Title: A Phase 1/2, Randomized, Observer-Blind, Placebo-Controlled Trial to Evaluate the Safety and Immunogenicity of TAK-019 by Intramuscular Injection in Healthy Japanese Male and Female Adults Aged 20 Years and Older

NCT Number: NCT04712110

Protocol Approve Date: 09-Apr-2021

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

PROTOCOL

<Title>

A Phase 1/2, Randomized, Observer-Blind, Placebo-Controlled Trial to Evaluate the Safety and Immunogenicity of TAK-019 by Intramuscular Injection in Healthy Japanese Male and Female Adults Aged 20 Years and Older

<Short Title>

A Phase 1/2 Placebo-Controlled 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-019-1501		
IND Number:	022430	**EudraCT Number:**	2020-004042-11
Investigational Medicinal Product (s):	TAK-019		
Takeda Approval Date:	9 April, 2021		
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

Date	Amendment version	Region
9-April-2021	1 (Ver 2.0)	All trial sites in Japan

This document describes the changes in reference to the Protocol Incorporating Amendment No. 1 (Ver 2.0).

The primary purpose of this amendment is to change the study design to Open-Label trial after the database lock for the primary analysis (i.e., Day 50 data). The following is a summary of the changes made in the amendment:

- Change the study design to Open-Label trial after the database lock of Day 50.
  Justification: In February 2021, the first SARS-CoV-2 vaccine was approved in Japan. And immunization program has started in Japan since February 2021.

  In order to provide an opportunity of vaccination of the approved SARS-CoV-2 vaccine in the subjects who received placebo in TAK-019-1501 study, the trial will be unblinded after the database lock of Day 50 data so that the subjects will be informed about the vaccination assignment (TAK-019 or Placebo) in the trial.

- Section 4.1 'Background' was updated to reflect with the latest information (availability of SARS-CoV-2 vaccine in Japan and overseas clinical trials).

- Addition of a scenario that the trial will be switched to a post-marketing clinical trial.

  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).

- Correction of inconsistencies within the original protocol.

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2.0 TRIAL SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited		**Product Name:** TAK-019
Trial Title: A phase 1/2, randomized, observer-blind, placebo-controlled trial to evaluate the safety and immunogenicity of TAK-019 by intramuscular injection in healthy Japanese male and female adults aged 20 years and older		
IND No.: 022430		**EudraCT No.:** 2020-004042-11
Trial Identifier: TAK-019-1501	**Phase:** 1/2	**Blinding Schema:** Observer-Blind
Indication: Prevention of infection disease caused by Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2).		

Trial Design:

This is a phase 1/2 randomized, observer-blind, placebo-controlled trial to evaluate the safety and immunogenicity of 2 doses of TAK-019 by intramuscular (IM) injection 21 days apart in healthy Japanese male and female adults.

The trial is planned to enroll 200 subjects. (150 subjects in the TAK-019 arm and 50 subjects in the placebo arm). Of them, 140 subjects will be stratified by age as ≥ 20 years to < 65 years (100 subjects in the TAK-019 arm and 40 subjects in the placebo arm), and 60 subjects will be stratified by age of ≥ 65 years (50 subjects in the TAK-019 arm and 10 subjects in the placebo arm).

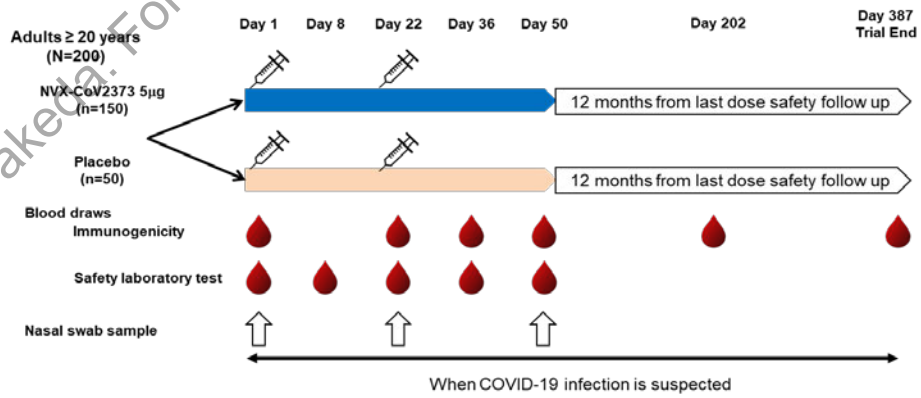
Once all screening assessments following informed consent are completed and eligibility is confirmed, the subject will receive the first dose of TAK-019 or saline placebo, by IM injection. And the subject will receive the second dose of TAK-019 or saline placebo after 21 days of the first vaccination (Day 22). All subjects will be followed up for safety and immunogenicity for 12 months after the last 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 each vaccination (including the day of vaccination). All subjects will be followed for unsolicited AEs for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days]) + 28 days following second vaccination [day of vaccination + 27 subsequent days]).

All subjects will be followed for serious adverse event (SAEs), adverse event of special interest (AESI), medically attended adverse events (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, Day 22, and Day 50) and in case of clinical symptoms suspected for Coronavirus Disease 2019 (COVID-19) throughout the trial.

The primary analysis will be performed for safety and immunogenicity after all subjects have completed the Day 50 visit. After the database lock of the primary analysis (Day 50 data), the trial will be unblinded and changed to an Open-Label study. After the database lock of Day 50 data, the subjects will be informed about the vaccination assignment (TAK-019 or Placebo) and obtain reconsent about study continuation from the subjects.

Schematic of phase 1/2 Trial



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

Primary Objectives:

To evaluate the safety and immunogenicity of 2 doses of TAK-019 by IM injection in healthy Japanese male and female adults aged ≥ 20 years, given 21 days apart.

Safety:

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

- Solicited local and systemic AEs for 7 days following each vaccination (day of vaccination + 6 subsequent days).
- Unsolicited AEs for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days] + 28 days following second vaccination [day of vaccination + 27 subsequent days].
- SAEs, AESI, MAAEs, AEs leading to trial withdrawal or discontinuation of vaccination and SARS-CoV-2 infection until Day 50.

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 on Day 36.

Secondary Objectives:

Safety:

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

- SAEs, AESI, MAAEs, AEs leading to trial withdrawal or discontinuation of vaccination and SARS-CoV-2 infection throughout the trial.

Immunogenicity:

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

- Serum IgG antibody levels to SARS-CoV-2 rS protein on Day 22, Day 50, Day 202, and Day 387.
- Serum neutralizing antibody titers to wild-type virus on Day 22, Day 36, Day 50, Day 202, and Day 387.

Exploratory Objectives:

[redacted]

Subject Population:

Healthy Subjects: Yes

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

Planned Number of Subjects: 200 subjects (150 subjects in the TAK-019 arm and 50 subjects in the placebo arm). Subjects will be stratified by age as ≥ 20 years to < 65 years (100 subjects in the TAK-019 arm and 40 subjects in the placebo arm), and ≥ 65 years (50 subjects in the TAK-019 arm and 10 subjects in the placebo arm).

Planned Number of Trial Arms: 2 arms

- Arm 1: (n=150 subjects), Investigational Product (TAK-019).
- Arm 2: (n=50 subjects), Placebo (0.9% sodium chloride).

Planned Number of Trial Sites: 2 sites

Key Inclusion Criteria:

- 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 trial procedures and are available for the duration of

follow-up.

Key Exclusion Criteria:

1. Subjects who received any other SARS-CoV-2 or other experimental novel coronavirus vaccine prior to the trial.
2. Subjects who have close contact of anyone known to have COVID-19 within 30 days prior to the trial vaccination.
3. Subjects who were tested positive for SARS-CoV-2 prior to the trial or before the trial vaccination.
4. Subjects who are on current treatment with other investigational agents for prophylaxis of COVID-19.
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 vaccination.
7. Subjects with known hypersensitivity or allergy to any of the investigational vaccine components.
8. 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.
9. Subjects with known or suspected impairment/alteration of immune function, including history of any autoimmune disease or neuro-inflammatory disease.
10. Abnormalities of splenic or thymic function.
11. Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
12. Subjects with any serious chronic or progressive disease (eg, neoplasm, insulin dependent diabetes, cardiac, renal or hepatic disease).
13. Subjects with body mass index (BMI) greater than or equal to 30 kg/m^2 (BMI= weight in kg/ height in $meters^2$).
14. Subjects participating in any clinical trial with another investigational product within 30 days prior to the trial vaccination or intend to participate in another clinical trial at any time during the conduct of this trial.
15. 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 trial dose administration.
16. Subjects with acute or chronic clinically significant disease including pulmonary, cardiovascular, hepatic or renal abnormality evaluated by physical examination.
17. Subjects involved in the trial conduct or their first-degree relatives.
18. Subjects who have history or infection of hepatitis B, hepatitis C, and human immunodeficiency virus infection.
19. Female subjects who are pregnant or breastfeeding.

Trial Vaccine and Placebo:

Investigational vaccine: TAK-019 for injection as a 0.5 mL volume will be used. The investigational vaccine contains 5 µg of SARS-CoV rS plus 0.05 mg of Matrix-M1 adjuvant.

Placebo: 0.9% sodium chloride.

Route of Administration: IM injection in the upper arm.

Duration of the Trial and Subject Participation:

The trial participation for each subject is for 12 months following the last IMP vaccination.

Criteria for Evaluation and Analyses:

Primary Endpoints:

Safety:

- Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following each 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 each vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with unsolicited AEs for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days] + 28 days following second vaccination [day of vaccination + 27 subsequent days]).
- Percentage of subjects with SAE until Day 50.
- Percentage of subjects with AESI until Day 50.
- Percentage of subjects with MAAEs until Day 50.
- Percentage of subjects with any AE leading to discontinuation of vaccination.
- Percentage of subjects with any AE leading to subject's withdrawal from the trial until Day 50.
- Percentage of subjects with SARS-CoV-2 infection until Day 50.

Immunogenicity:

- Geometric mean titers (GMT), geometric mean fold rise (GMFR), seroconversion rate (SCR; defined at proportion of subjects with ≥ 4-fold rises in titer if naïve at baseline OR proportion of subjects with ≥ 2-fold rises in titer if seropositive at baseline), and seroresponse rate (SRR; defined at proportion of subjects with ≥ 95 percentile in titer at baseline (Day 1) for all subjects) of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 36.

Secondary Endpoints:

Safety:

- Percentage of subjects with SAE throughout the trial.
- Percentage of subjects with AESI throughout the trial.
- Percentage of subjects with MAAEs throughout the trial.
- Percentage of subjects with any AE leading to subject's withdrawal from the trial from the day of vaccination throughout the trial.
- Percentage of subjects with SARS-CoV-2 infection throughout the trial.

Immunogenicity:

- GMT, GMFR, SCR, and SRR of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 22, Day 50, Day 202, and Day 387.
- GMT, GMFR, SCR, and SRR of serum neutralizing antibody titers to wild-type virus on Day 22, Day 36, Day 50, Day 202, and Day 387.

Exploratory Endpoints:

[redacted]

Statistical Considerations:

All analyses will be performed descriptively by treatment groups, unless otherwise specified.

Safety analysis:

Analyses will be performed using the Safety Analysis Set.

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

Unsolicited AEs for 49 days following first vaccination will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and tabulated by the System Organ Class and the Preferred Term.

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

For continuous variables of laboratory tests and 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.

Immunogenicity Analysis:

Analyses will be conducted using the Per-protocol Set. SCR and SRR of each endpoint at each time point will be calculated along with its 95% confidence interval (CI) in each treatment group.

For antibody titer values and changes from baseline, GMT and GMFR, and summary statistics and 95% CIs of each endpoint at each time point will be calculated in each treatment group.

Sample Size Justification:

The objective of this trial is to evaluate the safety and immunogenicity of TAK-019 in the Japanese population. This trial is designed to be descriptive, and therefore the sample size was not determined based on formal statistical power calculations. The sample size for the trial is based on clinical and practical consideration and is considered sufficient to evaluate the objective of the trial. With 150 subjects in the TAK-019 group, the probability to observe at least one AE of 2% event rate is 95%. Considering the risk of disease burden of COVID-19, the number of subjects in the placebo group in this trial was set as minimum as possible especially in the subjects ≥ 65 years old.

Interim Analysis:

An interim analysis is not planned in the trial.

The primary analysis will be performed for safety and immunogenicity after all subjects have completed the Day 50 visit. After the primary analysis, the trial will be unblinded only for the Sponsor personnel. After the database lock of the primary analysis data (i.e., Day 50 data), the trial will be unblinded and changed to an Open-Label study

Data Monitoring Committee:

No Independent Data Monitoring Committee will be used for this trial.

2.1 Schedule of Trial Procedures

Procedure	Day 1 [a]		Day 8	Day 22 [b]	Day 36 [b]	Day 50 [b]	Day 202 [b]	Day 387 [b] or Early Termination / Trial End [c]
	Before vaccination	After vaccination						
Visits number	1		2	3	4	5	6	7
Days Post Dose 1	0		7	21	35	49	201	386
Days Post Dose 2	-		-	0	14	28	180	365
Visit window (Days)	-		+3	+3	+3	+3	±7	±14
Signed informed consent [d]	X							
Assessment of eligibility criteria [e]	X			X				
Demographics	X [f]							
Medical history [g]	X							
Medication history [g]	X			X				
Physical examination [h]	X		X	X		X		X
Vital signs	X	X [i]	X	X [i]		X		X
Pregnancy test [j]	X			X		X	X	X
Oral body temperature [k]	X	X	X	X		X		X
Randomization	X							
Vaccine administration		X		X				
Dispensing eDiary		X						
Assessment of eDiary			X	X	X	X		
Solicited and unsolicited AEs [l]		X	X	X	X	X		
Concomitant medications [m]	X		X	X	X	X		
SAEs [n]		X	X	X	X	X	X	X
AEs leading to IMP withdrawal		X	X	X				
AEs leading to withdrawal from trial		X	X	X	X	X	X	X
AESI and MAAEs		X	X	X	X	X	X	X
Blood draw for immunogenicity tests	X			X [o]	X	X	X	X
Blood draw for safety laboratory test [p]	X [f]		X	X	X	X		
Nasal swab sample collection [q]	X [f]			X		X		

Abbreviations: AE: adverse event; AESI: adverse event of special interest; BMI: body mass index; COVID-19: coronavirus disease 2019; eDiary: electronic diary; IMP: investigational medicinal product; MAAE: medically-attended AE; PCR: polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: Severe Acute Respiratory Syndrome coronavirus-2.

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

[b] The date of the second vaccination (Day 22 [Visit 3]) is used as the starting date to define the date of visit. Each of the visit dates is therefore defined as follows; Day 36 (Visit 4) is on the 14th day (+3 days) after the second vaccination, Day 50 (Visit 5) is on the 28th day (+3 days) after the second vaccination, Day 202 (Visit 6) is on the 180th day (±7 days) after the second vaccination, and Day 387 (Visit 7) is on the 365th day (±14 days) after the second vaccination. In case where the second vaccination is not done for some reason, the date of the first vaccination (Day 1 [Visit 1]) is used as the starting date to define each of the visit dates.

[c] For the subjects who discontinue or 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.

[d] 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.

[e] Assessment of eligibility by review of all inclusion and exclusion criteria or contraindications will be documented before each vaccination at Day 1 and at Day 22.

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

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

[h] Height and weight will be measured at Day 1 before vaccination only and BMI will be calculated. On the day of vaccinations ie, Day 1 and Day 22, 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.

[i] On the day of vaccinations, 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.

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

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

[l] Solicited local and systemic AEs will be collected for 7 days after each vaccination (day of vaccination + 6 subsequent days) and unsolicited AEs will be collected for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days] + 28 days following second vaccination [day of second vaccination + 27 subsequent days]).

[m] All concomitant medications information will be collected for 28 days following each vaccination until Day 50. Follow up for concomitant medications associated with SAEs, AEs leading to withdrawal from trial and treatments for COVID-19 infection will be performed 365 days following the second vaccination.

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

[o] Blood collection for the immunogenicity test on Day 22 should be performed before vaccination.

[p] Refer to Table 9.b for the list of the safety laboratory tests to be performed.

[q] Nasal swabs will be collected at pre-specified time points (Day 1, Day 22, and Day 50) and in case of suspected for COVID-19 clinical symptoms throughout the trial. For the sample on Day 1, nasal swabs taken within 14 days before Day 1 (Day -14 to Day 1) can be used. If subjects show a sign of SARS-CoV-2 infection during the trial (from Day 1 to Day 387), 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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bAb	binding antibody
BMI	body mass index
CI	confidence interval
CoV	coronavirus
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
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
HIV	human immunodeficiency virus
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
PCR	polymerase chain reaction
PPS	Per-protocol Set
PTE	pretreatment event

QTL	quality tolerance limits
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*
SRR	seroresponse rate
SUSAR	suspected unexpected serious adverse reaction
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Coronaviruses (CoVs) 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).

CoVs 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 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].

COVID-19 has spread throughout China and to over 216 other countries and territories, including Japan [6]. On 11 March 2020, the World Health Organization (WHO) officially declared COVID-19 a pandemic [7]. As of 30 August 2020, the WHO reported close to 25 million confirmed cases and over 838 thousand deaths globally [8]. In Japan, the Ministry of Health, Labour, and Welfare (MHLW) reported 66,481 confirmed and probable cases of COVID-19, with 1,263 deaths in Japan [9]. 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) [10].

A guideline on Clinical Management of Patients with COVID-19 has been published and is continually being updated as the evidence base develops. Therapies that are under investigation include antiviral therapies, immune-based therapies such as blood-derived products, immunomodulators and adjunctive therapies to address serious potential complications [10].

Novavax, Inc. is developing a recombinant vaccine (NVX-CoV2373) formulated with the saponin-based Matrix-M1 as an immunologic adjuvant for the prevention of disease caused by SARS-CoV-2 outside Japan. The development of NVX-CoV2373 in Japan will be carried out by Takeda Pharmaceutical Company Limited (development code TAK-019). TAK-019 is SARS-CoV-2 recombinant spike (rS) protein nanoparticle vaccine (SARS-CoV-2 rS). TAK-019 is constructed from the full-length wild type SARS-CoV-2 S glycoprotein (GP) based upon the GenBank gene sequence MN908947, nucleotides 21563-25384, from the 2019 SARS-CoV-2 genome. The S protein is a type 1 trimeric GP of 1273 amino acids that is produced as an inactive S0 precursor. The S-gene was codon optimized for expression in *Spodoptera frugiperda* (Sf9)

insect cells. TAK-019 is intended for administration with Matrix-M1 adjuvant, which is a saponin-based adjuvant that has previously shown to enhance the immunogenicity of other nanoparticle vaccines in nonclinical and clinical studies.

Nonclinical Studies

As non-clinical pharmacological evaluations, immunogenicity evaluation using animal models of mice, hamsters, cynomolgus macaques and baboons, and protective efficacy evaluation using mice, hamsters and cynomolgus 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 spike 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-M1 adjuvant by intramuscular (IM) injection. SARS-CoV-2 rS with or without 50 µg Matrix-M1 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 in rat is underway.

Clinical Studies

Phase 1/2 study outside Japan

Currently, a phase 1/2 study (2019nCoV-101 study) is underway in the United States and Australia to evaluate the safety and immunogenicity of TAK-019 in healthy adults aged 18 to 59 years. The interim data of the study have been reported [11]. Results of an interim analysis for the phase 1 portion of the trial at Day 35 showed that SARS-CoV-2 rS with Matrix-M1 adjuvant was well tolerated and elicited robust immunogenicity. There were no serious adverse events (SAEs) or adverse events of special interest (AESI) reported. Local reaction was mainly mild in severity and of short duration (mean ≤ 2 days). The second vaccination showed more solicited local and systemic adverse events than the first vaccination. The adjuvant significantly enhanced immune responses (anti-S immunoglobulin G [IgG], human angiotensin-converting enzyme 2 receptor binding inhibition antibody, and neutralizing antibody). The 2-dose (5 µg and 25 µg) of SARS-CoV-2 rS /Matrix-M1 adjuvant 50 µg induced higher antibody responses than the mean responses in convalescent sera from clinically severe COVID-19 patients.

Please refer investigator's brochure (IB) for further details.

In addition, currently a phase 2b trial in South Africa, a phase 3 trial in the United Kingdom and a phase 3 in the United States are underway to evaluate the efficacy, safety and immunogenicity of TAK-019.

In the United Kingdom phase 3 study, the vaccine demonstrated overall efficacy against mild, moderate and severe disease of 89.7% (95% CI: 80.2, 94.6) for all circulating strains and 96.4% (95% CI: 73.8, 99.5) for the original COVID-19 strain. In the phase 2b trial taking place in South Africa, overall efficacy of 48.6% (95% CI: 28.4, 63.1) and 55.4% (95% CI: 35.9, 68.9) among the HIV- negative trial participants was shown in a region where the vast majority of strains are B1.351 escape variants. Across both trials, NVX-CoV2373 demonstrated 100% protection against severe disease, including all hospitalization and death[12].

Benefit-Risk Assessment

TAK-019 is a nanoparticle vaccine manufactured by the Baculovirus-Sf9 platform technologies. By using this technologies, it is possible to cut out only the target part from the pathogen and produce nanoparticles of the target antigen by gene recombination. In comparison with other vaccines produced by cell culture or other methods, it is possible to efficiently produce a large amount of the target antigen.

In overseas clinical trials, TAK-019 induces the SARS-CoV-2 binding antibody level and neutralizing antibody titer comparable to those in serum taken from COVID-19 patients recovered from the infection, indicating that TAK-019 will show similar level of immunogenicity and prophylactic effect against SARS-CoV-2 in Japanese adult.

As the results of overseas clinical trials reported to date, TAK-019 is well-tolerated and SAEs are not reported. Since there is a risk of disease enhancement that is known for several vaccines [13,14,15,16], the possibility to increase a risk of COVID-19 disease enhancement cannot fully be denied; however, no COVID-19 disease enhancement by TAK-019 is reported to date. Since this is a placebo-controlled trial and a part of the subjects will receive placebo, the subjects will potentially have an opportunity loss to enter other COVID-19 vaccine studies or receive approved SARS-CoV-2 vaccines.

Considering the subject's risk of COVID-19 outside the trial, and the nonclinical and clinical data to date, the Sponsor considers the potential benefits of participation to exceed the risks.

4.2 Rationale for the Proposed Trial

CoVs are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as MERS and SARS.

The primary objective of this trial is to evaluate safety and immunogenicity of TAK-019 by intramuscular injection compared with placebo in the Japanese healthy population. Till date, a total of 4 clinical trials are ongoing outside of Japan. The interim analysis of ongoing phase 1 study

outside Japan (Study 2019Cov-101) shows 2 doses regimens of SARS-CoV-2 rS 5 µg with Matrix-M1 50 µg were well tolerated and induced robust immune responses with high levels of neutralizing antibodies and binding antibodies against spike protein in healthy adults 18 to 59 years of age [11]. In addition, there was no concern observed in nonclinical toxicology study. Both nonclinical and overseas clinical data to date support initiation of the clinical trial for TAK-019 in Japan.

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

The primary objective is to evaluate the safety and immunogenicity of 2 doses of TAK-019 by IM injection in healthy Japanese male and female adults aged ≥ 20 years, given 21 days apart.

Safety:

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

- Solicited local and systemic adverse events (AEs) for 7 days following each vaccination (day of vaccination + 6 subsequent days).
- Unsolicited AEs for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days] + 28 days following second vaccination [day of vaccination + 27 subsequent days]).
- SAEs, AESI, medically-attended AEs (MAAEs), AEs leading to trial withdrawal or discontinuation of vaccination and SARS-CoV-2 infection until Day 50.

Immunogenicity:

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

- Serum IgG antibody levels to SARS-CoV-2 rS protein on Day 36.

5.1.2 Secondary Objectives

Safety:

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

- SAEs, AESI, MAAEs, AEs leading to trial withdrawal or discontinuation of vaccination and SARS-CoV-2 infection throughout the trial.

Immunogenicity:

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

- Serum IgG antibody levels to SARS-CoV-2 rS protein on Day 22, Day 50, Day 202, and Day 387.
- Serum neutralizing antibody titers to wild-type virus on Day 22, Day 36, Day 50, Day 202, and Day 387.

[redacted]

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

Safety:

- Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following each 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 each vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with unsolicited AEs for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days] + 28 days following second vaccination [day of vaccination + 27 subsequent days]).
- Percentage of subjects with SAE until Day 50.
- Percentage of subjects with AESI until Day 50.
- Percentage of subjects with MAAEs until Day 50.
- Percentage of subjects with any AE leading to discontinuation of vaccination.
- Percentage of subjects with any AE leading to subject's withdrawal from the trial until Day 50.
- Percentage of subjects with SARS-CoV-2 infection until Day 50.

Immunogenicity:

- Geometric mean titers (GMT), geometric mean fold rise (GMFR), seroconversion rate (SCR; defined at proportion of subjects with ≥ 4-fold rises in titer if naïve at baseline OR proportion of subjects with ≥ 2-fold rises in titer if seropositive at baseline), and seroresponse rate (SRR; defined at proportion of subjects with ≥ 95 percentile in titer at baseline (Day 1) for all subjects) of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 36.

5.2.2 Secondary Endpoints

Safety:

- Percentage of subjects with SAE throughout the trial.
- Percentage of subjects with AESI throughout the trial.

- Percentage of subjects with MAAEs throughout the trial.
- Percentage of subjects with any AE leading to subject's withdrawal from the trial from the day of vaccination throughout the trial.
- Percentage of subjects with SARS-CoV-2 infection throughout the trial.

Immunogenicity:

- GMT, GMFR, SCR, and SRR of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 22, Day 50, Day 202, and Day 387.
- GMT, GMFR, SCR, and SRR of serum neutralizing antibody titters to wild-type virus on Day 22, Day 36, Day 50, Day 202, and Day 387.

[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a phase 1/2 randomized, observer-blind, placebo-controlled trial to evaluate the safety and immunogenicity of 2 doses of TAK-019 by IM injection 21 days apart in healthy Japanese male and female adults.

The trial is planned to enroll 200 subjects (150 subjects in the TAK-019 arm and 50 subjects in the placebo arm). Of them, 140 subjects will be stratified by age as ≥ 20 years to < 65 years (100 subjects in the TAK-019 arm and 40 subjects in the placebo arm), and 60 subjects will be stratified by age of ≥ 65 years (50 subjects in the TAK-019 arm and 10 subjects in the placebo arm).

Once all screening assessments following informed consent are completed and eligibility is confirmed, the subject will receive the first dose of TAK-019 or saline placebo, by IM injection. And the subject will receive the second dose of TAK-019 or saline placebo after 21 days of the first vaccination (Day 22). All subjects will be followed up for safety and immunogenicity for 12 months after the last trial vaccination.

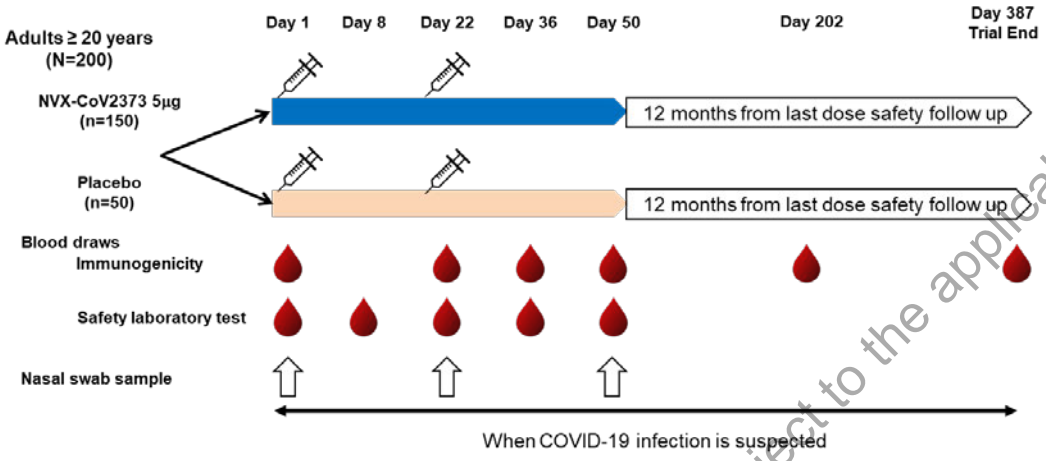
Each subject will be provided with an electronic diary (eDiary). Oral body temperature and solicited local and systemic adverse events (AEs) will be recorded in the eDiary by the subjects for 7 days after each vaccination (including the day of vaccination). All subjects will be followed for unsolicited AEs for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days]) + 28 days following second vaccination [day of vaccination + 27 subsequent days]).

All subjects will be followed for SAEs, AESI, 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, Day 22, and Day 50) and in case of clinical symptoms suspected for COVID-19 throughout the trial.

The primary analysis will be performed for safety and immunogenicity after all subjects have completed the Day 50 (the trial visit after 28 days from the date of the second vaccination) visit. After the database lock of the primary analysis (i.e., Day 50 data), the trial will be unblinded and changed to an Open-Label study. The subjects will be informed about the vaccination assignment (TAK-019 or Placebo) and reconsent about study continuation will be obtained from subjects.

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

Figure 6.a Schematic of Trial Design



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

6.2 Justification for Trial Design, Dose, and Endpoints

Since this is the first trial to evaluate safety and immunogenicity of TAK-019 in Japanese population, eligible participants will be healthy Japanese adults. In overseas phase 1 clinical trials, TAK-019 has been well tolerated in healthy young adults and any safety concerns for older adults have not been reported as this time. Since it has been known that the high risk of disease burden with COVID-19 is in older adults (≥ 65 years old), it is important to evaluate safety and immunogenicity of TAK-019 in Japanese older adults. Therefore, in order to enroll certainly older adults in the trial, subjects will be stratified by age as ≥ 20 years to < 65 years and ≥ 65 years.

The trial design (assessment timing and period of immunogenicity and safety endpoints, having the placebo arm, 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 [17]. In addition, to ensure comparison with overseas results, the same immunogenicity and safety endpoints (solicited AEs) which are evaluating in overseas phase 3 trial in U.S. have been set in this trial.

The dose of TAK-019 (5 µg of SARS-CoV-2 rS and 50 µg of Matrix-M1), the administration route (IM injection), and the schedule (2 doses administered 21 days apart) for this trial have been selected based on assessment of available safety and immunogenicity data from overseas phase 1 studies of the 2019nCoV-201 trial.

Please refer to the IB for further details.

6.3 Planned Duration of Subject's Participation in the Trial

The trial participation for each subject is for 12 months following the second trial vaccination.

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 including laboratory test results.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

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 laboratory tests), 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. 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 vaccination until 3 months after the last trial 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 9.1.14.

7.2 Exclusion Criteria

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

1. Subjects who received any other SARS-CoV-2 or other experimental novel coronavirus vaccine prior to the trial.
2. Subjects who have close contact of anyone known to have COVID-19 within 30 days prior to the 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).

3. Subjects who were tested positive for SARS-CoV-2 prior to the trial or on the test before the trial vaccination.
4. Subjects who are on current treatment with other investigational agents for prophylaxis of COVID-19.
5. Subjects who 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 vaccination.
7. Subjects with a known hypersensitivity or allergy to any of the investigational vaccine components (including excipients as summarized in Section 8.1).
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 any illness or history of 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 first administration of 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 first administration of IMP.
    d. Receipt of immunoglobulins and/or any blood products within the 3 months preceding the first administration of IMP, or planned administration during the trial
    e. Receipt of immunostimulants within 60 days preceding the first 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 first administration of IMP or planned administration during the trial.
    g. Known human immunodeficiency virus (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 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 any dose).
18. Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to 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 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 infection.
23. Subjects with history of substance or alcohol abuse within 2 years prior to 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 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 last dose of IMP.
27. Any positive or indeterminate pregnancy test (Section 9.1.14).

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 should be administrated before/after 14 days for inactivated vaccines or 28 days for live vaccines prior to 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 administration of IMP. These situations are listed below. In the event that a subject meets a criterion for delay of IMP administration, the subject may receive the IMP once the window for delay has passed as long as the subject is otherwise eligible for trial participation.

The criteria should be adapted to reflect single or multiple doses.

- 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. Investigational medicinal product 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 during the trial (the double-blind phase up to the database lock of Day 50 data and the Open-Label phase after the database lock of Day 50 data) 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 9.1.15.

7.6 Criteria for Premature Discontinuation of Investigational Medicinal Product Administration

There are also circumstances under which receipt of further IMP administration is a contraindication in this trial. These circumstances include anaphylaxis or severe hypersensitivity reactions following the initial vaccination. If these reactions occur, the subject must not receive additional IMP but is encouraged to continue in trial participation for safety follow-up.

Early termination of a subject's trial participation will by default prevent the subject from receiving further doses of IMP, as the subject will no longer be participating in the trial. In addition to criteria for early termination of a subject's participation (see Section 7.5), other situations may apply in which subjects may continue participating in the trial (eg, contributing safety data according to the protocol) but IMP administration is discontinued. Even if the subject is deemed ineligible to receive further doses of IMP, all efforts should be made to continue the collection of safety data according to protocol.

In addition, the primary reason for premature discontinuation of IMP administration should be recorded in the eCRF ("end of IMP administration" page) using the following categories:

1. Adverse Event: The subject has experienced an AE (irrespective of being related/unrelated to the IMP or trial-related procedures) for which subsequent IMP administration(s) impose an unacceptable risk to the subject's health, but the subject will continue trial participation for safety, or a subset of other trial procedures.
2. Lost to follow-up: The subject did not return to the site and at least three 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 an AE). The reason for withdrawal, if provided, should be recorded in the eCRF.
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 prior to the next IMP administration.
6. Protocol deviation: A protocol deviation is any change, divergence, or departure from the trial design or procedures of a trial protocol. The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety or rights.
7. Pregnancy: Any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further IMP administration. Pregnant subjects should, however, be asked to continue participating in the trial contributing data to the safety follow-up

according to the protocol. In addition, the site should maintain contact with the pregnant subject and complete a "Clinical Trial Pregnancy Form" as soon as possible. If the subject agrees, she should be followed-up until the birth of the child, or spontaneous or voluntary termination; when pregnancy outcome information becomes available, the information should be captured using the same form. Data obtained from the "Clinical Trial Pregnancy Form" will be captured in the safety database.

8. Other.

For criteria which also lead to early termination of a subject's trial participation, please refer to Section 7.5.

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. The sites will use commercially available saline solution standardized by the Japanese Pharmacopeia as the placebo.

Details regarding the dosage form description and strengths, or composition for the extemporaneous preparation, of the IMP can be found in the pharmacy manual. The IMP will be packaged to support randomization.

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Dosage Form and contents

Code of IMP: TAK-019

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

Composition and contents: Table 8.a describes the components in IMP 0.5 mL for a dose.

Table 8.a Components and content in 0.5 mL of TAK-019 injection

	Component	Content	Indication
Active substance	SARS-CoV-2 rS	5 µg	-
Additive	Sodium hydrogen phosphate buffer	25 mM	Buffer
	Sodium chloride	8.8 mg	Isotonic agent
	Polysorbate 80	0.05 mg	Aggregation inhibitor
	Matrix-M1[a]	0.05 mg	Immunologic adjuvant
Water for injection		Adequate amount	Solvent

[a] Matrix-M1 is an additive composed of saponin derived from the bark of the *Quillaja saponaria* Molina tree as a main component and cholesterol (semisynthetic substance derived from plants) and phosphatidylcholine (derived from egg) as other components.

Code of IMP: placebo

Dosage form: Injection liquid with colorless.

Composition and contents: Saline solution standardized by the Japanese Pharmacopeia (for details refer to the package insert).

8.1.1.2 Package and Labeling

TAK-019 will be packaged in cartons with 10 vials and labeled.

The label of TAK-019 will be written in English, refer to the pharmacy manual for details.

The placebo that will not be labeled in this trial as commercially available saline solution will be used.

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 placebo (saline solution) should be stored according to the package insert.

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 upper arm as explained in the pharmacy manual.

Table 8.b describes the doses that will be provided to each arm.

Table 8.b IMP doses

Trial Arm	Dose	Description		Timing	
		TAK-019	Placebo	Dose 1	Dose 2
1	1 dose TAK-019	SARS-CoV-2 rS 5 µg plus Matrix-M1 50 µg	None	Day 1	Day 22
2	1 dose Placebo	None	Placebo (0.9% sodium chloride)	Day 1	Day 22

Abbreviations: IMP: investigational medicinal product.

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 Assignment and Dispensing Procedures

Randomization schedule in the randomization manual provided by the Sponsor will be used to assign IMP to the subjects according to the randomization table.

Where a subject does not meet all the eligibility criteria but is randomized in error, or 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 blinded to the IMP allocation 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 IMP 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 the IMP.

Prior to subsequent IMP administration, the Investigator must confirm if the subject is eligible to receive vaccination by evaluating the criteria for delay of IMP administration outlined in Sections 7.4 (Criteria for Delay of Investigational Medicinal Product Administration), 7.5 (Criteria for Early Termination of a Subject's Trial Participation), and 7.6 (Criteria for Premature Discontinuation of Investigational Medicinal Product Administration).

Standard immunization practices are to be observed and care should be taken when administering an IMP intramuscularly. In addition, WHO recommendations to reduce anxiety and pain at the time of vaccination should be followed [18]. Before 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

Randomization personnel of the Sponsor or designee will generate the randomization table(s). Randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Medicinal Product Blind Maintenance

This trial is an observer-blind trial. The subjects, data collectors (eg, Investigator) and data evaluators are blinded to the material administered. Randomization and IMP preparation must be done by designated unblinded site staff who must not be involved with data collection of any sort including safety evaluation of the subject after administration of IMP.

The blind will be maintained by the unblinded designee.

8.5 Unblinding Procedure

The IMP blind shall not be broken by the Investigator unless information concerning the IMP is necessary for the medical treatment of a subject, or in cases of pregnancy. In the event of a medical emergency or pregnancy, if possible, the Sponsor should be contacted before the IMP blind is broken to discuss the need for unblinding.

For unblinding a subject, the IMP blind can be obtained by the Investigator, by contacting the Sponsor.

The Sponsor's pharmacovigilance department must be notified as soon as possible if the IMP blind is broken by the Investigator; and the completed SAE or pregnancy form, if applicable, must be sent within 24 hours. The date, time, and reason the blind is broken must be recorded in the source document and the same information (except the time) must be recorded on the eCRF.

If any subject is unblinded, the Investigator will discuss with the Sponsor about study continuation of the subject.

The Primary analysis will be performed for safety and immunogenicity after all subjects have completed the Day 50 visit. After the database lock of the primary analysis data (Day 50 data), the trial will be unblinded and changed to an Open-Label study. The subjects will be informed about the vaccination assignment (TAK-019 or Placebo) and reconsent about study continuation will be obtained from the subjects.

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.

A unique subject number will be assigned to each subject by the appropriate coding (eg, randomization schedule) after informed consent is obtained. If all eligibility criteria are fulfilled, this subject number will be used throughout the trial. Subject numbers assigned to subjects who fail screening should not be reused (Section 9.1.15).

After the database lock of the primary analysis data (Day 50 data), the trial will be unblinded and changed to an Open-Label study. After the database lock of Day 50 data, the subjects will be informed about the vaccination assignment (TAK-019 or Placebo) and reconsent about study continuation will be obtained from the subjects. The vaccination assignment information will be given to the subjects according to the initiation schedule of vaccination program of approved SARS-CoV-2 vaccine for each age group by local Japanese governments. Hence, the timing to provide the information of the vaccination assignment might be different by subject.

If the subjects will receive the approved SARS-CoV-2 vaccine, the subjects 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, 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/preexisting problem.

Medical history (including corresponding medication) to be obtained will include any significant conditions or diseases that have disappeared or resolved at or prior to signing of ICF.

Adverse medical occurrences emerging during the time between signing of ICF and the first 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) and concomitant medications (if the stop date is on or after Day 1, irrespective of the start date).

<Periods to collect medical and medications information>

a) Medications: 2 months prior to Day 1 (day of the first vaccination).

b) Vaccines: 2 weeks (for inactivated vaccines) and 4 weeks (for live vaccines) prior to Day 1 (day of the first vaccination).

c) Blood products: 3 months prior to Day 1 (day of the first vaccination).

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

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

Any other SARS-CoV-2 or other experimental coronavirus vaccine are prohibited throughout the trial. Other licensed vaccines should be administrated before/after 14 days for inactivated vaccines or 28 days for live vaccines prior to trial dose administration.

These data must be written in the source documents.

9.1.3 Documentation of Randomization

Only subjects who have a signed ICF, and meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization. The randomization schedule will be created by the Sponsor and provided to the sites. The randomization specification will be approved by the Sponsor's trial statistician, or designee.

If the subject is ineligible for randomization, 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 before 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, 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 vaccination arm.

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 predose measurement at 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 specified visit time points (Day 1, Day 22, Day 36, Day 50, Day 202, and Day 387).

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 50 mL, and the approximate total volume of blood for the trial is maximum 300 mL (Table 9.a).

The collected samples may be used for measurement of the endpoints defined in this trial as well as exploratory assessments of other immunogenicity (Section 9.4). Genetic tests will not be conducted by use of the collected samples in the trial. A protocol and report will be prepared when the exploratory assessments of other immunogenicity are conducted.

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. 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 50), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations must be recorded in the eCRF by the Investigator. Medications used for treatment of SAEs and COVID-19 must be recorded in the eCRF during the trial. When subjects receive approved SARS-CoV-2 vaccine, it must be recorded in the eCRF as well.

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 Section 10.4 and Section 10.5.

9.1.10 Clinical Safety Laboratory Variables

The local laboratory will provide the sites with appropriate material for blood sampling before start of the clinical trial.

9.1.11 Hematology and Blood Chemistry

All samples will be collected in accordance with acceptable laboratory procedures. The collected samples will be disposed after used for the trial purposes.

Table 9.a shows the volume of blood collected for laboratory tests at each prespecified visit. The total volume of blood is 65 mL, and the maximum volume of blood at any single visit is approximately 22 mL. Laboratory values will be determined by local laboratory. The blood samples are to be collected in fasting state.

Table 9.a Volume and Numbers of Sampling

Laboratory tests	Volume/sampling	Number of sampling	Total volume
Hematology	3.8 mL	5	19 mL
Blood chemistry	7 mL	5	35 mL
Immunogenicity	50 mL	6	300 mL
Serology (before the first vaccination only)	11 mL	1	11 mL
Total			365 mL

The Investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is not clinically significant or clinically significant. Abnormal clinical laboratory values which are confirmed as clinically significant by repeated tests must be followed until well-explained or resolved to acceptable level.

Table 9.b lists the clinical safety laboratory tests that will be performed.

Table 9.b Clinical Safety Laboratory Tests

Hematology	Blood Chemistry
Hemoglobin	Alanine aminotransferase (ALT)
Hematocrit	Aspartate aminotransferase (AST)
Platelet count	Alkaline phosphatase (ALP)
Complete white blood cell count	Lipase
Prothrombin time	Total bilirubin
Activated partial thromboplastin time	Urea (blood urea nitrogen)
	Creatinine
Serology (at screening only)	**Other analyses**
Hepatitis B surface antigen Hepatitis C virus antibody Human immunodeficiency virus (HIV) antibody types 1 and 2	Urine drug screen (amphetamines, methamphetamines, methadone, barbiturates, benzodiazepines, cocaine, opiates, methylenedioxymethamphetamine, phencyclidine, and tetrahydrocannabinol) Female subjects of childbearing potential only: urine pregnancy test (human chorionic gonadotropin)

9.1.12 Nasal Swab Sample

Nasal swab samples will be collected for polymerase chain reaction (PCR) testing of SARS-CoV-2 infection on Day 1, Day 22, and Day 50 in all subjects. For the sample on Day 1, nasal swabs taken within 14 days before Day 1 (Day -14 to Day 1) can be used.

Also, subjects will consult with the Investigator about the necessity of a PCR test throughout the trial (Day 1 to Day 387), 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 PCR test is necessary by the information obtained from the subject according to the guidance for COVID-19 medical treatment [10]. When the Investigator judges the necessity of a PCR test, an ad-hoc trial visit or home visit by medically qualified staff will be arranged as soon as possible (at least within 72 hour) to collect a nasal swab sample from the subject.

Subjects may be asked to submit follow-up nasal samples after consultation with the Investigator. If a nasal swab sample is unavailable in the trial for some reason (eg, emergency admission to the hospital or COVID-19 intensive care ward), PCR 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 PCR test, all clinical findings will be recorded in the eCRF including relevant concomitant medications 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 nasal swab samples:

- Fever (temperature ≥ 37.5ºC) 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 #2 of Section 7.2, by the information from the subject.

9.1.13 Contraception and Pregnancy Avoidance Procedure

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

For female subjects of childbearing potential, pregnancy testing will be performed on Day 1 and Day 22 prior to vaccination, and on Day 50, Day 202 and Day 387. 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). In addition to a negative pregnancy test at Day 1, subjects also must have a negative pregnancy test prior to receiving vaccination on Day 22. 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.

9.1.14 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 IMP or in the partner of the male subject having received IMP must be reported to the Sponsor promptly. If the subject becomes pregnant during the trial, she will not receive any further doses of IMP. 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 IMP administration should be reported immediately, using a pregnancy notification form, to the contact listed in the ISF.

Should the pregnancy occur after administration of a blinded IMP, the Investigator must inform the subject of their right to receive information concerning the IMP they were administered. The individual blind will be broken by the Investigator and procedures must be followed as described in Section 8.5.

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

9.1.15 Documentation of Subjects Who Are Not Randomized

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 non-randomization 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 fail screening should not be reused.

9.2 Monitoring Subject Compliance

The 2 doses of 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 vaccine will be reported in the eCRF. If a subject is not administered the 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. For the date of visits on Day 36 (Visit 4), Day 50 (Visit 5), Day 202 (Visit 6), and Day 387 (Visit 7), the date of the second vaccination (Day 22 [Visit 3]) is used as the starting date to define the date of visit. Each of the visit dates is therefore defined as follows; Day 36 (Visit 4) is on the 14th day (+3 days) after the second vaccination, Day 50 (Visit 5) is on the 28th day (+3 days) after the second vaccination, Day 202 (Visit 6) is on the 180th day (±7 days) after the second vaccination, and Day 387 (Visit 7) is on the 365th day (±14 days) after the second vaccination. In case where the second vaccination is not done for some reason, the date of the first vaccination (Day 1 [Visit 1]) is used as the starting date to define each of the visit dates. 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 at Day 387 (Visit 7) should be performed.

The screening procedures (Day 1 before vaccination) will be carried out within 14 days prior to 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) 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.
- Complete physical examination and other vital signs as listed in Section 9.1.4 and Section 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.
- Blood sampling for laboratory tests.

9.3.1 Pre Vaccination Procedures (Day 1 and Day 22)

The following will be checked and recorded by the Investigator or designee prior to vaccination at Day 1 and Day 22. Please refer to Section 2.1 for further details.

1. Assess eligibility by review of inclusion/exclusion criteria.
2. Prior and concomitant medications.
3. Complete physical examination and other vital signs as listed in Section 9.1.4 and Section 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. Blood sampling for laboratory tests (Day 1* and Day 22).
8. Nasal swab sample collection(Day 1* and Day 22).

   *For the sample on Day 1, the sample taken within 14 days before Day 1 (Day -14 to Day 1) can be used.

9.3.2 Vaccination Procedures (Day 1 and Day 22)

After confirming eligibility and randomizing the subject (on Day 1), perform IMP administration according to the procedures described in Section 8.2.1. At later clinic visits that involve vaccination (Day 22), confirm that the subject does not meet any criteria for delaying, or premature discontinuation of IMP administration, as described in Section 7.4.

9.3.3 Post Vaccination Procedures (Day 1 and Day 22)

After 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, observation for solicited local (injection site) reactions, and body temperature measurement.

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 each 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.
- The collection and reporting of unsolicited AEs and medications in the eDiary will continue for 21 days following the first vaccine administration (day of vaccination + 20 subsequent days) and for 28 days following the second vaccine administration (day of vaccination + 27 subsequent days).

9.3.4 Site Visits After Vaccination (Day 8 Day 36, Day 50, and Day 202)

Site visits that do NOT include a vaccination will be performed on Day 8, Day 36, Day 50, and Day 202. At the site visit, the Investigator will record unsolicited AEs and concomitant medications 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 50
- Pregnancy test in women of childbearing potential: Day 50, Day 202
- Confirmation of solicited AEs by the eDiary and unsolicited AEs and concomitant medications: Day 8, Day 36, Day 50
- Blood sampling for immunogenicity: Day 36, Day 50, Day 202
- Blood sampling for laboratory tests: Day 8, Day 36, Day 50

- Nasal swab sample collection: Day 50

9.3.5 Final (End of Trial) Visit

The final (end of trial) visit will be performed on Day 387. If a subject terminates earlier, the final (end of trial) visit procedures should be performed at their last trial visit, if possible. The Investigator must complete the End of Trial eCRF page for all subjects who received IMP.

9.3.6 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 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) [19].

If a solicited local or systemic AE continues beyond 7 days after dosing, the subject will capture the AE in the eDiary until resolution. The solicited AEs recorded in eDiaries beyond Day 7 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 injection.
- Solicited AE that leads to subject withdrawal from IMP.
- 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. 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 Preferred Terms)
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

Categories	Diagnoses (as MedDRA Preferred Terms)
	unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis).
Gastrointestinal Disorders	Crohn's disease, celiac disease, ulcerative colitis, and ulcerative proctitis.
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.
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.

[a] For Hashimoto thyroiditis: new onset only.

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

Categories	Diagnoses (as MedDRA System Organ Class/Preferred Term)
Respiratory/Infectious Disorders	ARDS, pneumonitis, and septic shock-like syndrome
Cardiac Disorders	Acute cardiac injury, and arrhythmia
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.

[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 [20].

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.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.d).

Table 10.d Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizure (including seizure and epilepsy)	Pulmonary fibrosis (including interstitial lung disease)
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
Hepatic necrosis	Spontaneous abortion / stillbirth and fetal death

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

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 IMP discontinuation or 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 re-test 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. I 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 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 first administered study drug (Visit 1) or until discontinuation prior to study drug administration. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug (Visit 1). Routine collection of AEs will continue until Visit 7.

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*, if necessary (see Section 10.4.4). All findings in subjects experiencing AEs must also be documented in the subject's source documents. Any unsolicited AEs will be collected for 49 days following first vaccination via eDiary. AEs leading to discontinuation (from the trial or from the vaccination regimen) are collected throughout the trial. Even if the subject is deemed ineligible to receive further doses of IMP, all efforts should be made to continue the collection of safety data according to protocol.

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.

**SAE reporting will be done by eCRF. If the eCRF system is unavailable, a paper Sponsor SAE form/paper CRF should be completed and the event must be entered into the eCRF once access is restored.*

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 administration of each IMP dose (including the day of 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 after Day 7 following each 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 up to Day 387. 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 first administered the IMP (Day 1). Routine collection of SAEs will continue until the end of the trial (Day 387).

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 a formal diagnosis can be made 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 (SUSAR) 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. These SAEs will be processed by the Sponsor's pharmacovigilance department. 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 [redacted] 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 informed consent forms, 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 unblinding of IMP assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

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

13.1.1 Analysis Sets

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 randomized subjects who receive at least 1 dose of the treatment. Immunogenicity Analyses 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 Analyses will be conducted using the SAS defined as all subjects who receive at least 1 dose of the treatment. The detail of the definitions for the analysis sets will be documented in the SAP.

Subject evaluability criteria for each Analysis Set will be specified in the SAP, and be fixed before unblinding of IMP assignment

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

(1) Primary Endpoints

- GMT, GMFR, SCR, and SRR of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 36.

(2) Analysis for Primary Endpoints

Analyses will be conducted using the PPS.

SCR and SRR of each endpoint at Day 36 will be calculated along with its 95% confidence interval (CI) in each treatment group.

For antibody titer values and the changes from baseline, GMT, GMFR, summary statistics, and 95% CIs of each endpoint at Day 36 will be calculated in each treatment group.

A detailed analysis method will be specified in the SAP.

(3) Secondary Endpoints

- GMT, GMFR, SCR, and SRR of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 22, Day 50, Day 202, and Day 387.
- GMT, GMFR, SCR, and SRR of serum neutralizing antibody titters to wild-type virus on Day 22, Day 36, Day 50, Day 202, and Day 387.

(4) Analysis for Secondary Endpoints

Analyses will be conducted using the PPS. SCR and SRR of each endpoint at each time point will be calculated along with its 95% CI in each treatment group.

For antibody titer values and the changes from baseline, GMT, GMFR, summary statistics and 95% CIs of each endpoint at each time point will be calculated in each treatment group.

A detailed analysis method will be specified in the SAP.

13.1.4 Safety Analysis

(1) Primary Endpoints

- Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following each 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 each vaccination (day of vaccination + 6 subsequent days).
- Percentage of subjects with unsolicited AEs for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days] + 28 days following second vaccination [day of vaccination + 27 subsequent days]).
- Percentage of subjects with SAE until Day 50.
- Percentage of subjects with AESI until Day 50.
- Percentage of subjects with MAAEs until Day 50.
- Percentage of subjects with any AE leading to discontinuation of vaccination.
- Percentage of subjects with any AE leading to subject's withdrawal from the trial until Day 50.
- Percentage of subjects with SARS-CoV-2 infection until Day 50.

(2) Secondary Endpoints

- Percentage of subjects with SAE throughout the trial.
- Percentage of subjects with AESI throughout the trial.

- Percentage of subjects with MAAEs throughout the trial.
- Percentage of subjects with any AE leading to subject's withdrawal from the trial from the day of vaccination throughout the trial.
- Percentage of subjects with SARS-CoV-2 infection throughout the trial.

(3) Analysis for Safety Endpoints

Analyses will be performed using the SAS.

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

Unsolicited AEs for 49 days following first vaccination will be coded using the MedDRA dictionary and tabulated by the System Organ Class and the Preferred Term.

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

For continuous variables of laboratory tests and 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.

A detailed analysis method will be specified in the SAP.

13.2 Interim Analysis and Criteria for Early Termination

An interim analysis is not planned in the trial.

The primary analysis will be performed for safety and immunogenicity after all subjects have completed the Day 50 visit. After the primary analysis, the trial will be unblinded only for the Sponsor personnel. After the database lock of the primary analysis (i.e, Day 50 data), the trial will be unblinded and changed to an Open-Label study.

13.3 Determination of Sample Size

The objective of this trial is to evaluate the safety and immunogenicity of TAK-019 in the Japanese population. This trial is designed to be descriptive, and therefore the sample size was not determined based on formal statistical power calculations. The sample size for the trial is based on clinical and practical consideration and is considered sufficient to evaluate the objective of the trial. With 150 subjects in the TAK-019 group, the probability to observe at least one AE of 2% event rate is 95%. Considering the risk of disease burden of COVID-19, the number of subjects in the placebo group in this trial was set as minimum as possible especially in the subjects ≥ 65 years old.

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 (QTL) 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 [redacted] 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

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