Title: A Phase II, Randomized, Double-blind, Safety and Immunogenicity Trial of Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine in Healthy Elderly Adults

NCT Number: NCT02661490

Protocol Approve Date: 16 November 2015

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

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

A Phase II, Randomized, Double-blind, Safety and Immunogenicity Trial of Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine in Healthy Elderly Adults

NOR-204 Safety and Immunogenicity of Norovirus GI.1/GII.4 Bivalent VLP Vaccine in an Elderly Population

Sponsor:	Takeda Vaccines, Inc. One Takeda Parkway Deerfield, Illinois 60015 USA		
Trial Identifier:	NOR-204		
IND Number:	014421	**EudraCT Number:**	Not Applicable
Vaccine Name	Norovirus GI.1/GII.4 Bivalent VLP Vaccine		
Date:	16 November 2015		
Version:	Version 2.0		

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site. Contact information is also provided in Table 1-1. The Sponsor will provide Investigators with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the trial site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Table 1-1 Contact Information

Issue	Contact
Serious adverse event and pregnancy reporting	PPD

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the Sponsor. I agree to conduct this trial in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of trial subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.4 of this protocol.
- Terms outlined in the Clinical Trial Site Agreement.
- Appendix A – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix B of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

Location of Facility (Country)

1.3 Protocol Amendment 1 Summary of Changes

1.3.1 Amendment History

Date	Amendment Number	Amendment Type	Region
29 July 2015	Initial Protocol	Not applicable	Global
16 November 2015	1	Substantial	Global

1.3.2 Summary of Changes

Amendment to Protocol Version 1.0 dated 29 July 2015

Rationale for the Amendment:

- Reduction of assessment time points for exploratory endpoints: CCI [redacted]
- CCI [redacted].
- CCI [redacted]

Minor grammatical and editorial changes are included for clarification and consistency purposes only.

New text is bold italics; redundant text is double strikethrough.

Section	Description of change
1.0	Administrative update: **1.1 Contact page 2** *should be read as follows:* PPD [redacted]
2.0; 2.1; 5.1.3; 5.2.3	Update in exploratory objectives and endpoints: **2.0 TRIAL SUMMARY** **Background and Rationale page 19** *should be read as follows:* In addition, CCI [redacted] Peripheral Blood Mononuclear Cells (PBMCs) will be collected on Day 1 (prior to vaccination), ~~Day 8,~~ Day 36, Day 57, ~~Day 211~~ and Day 393 to evaluate specific cell-mediated immune response. CCI [redacted]), ~~Day 8, Day 29 (prior to vaccination),~~ ***Day 36,*** Day 57, ~~Day 211~~ and Day 393 to evaluate the mucosal response. CCI [redacted] ***on serologic specimens collected on Day 1 (prior to vaccination),*** CCI [redacted]. ***Additionally, anti-NoV antibody titers of a panel of NoV strains not represented in the vaccine as measured by Histoblood Group***

CCI [redacted]

…

Exploratory Objectives page 21 *should be read as follows*:

CCI [redacted]

Exploratory Endpoints pages 23-24 *should be read as follows*:

CCI [redacted]

CCI

2.1 Schedule of Trial Procedures pages 26-27 *should be read as follows:*

Procedure		**Day 1**	**Day 8**	**Day 29**	**Day 36**	**Day 57**	**Day 211**	**Day 393/E.T.[1]**
Visit Number		1	2	3	4	5	6	7
Visit Windows			+4 days	+4 days	+4 days	+4 days	+7 days	+14 days
Procedures								
Signed informed consent		X						
Pregnancy test[a]		X		X				
Assessment of eligibility criteria[b]		X		X				
Demographics		X						
Medical history		X						
Medication history		X						
Concomitant medications		X	X	X	X	X	X	X
Physical Examination	Complete[c]	X						
	Symptom Directed		(X)	(X)	(X)	(X)	(X)	(X)
Vital Signs		X	X	X	X	X	X	X
Height, weight and Body		X						

Mass Index (BMI)							
Randomization	X						
Investigational vaccine administration	X		X				
Post vaccination assessment[d]	X		X				
Diary card[e] training and hand out to the subject	Days 1-7	Days 8-28	Days 29-35	Days 36-56			
Diary card[e] review with the subject and collection		Days 1-7	Days 8-28	Days 29-35	Days 36-56		
Solicited Adverse Events (AEs)	X		X				
Unsolicited AEs[f]	X	X	X	X	X		
Serious Adverse Events (SAEs)[g]	X	X	X	X	X	X	X
Adverse Events of Special Interest (AESI)	X	X	X	X	X	X	X
Blood Draw for Immunogenicity (~ 10 mL)[h]	X[i]	X	X[i]	X	X	X	X
CCI [redacted]							
CCI [redacted]							

…

…[h] *should be read as follows:*

Blood draw for immunogenicity includes anti-norovirus (anti-NoV) specific GI.1 and GII.4 Histoblood Group Antigen (HBGA) binding assays, Pan Immunoglobulin Enzyme-linked Immunosorbent Assay (Pan-Ig ELISA) on Day 1 (prior to vaccination), Day 8, Day 29 (prior to vaccination), Day 36, Day 57, Day 211 and Day 393); IgA ELISA on Day 1 (prior to vaccination), Day 8, Day 29 (prior to vaccination), Day 36, Day 57, Day 211, Day 393) and HBGA binding assay using a panel of NoV strains not represented in the vaccine on Day 1 (prior to vaccination), ~~Day 8, Day 29 (prior to vaccination),~~ Day 36, Day 57, ~~Day 211~~ and Day 393). Geometric Mean Titer (GMT), Blocking Titer 50 (BT_{50}), Geometric Mean Fold Rise (GMFR), and percentage of subjects with ≥4-fold antibody rise from baseline will be determined for all available subjects in each age group. CCI [redacted] ***will be assessed on serologic specimens collected on Day 1 (prior to vaccination),*** CCI [redacted]

…[k] *should be read as follows:*

CCI [redacted]

5.1.3 Exploratory Objectives page 36 *should be read as follows:*

CCI

[redacted]

5.2.3 Exploratory Endpoints page 38-39 *should be read as follows*:

…

CCI

[redacted]

	CCI [redacted]
2.0; 5.2.3; 6.1	Clarified that the breadth of immunogenicity will be assessed in a subset of subjects. **6.1 Trial Design page 41** *should be read as follows:* … CCI [redacted]
2.0; 2.1; 5.1.3; 5.2.3; 6.1; 6.2	CCI [redacted] in a subset of subjects. **6.1 Trial Design page 41** *should be read as follows:* … CCI [redacted] **6.2 Justification of Trial Design, Dose and Endpoints page 43** *should be read as follows:* … ***Additionally,*** CCI [redacted] ***in the same subset of subjects is evaluated in order to broaden the assessment of the immune response.***
2.0; 2.1; 5.2.3; 6.1;	Salivary specimen collection added on Day 36 and removed on Day 8, Day 29, and Day

9.1.6; 9.3.4; 9.3.7	211. **6.1 Trial Design page 40** *should be read as follows:* … CCI [redacted] **9.1.6 Immunogenicity Assessments page 58** *should be read as follows*: … CCI [redacted] **9.3.4 Pre-Vaccination Procedures, Day 29 page 61** *should be read as follows:* … CCI [redacted] **9.3.7 Clinic Visits after Vaccination (Day 8, Day 36, Day 57, Day 211) page 63** *should be read as follows:* … CCI [redacted]
2.0; 2.1; 5.2.3; 6.1; 9.1.7; 9.3.7	Removal of blood sample collection on Day 8 and Day 211 CCI [redacted]. **6.1 Trial Design page 40** *should be read as follows:* … CCI [redacted] **9.1.7 Processing, Labeling and Storage of PBMC samples page 58** *should be read as follows:* CCI [redacted]

	CCI **9.3.7 Clinic Visits after Vaccination (Day 8, Day 36, Day 57, Day 211) page 63** *should be read as follows:* … CCI
2.0; 2.1; 5.2.3; 6.1	Removal of blood sample collection for norovirus strains not represented in the vaccine as measured by Histoblood Group Antigen (HBGA) binding assay on Day 8, Day 29, and Day 211. *Wording already mentioned* (*refer to page 10)*
9.1.7	Update in blood volume required for CCI According to the reduction of the number of time points the blood volume collected is reduced to a total of 350 mL instead of 490 mL for the subjects included in the CCI. **9.1.7 Processing, Labeling and Storage of PBMC samples page 58** *should be read as follows:* … Each of these time points requires approximately 70 mL of blood to isolate and cryopreserve PBMCs for later testing. The total blood volume for CCI will be approximately ~~420~~***280*** mL (~~***6 4***~~ x 70 mL). CCI.

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2.0 TRIAL SUMMARY

Name of Sponsor: Takeda Vaccines, Inc. One Takeda Parkway Deerfield, IL 60015 USA		**Product Name:** Norovirus GI.1/GII.4 Bivalent VLP Vaccine
Trial Title: A Phase II, Randomized, Double-blind, Safety and Immunogenicity Trial of Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine in Healthy Elderly Adults.		
IND No.: 014421		**EudraCT No.:** Not Applicable
Trial Identifier: NOR-204	**Phase:** II	**Trial Blinding Scheme**: Double-blind

Background and Rationale:

Noroviruses (NoVs) have emerged as the single most significant cause of epidemic outbreaks of non-bacterial gastroenteritis worldwide. These outbreaks commonly result in significant morbidity and mortality in almost all age groups and represent a serious burden to public health. Those most at risk are the elderly, the very young, and immunocompromised individuals. Noroviruses cause acute debilitating illness characterized by vomiting, diarrhea and abdominal pain. There are no substantial differences in clinical presentation between adults and children, however the elderly are more prone to complications and have the highest mortality rate.

The investigational norovirus (NoV) vaccine under development at Takeda contains NoV virus-like particles (VLPs) as the antigens. NoV VLPs are non-infectious because they lack the viral genomic ribonucleic acid (RNA) but are immunogenic because they preserve particulate antigen conformation and structure that mimic functional interactions of the virus with cellular receptors. NoV strains drift from year to year, and both genogroup I (GI) and genogroup II (GII) cause disease in all age groups. Although numerous genotypes are reported, the GII, genotype 4 (GII.4) type remains dominant and is currently responsible for the majority of outbreaks worldwide. The rationale for developing a bivalent vaccine is based on known epidemiology that both GI, genotype 1 (GI.1) and GII.4 genotypes circulate and do not cross-protect in nature.

The 2 NoV GI.1/GII.4 Bivalent VLP Vaccine formulations (Formulations A and B) tested in trial **NOR-204** contain the adjuvant aluminum hydroxide ($Al(OH)_3$) which has been shown to enhance the antigenicity of vaccines. Formulation B also contains monophosphoryl lipid A (MPL) as adjuvant. This combination of both MPL and aluminum salt is used in the commercially available vaccines Cervarix®, a human papilloma virus (HPV) vaccine, and Fendrix® indicated for hepatitis B prevention for patients with renal insufficiency. Aluminum salt-based adjuvants are used in multiple vaccines and have an acceptable safety profile. The aluminum concentration per dose was selected empirically from data that demonstrated that this amount of aluminum enhanced the antigenicity of the vaccine.

A population aged ≥65 years has been studied only in a limited fashion in the early steps of the clinical development of the NoV GI.1/GII.4 Bivalent VLP Vaccine. Data are available from trial **LV03-104** for 10 subjects aged 65-85 years for the 50/50 □g GI.1 and GII.4 formulation adjuvanted with MPL and $Al(OH)_3$. Response patterns to both VLP components of the vaccine were similar but point estimates of titers to the GII.4 component were lower than those to the GI.1 component. Pan-immunoglobulin (Pan-Ig) and immunoglobulin A (IgA) responses to both VLP components were similar in the 3 age groups (18–49, 50–65 and 65–85 years), however immunoglobulin G (IgG) responses showed some age-dependent variation with IgG Geometric Mean Titers (GMT) lower in those aged 65–85 years.

Trial **NOR-107** was designed to evaluate various dosages of antigens of the bivalent vaccine ranging from 15 µg to 150 µg, with and without MPL adjuvant (0 µg, 15 µg, and 50 µg) in 420 healthy subjects aged 18–<65. There was no trend towards an increased systemic reactogenicity profile with increasing antigen content in adjuvanted and unadjuvanted formulations. The majority of the reactions observed were mild to moderate in all groups and there were no Serious Adverse Events (SAEs) related to the vaccine reported. The immune responses to both VLP antigens were similar with and without the MPL adjuvant. Trial **NOR-107** data supported the selection of the NoV GI.1/GII.4 Bivalent VLP Vaccine containing 15 µg of GI.1 VLP combined with 50 µg of GII.4-VLP and the choice of the 2 vaccine formulations without MPL (Formulation A) and with MPL (Formulation B). Formulation A without MPL was

selected for further development in subjects aged 18-60 years. Natural decline of the immune system affects older adults, thus a vaccine formulation containing both $Al(OH)_3$ and MPL (Formulation B) may provide additional benefit for subjects aged ≥60 years.

The present phase II trial, **NOR-204**, is designed to address the safety and immunogenicity of 2 formulations of the NoV GI.1/GII.4 Bivalent VLP Vaccine (Formulation A and Formulation B) in an elderly population when given according to either a 1-dose regimen or 2-dose regimen 28 days apart. The trial population will be stratified into four age groups including: 18–49 years, 60–74 years, 75–84 years, and 85 years and above. The 18–49 age group is added to the trial to provide a head-to-head comparison in order to limit eventual trial bias in results interpretation that may occur with historical comparisons. Elderly subjects (age groups 60-74 years, 75-84 years, and 85 years and above) will be randomized to receive either 1 or 2 doses of the NoV GI.1/GII.4 Bivalent VLP Vaccine (Formulation A or Formulation B). The 18–49 age group will receive only one NoV GI.1/GII.4 Bivalent VLP Vaccine dose (Formulation A) as it has been shown in trials **LV03-104** and **LV03-105** that in this age group an additional dose did not provide a substantial benefit in terms of immune response. Immunogenicity and safety evaluation will be done in each age group at various time points throughout the trial. CCI [redacted]. Peripheral Blood Mononuclear Cells (PBMCs) will be collected on Day 1 (prior to vaccination), Day 36, Day 57, and Day 393 to evaluate specific cell-mediated immune response. CCI [redacted] on serologic specimens collected on Day 1 (prior to vaccination), CCI [redacted] CCI [redacted]

The primary trial objective is the Day 57 immunogenicity assessment (28 days after the last vaccination) and safety assessment for the trial period. The trial will be conducted in accordance with the protocol, the International Conference on Harmonization and Good Clinical Practice (ICH-GCP) Guidelines and applicable regulatory requirements.

Trial Design:

This is a phase II, randomized, controlled, double-blind, multi-site trial of 2 formulations of the NoV GI.1/GII.4 Bivalent VLP Vaccine: Formulation A composed of a mixture of 15 µg of GI.1 NoV VLP and 50 µg of GII.4 NoV VLP (consensus of 3 strains) adjuvanted with $Al(OH)_3$ without MPL, and Formulation B composed of a mixture of 15 µg of GI.1 NoV VLP and 50 µg of GII.4 NoV VLP (consensus of 3 strains) adjuvanted with $Al(OH)_3$ and with MPL. Approximately 325 subjects will be allocated to 4 age groups (namely 18–49, 60–74, 75–84, and ≥85 years of age). In the elderly age groups (60–74, 75–84, and ≥85 years) subjects will be randomized to a 1:1:1:1 ratio for the dose regimen and for the formulation. Each subject will receive 1 or 2 doses of the NoV GI.1/GII.4 Bivalent VLP Vaccine, either Formulation A or Formulation B (Table 1 and Figure 1). There will be an interval of 28 days between the two vaccine administrations. The 18–49 age group will receive only one NoV G.1/GII.4 Bivalent VLP Vaccine dose (Formulation A).

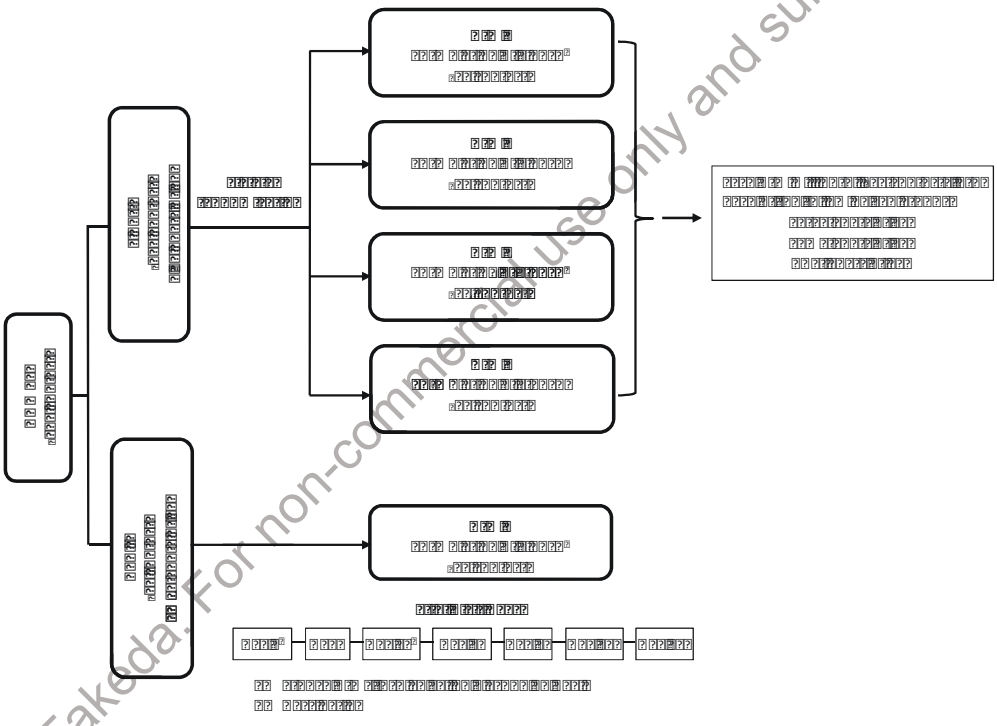
All age groups will be enrolled in parallel. In order to remain blinded and to have the same trial time point with both dosing regimens relative to the last vaccination, subjects randomized in the 1-dose groups will receive 1 dose of Saline Placebo followed by 1 dose of the investigational NoV GI.1/GII.4 Bivalent VLP Vaccine 28 days later.

Subjects will provide pre- and post-immunization serologic specimens and will be followed for safety assessment up to 1 year after the last trial vaccine dose, i.e. through and including a last visit scheduled on Day 393 (complete follow-up of 365 days after the second vaccine administration).

Table 1 Subject Distribution for Trial NOR-204

Age groups (years)	Number of subjects	Day 1	Day 29
18–49	25	Saline Placebo	Formulation A
60–74	25	Saline Placebo	Formulation A
	25	Formulation A	Formulation A
	25	Saline Placebo	Formulation B
	25	Formulation B	Formulation B
75–84	25	Saline Placebo	Formulation A
	25	Formulation A	Formulation A
	25	Saline Placebo	Formulation B
	25	Formulation B	Formulation B
≥85	25	Saline Placebo	Formulation A
	25	Formulation A	Formulation A
	25	Saline Placebo	Formulation B
	25	Formulation B	Formulation B
Total evaluable subjects	325		

Figure 1 Schematic of Trial NOR-204 Design



Primary Objective:
To select for further development a formulation and a dose regimen of the NoV GI.1/GII.4 Bivalent VLP Vaccine that is immunogenic and safe in an elderly population aged 60 years and above.

Secondary Objectives:

- To assess the immunogenicity of the NoV GI.1/GII.4 Bivalent VLP Vaccine in both adults aged 18–49 years and elderly population aged ≥60 years, by treatment arm;
- To assess the safety profile of the NoV GI.1/GII.4 Bivalent VLP Vaccine in both adults aged 18–49 years and elderly population aged ≥60 years, by treatment arm throughout the trial.

Exploratory Objectives:

CCI [redacted]

Subject Population:
Healthy subjects: yes
Planned minimum age: 18 years
Planned number of subjects: approximately 325 subjects
Planned number of Arms: 5

- **Arm 1:** NoV GI.1/GII.4 Bivalent VLP Vaccine, Formulation A, 1-dose regimen (subjects ≥60 years).
- **Arm 2:** NoV GI.1/GII.4 Bivalent VLP Vaccine, Formulation A, 2-dose regimen (subjects ≥60 years).
- **Arm 3:** NoV GI.1/GII.4 Bivalent VLP Vaccine, Formulation B, 1-dose regimen (subjects ≥60 years).
- **Arm 4:** NoV GI.1/GII.4 Bivalent VLP Vaccine, Formulation B, 2-dose regimen (subjects ≥60 years).
- **Arm 5**: NoV GI.1/GII.4 Bivalent VLP Vaccine, Formulation A, 1-dose regimen (Subjects 18–49 years).

Criteria for Inclusion:

- The subject is aged 18–49 years, or 60 years and older at the time of enrollment;
- Individuals who are in good health, or in stable health status with no exclusionary medical or neuropsychiatric conditions at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the Investigator;
- The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements;
- Individuals who can comply with trial procedures and are available for the duration of follow-up.

Criteria for Exclusion:

- Subjects with known hypersensitivity or allergy to any of the NoV GI.1/GII.4 Bivalent VLP Vaccine components;
- Subjects with known or suspected impairment or alteration of immune function including any autoimmune disease or history of neuro-inflammatory disease;
- Any unstable medical or neuropsychiatric condition, which in the Investigator's opinion poses a risk of unusual magnitude for the subject's age group of hospitalization, death, or an event meeting the definition of a SAE within 2 months of immunization. (The intent of this criterion is to recognize and allow for the frequent existence of significant health concerns in this population, but exclude those subjects who are experiencing an acute decline in health status.);
- Subjects who received any inactivated vaccines within 14 days or any live vaccines for 28 days prior to enrollment in this trial;
- Female subjects who are pregnant or breastfeeding;

- Any condition or circumstance that the Investigator determines would interfere with trial evaluation or interpretation.

A full list of exclusion criteria is presented in the protocol.

Trial Vaccines:

Norovirus GI.1/GII.4 Bivalent VLP Vaccine: two vaccine formulations will be evaluated in this trial:

- Formulation A (per dose): 15 µg of GI.1 NoV VLP; 50 µg of GII.4 NoV VLP (consensus of 3 strains) without MPL, all of which are adsorbed to $Al(OH)_3$ adjuvant (500 µg aluminum).
- Formulation B (per dose): 15 µg of GI.1 NoV VLP; 50 µg of GII.4 NoV VLP (consensus of 3 strains) with 15 µg of MPL, all of which are adsorbed to $Al(OH)_3$ adjuvant (500 µg aluminum).

Control: Placebo (saline) will be 0.9% sodium chloride for injection without preservative. It will be used as a control to maintain the trial blinding in subjects who are in the 1-dose groups of NoV GI.1/GII.4 Bivalent VLP Vaccine.

All vaccines will be administered by intramuscular (IM) route into the middle third of the deltoid muscle, preferably in the non-dominant arm.

Duration of the Trial:	**Period of Evaluation:**
The overall trial duration is approximately 13 months.	393 days

Main Criteria for Evaluation and Analyses:

Primary endpoints:

Immunogenicity

- Percentage of subjects with a 4-fold rise or greater in serum anti-NoV antibody titers for both GI.1 VLP and GII.4 VLP as measured by HBGA binding assay on Day 57 (28 days after the last vaccination).

Safety

- Percentage of subjects with solicited local Adverse Events (AEs) (pain, erythema, induration, and swelling at the injection site) for 7 days (the day of vaccination and the following 6 days) after each vaccination;
- Percentage of subjects with solicited systemic AEs (headache, fatigue, myalgia, arthralgia, vomiting, and diarrhea) for 7 days after each vaccination;
- Percentage of subjects with elevated daily body temperature ≥38°C (defined as fever) for 7 days after each vaccination;
- Percentage of subjects with any unsolicited AEs from Day 1 through Day 28 (post-vaccination 1) and from Day 29 through Day 57 (post-vaccination 2), inclusive;
- Percentage of subjects with SAEs throughout the trial.

Secondary endpoints:

Immunogenicity

HBGA binding assay

- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GI.1 VLP and anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay (Day 8, Day 29, Day 36, Day 211, and Day 393);
- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMT of anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay (Day 1, Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);

- GMT of anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay (Day 1, Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- Geometric Mean Fold Rise (GMFR) of anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMFR of anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393).

Pan-Ig Enzyme-linked Immunosorbent Assay (ELISA)

- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GI.1 VLP and anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMT of anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA (Day 1, Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMT of anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA (Day 1, Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMFR of anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMFR of anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211 and Day 393).

Safety

- Percentage of subjects with Adverse Events of Special Interest (AESI) throughout the trial;
- Percentage of subjects with any AE leading to subject's withdrawal throughout the trial.

Exploratory Endpoints:

CCI

[redacted]

CCI [redacted]

Statistical Considerations:

Analysis of Demographics and Other Baseline Characteristics

Age, gender, race and other baseline characteristics will be summarized descriptively by age group and treatment arm based on the set of all randomized subjects.

Immunogenicity Analysis

Descriptive summary statistics including 95% confidence intervals (CI) for the primary, secondary, and exploratory endpoints, including percentage of subjects with ≥4-fold rise, GMT, BT_{50} and GMFR, will be computed for all available assays for each time point by treatment arm, separately for each age group. Within each age group, analysis of covariance (ANCOVA) with treatment arm as a factor and Fisher's exact test will be conducted for continuous and binomial outcomes, respectively. Pre-vaccination titers will be used as a covariate in the ANCOVA analyses. CCI [redacted]

Safety Analysis

Reactogenicity will be assessed for 7 days (the day of vaccination and the following 6 days) after each vaccination via collection of solicited AEs, including local AEs (injection site: pain, erythema, induration and swelling) and systemic AEs (headache, fatigue, myalgia, arthralgia, vomiting, and diarrhea). In addition, other indicators of reactogenicity will be collected (eg, body temperature).

For each solicited AE, the percentage of subjects will be summarized by event severity, for each day (from Day 1 to Day 7) and overall. In addition, summaries will be provided for the intervals of Days 1 to 3 after each vaccination, and Days 4 to 7 after each vaccination. A summary of the day of first onset of each event will also be provided. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs, SAEs and AESI will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term (PT) for each treatment arm. AEs leading to subject withdrawal from the trial will also be summarized. A detailed Statistical Analysis Plan (SAP) will be prepared for the trial.

Sample Size Justification:
This is a phase II trial designed primarily to be descriptive. Therefore the sample size was not determined based on formal statistical power calculations but rather to provide a reasonable clinical database to assess safety and immunogenicity in an elderly population.

Interim Analysis:
A review of safety data will be performed by the Data Monitoring Committee (DMC) as soon as the first approximately 100 subjects have completed the Day 36 Visit (8 days post last vaccination) to verify if safety results observed in the present trial are consistent with what has been observed in previous trials with the NoV GI.1/GII.4 Bivalent VLP Vaccine performed by Takeda. In order to have a good representation of the entire trial population, efforts will be made in terms of enrollment to have those first approximately 100 subjects equally distributed in each permutation.
An interim analysis on safety and immunogenicity data is planned when all subjects have completed the Day 57 Visit (28 days after last vaccination). This analysis will include group results but not individual subject information. This analysis will be performed by a separate set of unblinded statisticians and programmers at a selected independent Contract Research Organization (CRO) who will have access to individual treatment assignments but will not be involved in subsequent trial conduct. Except for the unblinded pharmacist and unblinded administrator, the personnel involved in the conduct of the trial including those at the Sponsor site, the CRO, and the trial sites, will remain blinded to the individual subject data (including treatment assignment) until unblinding after database lock for data through Day 393.

Data Monitoring Committee:
An overall DMC is established to evaluate overall safety of the Takeda Norovirus vaccine program on an ongoing basis. The composition, role and responsibilities of the DMC are presented in a separate DMC Charter.

2.1 Schedule of Trial Procedures

Procedure		Day 1	Day 8	Day 29	Day 36	Day 57	Day 211	Day 393/ E.T.[1]
Visit Number		1	2	3	4	5	6	7
Visit Windows			+4 days	+4 days	+4 days	+4 days	+7 days	+14 days
Procedures								
Signed informed consent		X						
Pregnancy test[a]		X		X				
Assessment of eligibility criteria[b]		X		X				
Demographics		X						
Medical history		X						
Medication history		X						
Concomitant medications		X	X	X	X	X	X	X
Physical Examination	Complete[c]	X						
	Symptom Directed		(X)	(X)	(X)	(X)	(X)	(X)
Vital Signs		X	X	X	X	X	X	X
Height, weight and Body Mass Index (BMI)		X						
Randomization		X						
Investigational vaccine administration		X		X				
Post vaccination assessment[d]		X		X				
Diary card[e] training and hand out to the subject		Days 1-7	Days 8-28	Days 29-35	Days 36-56			
Diary card[e] review with the subject and collection			Days 1-7	Days 8-28	Days 29-35	Days 36-56		
Solicited Adverse Events (AEs)		X		X				
Unsolicited AEs[f]		X	X	X	X	X		
Serious Adverse Events (SAEs)[g]		X	X	X	X	X	X	X
Adverse Events of Special Interest (AESI)		X	X	X	X	X	X	X
CCI								
CCI								
CCI								

Note: If the administration of Dose 2 is changed within the allowable window, subsequent visits should be calculated from the Day of the second dose (eg, if Dose 2 is given on trial Day 31, the next visit should be scheduled for trial Day 38).

Footnotes:

a. In female subjects of childbearing potential, urine pregnancy tests will be performed before each vaccination. Subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the trial procedures.
b. Continuing eligibility (by review of relevant inclusion/exclusion criteria) will be documented before each vaccination.
c. A complete physical examination is performed on Day 1. At other visits, subjects may undergo a brief symptom-directed physical examination and, if performed, should assess clinically significant changes from baseline.
d. After vaccination on Day 1 and Day 29, the subject will be observed for at least 30 minutes including observation for solicited AEs, unsolicited AEs, and body temperature measurement.
e. Diary cards will be completed from Day 1 through Day 56. Daily diary of solicited AEs from Day 1 through Day 7 and Day 29 through Day 35 (the day of vaccination and for 6 days following each vaccination). Information about unsolicited AEs and medications will be collected from Day 1 through Day 56.
f. AEs including solicited local and systemic events and unsolicited AEs will be collected with the help of the diary card and by interview and categorized by the Investigator as mild, moderate or severe and relatedness to vaccine.
g. SAEs will be reported to the Sponsor or their designee within 24 hours of the Investigator becoming aware of the event throughout the trial. Note: For this trial, SAE reporting will be done by use of the electronic Case Report Form (eCRF). If the Electronic Data Capture (EDC) system is unavailable, a paper Sponsor SAE form/paper CRF should be completed and the event must be entered into the EDC once access is available.
h. CCI [redacted]
i. Samples will be taken prior to vaccination.
j. CCI [redacted]
k. CCI [redacted]
l. Day 393/E.T. Early Termination. In case of Early Termination same safety procedures will apply. Refer to section 7.5 and 9.3.8.

3.0 TRIAL REFERENCE INFORMATION

3.1 Trial-Related Responsibilities

The Sponsor will perform all trial-related activities with the exception of those identified in the Trial-Related Responsibilities template. The identified vendors for specific trial-related activities will perform these activities in full or in partnership with the Sponsor.

3.2 Principal Investigator

The Sponsor will select a Principal Coordinating Investigator from the Investigators who participate in the trial. Selection criteria for this Investigator will include significant knowledge of the trial protocol, the investigational vaccine, their expertise in the therapeutic area and the conduct of clinical research as well as trial participation. The Signatory Principal Investigator/Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the trial.

3.3 List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
$Al(OH)_3$	Aluminum Hydroxide, Alhydrogel®
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
BT_{50}	Blocking Titer 50
CFR	Code of Federal Regulations
CI	Confidence Interval
CCI	[redacted]
CRO	Contract Research Organization
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GI	Genogroup I
GII	Genogroup II
GI.1	Genogroup I, Genotype 1
GII.4	Genogroup II, Genotype 4
HBGA	Histoblood Group Antigen
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFNγ	Interferon Gamma
Ig	Immunoglobulin
IL-2	Interleukin 2
IL-21	Interleukin 21
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MPL	Monophosphoryl Lipid A
NoV	Norovirus
NoVs	Noroviruses

Cont.

Pan-Ig	Pan Immunoglobulin
PBMC	Peripheral Blood Mononuclear Cell
PFS	Prefilled Syringe
PPS	Per-Protocol Analysis Set
PT	Preferred Term
PV	Pharmacovigilance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF-α	Tumor Necrosis Factor-alpha
US	United States
USA	United States of America
VLP	Virus Like Particle

3.4 Corporate Identification

TV	Takeda Vaccines, Inc.
VBU	Vaccine Business Unit

4.0 INTRODUCTION

4.1 Background

Noroviruses (NoVs) cause acute debilitating illness characterized by vomiting, diarrhea and abdominal pain. NoVs are non-cultivatable human caliciviruses that have emerged as the single most significant cause of epidemic outbreaks of viral gastroenteritis worldwide [1, 2]. Endemic norovirus (NoV) disease occurs year round but exhibits seasonality, with a pronounced winter peak in countries in the northern hemisphere. These outbreaks can occur in all age groups, and commonly result in significant morbidity and mortality, particularly in the elderly, the immunocompromised subjects, and the very young subjects [3-7]. According to the Centers for Disease Control and Prevention (CDC), 21 million cases of acute gastroenteritis are due to NoVs each year in the United States (US) [8].

NoVs comprises a genetically diverse family consisting of 6 genogroups (GI–GVI), 3 of which (genogroup I [GI], genogroup II [GII], and genogroup IV [GIV]) cause human disease. NoV strains drift from year to year, and although both GI and GII genogroups and numerous genotypes are reported, the GII, genotype 4 (GII.4) type remains dominant causing the majority of outbreaks worldwide [9-11]. Recently, surveillance systems have shown an increase in NoV activity globally during late 2012 due to the emergence of a new NoV GII.4 variant, termed Sydney 2012 [12].

Norovirus Vaccine

The rationale for developing a bivalent vaccine is based on known epidemiology that both GI, genotype 1 (GI.1) and GII.4 circulate and do not cross-protect in nature. NoV Virus Like Particles (VLPs) are non-infectious particles because they do not contain viral genomic ribonucleic acid (RNA); however they are immunogenic because they preserve the particulate antigen conformation and structure that mimic functional interactions of the virus with cellular receptors.

The NoV GI.1/GII.4 Bivalent VLP Vaccine under development at Takeda is based on NoV GI.I and GII.4 VLPs as the antigens. These 2 genotypes cause the vast majority of NoV outbreaks. The GI.1 VLP represents a single GI.1 strain and the GII.4 VLP represents a consensus sequence of 3 GII.4 strains.

The 2 NoV GI.1/GII.4 Bivalent VLP Vaccine formulations tested in trial **NOR-204** (Formulations A and B) contain the adjuvant aluminum hydroxide ($Al(OH)_3$) which has been shown to enhance the antigenicity of vaccines [13, 14]. Formulation B also contains monophosphoryl lipid A (MPL) as adjuvant. This combination of both, MPL and aluminum salt is used in the commercially available vaccines Cervarix®, a human papilloma virus (HPV) vaccine, and Fendrix® indicated for hepatitis B prevention for patients with renal insufficiency. Aluminum salt-based adjuvants are used in multiple vaccines and have an acceptable safety profile [14]. The aluminum concentration per dose was selected empirically from data that demonstrated that this amount of aluminum enhanced the antigenicity of the vaccine.

Selection of the NoV GI.1/GII.4 Bivalent VLP Vaccine formulations for trial **NOR-204** is based on safety and immunogenicity data observed in adults 18–64 years of age in trial **NOR-107** described below.

Preclinical Safety and Toxicology

A Good Laboratory Practice (GLP) safety trial was performed in rabbits to evaluate safety and toxicology of NoV GI.1/GII.4 Bivalent VLP Vaccine with MPL and $Al(OH)_3$. Five, 0.5 mL doses of NoV GI.1/GII.4 Bivalent VLP Vaccine, each containing 300 µg of total VLP (150 µg of GI.1 VLP and 150 µg of GII.4 cVLP) with 500 µg of $Al(OH)_3$ and 50 µg of MPL were administered by single daily intramuscular (IM) injection on Days 1, 15, 29, 43, and 57. The vaccine was well tolerated in rabbits. No mortality and no systemic toxicity were observed. Refer to current version of the Investigator Brochure for more details [15].

Clinical Safety and Immunogenicity

The safety of the NoV GI.1/GII.4 Bivalent VLP Vaccine given by the IM route was evaluated in 2 completed trials in 234 healthy US adult subjects. Trial **LV03-104** included 102 subjects (aged 18–49 years, 50–64 years, 65–85 years). Trial **LV03-105** included 132 subjects (aged 18–50 years). Both trials compared the NoV GI.1/GII.4 Bivalent VLP Vaccine with Saline Placebo given by IM injection as a 2-dose regimen, 28 days apart. In both trials combined, 133 adults received at least 1 dose of the NoV GI.1/GII.4 Bivalent VLP Vaccine and 101 adults received at least 1 dose of Saline Placebo. No allergic reactions, neurologic adverse events (AEs), or serious adverse events (SAEs) related to the vaccine were reported in either trial. No increase in severity or frequency of symptoms was observed with increased VLP dosages or with increased age or after Dose 2 of vaccine compared with Dose 1. The IM NoV GI.1/GII.4 Bivalent VLP Vaccine was well tolerated.

The completed dosage escalation trial, **LV03-104**, which compared 5/5, 15/15, 50/50 and 150/150 µg dosages of the GI.1 and GII.4 VLPs in adults showed the percentage of subjects with at least a four-fold rise in antibody levels (seroresponse rate) and Geometric Mean Fold Rise (GMFR) were lower for the GII.4 VLP than for the GI.1 VLP at equivalent antigen dosages. Similar post-vaccination immunogenicity data were obtained in the completed GII.4 challenge trial **LV03-105** that evaluated a candidate vaccine containing 50/50 µg VLP.

Trial **LV03-104** comprised a group of 10 subjects aged 65-85 years who received the NoV formulation at 50/50 µg. Response patterns to both VLP components of the vaccine were similar but point estimates of titers to the GII.4 component were lower than those to the GI.1 component. Pan-Immunoglobulin (Pan-Ig) and immunoglobulin A (IgA) responses to both VLP components were similar in the 3 age groups, but immunoglobulin G (IgG) responses showed some age-dependent variation with IgG Geometric Mean Titers (GMT) lower in those aged 65-85 years.

Trial **NOR-107** was designed to evaluate various dosages of antigen of the bivalent vaccine ranging from 15 to 150 µg, with and without MPL adjuvant (0 µg, 15 µg, and 50 µg) in 420 healthy adult subjects. There was no trend towards an increased systemic reactogenicity profile with increasing antigen content in adjuvanted and unadjuvanted formulations. The majority of the reactions observed were mild to moderate in all groups and there were no SAEs related to the vaccine reported. The immune responses to both VLP antigens were similar with and

without the MPL adjuvant. The ongoing trial **NOR-201** was designed to evaluate 2 NoV GI.1/GII.4 VLP antigen formulations (15 µg/50 µg and 50 µg/50 µg), adjuvanted with 50 µg of MPL and 500 µg $Al(OH_3)$ in approximately 450 adults aged 18–49 years. The preliminary results of this trial are consistent with the observations of trial **NOR**-107 trial and confirm that 15 µg of GI.1 VLP combined with 50 µg of GII.4-VLP, provide a superior immune response to the GII.4 component than did the 50 µg of GI.1 VLP combined with 50 µg of GII.4 VLP.

4.2 Rationale for the Proposed Trial

NoV outbreaks can occur in all age groups. There are no substantial differences in clinical presentation between adults and children, however elderly are more susceptible to complications and are at greater risk of NoV associated deaths.

The clinical significance of NoVs was underestimated prior to the development of diagnostic assays to detect these enteric viruses. NoV-related illnesses and outbreaks exact a significant socioeconomic toll on hospitals, schools, businesses and other closed settings such as hospitals and long care settings.

Elderly population will increase dramatically in the next few years reaching approximately 30% of the total population by year 2030. Aging and more explicitly, the natural decline of the immune system increases their susceptibility to infection and compromises responsiveness to vaccines [16]. New vaccine strategies might be beneficial to this age group and there might be potential for specific vaccine formulations or dose regimens adapted to their age.

Preliminary data in a population aged ≥65 years are available from trial **LV03-104** as previously described, however those findings need to be further explored in a larger trial.

The present phase II trial, **NOR-204**, is designed to address the safety and immunogenicity of 2 formulations of the NoV GI.1/GII.4 Bivalent VLP Vaccine (Formulation A and Formulation B) in an elderly population when given according to either a 1-dose regimen or 2-dose regimen 28 days apart. The 2 NoV GI.1/GII.4 Bivalent VLP Vaccine formulations (Formulation A and Formulation B) are selected based on safety and immunogenicity data from trial **NOR-107**.

The trial population will be stratified into four age groups including: 18–49 years, 60–74 years, 75–84 years, and 85 years and above. The 18–49 age group is added to the trial to provide a head-to-head comparison in order to limit eventual trial bias in results interpretation that may occur with historical comparisons. Elderly subjects (age groups 60–74 years, 75–84 years, and 85 years and above) will be randomized to receive either 1 or 2 doses of the NoV GI.1/GII.4 Bivalent VLP Vaccine (Formulation A or Formulation B). The 18–49 age group will receive only 1 NoV GI.1/GII.4 Bivalent VLP Vaccine dose of Formulation A that is considered the formulation for further development in this age group by Takeda. Subjects allocated to the 1-dose regimen of the NoV GI.1/GII.4 Bivalent VLP Vaccine will receive 1 injection with Saline Placebo on Day 1 to respect trial blinding. Twenty-eight days later (Day 29), they will receive their vaccination with the Formulation A vaccine.

Immunogenicity and safety evaluation will be done in each age group at various time points throughout the trial. The primary trial objective is the Day 57 immunogenicity assessment (28 days after the last vaccination) and safety assessment for the trial period.

The trial will be conducted in accordance with the protocol, the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines and applicable regulatory requirements.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

The primary, secondary, and exploratory objectives of this trial are listed in the following sections.

5.1.1 Primary Objective

To select for further development a formulation and a dose regimen of the NoV GI.1/GII.4 Bivalent VLP Vaccine that is immunogenic and safe in an elderly population aged 60 years and above.

5.1.2 Secondary Objectives

- To assess the immunogenicity of the NoV GI.1/GII.4 Bivalent VLP Vaccine in both adults aged 18–49 years and elderly population aged ≥60 years, by treatment arm;
- To assess the safety profile of the NoV GI.1/GII.4 Bivalent VLP Vaccine in both adults aged 18–49 years and elderly population aged ≥60 years, by treatment arm throughout the trial.

5.1.3 Exploratory Objectives

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

Immunogenicity

- Percentage of subjects with a 4-fold rise or greater in serum anti-NoV antibody titers for both GI.1 VLP and GII.4 VLP as measured by Histoblood Group Antigen (HBGA) binding assay on Day 57 (28 days after the last vaccination).

Safety

- Percentage of subjects with solicited local AEs (pain, erythema, induration, and swelling at the injection site) for 7 days (the day of vaccination and the following 6 days) after each vaccination;
- Percentage of subjects with solicited systemic AEs (headache, fatigue, myalgia, arthralgia, vomiting, and diarrhea) for 7 days after each vaccination;
- Percentage of subjects with elevated daily body temperature ≥38°C (defined as fever) for 7 days after each vaccination;
- Percentage of subjects with any unsolicited AEs from Day 1 through Day 28 (post-vaccination 1) and from Day 29 through Day 57 (post-vaccination 2), inclusive;
- Percentage of subjects with SAEs throughout the trial.

5.2.2 Secondary Endpoints

Immunogenicity

HBGA binding assay

- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GI.1 VLP and anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay (Day 8, Day 29, Day 36, Day 211, and Day 393);
- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMT of anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay (Day 1, Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMT of anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay (Day 1, Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMFR of anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMFR of anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393).

Pan-Ig Enzyme-linked Immunosorbent Assay (ELISA)

- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GI.1 VLP and anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);

- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- Percentage of subjects with a 4-fold rise or greater of serum anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMT of anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA (Day 1, Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMT of anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA (Day 1, Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMFR of anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMFR of anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393).

Safety

- Percentage of subjects with Adverse Events of Special Interest (AESI) throughout the trial;
- Percentage of subjects with any AE leading to subject's withdrawal throughout the trial.

5.2.3 Exploratory Endpoints

CCI

[redacted]

CCI

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a phase II, randomized, controlled, double-blind, multi-site trial of the NoV GI.1/GII.4 Bivalent VLP Vaccine adjuvanted with 500 µg $Al(OH)_3$ without MPL (Formulation A) and with 15 µg of MPL (Formulation B). Approximately 325 subjects will be allocated to 4 age groups (18–49, 60–74, 75–84, and ≥85 years of age). Subjects in the elderly age groups (60–74, 75–84, and ≥85 years of age) will be randomized to a 1:1:1:1 ratio for the dose regimen and for the formulation. Each subject will receive 1 or 2 doses of the NoV GI.1/GII.4 Bivalent VLP Vaccine, either Formulation A or Formulation B. There will be an interval of 28 days between the two vaccine administrations. The 18–49 year old subjects will receive only one NoV G.1/GII.4 Bivalent VLP Vaccine dose (Formulation A).

All age groups will be enrolled in parallel. In order to maintain blinding and to have the same trial time point with both dosing regimens relative to the last vaccination, subjects randomized into the 1-dose groups will receive 1 dose of Saline Placebo on Day 1 followed by 1 dose of the investigational NoV GI.1/GII.4 Bivalent VLP Vaccine 28 days later. Subjects who receive the Saline Placebo first will undergo exactly the same follow up as the other subjects who receive the first dose of NoV GI.1/GII.4 Bivalent VLP Vaccine on Day 1.

Screening, pre-vaccination blood draw, pre-vaccination saliva collection, urine pregnancy test (if applicable), randomization, and vaccination will occur on Day 1. Screening will include demographic characteristics, medical history, medication history, concomitant medications, physical examination, height, weight, body mass index (BMI), vital signs, and eligibility criteria assessment. Written informed consent will be obtained prior to any trial specific procedures on Day 1. Six additional clinical visits are planned on Day 8, Day 29, Day 36, Day 57, Day 211 and Day 393 for all the subjects. During these visits, post-immunization serologic specimens will be collected and subjects will be followed for safety assessment up to 1 year after the last trial vaccine dose (ie, through and including a last visit scheduled on Day 393). Diary cards will be completed from Days 1 through 56. Solicited AEs will be assessed for 7 days (the day of vaccination and the following 6 days) after each vaccination and unsolicited AEs will be assessed for 28 days following each vaccination; SAEs and AESI will be assessed throughout the trial. The final trial visit is scheduled on Day 393.

CCI [redacted]

CCI [redacted]

CCI [redacted].

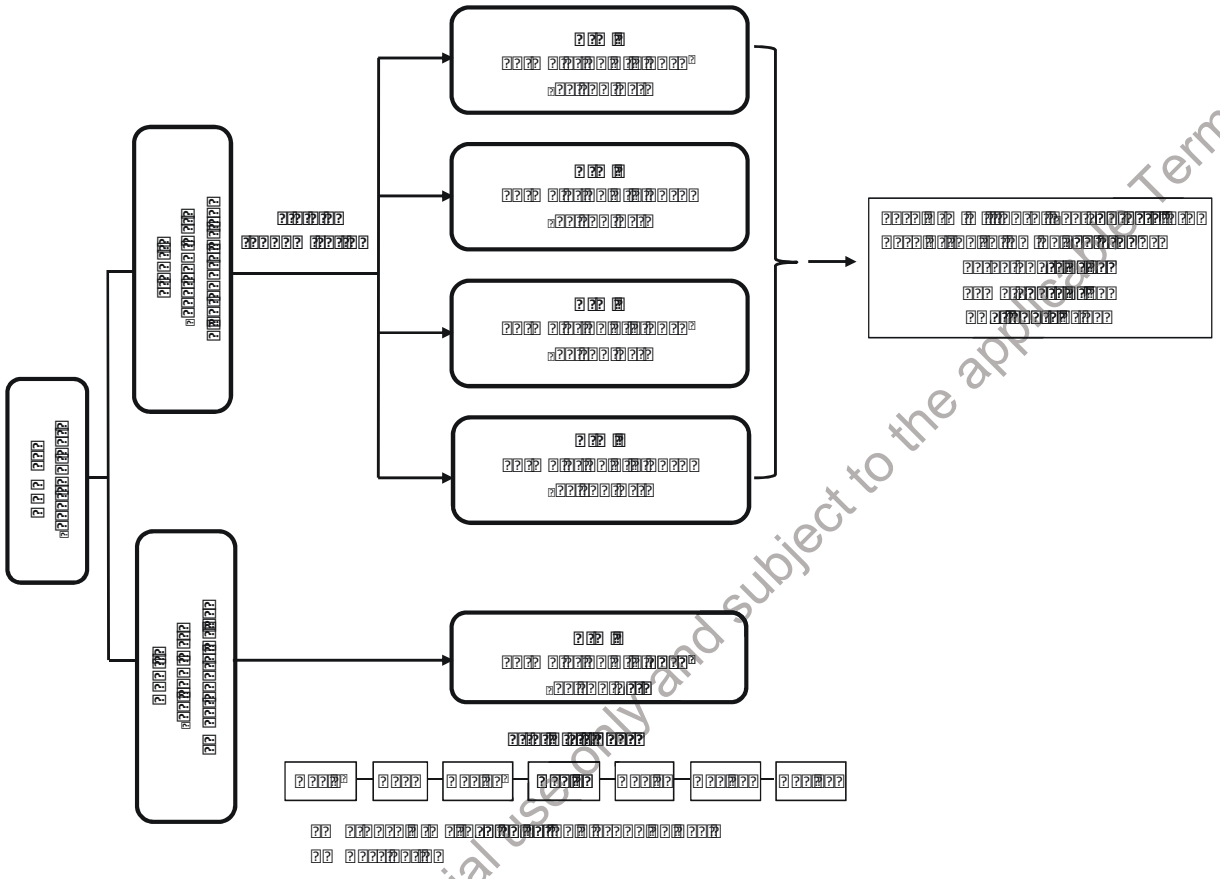
CCI [redacted]

A review of safety data will be performed by the Data Monitoring Committee (DMC) as soon as the first approximately 100 subjects have completed the Day 36 Visit (8 days after last vaccination). Refer to Section 11.1.1.

An interim analysis on safety and immunogenicity data is planned when all subjects have completed the Day 57 Visit (28 days after last vaccination). Refer to Section 13.2. The final Clinical Study Report (CSR) will include analyses of all safety and immunogenicity data through Day 393 as well as individual subject data (including data listings and subject treatment assignments).

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

Figure 6-a Schematic of Trial NOR-204 Design



6.2 Justification for Trial Design, Dose, and Endpoints

The purpose of this trial is to evaluate the safety and immunogenicity of 2 NoV GI.1/GII.4 Bivalent VLP Vaccine formulations in an elderly population. Elderly are expected to have a pattern of response similar to younger adults; however the potential impact of pre-existing specific antibody level in relation with individual history against wild NoV circulation has to be clarified. Also elderly subjects undergo immune system alterations such as decline of B cell functions, changes in T cell populations with a restricted pool of naïve T cells that affect their susceptibility to diseases and also their response to vaccine antigens. Thus it is of importance to test different NoV formulations and dose regimens than the one anticipated for an adult population. This may help to circumvent an eventual low antibody response or a rapid decline of antibodies in relation to the immunosenescence. The 2 NoV formulations (Formulations A and B) tested in trial **NOR-204** are based on the interim results of trial **NOR-107.**

Subjects enrolled in the trial will be adults between 18 years and 49 years for the youngest age group, and 60 years and over for the elderly group. They will be members of the community at large. The age group ≥60 years and in particular those aged ≥85 years will comprise both healthy elderly subjects and also subjects with a broad spectrum of diagnoses consistent with an aging population. However all subjects must be in stable health conditions and judged eligible

for the trial when assessed against the inclusion and exclusion criteria. The stable health status is imposed to control short and long term attritions as the trial is expected to last approximately 13 months for each participant.

The gender ratio will not be strictly controlled in this trial. From a demographic point of view it is known that there are more females in the elderly population, thus it is anticipated that the trial will be representative of this bias, particularly for the age strata 75-84 and ≥85. However, sites will be instructed to ensure the inclusion of a reasonable number of male participants and to do their best effort to approach a 1/1 female/male ratio or at least not to exceed a 3/2 female/male ratio.

The number of subjects planned for enrollment and the descriptive trial design are consistent with a phase II stage clinical development. The descriptive trial design is consistent with early stage of development.

The collection of solicited and unsolicited AEs following vaccination is consistent with vaccine evaluation trials. Additionally, the 1-year follow up will provide safety profile information that is particularly critical for an elderly population prone to complications and development of autoimmune diseases. Subjects who receive Saline Placebo first (ie, subjects part of the 1-dose regimen groups) will have the same safety follow up as those in the 2-dose regimen groups. The safety assessments used in the trial, including monitoring for AEs, physical examinations, and vital signs assessments are widely used and generally recognized as reliable, accurate and relevant. They represent the standard for good clinical practice to ensure the safety of each subject.

The planned safety data review after the first approximately 100 subjects are enrolled in this trial (see Section 11.1.1) is intended to verify if safety results observed in the present trial are consistent with what has been observed in previous trials with the NoV GI.1/GII.4 Bivalent VLP Vaccine performed by Takeda. The collection of blood at the given time points, the selection of assays for the assessment of immune response to vaccination, and the selected vaccine formulations are based on experience from previous trials with the NoV GI.1/GII.4 Bivalent VLP Vaccine. Cognizant of the age of the elderly group and in an effort to limit the number of subjects exposed to the procedures, CCI [redacted] and time points have been selected to capture the eventual rapid changes and persistence over time in terms of cell mobilization after vaccination. CCI [redacted]

Please refer to the Investigator's Brochure [15] for further details.

6.3 Duration of Subject's Expected Participation in the Entire Trial

Subjects will be enrolled for approximately 393 days; that is to capture safety information 365 days after the last trial dose. Short term follow-up for AEs, SAEs, concomitant medications and AESI will be 28 days following each dose (Dose 1: through Day 28, collected on Day 29;

Dose 2: through Day 56, collected on Day 57). Final follow-up for SAEs and AESI will be performed 365 days following the last vaccination (ie, on Day 393).

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 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the trial.

- 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 Good Clinical Practice (GCP) that compromises the ability to achieve the primary trial objectives or compromises subject safety.

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)/Independent Ethics Committee (IEC) 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

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. The subject is aged 18–49 years, or 60 years and older at the time of enrollment;
2. Individuals who are in good health, or in stable health status with no exclusionary medical or neuropsychiatric conditions at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the Investigator;
3. The subject signs and dates 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 according to local regulatory requirements (Appendix C);
4. Individuals who can comply with trial procedures and are available for the duration of follow-up.

7.2 Exclusion Criteria

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

1. Individuals with known hypersensitivity or allergy to any of the NoV GI.1/GII.4 Bivalent VLP Vaccine components;
2. Individuals with a clinically significant active infection (as assessed by the Investigator) or body temperature ≥ 38°C/100.4°F within 3 days of the intended date of vaccination;
3. Individuals with the presence of significant acute or chronic, uncontrolled medical or neuropsychiatric illness. Uncontrolled was defined as:
    a. Requiring institution of new medical or surgical treatment within 3 months prior to immunization, or
    b. Requiring a change in medication dosage in the 3 months prior to immunization due to uncontrolled symptoms or drug toxicity (elective dosage adjustments in stable subjects were acceptable), or
    c. Hospitalization or an event fulfilling the definition of a serious adverse event within 3 months prior immunization.
4. Individuals with any unstable medical or neuropsychiatric condition, which in the Investigator's opinion poses a risk of unusual magnitude for the subject's age group of hospitalization, death, or an event meeting the definition of a SAE within 2 months of immunization. The intent of this criterion is to recognize and allow for the frequent existence of significant health concerns in this population; but exclude those subjects who are experiencing an acute decline in health status;

5. Individuals with any medical or neuropsychiatric condition which, in the Investigator's opinion, rendered the subject incompetent to provide informed consent or unable to provide valid safety observations and reports;
6. Individuals 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;
7. Individuals with any history of progressive or severe neurologic disorder, history of seizure, or history of neuro-inflammatory disease (eg, Guillain-Barré syndrome);
8. Individuals 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. Individuals with known or suspected autoimmune disease;
10. Individuals with known or suspected impairment/alteration of immune function, including:
    a. Chronic use of oral steroids (equivalent to 20 mg/day prednisone ≥ 12 weeks/≥ 2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1 (use of inhaled, intranasal, or topical corticosteroids is allowed).
    b. Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/≥2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1.
    c. Receipt of immunosuppressive therapy within 3 months prior to Day 1.
    d. Receipt of immunostimulants within 60 days prior to Day 1.
    e. Receipt of parenteral, epidural or intra-articular immunoglobulin preparation, blood products, and/or plasma derivatives within 3 months prior to Day 1 or planned during the full length of the trial.
    f. Human Immunodeficiency Virus (HIV) infection or HIV-related disease.
    g. Genetic immunodeficiency.
11. Individuals with abnormalities of splenic or thymic function;
12. Individuals with any significant disorder of coagulation or treatment with anticoagulant therapy that would increase the risk of IM injection. Persons receiving prophylactic antiplatelet medication such as low dose of acetylsalicylic acid are eligible;
13. Individuals with any serious chronic or progressive disease according to judgment of the Investigator: cancer (malignancy other than resolved/excised skin lesion), insulin dependent Type I diabetes (Type II diabetes is accepted), cardiac, renal or hepatic disease;
14. Individuals with BMI greater than or equal to 35 kg/m^2 (= weight in kg/[height in meters ^{2}]);
15. Individuals participating in any clinical trial with another investigational product 30 days prior to first trial visit or intent to participate in another clinical trial at any time during the conduct of this trial;

16. Individuals who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial or who are planning to receive any vaccine within 28 days of investigational vaccine administration;
17. Individuals involved in trial conduct or their first degree relatives;
18. Individuals with history of substance or alcohol abuse within the past 2 years;
19. Females who are pregnant or breastfeeding;
20. If female of childbearing potential, sexually active with a male partner who has not been sterilized, and has not used any of the "acceptable contraceptive methods" for at least 2 months prior to trial entry:
    a. Of 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 birth control methods are defined as 1 or more of the following:
        i. Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring);
        ii. Barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse;
        iii. Intrauterine device (IUD);
        iv. Monogamous relationship with vasectomized partner. Partner must have been vasectomized for at least 6 months prior to the subjects' trial entry.
21. If female of childbearing potential and sexually active, refusal to use an "acceptable contraceptive method" from Day 1 and throughout the duration of the trial. In addition, they must be advised not to donate ova during this period (Section 9.1.10);
22. Females with any positive or indeterminate pregnancy test.

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 excluded medication or vaccine). Under these circumstances, a subject may be considered eligible for trial enrollment if the appropriate window for delay has passed, inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

7.3 Criteria for Delay of Vaccination and/or Blood Sampling

After enrollment, subjects may encounter clinical circumstances that warrant a delay in subsequent trial vaccination. These situations are listed below. In the event that a subject meets a criterion for delay of vaccination, the subject may receive trial vaccination once the window for delay has passed as long as the subject is otherwise eligible for trial participation and this is discussed by the Investigator or designee in conjunction with the medical monitor. Subsequent visits should be calculated from the day of the second dose (eg, if Dose 2 is given on trial Day 31, the next visit should be scheduled for trial Day 38).

- Individuals with a body temperature >38.0°C (100.4°F) within 3 days of intended trial vaccination.

In case of non-clinical circumstances that warrant a delay in subsequent trial vaccination, same rules will apply.

There are also circumstances under which receipt of further vaccines 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 vaccine administrations but is encouraged to continue trial participation for safety reasons.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the trial should be recorded in the electronic Case Report Form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.11.

1. Protocol violation: The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety or rights;
2. Adverse Event (AE): The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE;
3. Lost to follow-up: The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact subject will be considered unsuccessful after 3 phone calls and a written notice. Attempts to contact the subject must be documented;
4. Withdrawal by subject: The subject (or subject's legally acceptable representative) wishes to withdraw from the trial. The reason for withdrawal will be recorded in the eCRF. Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category);
5. Trial terminated by Sponsor;
6. Pregnancy: Any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further investigational vaccines. The site should maintain contact with the pregnant subject and complete a "Clinical Trial Pregnancy Form" as soon as possible. In addition, the subject 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. The subject should be reported as a withdrawal from trial and the reason for withdrawal (eg, pregnancy) recorded in detail in the eCRF and subject's source records;
7. Other.

   Note: The specific reason should be recorded in the "specify" field of the eCRF.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may terminate a subject's trial participation at any time during the trial when the subject meets the trial termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the trial. Should a subject's participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures as scheduled for the Final Visit.

Subjects withdrawn or discontinued from the trial should be followed for safety through to the End of Trial (Day 393). The safety follow up procedures will be described in the manual of study procedures.

Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all vaccines and materials provided directly by the Sponsor, and/or sourced by other means, that are required by the trial protocol, including important sections describing the management of clinical trial material.

8.1 Trial Vaccines and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

The term trial vaccine refers to all of the vaccines (including placebo) described below.

The 2 NoV GI.1/GII.4 Bivalent VLP Vaccines (Formulations A and B), and the Saline Placebo described in this protocol will be supplied by the Sponsor. Cook Pharmica, Bloomington (IN), United States of America (USA), manufactures the investigational NoV GI.1/GII.4 Bivalent VLP Vaccines, and Ajinomoto Althea, San Diego (CA), USA, manufactures the Saline Placebo.

8.1.1.1 *Sponsor-Supplied Investigational vaccine*

NoV GI.1/GII.4 Bivalent VLP Vaccines (Formulations A and B): The prefilled syringes (PFS) of the NoV GI.1/GII.4 Bivalent VLP Vaccines will be supplied in tamper-evident, single dose cartons. Each PFS and carton will contain a label that includes pertinent trial information and caution statements. The label text will either be in English or the specific country language, depending on local requirements. The vaccine kit to be used will be identifiable by a unique identification number and managed by IWRS.

The NoV GI.1/GII.4 Bivalent VLP Vaccines are presented in a single-use, glass PFS CCI [redacted]. Each PFS contains a single 0.5 mL liquid dose for IM injection, CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Saline Placebo (Control): The placebo (saline) control will be 0.9% sodium chloride for injection without preservative for single injection presented in the same PFS as the NoV GI.1/GII.4 Bivalent VLP Vaccines to maintain the trial blind. Details for administration of placebo (saline) will be specified in the pharmacy manual.

8.1.2 Storage

The NoV GI.1/GII.4 Bivalent VLP Vaccines (Formulations A and B) will be shipped in refrigerated and temperature monitored containers. From receipt and prior to use, investigational vaccines must be protected from light and stored at 2°C to 8°C in a refrigerator with controlled access available only to authorized trial personnel. The vaccines must not be frozen. In case of accidental freezing, frozen vaccines should never been administered to subjects. Vaccines are single use only.

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the Sponsor or designee for destruction. All Sponsor-supplied vaccines must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the vaccine storage area must be maintained per the Sponsor approved site procedures. All temperature deviations must be reported to the Sponsor or their designee. Further details will be provided in the Pharmacy Manual.

8.1.3 Dose and Regimen

All subjects will receive trial vaccination on Day 1 and Day 29 as shown in Table 8-1. Refer to Section 8.1.1 for dosage specifications of the NoV GI.1/GII.4 Bivalent VLP Vaccines and Saline Placebo.

Note: If Dose 2 is not given on Day 29, subsequent visits should be calculated from the actual Day given (eg, if Dose 2 is given on trial Day 31, the next visit should be scheduled for trial Day 38).

Trial Arms 1, 2, 3 and 4 will include subjects aged ≥60 years distributed into 3 age groups including: 60-74 years, 75-84 and ≥85 years. Trial Arm 5 will include subjects aged 18–49 years.

Subjects in Arm 1 (1-dose regimen) will receive 1 dose of Saline Placebo on Day 1 and 1 dose of Formulation A on Day 29.

Subjects in Arm 2 (2-dose regimen) will receive 1 dose of Formulation A on Day 1 and on Day 29.

Subjects in Arm 3 (1-dose regimen) will receive 1 dose of Saline Placebo on Day 1 and 1 dose of Formulation B on Day 29.

Subjects in Arm 4 (2-dose regimen) will receive 1 dose of Formulation B on Day 1 and on Day 29.

Subjects in Arm 5 (1-dose regimen) will receive 1 dose of Saline Placebo on Day 1 and 1 dose of Formulation A on Day 29.

Table 8-1 Subject Distribution for Trial NOR-204

Age groups (years)	Number of subjects	Dose regimen [(a)]	Day 1	Day 29
18–49	25	1	Saline Placebo	Formulation A
60–74	25	1	Saline Placebo	Formulation A
	25	2	Formulation A	Formulation A
	25	1	Saline Placebo	Formulation B
	25	2	Formulation B	Formulation B
75–84	25	1	Saline Placebo	Formulation A
	25	2	Formulation A	Formulation A
	25	1	Saline Placebo	Formulation B
	25	2	Formulation B	Formulation B
≥85	25	1	Saline Placebo	Formulation A
	25	2	Formulation A	Formulation A
	25	1	Saline Placebo	Formulation B
	25	2	Formulation B	Formulation B
Total evaluable subjects	325			

[a]One dose versus 2-dose regimen with the NoV GI.1/GII.4 Bivalent VLP Vaccine (Formulations A or B)

8.2 Trial Vaccine Assignment and Dispensing Procedures

The Investigator or Investigator's designee will access the IWRS on Day 1 to obtain the subject number. Details of randomization and the IWRS will be covered in the IWRS User Manual.

The Investigator or Investigator's designee will utilize the IWRS to randomize the subject into the trial. During this contact, the Investigator or designee will provide the necessary subject identifying information.

The trial vaccine identification numbers to be administered will be assigned by the IWRS.

The trial vaccine will be prepared and administered by the unblinded designee according to the instructions in the Pharmacy Manual. All investigational vaccine preparation will be documented.

All trial vaccines (NoV GI.1/GII.4 Bivalent VLP Vaccines and Saline Placebo) will be administered IM into the middle third of the deltoid muscle of the subject's arm, preferably the non-dominant arm.

The Investigator or designee will be responsible for overseeing the administration of investigational vaccine to subjects enrolled in the trial according to the procedures stipulated in this trial protocol. All the trial vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable laws and regulations for that specific trial.

If trial vaccines are lost or damaged, the site can request a replacement from the IWRS (refer to the IWRS manual supplied separately).

8.2.1 Precautions to be Observed in Administering the Investigational Vaccine

Prior to vaccination, a subject must be determined to be eligible for trial vaccination and it must be clinically appropriate in the judgment of the Investigator to vaccinate. Eligibility for

vaccination prior to first trial vaccine administration is determined by evaluating the entry criteria outlined in this protocol (Sections 7.1 and 7.2). Eligibility for subsequent trial vaccination is determined by following the criteria outlined in Section 7.0.

Trial vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering the trial vaccine, the injection site is to be disinfected with a skin disinfectant (eg, 70% alcohol). Allow the skin to dry. DO NOT inject intravascularly.

As with all injectable vaccines, trained medical personnel 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 schedule. Randomization information will be stored in a secured area, accessible only by authorized personnel. The randomization will be stratified by site and age group. The randomization ratio is 1:1:1:1 in subjects aged 60 years and older (ie, 1 dose versus 2 doses of each Formulation A or B). All subjects aged 18–49 years will receive one dose of NoV G.1/GII.4 Bivalent VLP Vaccine Formulation A and one dose of Saline Placebo.

CCI [redacted].

8.4 Investigational Vaccine Blind Maintenance

This trial is double-blind within each elderly age group. The subjects, data collectors (eg, Investigator), and data evaluators (eg, trial statisticians) are blinded to the material administered. The trial vaccine assignment will be maintained by the unblinded site staff designee.

The trial is open label for the 18–49 years age group since all subjects will receive the same trial vaccine.

8.5 Unblinding Procedure

The trial vaccine blind shall not be broken by the Investigator unless information concerning the trial vaccine is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the trial vaccine blind is broken to discuss the need for unblinding.

For unblinding a subject, the trial vaccine blind information can be obtained by the Investigator by accessing the IWRS.

The Sponsor's Pharmacovigilance (PV) Department or designee must be notified as soon as possible if the trial vaccine blind is broken by the Investigator. Any unblinded cases must be

reported as an SAE and the completed SAE forms for the event requiring unblinding must be sent within 24 hours to the Sponsor PV or designee. The date, time, and reason the blind was broken must be recorded in the source document and the same information (except the time) must be recorded on the eCRF.

Subjects withdrawn from the trial due to unblinding should be followed for safety through the end of the trial. Further details for dealing with safety follow up for subjects withdrawn from the trial will be provided.

8.6 Accountability and Destruction of Sponsor-Supplied Vaccine(s)

Trial vaccine supplies will be counted and reconciled at the site before being returned to the Sponsor or designee as noted below. Sites will maintain source documents in addition to entering data in the IWRS.

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

Upon receipt of Sponsor-supplied vaccines, 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 trial vaccine is received within the labeled storage conditions, and is in good condition. If quantity and conditions are acceptable, Investigator or designee will acknowledge receipt of the shipment by recording in IWRS.

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's essential document file.

The Investigator must maintain 100% accountability for all Sponsor-supplied vaccines received and administered during his or her entire participation in the trial. Proper vaccine accountability includes, but is not limited to:

- Verifying that actual inventory matches documented inventory;
- Verifying that the log is completed for the vaccine used to prepare each dose;
- Verifying that all containers 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 vaccines on a Sponsor-approved vaccine accountability log. The following information will be recorded at a minimum: protocol number and title, name of Investigator, site identifier and number, description of Sponsor-supplied vaccines, date and amount. The log should include all required information as a separate entry for each subject to whom Sponsor-supplied vaccine is administered.

The Investigator will be notified of any expiry date or retest date extension of clinical trial material during the trial conduct if applicable. 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 its designee for destruction.

Prior to site closure or at appropriate intervals throughout the trial, before any clinical trial materials are returned to the Sponsor or its designee for destruction, a representative from the Sponsor or its designee 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.

The pharmacist (or designated individual) at each site will be responsible for vaccine accountability and will document receipt, use, return, or destruction. Vaccine accountability documentation will be reviewed by the monitor during clinical monitoring visits.

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.

9.1.1 Informed Consent

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

Informed consent must be obtained prior to the subject entering into the trial, and before any protocol-directed procedures are performed.

After informed consent is obtained, a unique subject identification number will be assigned to each subject from the IWRS. 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.

9.1.2 Demographics, Medical History and Prior Medications

Demographic information to be obtained will include age, sex, and race as described by the subject.

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 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.

All medications, vaccines and blood products taken or received by the subjects within 3 months prior to the start of the trial are to be recorded on the source document (patient record) and entered on the Prior and Concomitant Medications eCRF. 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 described in the source documents and the eCRF.

Medications taken for prophylaxis are those intended to prevent the onset of AEs following vaccination. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

These data must be recorded in the source documents.

Prohibited Therapies (See Section 7.2)

- Parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within 3 months of trial vaccination;
- Immunosuppressive therapy within 3 months or systemic (eg, oral or parenteral) corticosteroid treatment within 60 days prior to trial vaccine administration;

- Administration of other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial. Any planned vaccinations during the trial should be discussed with the Sponsor and if given recorded on the trial eCRFs.

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 informed consent.

9.1.3 Documentation of Trial Entrance/Randomization

Only subjects, who have signed the ICF, meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance/randomization into the vaccination phase. The list of randomization assignments is produced by IWRS.

The randomization will be stratified by site and by age group for subjects aged 60 years and older (60-74, 75-84, and ≥85 years of age).

If the subject is found to be not eligible for randomization/trial phase, the Investigator should record the primary reason for failure on the screening log.

9.1.4 Physical Examination

Physical examinations must be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Site Responsibility Delegation Log. Complete physical examination will be performed on Day 1, the same day as the first vaccine administration. A detailed physical examination includes but is not limited to: height and weight, auscultation of heart and lungs, palpation of the abdomen, inspection of extremities (including skin over intended vaccination site), and a check of general appearance. Additional physical examinations may be performed if indicated by review of the subject's medical history. The findings should be documented in the subject's record and eCRF.

Symptom-directed physical examination may be performed during the trial visits if deemed necessary.

9.1.5 Vital Signs

During the physical examination on Day 1 and during subsequent trial visits, a subject should have their vital signs measured. Vital signs include systolic blood pressure/diastolic blood pressure, heart rate, body temperature.

9.1.6 Immunogenicity Assessments

Subjects in all treatment arms will undergo blood sampling for serological immunogenicity testing on Day 1 (prior to vaccination), Day 8, Day 29 (prior to vaccination), Day 36, Day 57, Day 211, and Day 393.

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood taken at any single visit is approximately 10 mL, and the approximate total volume of blood for the immunogenicity assessments is approximately 70 mL. Blood samples will be processed and stored per the Laboratory Guidelines.

CCI [redacted]

9.1.7 Processing, Labeling and Storage of PBMC Samples

CCI [redacted]

Instructions for the processing of samples will be provided in a Laboratory Guidelines in the Procedures Manual.

9.1.8 Safety Assessments

Safety assessments will include collection and recording of solicited local (injection site) and systemic AEs, unsolicited AEs (serious and non-serious), SAEs and AESI. Refer to Section 10.1 for safety definitions. Details on collection and reporting of AEs are in Section 10.4.

9.1.9 Contraception and Pregnancy Avoidance Procedure

For female subjects of child bearing potential, urine pregnancy testing will be performed on Day 1 and Day 29 prior to vaccination. 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. Subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the trial procedures. All pregnancy tests must be negative prior to receiving any dose of investigational vaccine. Exclusion criteria for female subjects of child bearing potential are detailed in Section 7.2, Exclusion Criterion n°20.

9.1.10 Pregnancy

To ensure subject safety and the safety of the unborn child, each pregnancy in a subject having received a trial vaccine must be reported to the Sponsor or their designee within 24 hours of the site learning of its occurrence using the supplied Pregnancy Form. If the subject becomes pregnant during the trial, she will not receive any further doses of trial vaccine. 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. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended.

Any pregnancy occurring following trial vaccine administration should be reported immediately, using a pregnancy notification form provided to the site. Should the pregnancy occur after administration of a blinded trial vaccine, the Investigator must inform the subject of

their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the Investigator and procedures must be followed as described in Section 8.5.

9.1.11 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 complete the eCRF. The IWRS should be contacted as a notification of non-randomization.

The primary reason for non-randomization is recorded in the eCRF using the following categories:

- Screen failure, did not meet inclusion criteria or did meet exclusion criteria;
- Withdrawal by subject;
- Trial terminated by Sponsor;
- Other: The reason should be documented in the subject's source records and in the eCRF as appropriate.

Subject numbers assigned to subjects who fail screening should not be reused.

9.2 Monitoring Subject Treatment Compliance

The Investigator/designee records all injections of trial vaccine given to the subject in the source document and eCRF.

9.3 Schedule of Observations and Procedures

The schedule for all trial-related procedures for all evaluations is shown in Section 2.1. Assessments should be completed at the designated visit/time points. For this protocol, all body temperatures are preferably taken orally. Please note, if Dose 2 is delayed, subsequent visits should be calculated from the second dose (eg, if Dose 2 is given on trial Day 31, the next visit should be scheduled for trial Day 38).

9.3.1 Pre-Vaccination Procedures, Day 1

1. Informed consent;
2. Demographics;
3. Prior and concomitant medication;
4. Medical history;
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;
6. "Complete" physical examination;
7. Height and weight, BMI;
8. Vital signs including body temperature, blood pressure and pulse rate;

9. Pregnancy testing for women of child-bearing potential;
10. Assessment of eligibility criteria;
11. Enrollment;
12. Randomization;
13. Blood sampling. Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in the Laboratory Guidelines in the Manual of Procedures;
14. CCI [redacted].

9.3.2 Vaccination Procedures, Day 1

After confirming eligibility and enrolling the subject, the IWRS assigned dose will be administered according to the procedures described in Section 8.2.

9.3.3 Post-Vaccination Procedures, Day 1

After vaccination, the subject will be observed for at least 30 minutes including observation for solicited AEs (Table 10-2), unsolicited AEs and body temperature measurement will be performed. The subject should be instructed on how to measure solicited AEs and body temperature as part of this observation period. All safety data collected during this time should be recorded in the subject's source documents and entered on the appropriate eCRF.

Diary Cards

Careful training of the subject on how to measure local AEs and body temperature, how to complete, and how often to complete the diary card and handing out of the Day 1 – Day 7 diary card to the subject. Training should be directed at the individual who will perform the measurements of local AEs and those who will enter the information into the diary card. If a person other than a subject enters information into the diary card, this person's identity must be documented in the trial file and this person must receive training. Training of the subject on how to measure an injection site reaction should be performed while the subject is under observation after vaccination.

The subject must understand that timely completion of the diary card on a daily basis is a critical component to trial participation. The subject should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card that are performed by the person completing the diary card should include a single strikethrough line with a brief explanation for any change and be initialed and dated.

Please note: Diary cards will be the only source document allowed for remote collection of solicited local and systemic AEs (including body temperature measurements).

The site should schedule the next trial activity (Day 8). The subject will receive a written reminder of the next planned trial activity. The subject will be reminded to complete the diary card daily to contact the site if there are any questions and to contact the site immediately (or as

soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All contact details will be provided to the subject.

9.3.4 Pre-Vaccination Procedures, Day 29

For Dose 2 (Day 29 +4 days), the Investigator or designee will:

1. Reassess eligibility (confirm that the subject does not meet any criteria for delaying or cancelling additional trial vaccination, as described in Section 6.4.3);
2. Take vital signs and perform a Symptom Directed Physical Examination (if applicable);
3. Perform pregnancy testing for women of child-bearing potential;
4. Collect concomitant medications;
5. Review of the diary cards with the subjects for events occurring from Day 8 to Day 28 and collection of the diary card;
6. Blood sampling. Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in the Laboratory Guidelines as provided in the Procedures Manual;
7. Perform safety follow up for SAEs and AESI (according to the Schedule of Trial Procedures).

9.3.5 Vaccination Procedures, Day 29

After confirming that the subject does not meet any criteria for delaying or cancelling additional dosing, administer the appropriate investigational vaccine (the unblinded pharmacist is responsible for preparation of the correct material).

9.3.6 Post-Vaccination Procedures, Day 29

After vaccination on Day 29, the subject will be observed for at least 30 minutes including observation for solicited AEs, unsolicited AEs and body temperature measurement will be performed. The subject should be reminded on how to measure solicited AEs and temperature as part of this observation period. All safety data collected during this time should be recorded in the subject's source documents and entered on the appropriate eCRF.

Diary Cards

Careful training of the subject on how to measure local AEs and body temperature, how to complete, and how often to complete the diary card and handing out of the Day 29 - Day 35 diary card to the subject. Training should be directed at the individual who will perform the measurements of local AEs and those who will enter the information into the diary card. If a person other than a subject enters information into the diary card, this person's identity must be documented in the trial file and this person must receive training prior to doing so. Training of the subject on how to measure an injection site reaction should be performed while the subject is under observation after vaccination.

The subject must understand that timely completion of the diary card on a daily basis is a critical component of trial participation. The subject should also be instructed to write clearly

and to complete the diary card in pen. Any corrections to the diary card that are performed by the person completing the diary card should include a single strikethrough line with a brief explanation for any change and be initialed and dated.

Please note: Diary cards will be the only source document allowed for remote collection of solicited local and systemic AEs (including body temperature measurements).

The site should schedule the next trial activity. The subject will receive a written reminder of the next planned trial activity. The subject will be reminded to complete the diary card daily, to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All contact details will be provided to the subject.

9.3.7 Clinic Visits after Vaccination (Day 8, Day 36, Day 57, Day 211)

Clinic Visits that do NOT include a vaccination will be performed on Days 8, 36, 57 and 211. Diary cards for the Day 1 – Day 7 period and the Day 29 – Day 35 period will be reviewed with the subject and collected at the clinic visits on Day 8 and Day 36, respectively. The diary cards for the Day 8 – Day 28 and the Day 36 – Day 56 follow-up periods will be handed out to the subject at the clinic visits on Day 8 and Day 36, respectively, and subsequently reviewed with the subject and collected on Day 36 and on Day 57. The healthcare professional reviewing these data will discuss the AEs (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are present and/or concomitant medications have been used.

Additionally, the following rules apply to the documentation of safety information collected by diary card:

- No corrections or additions to the diary card will be allowed after it is reviewed with the Investigator/designee;
- Any data that is identified as implausible or incorrect, and confirmed by the subject to be a transcription error should be corrected by the subject on the diary card (the correction should include a single strikethrough line and should be initialed and dated by the subject);
- Any blank or illegible fields on the diary card not otherwise corrected as above will be missing in the eCRF;
- The site must enter all readable entries on the diary card into the eCRF;
- Any newly described safety information should be written into the diary card by the subject and initialed and dated. Any new unsolicited safety information should be recorded in the subject source document as a verbally reported event and therefore captured as an AE and therefore entered on the AE eCRF;
- Starting on the day of vaccination, the subject will check for specific types of reactions at the injection site (solicited local AEs), any specific generalized symptoms (solicited systemic AEs), body temperature, any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals). These solicited AEs and body temperature will be recorded in the diary card. Assessments should preferably take place in the evening at day's end;

- Temperature measurement is to be performed using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check their body temperature. If the subject has taken their body temperature more than once during the day, the highest body temperature observed that day should be recorded on the diary card;
- The measurement of solicited local AEs is to be performed using the ruler provided by the site. The collection of body temperature, solicited local AEs, solicited systemic AEs will continue for a total of 7 days following vaccine administration on the diary card. The collection of unsolicited AEs and medications will continue for 28 days following each vaccine administration on the diary card.

Measurement of vital signs and collecting concomitant medication. A brief symptom-directed physical assessment may be performed. If performed, the corresponding information is to be documented in the source documents and eCRFs. Perform safety follow up for SAEs and AESI according to the Schedule of Trial Procedures.

In addition to vaccination days during which a blood sample is taken, blood will be obtained on Day 8, Day 36, Day 57 and Day 211 for serological immunogenicity testing. Blood samples for CCI [redacted] in addition to the blood sample taken at first vaccination (ie, Day 1). Blood should be taken from the subject using an aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in the Laboratory Guidelines as provided in the Procedures Manual.

CCI [redacted] Refer to the detailed collection and handling procedures outlined in the Laboratory Guidelines as provided in the Manual of Procedures.

The site should schedule the next trial activity clinic visit with subject. The subject will receive a written reminder of the next planned trial activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

9.3.8 Final Visit (Day 393)

The Final Visit will be performed on Day 393 and will include assessment of vital signs, symptom directed physical examination if deemed necessary, review of concomitant medications, blood draw for serological immunogenicity testing (all subjects) CCI [redacted] and safety follow up for SAEs and AESI (according to the Schedule of Trial Procedures).

If a subject terminates earlier, procedures specified for Day 393 should be performed if possible.

9.3.9 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. Biological samples will be processed and stored per the Laboratory Guidelines as provided in the Procedures Manual. The samples will be retained at sponsor contracted laboratories/facilities for up to but no longer than 20 years, or as required by applicable laws. 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.

Serum samples, PBMCs, or salivary specimens, will be used for the analyses defined in this protocol, but may also be used, with the permission of the subject to assess, improve or develop tests related to the disease or the vaccine under trial that will allow more reliable measurement of the response to the vaccine.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a trial vaccine; it does not necessarily have to have a causal relationship with trial vaccine 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 a trial vaccine whether or not it is considered related to the trial vaccine.

Unsolicited AEs will be graded by the Investigator in the following manner:

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.

10.1.2 Solicited Adverse Events (AEs)

The occurrence of selected indicators of reactogenicity (Table 10-1) will be measured/collected until Day 7 (day of first vaccination [Day 1] + 6 following days) and until Day 35 (day of second vaccination [Day 29] + 6 following days) and will be recorded on the "Local and Systemic AE" eCRF, as applicable. These will be summarized under the category "solicited adverse events" to differentiate them from other AEs which were not solicited. Any solicited local or systemic AE observed as continuing on Day 7 following first vaccination or Day 35 following second vaccination, will be recorded as an AE on the Adverse Event eCRF.

Table 10-1 Local and Systemic AEs

Local AEs (injection site):	Pain
	Erythema
	Induration
	Swelling
Systemic AEs:	Headache
	Fatigue
	Myalgia
	Arthralgia
	Vomiting
	Diarrhea
	Fever[a] Record temperature in °C /°F

[a] Body temperature will be taken (preferably orally) and recorded. Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method taken [17].

The intensity of solicited safety parameters will be assessed as described in Table 10-2.

Table 10-2 Intensity Assessment for Solicited Safety Parameters

Solicited Event	Grade	Assessment
Pain at injection site:	0	No pain
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without
	3	Severe: Prevents daily activity with or without treatment
Erythema[a] at injection site:	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Induration[a] at injection site:	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Swelling[a] at injection site:	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Headache:	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without
	3	Severe: Prevents daily activity with or without treatment
Fatigue:	0	None
	1	Mild No interference with daily activity
	2	Moderate: Interference with activity
	3	Sever Prevents daily activity
Myalgia:	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with activity
	3	Severe: Significant; prevents daily activity
Arthralgia:	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with activity
	3	Severe: Prevents daily activity
Vomiting:	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity.
Diarrhea:	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Fever[b]:	Record temperature in °C /°F (preferably oral)	

[a] Subjects are to record the greatest surface diameter in mm in the diary.
[b] Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method taken [17].

10.1.3 Adverse Events of Special Interest (AESI)

AEs will also be evaluated by the Investigator for the co-existence of AESI which are pre-defined AEs that will be specifically highlighted to the Investigator. The list of AESI is summarized in Appendix D.

10.1.4 Serious Adverse Events (SAEs)

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.

10.2 Causality of AEs

Relatedness (causality) to vaccine will also be assessed by the Investigator. The relationship of each AE, including solicited systemic AEs (solicited local AEs are considered related) to trial vaccines will be assessed using the following categories:

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

Not Related: There is no suspicion that there is a relationship between the trial vaccine and the AE; there are other more likely causes and administration of the trial vaccine 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 reasonable possibility that an event is due to a trial procedure. Otherwise, the relationship should be assessed as "No".

10.2.2 Outcome of AEs

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.
Resolving 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.

10.3 Additional Points to Consider for AEs

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 AEs;
- Necessitate therapeutic intervention;
- Require an invasive diagnostic procedure;
- Require vaccine discontinuation or a change in concomitant medication;
- Be considered unfavorable by the Investigator for any reason.

Diagnoses vs. 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, sign(s) or symptom(s) should be recorded appropriately as an AE.

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after starting administration of the trail vaccine, 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 after any change in investigational vaccine, 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 informed consent are not considered AEs. 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.

10.4 Procedures

10.4.1 Collection and Reporting of AEs

All AEs experienced within 28 days of each vaccine dose whether considered related with the use of the trial vaccine or not, must be collected and 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 pathologist's report should be supplied, if possible. All findings must be recorded on an AE eCRF and on the SAE form if necessary. All findings in subjects experiencing AEs must also be reported in the subject's source documents. Any unsolicited AE will be collected for 28 days following vaccination during site visits using the diary card and by interview, AE reporting beyond Day 57 will be spontaneous or retrospectively at Day 393.

AEs leading to the subject's withdrawal will be collected from Day 1 through to Day 393.

The following information will be documented for each Unsolicited AE:

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

10.4.2 Collection and Reporting of Solicited AEs

The occurrence of selected indicators of safety will be collected on diary cards by the subjects through seven days (day of vaccination and the following 6 days) and will be recorded on the appropriate eCRF. Any solicited local or systemic AE observed as continuing on the seventh day will be recorded as an unsolicited AE on the Adverse Event eCRF. Any solicited local or systemic AE that resolved before the seventh day but recurs at a later time (i.e. if discontinued and restarted), will be recorded as an unsolicited AE on the Adverse Event eCRF.

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

- Solicited local or systemic AEs that lead the subject to withdraw from the trial;
- Solicited local or systemic AEs that lead to the subject being withdrawn from the trial by the Investigator;
- Solicited local and systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.4).

10.4.3 Collection and Reporting of AESI

AEs will also be evaluated by the Investigator for the co-existence of AESI which are pre-defined AEs that will be specifically highlighted to the Investigator. The list of AESI is summarized in Appendix D.

AESI will be collected by close monitoring from Day 1 up to Day 393. AESI need to be reported to the Sponsor as soon as possible after the Investigator becomes aware of the event.

AESI must be recorded as an AE on the Adverse Event eCRF. AESI will be summarized separately at the end of the trial.

10.4.4 Collection and Reporting of SAEs

Collection of SAEs will commence from the time that the subject is first administered with the trial vaccine (Day 1). Routine collection of SAEs will continue until the end of the trial (Day 393).

SAEs should be reported according to the following procedure:

A Sponsor SAE form must be completed, in English, and signed by the Investigator immediately or within 24 hours of first onset or notification of the event. 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;
- Subject identification number;
- Investigator's name;
- Name of the trial vaccine(s) – if no unblinding is necessary, in a blinded way;
- Causality assessment.

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

Note: For this study, SAE reporting will be done by eCRF. If the Electronic Data Capture (EDC) system is unavailable, a paper Sponsor SAE form/paper CRF should be completed and the event must be entered into the EDC once access is available.

10.5 Follow-up Procedures

10.5.1 AEs

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 SAEs

If information not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, laboratory tests, discharge summary, postmortem results) should be sent to the Sponsor.

All SAEs should be followed up until resolution or 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.

Note: For this trial, SAE reporting will be done by eCRF. If the EDC system is unavailable, a paper Sponsor SAE form/paper CRF should be completed and the event must be entered into the EDC once access is available.

10.5.3 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The Sponsor or designee will be responsible for the reporting of all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), Investigators and IRBs or IECs, 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 Sponsor's 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 medicinal product or that would be sufficient to consider changes in the trial vaccine administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to their IRB or IEC in accordance with national regulations.

10.5.4 Post-Trial Events

Any AE that occurs outside of the protocol-specified observation period or after the end of the trial but considered to be caused by the trial vaccine(s) must be reported to the Sponsor. These

AEs will be processed by the Sponsor's Pharmacovigilance Department. Instructions for how to submit these AEs will be provided in a handout in the Investigator Site File.

11.0 TRIAL-SPECIFIC REQUIREMENTS

11.1 Trial-Specific Committees

No trial-specific committee will be used for this trial.

11.1.1 Data Monitoring Committee

An overall DMC is established to evaluate overall safety of the Takeda Norovirus vaccine program on an ongoing basis. The composition, role and responsibilities of the DMC are presented in a separate DMC Charter.

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 conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Low Level Term (LL), Preferred Term (PT) and their corresponding descriptive terms. Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 Electronic CRFs (eCRF)

Completed eCRFs are required for each subject who signs an informed consent.

The Sponsor or its 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 eCRFs are used to transmit the information collected in the performance of this trial to the Sponsor and regulatory authorities. 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 designees) and will be answered by the site. Reasons for significant corrections should additionally be included.

Corrections to 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.

The principal Investigator or designee 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.

Electronic CRFs will be reviewed for completeness and acceptability at the trial site during periodic visits by trial monitors. The Sponsor or its 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 records of the eCRF and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, source documents. Temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of vaccine disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Furthermore, International Conference on Harmonization (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.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

There will be 2 analysis time points in this trial:

(1) An interim analysis is planned after all subjects have completed the Day 57 Visit (28 days after last vaccination). Refer to Section 13.2.

(2) The final analysis is planned after all subjects have completed the Day 393 Visit.

Blinded data reviews will be conducted by the blinded trial team prior to unblinding of subject treatment assignment for the primary analysis. These reviews will assess the accuracy and completeness of the trial database and subject evaluability.

13.1.1 Analysis Sets

The analyses sets are defined as follows:

- *Safety Analysis Set*: will include all subjects who receive at least 1 dose of vaccine (NoV VLP vaccine or control placebo).
- *Full Analysis Set* (FAS): will include all subjects who are randomized and have received at least 1 dose of vaccine.
- *Per Protocol Set* (PPS): will include all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of subject's treatment assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving wrong trial treatment (3) receiving prohibited therapies, and (4) other major protocol violations that may be identified during blinded data reviews. The major protocol violation criteria will be finalized prior to the initial interim analysis.

The safety analysis will be based on the Safety Analysis Set. The primary immunogenicity analyses will be based on the PPS, and secondary immunogenicity analyses will be based on the FAS.

Summaries for safety and immunogenicity will be provided. Unless otherwise specified, descriptive summary statistics include mean, standard deviation (SD), median, minimum, and maximum values for continuous variables, and the number and percentage of subjects in specified categories for categorical variables.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Age, gender, race and other baseline characteristics will be summarized descriptively by treatment arm and by age group, based on the set of all randomized subjects.

13.1.3 Safety Analysis

All summaries and analyses of safety data are based on subjects in the Safety Analysis Set. Unless otherwise specified, the safety data will be summarized according to the treatment arms within each age group. Further grouping or sub-grouping may be investigated as appropriate (eg, all age classes ≥60 years together). In general, data imputation will not be performed for any missing safety data. The criteria for implausible measurements are defined in the statistical analysis plan, and any measurements meeting those criteria (eg, body temperature >42°C) will be excluded from the summaries and analyses.

Reactogenicity

Reactogenicity will be assessed for 7 days following each vaccination (the day of vaccination and the following 6 days) via collection of solicited AEs, including local AEs (injection site: pain, erythema, induration and swelling) and systemic AEs (headache, fatigue, myalgia, arthralgia, vomiting, and diarrhea). In addition, other indicators of reactogenicity will be collected (body temperature). The categories for each solicited AE are defined in Section 10.1.3. Solicited adverse event data (reactogenicity) will be captured daily for 7 days (on the day of vaccination and the following 6 days).

For each solicited AE, the percentage of subjects will be summarized by event severity for each day (from Day 1 to Day 7) and overall. In addition, summaries will be provided for the intervals of Days 1 to 3 following each vaccination, and Days 4 to 7 following each vaccination. A summary of the day of first onset of each event and the number of days subjects reported experiencing each event will also be provided. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

The occurrence of reactogenicity will also be summarized descriptively by the number of days subjects reported experiencing the symptom, by treatment group within each age group.

*Unsolicited AE*s

Unsolicited AEs, SAEs and AESI will be coded using the MedDRA and summarized by SOC and PT for each trial treatment arm in each age group. AEs leading to subject's withdrawal from the trial will also be summarized.

All unsolicited AEs up to 28 days after the last vaccination will be included in the analyses of all AEs. For SAEs and AEs leading to subject withdrawal from the trial, any AE collected during the trial will be included.

In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE) and by SOC and PT. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. Unsolicited AEs will be summarized as follows: by PT including events with frequency greater than 2%; by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to the investigational vaccine.

Unless otherwise specified, unsolicited AEs in the treatment arm and age groups will be summarized in the following 3 ways: 1) overall up to 28 days after the first and second vaccination, 2) with onset between 1 and 7 days after the first and second vaccination, and 3) with onset between 8 and 28 days after the first and second vaccination.

13.1.4 Immunogenicity Analysis

Descriptive summary statistics including 95% confidence intervals (CI) for the primary, secondary, and exploratory (CCI endpoints, including percentage of subjects with ≥4-fold rise, GMT, BT_{50} and GMFR will be computed for all available assays for each time point by treatment arm, separately for each age group. Within each age group, analysis of covariance (ANCOVA) with treatment arm as a factor and Fisher's exact test will be conducted for continuous and binomial outcomes, respectively. Pre-vaccination titers will be used as a covariate in the ANCOVA analyses.

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More specific details about the immunogenicity analyses will be provided in the SAP.

13.2 Interim Analysis

A review of safety data will be performed by the DMC as soon as the first approximately 100 subjects have completed the Day 36 Visit (8 days post last vaccination) to verify if safety results observed in the present trial are consistent with what has been observed in previous trials with the NoV GI.1/GII.4 Bivalent VLP Vaccine performed by Takeda. In order to have a good representation of the entire trial population, efforts will be made in terms of enrollment to have those first approximately 100 subjects equally distributed in each permutation.

An interim analysis on safety and immunogenicity data is planned when all subjects have completed the Day 57 Visit (28 days after last vaccination). This analysis will include group results but not individual subject information. This analysis will be performed by a separate set of unblinded statisticians and programmers at a selected independent Contract Research Organization (CRO) who will have access to individual treatment assignments but will not be involved in subsequent trial conduct. Except for the unblinded pharmacist and unblinded administrator, the personnel involved in the conduct of the trial including those at the Sponsor site, the CRO, and the trial sites, will remain blinded to the individual subject data (including treatment assignment) until unblinding after database lock for data through Day 393.

13.3 Determination of Sample Size

This trial is designed to be primarily descriptive. Therefore the sample size was not determined based on formal statistical power calculations but rather to provide a reasonable clinical database to assess safety and immunogenicity in an elderly population.

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 its designee (CRO) and by the IRB or IEC.

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 Investigator's Binder, trial vaccine, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs 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 medical monitor (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial site also may be subject to quality assurance audits by the Sponsor or designees. 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 (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). 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.

15.0 ETHICAL ASPECTS OF THE TRIAL

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

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local 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 or IEC. If any member of the IRB or IEC has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained. Those US sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, 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 or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the Sponsor or designee before commencement of the trial (ie, before shipment of the Sponsor-supplied Vaccine or trial specific screening activity). The IRB or IEC 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 of approval, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC 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 or IEC, and submission of the Investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the Sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC 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 (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the trial. The ICF and the subject information sheet (if applicable) 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 participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) 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 or IEC.

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 he or she 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 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 (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the subject signs the informed consent in the subject's medical record and eCRF. 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 relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record and eCRF, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The Sponsor and designees 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's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs 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 informed consent 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 eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The results of this trial are expected to be published in a scientific journal. It is anticipated that clinical and laboratory co-investigators will participate in authorship. The order of authorship and choice of journal will be determined by the PIs and the Sponsor. The data analysis center for this trial will provide the analyses needed for publication. Information regarding this trial will be posted on ClinicalTrials.gov.

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, at a minimum register all clinical trials conducted in subjects that it Sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation. The Sponsor contact information, along with Investigator's city, country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

The Sponsor will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

Trial completion corresponds to the date on which the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

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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Appendix A Responsibilities of the Investigator

Clinical research trials sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The Investigator agrees to assume the following responsibilities:

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. Ensure that trial related procedures, including trial specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
5. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the trial to the IRB/IEC, and issue a final report within 3 months of trial completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the trial, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an ICF does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject.
9. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied vaccines, and return all unused Sponsor-supplied vaccines to the Sponsor.
12. Report AEs to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.
13. Review and provide a signature as approval of the content of the clinical study report.

Appendix B Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of Investigator, including his or her name, address, and other personally identifiable information. In addition, Investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of Investigator for the trial and/or other clinical trials.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other vaccines used in other clinical trials that may contain the same chemical compound present in the investigational vaccine.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting Investigator site contact information, trial details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in Investigator's own country. Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the trial involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the trial.
7. A description of the subject's responsibilities.
8. A description of the conduct of the trial.
9. A statement describing the vaccination(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects following vaccine administration that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the trial.
17. The anticipated expenses, if any, to the subject for participating in the trial.
18. An explanation of whom to contact for answers to pertinent questions about the research (Investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the Sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
24. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the trial. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the investigational vaccine(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical trials;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the trial to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that trial results are published.
25. Female subjects of childbearing potential (eg, non-sterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Day 1 and throughout the duration of the trial. Pregnancy tests will be performed on Day 1 and Day 29 prior to vaccination for all female subjects of childbearing potential. If a subject is found to be pregnant during trial, no further vaccine

doses will be administered and the Investigator will offer the subject the choice to receive unblinded treatment information.

26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Adverse Events of Special Interest (AESI)

Cardiac Disorders

- Endocarditis
- Myocarditis
- Pericarditis

Gastrointestinal Disorders

- Celiac Disease
- Crohn's Disease
- Inflammatory Bowel Disease (non-specific)
- Ulcerative Colitis
- Ulcerative Proctitis

Immune System Disorders

- ANA Increased
- Anti-ds DNA Increased
- Anti-Phospholipid Syndrome
- Autoimmune Glomerulonephritis
- Autoimmune Hemolytic Anemia
- Autoimmune Hepatitis
- Idiopathic thrombocytopenic purpura (ITP)
- Serum Sickness

Infections and Infestations

- Fever of Unknown Origin
- Sinusitis

Musculoskeletal and Connective Tissue Diseases

- ANCA-Associated Vasculitis
- Arthritis/Bursitis (non-specified)
- Behcet's Syndrome
- Cutaneous Lupus
- Dermatomyositis
- Juvenile Rheumatoid Arthritis
- Mixed Connective Tissue Disease
- Mono-Articular Arthritis
- Pauci-Articular Arthritis
- Polymyalgia Rheumatica
- Polymyositis
- Reactive Arthritis
- Rheumatoid Arthritis
- Sarcoidosis
- Scleroderma
- Sjorgen's Syndrome
- Systemic Lupus Erythematosis
- Temporal Arteritis
- Wegener's Granulomatosis

Neuroinflammatory Disorders

- Acute disseminated encephalomyelitis (ADEM)
- Bell's Palsy/Facial Palsy
- Encephalitis
- Demyelinating Disease
- Guillain Barre Syndrome
- Hypoaesthesia (non-specific)
- Multiple Sclerosis
- Myasthenia Gravis
- Myelitis/Transverse Myelitis
- Neuritis
- Optic Neuritis
- Paraesthesia (non-specific)
- Uveitis

Renal and Urinary Disorders

- Glomerulonephritis
- Hematuria
- Nephritis
- Proteinuria
- Renal failure

Skin

- Alopecia
- Dermatomyositis
- Erythema Nodosum
- Psoriasis and Psoriatic Arthropathy
- Stevens-Johnson Syndrome
- Toxic Epidermal Necrolysis (TEN)
- Vitiligo

Thyroid Disorders

- Graves' (Basedow's) Disease
- Goiter (non-specified)
- Hyperthyroidism
- Hypothyroidism
- TSH High
- Thyroid Disorder (non-specific)
- Thyroiditis

Vascular Disorders

- Pulmonary Embolism
- Raynaud's Phenomenon
- Vasculitis

Others

- Aphthous Stomatitis
- Insulin-dependent diabetes mellitus (IDDM)