicable, in accordance with national regulations in the countries where the trial is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational vaccine or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the trial. The investigational site also will also forward a copy of all expedited reports to their IRB in accordance with national regulations.

10.5.4 Post-Trial Events

Any SAE that occurs outside of the protocol-specified observation period or after the end of the trial but is considered to be caused by the IMP must be reported to the Sponsor. Instructions for how to submit these SAEs will be provided in a handout in the ISF.

11.0 TRIAL-SPECIFIC REQUIREMENT(S)

11.1 Trial-Specific Committee

No independent data monitoring committee will be used for this trial.

11.2 Halting Rules

Although the Sponsor has every intention of completing this trial, they reserve the right to discontinue it at any time for clinical or administrative reasons (see Section 6.4.1).

12.0 DATA HANDLING AND RECORD KEEPING

The full details of procedures for data handling will be documented in the data management plan. AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

12.1 Electronic CRFs

Completed eCRFs are required for each subject who provides a signed informed consent.

The Sponsor or designee will supply investigative sites with access to eCRFs. The Sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this trial to the Sponsor and regulatory authorities. The eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Sponsor personnel or designee and will be answered by the site.

All corrections must be initialed and dated. Corrections to the eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The Investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

All data will have separate source documentation; no data will be recorded directly onto the eCRF.

After the lock of the trial database, any change of, modification of or addition to the data on the eCRFs should be followed by the procedure of the Sponsor or designee (contract research organization [CRO]) on the change and modification of the eCRF. The Investigator must confirm and ensure the data change for completeness and accuracy.

The eCRFs will be reviewed for completeness and acceptability at the trial site during periodic visits by trial monitors. The Sponsor or designee will be permitted to review the subject's medical and hospital records pertinent to the trial to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

12.2 Record Retention

The Investigator agrees to keep the records stipulated in Appendix A and those documents that include (but are not limited to) the trial-specific documents, the identification log of all

participating subjects, medical records, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICF), electronic copy of eCRFs, including all query responses, and detailed records of vaccine disposition to enable evaluations or audits from regulatory authorities, the Sponsor or designee. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility.

Furthermore, ICH E6 Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified vaccine indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical trial site agreement between the Investigator and Sponsor.

Refer to the clinical trial site agreement for the Sponsor's requirements on record retention. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

The Investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, source worksheets, all original signed and dated ICFs, electronic copy of eCRFs, including all query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. The Investigator and the head of the study site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the Sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the Sponsor.

1) The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2) The day 3 years after the date of early termination or completion of the study.

In addition, the Investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to the database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A data review will be conducted prior to the database lock. This review will assess the accuracy and completeness of the trial database, subject evaluability, and appropriateness of the planned statistical methods.

The primary analysis of the **Main Part** will be performed for immunogenicity and safety after all subjects have completed the Day 29 visit in the **Main Part**.

An interim analysis will be performed for immunogenicity and safety after all subjects have completed the **Extension Part** Day 29 visit.

13.1.1 Analysis Sets

Subject evaluability criteria for each Analysis Set will be specified in the SAP, and be fixed before the database lock.

MAIN PART

The Full Analysis Set (FAS), Per-protocol Set (PPS), and Safety Analysis Set (SAS) are defined for this trial. The FAS is defined as all enrolled subjects who receive at least 1 dose of the trial vaccination. Immunogenicity analysis will be conducted using the PPS defined to include subjects in the FAS and who have evaluable immunogenicity data and do not have significant protocol deviations which influence the immunogenicity assessment. Safety analysis will be conducted using the SAS defined as all subjects who receive at least 1 dose of the trial vaccination. The detail of the definitions for the analysis sets will be documented in the SAP.

EXTENSION PART

The FAS, PPS, and SAS in **Extension Part** are defined for this trial. The FAS in **Extension Part** is defined as all subjects enrolled in **Extension Part** who receive at least 1 dose of the trial vaccination in **Extension Part**. Immunogenicity analysis will be conducted using the PPS in **Extension Part** defined to include subjects in the FAS in **Extension Part** and who have evaluable immunogenicity data and do not have significant protocol deviations which influence the immunogenicity assessment. Safety analysis will be conducted using the SAS in **Extension Part** defined as all subjects who receive at least 1 dose of the trial vaccination in **Extension Part**. The detail of the definitions for the analysis sets will be documented in the SAP.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline and demographic information will be analyzed by using the SAS.

13.1.3 Immunogenicity Analysis

MAIN PART

(1) Primary Endpoints

- GMT ratio of neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 15 after a single booster vaccination (14 days after the booster vaccination) compared with that observed on Day 36 (14 days after the second vaccination) in subjects from Study TAK-019-1501.

(2) Analysis for Primary Endpoints

For immunogenicity endpoints, analyses will be conducted using the PPS.

For neutralizing antibody titer values to the ancestral strain (wild-type virus), summary statistics, GMT, and the two-sided 95% CIs will be calculated.

For GMT ratio of serum neutralizing antibody titers to the ancestral strain (wild-type virus) between booster vaccination group in the proposed study and the 2 doses primary vaccinations group in Study TAK-019-1501 (called study group), point estimate and the two-sided 95% CIs will be provided using a 2-way analysis of variance (ANOVA) model. The 2-way ANOVA model will include log-transformed (common log) serum neutralizing antibody titers to the ancestral strain (wild-type virus) 14 days after vaccination as dependent variable, and categorized age (20<= - <65, 65<=) and study group as independent variable. Each estimate by the model will be back transformed to the original scale. The lower limit of two-sided 95% CI of the GMT ratio will be compared with non-inferiority margin of 0.67 to assess the non-inferiority of neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 15 after a single booster vaccination compared with that observed on Day 36 (14 days after 2nd vaccination) in subjects from Study TAK-019-1501. If the lower limit of the 95% CI will be ≥0.67, the immune response to a single heterologous booster vaccination of TAK-019 will be considered to be non-inferior of that to the primary series of TAK-019.

As a sensitivity analysis, statistical results will be demonstrated appropriately based on the different model with the primary analysis (eg, add other subject characteristics to the model as factors).

A detailed analysis method will be specified in the SAP.

(3) Secondary Endpoints

- GMT, GMFR, and SCR (defined at proportion of subjects with ≥4-fold rises from baseline [Day 1]) of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 8, Day 15, Day 29, Day 91, Day 181, and Day 366.
- GMT, GMFR, and SCR of serum neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 8, Day 15, Day 29, Day 91, Day 181, and Day 366.

(4) Analysis for Secondary Endpoints

Analyses will be conducted using the PPS. SCR of each immunogenicity endpoint at each time point will be calculated along with its 95% CI. For antibody titer values and GMFR from baseline, summary statistics, GMT, and the two-sided 95% CIs of each endpoint at each time point will be calculated.

EXTENSION PART

(5) Secondary Endpoints

- GMT, GMFR, and SCR (defined at proportion of subjects with ≥4-fold rises from baseline [**Extension Part** Day 1]) of serum IgG antibody levels to SARS-CoV-2 rS protein on **Extension Part** Day 15, Day 29, Day 91, Day 181, and Day 366.
- GMT, GMFR, and SCR of serum neutralizing antibody titers to the ancestral strain (wild-type virus) on **Extension Part** Day 15, Day 29, Day 91, Day 181, and Day 366.

(6) Analysis for Secondary Endpoints

Analyses will be conducted using the PPS in **Extension Part**. SCR of each immunogenicity endpoint at each time point will be calculated along with its 95% CI. For antibody titer values, summary statistics, GMT and GMFR from baseline (**Extension Part** Day 1), and 95% CIs of each endpoint at each time point will be calculated.

A detailed analysis method will be specified in the SAP.

13.1.4 Safety Analysis

MAIN PART

(1) Primary Endpoints

- Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following the first single booster vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with solicited systemic AEs: fever, fatigue, malaise, myalgia, arthralgia, nausea/vomiting, and headache for 7 days following the first single booster vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with unsolicited AEs for 28 days following the first single booster vaccination (day of vaccination + 27 subsequent days).
- Percentage of subjects with SAEs until Day 29.
- Percentage of subjects with AESIs until Day 29.
- Percentage of subjects with MAAEs until Day 29.

- Percentage of subjects with any AEs leading to subject's withdrawal from the trial until Day 29.
- Percentage of subjects with SARS-CoV-2 infection until Day 29.

(2) Secondary Endpoints

- Percentage of subjects with SAEs throughout the trial.
- Percentage of subjects with AESIs throughout the trial.
- Percentage of subjects with MAAEs throughout the trial.
- Percentage of subjects with any AEs leading to subject's withdrawal from the trial from the day of the first single booster vaccination throughout the trial.
- Percentage of subjects with SARS-CoV-2 infection throughout the trial.

[redacted]

(4) Analysis for Safety Endpoints

Analyses will be performed using the SAS.

Solicited local and systemic AEs will be summarized for each day post the first single booster vaccination and the total duration (day of vaccination + 6 subsequent days).

Unsolicited AEs for 28 days following the first single booster vaccination will be coded using the MedDRA dictionary and tabulated by the System Organ Class (SOC) and the Preferred Term (PT).

The percentage of subjects with SARS-CoV-2 infection will be summarized.

For continuous variables of vital signs, the observed values and the changes from baseline (Day 1 in the **Main Part**) will be summarized for each scheduled time point using descriptive statistics. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled time point will be provided.

A detailed analysis method will be specified in the SAP.

EXTENSION PART

(5) Secondary Endpoints

- Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following the second single booster vaccination (day of vaccination + 6 subsequent days).

- Percentage of subjects with solicited systemic AEs: fever, fatigue, malaise, myalgia, arthralgia, nausea/vomiting, and headache for 7 days following the second single booster vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with unsolicited AEs for 28 days following the second single booster vaccination (day of vaccination + 27 subsequent days).
- Percentage of subjects with SAEs until **Extension Part** Day 29.
- Percentage of subjects with AESIs until **Extension Part** Day 29.
- Percentage of subjects with MAAEs until **Extension Part** Day 29.
- Percentage of subjects with any AEs leading to subject's withdrawal from the trial until **Extension Part** Day 29.
- Percentage of subjects with SARS-CoV-2 infection until **Extension Part** Day 29.
- Percentage of subjects with SAEs throughout the trial.
- Percentage of subjects with AESIs throughout the trial.
- Percentage of subjects with MAAEs throughout the trial.
- Percentage of subjects with any AEs leading to subject's withdrawal from the trial from the day of the second single booster vaccination throughout the trial.
- Percentage of subjects with SARS-CoV-2 infection throughout the trial.

[redacted]

(7) Analysis for Safety Endpoints

Analyses will be performed using the SAS in **Extension Part**.

Solicited local and systemic AEs will be summarized for each day post the second single booster vaccination and the total duration (day of vaccination + 6 subsequent days).

Unsolicited AEs for 28 days following the second single booster vaccination will be coded using the MedDRA dictionary and tabulated by the SOC and the PT.

The percentage of subjects with SARS-CoV-2 infection will be summarized.

For continuous variables of vital signs, the observed values and the changes from baseline (**Extension Part** Day 1) will be summarized for each scheduled time point using descriptive statistics. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled time point will be provided.

A detailed analysis method will be specified in the SAP.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned for the **Main Part**.

An interim analysis of immunogenicity and safety is planned for the **Extension Part** after all subjects have completed **Extension Part** Day 29 (immunogenicity data through **Extension Part** Day 15 and safety data through **Extension Part** Day 29).

13.3 Determination of Sample Size

MAIN PART

In Study TAK-019-1501, GMT and geometric SD of serum neutralizing antibody titers to wild-type virus after the primary vaccinations on Day 36 (14 days after the 2nd vaccination) were 884.4 and 2.80 respectively in the vaccine group.

There is no immunogenicity data of serum neutralizing antibody titers to the ancestral strain (wild-type virus) after a booster vaccination of TAK-019 in Japanese subjects available. However, an estimate has been made on the results of the primary vaccination in Study TAK-019-1501 and the homoeologous booster vaccination in Study 2019nCoV-101 (Part 2). The assumption was made that neutralizing antibody titers on Day 15 in the proposed study would be equivalent to titers on Day 36 in Study TAK-019-1501 (ie, assuming GMT ratio to be 1 and geometric SD to be 2.80). With the guidance document, Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1) Evaluation of Vaccines Against Variants, issued by the PMDA [16], in mind, the non-inferiority margin of GMT ratio between booster vaccination group in the proposed study and the primary vaccination group in Study TAK-019-1501 is set as 0.67 fold. This results in 132 subjects be required as the number of evaluable subjects in PPS to ensure 90% power with the lower limit of 2-sided 95% CI of the GMT ratio exceeding the non-inferiority margin. Considering around 10% non-evaluable subjects, 150 subjects will be required into the proposed study.

EXTENSION PART

The number of subjects in this part is not based on statistical power considerations as this is an **Extension Part** of Study TAK-019-3001 following the **Main Part**.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Trial-Site Monitoring Visits

Monitoring visits to the trial site will be made periodically during the trial to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The Investigator and institution guarantee access to source documents by the Sponsor or designee (CRO) and by the IRB.

All aspects of the trial and its documentation will be subject to review by the Sponsor or designee (as long as blinding is not jeopardized), including but not limited to the ISF, IMP records, subject medical records, ICF documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of CRFs and associated source documents. It is important that the Investigator and other trial personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator should consult with the Sponsor (and IRB as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

The Investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the Sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the Sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the Sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The Investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial site also may be subject to quality assurance audits by the Sponsor or designee. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the vaccine is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of foreign governments. If the trial site is contacted for an inspection by a regulatory body, the

Sponsor should be notified immediately. The Investigator and institution guarantee access for quality assurance auditors to all trial documents as described in Section 14.1.

14.4 Trial Risk Management

The ICH E6 addendum (R2) guidance encourages a risk-based approach to the management of clinical trials and includes requirements for risk control and risk reporting. Before initiation of the trial, Takeda or designee will establish quality tolerance limits (QTLs) taking into consideration the medical and statistical characteristics of the variables and the statistical design of the trial.

At the end of the trial, the quality management approach implemented will be described in the clinical study report (CSR). If applicable, the CSR will summarize important deviations from the predefined QTL and the remedial actions taken.

15.0 ETHICAL ASPECTS OF THE TRIAL

This trial will be conducted with the highest respect for the trial subjects according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki [1], and the ICH Harmonised Tripartite Guideline for GCP E6 (R2) [2]. Each Investigator will conduct the trial according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

15.1 Institutional Review Board Approval

IRBs must be constituted according to the applicable state and federal requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

The Sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject ICF must be obtained and submitted to the Sponsor or designee before commencement of the trial (ie, before shipment of the IMP or trial specific screening activity). The IRB approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The Sponsor will notify the site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from the competent authority to begin the trial. Until the site receives notification/approval no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB, and submission of the Investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the Sponsor or designee.

Incentives should not be used to exert undue influence on subjects for participation. Payments to subjects must be approved by the IRB and Sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for the purpose of conducting the trial. The ICF and the subject information sheet further explain the nature of the trial, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the subject and the fact that the subject is free to withdraw at any time without giving a reason and without prejudice to the subject's further medical care.

Re-consent, re-affirmation of consent: The Investigator should assess the need to re-consent / re-affirmation of consent in situations wherein there has been substantial changes to the subject's status of condition since the original consent. The process should comply with relevant local regulations.

The Investigator is responsible for the preparation, content, and IRB approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet must be approved by both the IRB and the Sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the Investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the trial and (2) decide whether or not to participate in the trial. If the subject determines that they will participate in the trial, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, at the time of consent and prior to the subject entering into the trial. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The Investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to the subject entering into the trial; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet will be stored in the ISF. The Investigator must document the date the subject signs the ICF in the subject's medical record and CRF. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by the subject in the same manner as the original ICF. The date the revised consent was obtained should be recorded in the subject's medical record and CRF, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The Sponsor and designee affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this trial, a subject's source data will only be linked to the

Sponsor's clinical trial database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee, representatives from any regulatory authority, the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's trial participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the ICF process (see Section 15.2).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's CRF).

15.4 Clinical Trial Registration, Publication and Disclosure Policy

15.4.1 Publication and Disclosure

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the study. During and after the study, only the Sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator.

The Investigator needs to obtain a prior written approval from the Sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, the Sponsor will, as a minimum register all clinical trials conducted in subjects that it sponsors anywhere in the world, on publicly accessible websites such as Japan Registry of Clinical Trials (jRCT), ClinicalTrials.gov and/or others according to local requirements, before trial initiation. The Sponsor contact information, along with the investigator's city, country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda clinical trial disclosure policy aims to comply with the clinical trial data disclosure requirements of all relevant regions. The Sponsor will post the results of this clinical trial regardless of outcome, on publicly accessible websites such as ClinicalTrials.gov and/or others, as required by applicable laws and/or regulations.

Completion of trial corresponds to the date on which the final subject will be examined or receive an intervention for the purpose of final collection of data (usually corresponds to last subject last visit).

If the deadline for results disclosure cannot be met, an application for extension with scientific justification will be provided.

15.4.4 Publication of Trial Results

The results of this trial are expected to be published in a peer-reviewed scientific journal publication of trial results will follow Takeda publication policies, applicable international standards and guidelines for good publication practice, applicable laws, and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the trial must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the Sponsor or Sponsor's designee will obtain clinical trial insurance against the risk of injury to clinical trial subjects. Refer to the clinical trial site agreement regarding the Sponsor's policy on subject compensation and treatment for injury. If the Investigator has questions regarding this policy, he or she should contact the Sponsor or Sponsor's designee.

16.0 REFERENCES

1. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH harmonised guideline. Integrated Addendum to ICH E6 (R2): Guideline for Good Clinical Practice E6.
3. Su S, Wong G, Shi W, Liu J, Lai A, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol. 2016;24(6):490-520.
4. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
5. World Health Organization (WHO). Naming the coronavirus disease (COVID-19) and the virus that causes it. Country & Technical Guidance - Coronavirus disease (COVID-19). Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it. (accessed 20 January 2022).
6. WHO. Coronavirus disease 2019 (COVID-19) Situation Report – 51. 11 March 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10. (accessed 20 January 2022).
7. WHO. Coronavirus disease 2019 (COVID-19) Weekly epidemiological update on COVID-19 - 8 June 2022. Edition 95. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---8-june-2022. (accessed 13 June 2022).
8. Ministry of Health, Labour and Welfare (MHLW). Status of COVID-19 prevalence and initiatives of MHLW. 22 June 2022. Available from: https://www.mhlw.go.jp/stf/newpage_26173.html. (accessed 13 June 2022).
9. MHLW. Clinical Management of Patients with COVID-19, version 6.1. 28 December 2021. Available from: https://www.mhlw.go.jp/content/000875183.pdf (accessed 18 January 2022).
10. MHLW. Development of medications and vaccines. Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00223.html. (accessed 18 June 2022).

11. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet. 2021 Dec 18;398(10318):2258-76.
12. Centers for Disease Control and Prevention (CDC). The Possibility of COVID-19 after Vaccination: Breakthrough Infections – Updated 17 December 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness/why-measure-effectiveness/breakthrough-cases.html. (accessed 18 January 2022).
13. Prime Minister's Office of Japan. Novel Coronavirus Vaccines. Available from: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html. (accessed 31 January 2022).
14. MHLW. Announcements on Booster Vaccination (4th Dose). Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/vaccine_fourth-dose.html. (accessed on 13 June 2022).
15. Pharmaceuticals and Medical Devices Agency (PMDA). Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2. 02 September 2020. Available from: https://www.pmda.go.jp/files/000237021.pdf (accessed 18 January 2022).
16. PMDA. Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1) Evaluation of Vaccines Against Variants. 05 April 2021. Available from: https://www.pmda.go.jp/files/000240416.pdf (accessed 18 January 2022).
17. WHO. Reducing pain at the time of vaccination: WHO position paper. Vaccine. 2015, 90, 505-16.
18. Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007 [cited 20 January 2022]. Available from: https://www.fda.gov/media/73679/download
19. CDC. Clinical Considerations: Myocarditis and Pericarditis after Receipt of mRNA COVID-19 Vaccines Among Adolescents and Young Adults. Available from: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html. (accessed 27 June 2022).
20. Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices - United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(27):977-82.
21. Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. July 2017 [cited

20 January 2022]. Available from:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf