Title: A Phase 2, Long-Term Immunogenicity Follow-up Trial of Adult and Elderly Subjects who have Previously Received an Intramuscular Injection of Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine

NCT Number: NCT03039790

Protocol Approve Date: 27 March 2018

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.

A Phase 2, Long-Term Immunogenicity Follow-up Trial of Adult and Elderly Subjects who have Previously Received an Intramuscular Injection of Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine

Long-Term Immunogenicity of the Norovirus GI.1/GII.4 Bivalent VLP Vaccine in Adults

Sponsor:	Takeda Vaccines, Inc. 40 Landsdowne Street, Cambridge, MA 02139, USA		
Study Identifier:	NOR-213		
IND Number:	014421	**EudraCT Number:**	2016-004288-37
Vaccine Name:	Not Applicable		
Date:	27 March 2018		
Version:	3.0		

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.a.

The sponsor will provide investigators with site-specific 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 trial related responsibilities is given in Section 3.1 and relevant guidelines will be provided to the site.

Table 1.a 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 (ie subjects) 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 [1].
- International Council for Harmonization (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline [2].
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.

SIGNATURES

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure IB), 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 Council for Harmonization, E6 Good Clinical Practice: Consolidated Guideline [2].
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.
- Regulatory requirements for reporting serious adverse events defined in Section 10.4 of this protocol.
- Terms outlined in the Clinical Study 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 C 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 Summary of Changes

This document describes the changes in reference to the protocol incorporating Amendment N° 2.0.

The purpose of this amendment is to update the protocol to remove reference to trial NOR-222. This trial will no longer be included in the vaccine development plan. Full details on changes of text are given in Section 1.3.2.

1.3.1 Amendment History

Date	Amendment Number	Protocol Version	Amendment Type	Region
05 December 2016	Not applicable	1.0	Not applicable	Global
02 October 2017	1.0	2.0	Non-substantial	Global
27 March 2018	2.0	3.0	Non-substantial	Global

1.3.2 Summary of Changes

Amendment to Protocol Version 2.0 02 October 2017

Rationale for the Amendment:

The reason for this amendment is to remove NOR-222 from the long-term follow-up due to it being cancelled. Accordingly, sample size has been reduced and interim analysis (IA) language has been modified to state that the IA will be performed when all participants have provided one blood sample corresponding to at least their first year of participation in NOR-213.

Section	Description of change
2.0 Trial summary	Adapted to reflect the changes in the body of the protocol.
2.1 Schedule of Trial Procedures	Removal of text pertaining to NOR-222 from the table.
3.3 List of Abbreviations	Geometric mean blocking titer ***(50%)***
4.2 Rationale for the Proposed Trial	Completed or ongoing trials have included a safety and immunogenicity follow-up of maximum 1 year. NOR-213 is designed to capture data from adults and older adults previously vaccinated with NoV vaccine, providing the opportunity to evaluate long-term immunogenicity data up to 5 years following the first dose of NoV vaccine. ~~Four~~ ***Three*** trials have been selected for this purpose: NOR-107 (adults aged 18 to 64 years, 1 or 2 doses 11 compositions of GI.1/GII.4/MPL, 167 or 500 µg aluminum as $Al(OH)_3$), NOR-210 (adults aged 18 to 49 years, 1 dose 15/50/0 µg GI.1/GII.4, 500 µg aluminum as $Al(OH)_3$) ***and***~~,~~ NOR-204 (adults aged 18 to 49 and ≥60 years, 1 or 2 doses 15/50/0 or 15/50/15 µg GI.1/GII.4/MPL, 500 µg aluminum as $Al(OH)_3$)~~ and NOR-222 (adults aged 18 to 49 years, 1 dose 15/50/0 µg GI.1/GII.4, 500 µg aluminum as $Al(OH)_3$)~~. Subjects who participated in trials NOR-107 and NOR-210 will enter NOR-213 during the 3rd and 2nd year post-vaccination, respectively. NOR-204 is ongoing, and subjects participating in NOR-213 will enter the trial during the 2nd year post-vaccination. ~~NOR-222 has not yet started and subjects participating in NOR-213 will enter the trial during the 1st year post-vaccination~~. The rationale for the selection of these trials is based on the opportunity to obtain long-term follow-up data for immunogenicity of the NoV vaccine in adult and elderly populations.

Section	Description of change
5.2 Endpoints	*All primary, secondary* CCI *evaluations will be performed at yearly intervals ~~from at least 1 year and~~ up to 5 years after primary vaccination.*
6.1 Trial Design	This phase 2, multi-site trial is designed to evaluate descriptively the long-term immunogenicity of at least 1 NoV vaccine administration. Subjects previously enrolled in NOR-107, NOR-210 and NOR-204 ~~as well as those who will be part of NOR-222~~ will be invited to participate in this long-term follow-up trial ~~for~~ ***corresponding to*** a duration of up to 5 years post-***primary*** vaccination. The timing of subject entry into NOR-213 with respect to the anniversary of the primary vaccination trial means the duration of subject participation in the present trial will be different. Following inclusion in NOR-213 subjects will have yearly blood draws. Subjects from NOR-107 will enter this trial at the time of their 3rd year post-primary vaccination. For NOR-210 and 204, entry will correspond to their 2nd year post-primary vaccination~~, and for NOR-222, this will be the time of their 1st year post-primary vaccination~~. Trial procedures will include a maximum of ~~5~~ ***4*** visits over ~~5~~ ***3*** years. At each visit, a blood sample, including peripheral blood mononuclear cell (PBMC) isolation (only for the subset of subjects initially included in NOR-107 and NOR-204 trials), CCI [redacted]. At each contact with the subject, fatal and life threatening serious adverse events (SAEs), NoV vaccine-related SAEs, potential immune–mediated events of medical significance and any procedure-related medical occurrences will be recorded. An interim analysis (IA) is planned when all subjects have ~~completed at least the one-year follow-up visit~~***provided one blood sample corresponding to at least their first year of participation in NOR-213***. It is expected that ~~approximately 800~~ ***up to 575*** subjects who participated in the selected trials will be available for enrollment.
	Figure 6a. Removal of NOR-222.
6.2 Justification for Trial Design, Dose, and Endpoints	Subjects who participated in trials NOR-107, NOR-210 and NOR-204 will have already reached 1 year or more post-primary vaccination with NoV vaccine at the time of trial NOR-213 start. ~~Subjects in NOR-222 will be invited to participate in NOR-213 1 year following primary vaccination.~~
6.3 Duration of Subject's Expected Participation in the Entire Trial	~~The total estimated duration of trial participation is approximately 4 years for subjects who previously participated in NOR-222.~~
7.1 Inclusion Criteria	2. Male and female subjects who previously received at least 1 dose of NoV vaccine in trials NOR-107, NOR-210 ***and***~~,~~ NOR-204~~ and NOR-222~~, have baseline and post-vaccination data, and completed the primary vaccination trial protocol as initially described.
8.1.4 NOR-222	Deletion of the section describing trial NOR-222.
9.1.6 Immunogenicity Assessments	CCI [redacted]
9.1.8 Safety Assessments	At every subject contact, fatal and life threatening SAEs, NoV vaccine-related SAEs, potential immune–mediated events of medical significance and any procedure-related medical occurrences will be collected ~~up to 5 years~~***throughout the trial***.

Section	Description of change
13.2 Interim Analysis and Criteria for Early Termination	An IA will be performed after all subjects have ***provided one blood sample corresponding to at least their first year of participation in NOR-213*** ~~completed at least the 1-year follow-up visit~~ and the data for that trial segment have been sufficiently reviewed for accuracy and correctness. An interim report will be developed based on these data. The final CSR will include the description of the immunogenicity results ~~for the duration of the trial (~~corresponding to ***up to*** 5 years post-primary vaccination~~)~~ as well as safety data. The sponsor may consider terminating or amending the trial after review of the IA.
16.0 References	Global Investigator's Brochure. Norovirus Bivalent VLP Vaccine. Edition ***6***4.0, 224 ~~December~~ ***November*** 2017~~6~~.

Amendment to Protocol Version 1.0 05 December 2016

Rationale for the Amendment:

- At the request of the first site to participate in trial NOR-213, the previous 3-digit identification number used during the primary vaccination trial will be kept instead of using a new chronological entry order. This is easier for the sites from a logistical point of view, will facilitate the subject traceability.
- Clarification about safety data collection in the source document in relation to the sponsor requirement for the eCRF. As there is no new vaccine administration in NOR-213 and appropriate safety follow-up was carried out in the primary vaccination trials (vaccine composition containing monophosphoryl lipid A (MPL): 12 months of safety follow-up, vaccine composition with no MPL: 6 months of safety follow-up) it was considered that a targeted long-term safety follow-up was sufficient. Recording of adverse events (AEs) in the subject's eCRF will be limited to fatal and life threatening serious adverse events (SAEs), NoV vaccine-related SAEs, potential immune–mediated events of medical significance and any procedure-related medical occurrences during the entire duration of NOR-213.

CCI [redacted]

Section	Description of change
Title page	Correction of a typographical error in the title: Long-Term Immunogenicity of Norovirus GI.*1*/GII.4 Bivalent VLP Vaccine in Adults. Modification of the sponsor address.
Trial summary	Adapted to reflect the changes in the body of the protocol.
Section 2.1 Schedule of Trial Procedures (Footnoted)	Clarification about safety information to be recorded in source documents: (d~~)AE collection and r~~***R****eporting* ***of AEs*** in the subject's eCRF is limited to fatal and life threatening SAEs, NoV vaccine-related SAEs, ~~and important medical events (~~potential immune–mediated events~~)~~ ***of medical significance*** and any procedure-related medical occurrences~~. However, all findings in subjects experiencing any AEs~~***; and*** must be recorded in the subject's source documents

CCI [redacted]

Section	Description of change
Section 6.1 Trial Design	Modification to text concerning sample re-testing: ~~Where possible,~~ CCI [redacted] .
	Clarification about safety information to be recorded: At each contact with the ~~participants~~***subject***, fatal and life threatening serious adverse events (SAEs), NoV vaccine-related SAEs, ~~and important medical events (~~ potential immune–mediated events~~)~~ ***of medical significance*** and any procedure-related medical occurrences will be recorded.
Section 9.1.2 Documentation of Trial Entrance	Clarification for the subject identification number: After informed consent is obtained, each subject will ***be identified with the same*** ~~receive a~~ unique subject number ***allocated for*** ~~that will link the subject to~~ the primary vaccination trial. ~~and corresponding primary trial identifier, the site number and a new chronological number~~**.**
Section 9.1.8 Safety assessments	Clarification about safety data collection: At every subject contact, fatal and life threatening SAEs, NoV vaccine-related SAEs, ~~and important medical events (~~ potential immune–mediated events~~)~~ ***of medical significance,*** and any procedure-related medical occurrences will be collected up to 5 years.
Section 9.3.2	Clarification about safety data collection: At every subject contact, fatal and life threatening SAEs, NoV vaccine-related SAEs, ~~and important medical events (~~ potential immune–mediated events~~)~~ ***of medical significance***, any procedure-related medical occurrences and concomitant medication related to AEs and SAEs will be collected.
Section 10.4.1 Collection and Reporting of AEs	Clarification about safety information to be collected in source documents: For this study, ~~AE collection and~~ rep~~c~~ort~~d~~ing ***of AEs*** in the subject's eCRF is limited to fatal and life threatening SAEs, NoV vaccine-related SAEs, ~~and important medical events (~~ potential immune–mediated events~~)~~ ***of medical significance,*** and any procedure-related medical occurrences~~. All findings in subjects experiencing any AEs~~***; and*** must ~~also~~ be rep~~c~~ort~~d~~ed in the subject's source documents.
Section 10.4.4 Collection and Reporting of SAEs	Clarification about safety information to be collected in source documents: *Note*: (2) For this study, ~~SAE collection and~~ rep~~c~~ort~~d~~ing ***of SAEs*** in the subject's eCRF is limited to fatal and life threatening SAEs, NoV vaccine-related SAEs, ~~and important medical events (~~ potential immune–mediated events~~)~~ ***of medical significance,*** and any procedure-related medical occurrences~~. However, all findings in subjects experiencing any AEs~~***; and*** must be recorded in the subject's source documents.
Section 13.1.4	Modification to text concerning sample re-testing: Immunogenicity measurements obtained at baseline and post-vaccination visits during the primary vaccination trial ~~will~~ ***may*** be accessed from databases to contribute to designated summaries of immunogenicity endpoints over time following vaccination.
	Modification to text concerning sample re-testing: CCI [redacted]
Throughout	CCI [redacted]

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2.0 TRIAL SUMMARY

Name of Sponsor: Takeda Vaccines, Inc. 40 Landsdowne Street, Cambridge, MA 02139, USA	**Product Name:** Norovirus GI.1/GII.4 Bivalent Virus-Like Particle (VLP) Vaccine	
Trial Title: A Phase 2, Long-Term Immunogenicity Follow-up Trial of Adult and Elderly Subjects who have Previously Received an Intramuscular Injection of Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine.		
IND No.: 014421	**EudraCT No:** 2016-004288-37	
Trial Identifier: NOR-213	**Phase:** 2	**Trial Blinding Scheme:** Not applicable

Background and Rationale:

Noroviruses 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. Those most at risk are the elderly, the very young and immunocompromised individuals.

Currently, no vaccine exists for protection against acute gastroenteritis (AGE) due to norovirus and treatment remains symptomatic. Human noroviruses are difficult to cultivate and so far, it has not been possible to develop a live attenuated or an inactivated norovirus vaccine. The investigational vaccine being developed by Takeda, norovirus genotypes GI.1/GII.4 bivalent virus-like particle (VLP) vaccine (NoV vaccine), contains GI.1 Norwalk Virus VLP and norovirus GII.4 consensus VLP which represents a consensus sequence of 3 GII.4 strains, as antigens. Norovirus VLPs are non-infectious because they do not contain viral ribonucleic acid but are immunogenic because they preserve particulate antigen conformation and structure that mimic the functional interactions of the virus with cellular receptors. The rationale for developing a bivalent vaccine is based on known epidemiology that both GI.1 and GII.4 genotypes circulate and do not cross-protect in nature. The intramuscular (IM) NoV vaccine has been evaluated as different compositions of GI.1/GII.4 VLP adjuvanted with aluminum as aluminum hydroxide ([$Al(OH)_3$]; adults and children) or $Al(OH)_3$ combined with monophosphoryl lipid A (MPL) (adults).

Safety and immunogenicity data are available from several Takeda trials in which subjects received at least 1 dose of a NoV vaccine composition under development. Data related to the primary objective of NOR-107 showed the optimal NoV vaccine composition among those evaluated, contains 15 µg GI.1 VLP, 50 µg GII.4 VLP, 500 µg aluminum as $Al(OH)_3$ in adults. No clear benefit on vaccine immunogenicity was suggested from including 50 µg or 15 µg MPL in the NoV vaccine formulation or from administering 2 doses 28 days apart. A single dose of 15 µg GI.1 VLP, 50 µg GII.4 VLP, 500 µg aluminum as $Al(OH)_3$ was tested in trial NOR-210, confirming a robust immune response up to 28 days after vaccination. The different compositions of the NoV vaccine have been well-tolerated, and have an acceptable safety profile.

Completed or ongoing trials have included a safety and immunogenicity follow-up of maximum 1 year. NOR-213 is designed to capture data from adults and older adults previously vaccinated with NoV vaccine, providing the opportunity to evaluate long-term immunogenicity data up to 5 years following the first dose of NoV vaccine. Three trials have been selected for this purpose: NOR-107 (adults aged 18 to 64 years, 1 or 2 doses 11 compositions of GI.1/GII.4/MPL, 167 or 500 µg aluminum as $Al(OH)_3$), NOR-210 (adults aged 18 to 49 years, 1 dose 15/50/0 µg GI.1/GII.4, 500 µg aluminum as $Al(OH)_3$) and NOR-204 (adults aged 18 to 49 and ≥60 years, 1 or 2 doses 15/50/0 or 15/50/15 µg GI.1/GII.4/MPL, 500 µg aluminum as $Al(OH)_3$). Subjects who participated in trials NOR-107 and NOR-210 will enter NOR-213 during the 3rd and 2nd year post-vaccination, respectively. NOR-204 is ongoing, and subjects participating in NOR-213 will enter the trial during the 2nd year post-vaccination. The rationale for the selection of these trials is based on the opportunity to obtain long-term follow-up data for immunogenicity of the NoV vaccine in adult and elderly populations.

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

Trial Design:

This phase 2, multi-site trial is designed to evaluate descriptively the long-term immunogenicity of at least 1 NoV vaccine administration. Subjects previously enrolled in NOR-107, NOR-210 and NOR-204 will be invited to participate in this long-term follow-up trial corresponding to a duration of up to 5 years post-primary vaccination. The timing of subject entry into NOR-213 with respect to the anniversary of the primary vaccination trial means the duration of subject participation in the present trial will be different. Following inclusion in NOR-213 subjects will have yearly blood draws. Subjects from NOR-107 will enter this trial at the time of their 3rd year post-primary vaccination. For NOR-210 and 204, entry will correspond to their 2nd year post-primary vaccination.

Trial procedures will include a maximum of 4 visits over 3 years. At each visit, a blood sample, including peripheral blood mononuclear cell (PBMC) isolation (only for the subset of subjects initially included in NOR-107 and NOR-204 trials), CCI [redacted]. At each contact with the subject, fatal and life threatening serious adverse events (SAEs), NoV vaccine-related SAEs, potential immune–mediated events of medical significance and any procedure-related medical occurrences will be recorded. An interim analysis (IA) is planned when all subjects have provided one blood sample corresponding to at least their first year of participation in NOR-213. It is expected that up to 575 subjects who participated in the selected trials will be available for enrollment. The schematic of trial NOR-213 is shown in Figure 2.a.

Figure 2.a Schematic of Trial NOR-213

Primary Vaccination Trial	Age	Doses	GI.1/GII.4 VLP/MPL (µg)	Blood draws*
NOR-204:	18 to 49 and ≥60 years	1 or 2 doses (Day 1/Day 29)	15/50/0 or 15/50/15	Days 1, 8, 29, 36, 57, 211, 393
NOR-210:	18 to 49 years	1 dose (Day 1)	15/50/0	Days 1, 8, 15, 29
NOR-107:	18 to 64 years	1 (Day 1) or 2 doses (Day 1/Day 28)	11 compositions	Days 1, 28, 35, 56, 208, 393

*Samples taken during the primary vaccination trial may be re-tested in NOR-213

Primary Objective:

- To evaluate the humoral response after at least 1 dose of NoV vaccine up to 5 years after IM injection as measured by histo-blood group antigen (HBGA) blocking assay.

Secondary Objective:

- To evaluate the humoral response after at least 1 dose of NoV vaccine up to 5 years after IM injection as measured by total-immunoglobulin (pan-Ig) enzyme-linked immunosorbent assay (ELISA).

CCI

Subject Population:

Subjects in good or stable health condition: Yes.

Planned minimum age: 18 years.

Planned Number of Subjects: Up to 575 subjects.

Criteria for Inclusion:

- The subject is aged over 18 years.
- Male and female subjects who previously received at least 1 dose of NoV vaccine in trials NOR-107, NOR-210 and NOR-204, have baseline and post-vaccination data, and completed the primary vaccination trial protocol as initially described.
- 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.
- Individuals who can comply with trial procedures and are available for the duration of the follow-up.

Criteria for Exclusion:

- Participation in any clinical trial is allowed, on condition that no investigational product is administered within 30 days prior to blood sampling.
- In the opinion of the investigator, the subject is not medically eligible to provide blood specimens.
- 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.

Trial Vaccine:

No investigational vaccine will be administered in this trial.

Duration of the Trial:	**Period of Evaluation:**
Up to 3 years	Up to 3 years

Main Criteria for Evaluation and Analyses:

All primary, secondary and exploratory evaluations will be performed at yearly intervals up to 5 years after primary vaccination.

The **primary endpoints** (*immunogenicity*) for this trial, as measured by HBGA blocking assay are:

- Geometric Mean Blocking Titers (50%; $GMBT_{50}$) of anti-norovirus GI.1 VLP antibodies.
- $GMBT_{50}$ of anti-norovirus GII.4 VLP antibodies.

The **secondary endpoints** (*immunogenicity*) for this trial, as measured by pan-Ig ELISA are:

- Geometric Mean Titers (GMT) of anti-norovirus GI.1 VLP antibodies.
- GMT of GII.4 VLP antibodies.

CCI [redacted]

Statistical Considerations:

The following analysis sets are defined for this trial:

Full Analysis Set (FAS): All subjects with data from at least 1 follow-up time point.

Per Protocol Set: All subjects in the FAS who do not have major protocol violations that potentially confound the primary endpoint.

Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics will be calculated for demographic and baseline characteristics (eg age, gender, race, etc) obtained during the primary vaccination trial.

Immunogenicity Analysis

Immunogenicity measured by HBGA blocking assay and pan-Ig ELISA will be evaluated using point estimates of parameters such as $GMBT_{50}$ and GMT on a yearly basis. Immunogenicity measurements obtained at baseline and post-vaccination visits during the primary vaccination trial may be accessed from databases to contribute to designated summaries of immunogenicity endpoints over time following vaccination.

Time points to be considered will include relevant ones from the primary vaccination trial and this follow-up trial. Descriptive statistics, including 95% CIs, will be calculated for the subject subsets (ie, groups) of interest. Analysis will be done by primary vaccination trial; however, additional subject groupings may be explored such as pooling similar dose levels across studies including subject subsets with/without MPL to consider subjects administered a 1-dose or 2-dose regimen. Where data permit (eg, demographic characteristic etc), additional exploration of the data may be presented in the statistical analysis plan (SAP). CCI [redacted]

Safety Analysis

Fatal and life threatening SAEs, NoV vaccine-related SAEs, potential immune–mediated events of medical significance and any procedure-related medical occurrences will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term (PT) by each primary vaccination trial.

Sample Size Justification:

This trial is descriptive and will only enroll subjects who previously received at least 1 dose of NoV vaccine, have baseline and post-vaccination data, and completed the primary vaccination trial according to protocol. Sample size will not be determined based on formal statistical power calculations.

Interim Analysis

An IA will be performed after all subjects have provided one blood sample corresponding to at least their first year of participation in NOR-213 and the data for that trial segment have been sufficiently reviewed for accuracy and correctness. An interim report will be developed based on these data.

The final clinical study report (CSR) will include the description of the immunogenicity results corresponding to up to 5 years post-primary vaccination as well as safety data. The sponsor may consider terminating or amending the trial after review of the IA.

Data Monitoring Committee:

No trial-specific committee is planned for this trial. An overall data monitoring committee is established to evaluate overall safety of the Takeda NoV vaccine program on an ongoing basis.

NOR-213 Version 3.0 (27 March 2018)

2.1 Schedule of Trial Procedures

Primary Vaccination Trial	NOR-107	NOR-210	NOR-204	NOR-213 Time After First Vaccination				
Vaccination 1 (day)	1	1	1	**Year 2**		**Year 3**	**Year 4**	**Year 5**
Vaccination 2 (day)	28	-	29					
Blood draw(s) (days)	**1, 28, 35, 56, 208, 393**	**1, 8, 15, 29**	**1, 8, 29, 36, 57, 211, 393**					
NOR-213				**Screening[a]**	**Trial Entry**	**Year 1**	**Year 2**	**Year 3/ Trial End/ ET**
NOR-107						**X[a, c]**		
NOR-210					**X[a, c]**			
NOR-204					**X[a, c]**			
Procedure								
Visit					X	X	X	X
Visit window					±2 m	±2 m	±2 m	±2 m
Signed informed consent				X				
Eligibility criteria checked				X				
Demographics				X				
Medical history/prior medication				X				
Concomitant medication[b]					X	X	X	X
Enrollment[c]				X				
AE recording[d]					X	X	X	X
Procedure-related medical occurrences					X	X	X	X
CCI [redacted]								

Notes: ET=Early Termination.

(a) Screening procedures to be performed prior to any trial procedures being performed. This should coincide with a scheduled visit.

(b) Concomitant medication related to adverse events (AEs) and serious adverse events (SAEs).

(c) After eligibility has been confirmed during the screening visit, subjects will be enrolled into the trial. Screening may coincide with the trial entrance visit.

(d) Recording of AEs in the subject's electronic case report form (eCRF) is limited to fatal and life threatening SAEs, NoV vaccine-related SAEs, potential immune–mediated events of medical significance and any procedure-related medical occurrences and must be recorded in the subject's source documents.

(e) CCI [redacted]

(f) CCI [redacted]

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 in the template for specific trial-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

The sponsor will select a Signatory Principal Investigator/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 used in the primary vaccination trials, 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 (CSR) and by doing so agrees that it accurately describes the results of the trial.

3.3 List of Abbreviations

AE	Adverse event
AGE	Acute gastroenteritis
$Al(OH)_3$	Aluminum hydroxide
CFR	Code of Federal Regulations
CSR	Clinical study report
CCI	[redacted]
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ET	Early termination
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good clinical practice
GI.1	Genotype I.1
GII.4	Genotype II.4
$GMBT_{50}$	Geometric mean blocking titer (50%)
GMT	Geometric mean titer
HBGA	Histo-blood group antigen
IA	Interim analysis
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonization
IEC	Independent ethics committee
IM	Intramuscular
IRB	Institutional review board
MedDRA	Medical dictionary for regulatory activities
MHRA	Medicines and Healthcare products Regulatory Agency
MPL	Monophosphoryl lipid A
NoV vaccine	Norovirus GI.1/GII.4 bivalent VLP vaccine
Pan-Ig	Total immunoglobulin
PBMC	Peripheral blood mononuclear cell
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term
SAE	Serious adverse event

SAP	Statistical analysis plan
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
VLP	Virus-like particle

3.4 Corporate Identification

TV	Takeda Vaccines, Inc
VBU	Vaccine Business Unit

4.0 INTRODUCTION

4.1 Background

Noroviruses have emerged as the single most significant cause of epidemic outbreaks of non-bacterial gastroenteritis worldwide [3, 4]. These outbreaks commonly result in significant morbidity and mortality in almost all age groups. Those most at risk are the elderly, the very young and immunocompromised individuals [5].

Currently, no vaccine exists for protection against acute gastroenteritis (AGE) due to norovirus and treatment remains symptomatic. Human noroviruses are difficult to cultivate and so far, it has not been possible to develop a live attenuated or an inactivated norovirus vaccine. The investigational vaccine being developed by Takeda, norovirus genotypes GI.1/GII.4 bivalent virus-like particle (VLP) vaccine (NoV vaccine), contains GI.1 Norwalk Virus VLP and norovirus GII.4 consensus VLP which represents a consensus sequence of 3 GII.4 strains, as antigens. Norovirus VLPs are non-infectious because they do not contain viral ribonucleic acid but are immunogenic because they preserve particulate antigen conformation and structure that mimic the functional interactions of the virus with cellular receptors. The rationale for developing a bivalent vaccine is based on known epidemiology that both GI.1 and GII.4 genotypes circulate and do not cross-protect in nature. The intramuscular (IM) NoV vaccine has been evaluated as different compositions of GI.1/GII.4 VLP adjuvanted with aluminum as aluminum hydroxide [$Al(OH)_3$] (adults and children) or $Al(OH)_3$ combined with monophosphoryl lipid A (MPL) (adults).

Safety and immunogenicity data are available from several Takeda trials in which subjects received at least 1 dose of a NoV vaccine composition under development [6-8]. Data related to the primary objective of NOR-107 showed the optimal NoV vaccine composition among those evaluated, contains 15 µg GI.1 VLP, 50 µg GII.4 VLP, 500 µg aluminum as $Al(OH)_3$ in adults. No clear benefit on vaccine immunogenicity was suggested from including 50 µg or 15 µg MPL in the NoV vaccine formulation or from administering 2 doses 28 days apart. A single dose of 15 µg GI.1 VLP, 50 µg GII.4 VLP, 500 µg aluminum as $Al(OH)_3$ was tested in trial NOR-210, confirming a robust immune response up to 28 days after vaccination.

The different compositions of the NoV vaccine have been well-tolerated, and have an acceptable safety profile.

Refer to the current IB for further information [9].

The trial will be conducted in accordance with the protocol, ICH-GCP Guidelines, and applicable regulatory requirements.

4.2 Rationale for the Proposed Trial

Completed or ongoing trials have included a safety and immunogenicity follow-up of maximum 1 year. NOR-213 is designed to capture data from adults and older adults previously vaccinated with NoV vaccine, providing the opportunity to evaluate long-term immunogenicity data up to 5 years following the first dose of NoV vaccine. Three trials have been selected for this purpose: NOR-107 (adults aged 18 to 64 years, 1 or 2 doses 11 compositions of GI.1/GII.4/MPL, 167 or

500 µg aluminum as $Al(OH)_3$), NOR-210 (adults aged 18 to 49 years, 1 dose 15/50/0 µg GI.1/GII.4, 500 µg aluminum as $Al(OH)_3$) and NOR-204 (adults aged 18 to 49 and ≥60 years, 1 or 2 doses 15/50/0 or 15/50/15 µg GI.1/GII.4/MPL, 500 µg aluminum as $Al(OH)_3$). Subjects who participated in trials NOR-107 and NOR-210 will enter NOR-213 during the 3rd and 2nd year post-vaccination, respectively. NOR-204 is ongoing, and subjects participating in NOR-213 will enter the trial during the 2nd year post-vaccination. The rationale for the selection of these trials is based on the opportunity to obtain long-term follow-up data for immunogenicity of the NoV vaccine in adult and elderly populations.

This trial will be conducted in accordance with the protocol, ICH-GCP Guidelines and applicable regulatory requirements.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

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

5.1.1 Primary Objective

- To evaluate the humoral response after at least 1 dose of NoV vaccine up to 5 years after IM injection as measured by histo-blood group antigen (HBGA) blocking assay.

5.1.2 Secondary Objective

- To evaluate the humoral response after at least 1 dose of NoV vaccine up to 5 years after IM injection as measured by total-immunoglobulin (pan-Ig) enzyme-linked immunosorbent assay (ELISA).

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5.2 Endpoints

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

All primary, secondary CCI aluations will be performed at yearly intervals up to 5 years after primary vaccination.

5.2.1 Primary Endpoints

The **primary endpoints** (*immunogenicity*) for this trial, as measured by HBGA blocking assay are:

- Geometric Mean Blocking Titers (50%; $GMBT_{50}$) of anti-norovirus GI.1 VLP antibodies.
- $GMBT_{50}$ of anti-norovirus GII.4 VLP antibodies.

5.2.2 Secondary Endpoints

The **secondary endpoints** (*immunogenicity*) for this trial, as measured by pan-Ig ELISA are:

- Geometric Mean Titers (GMT) of anti-norovirus GI.1 VLP antibodies.
- GMT of GII.4 VLP antibodies.

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[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

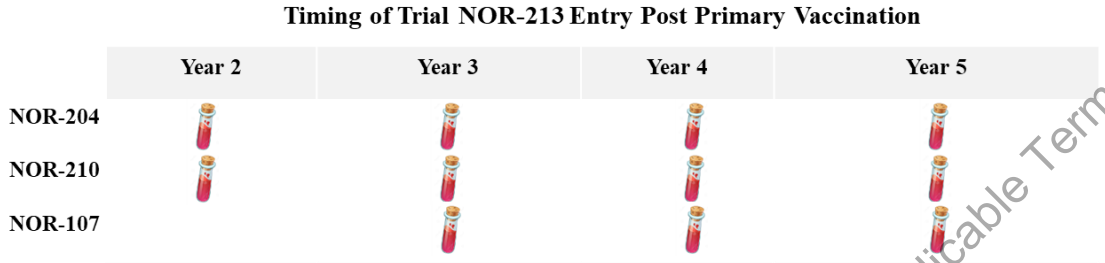
This phase 2, multi-site trial is designed to evaluate descriptively the long-term immunogenicity of at least 1 NoV vaccine administration. Subjects previously enrolled in NOR-107, NOR-210 and NOR-204 will be invited to participate in this long-term follow-up trial corresponding to a duration of up to 5 years post-primary vaccination. The timing of subject entry into NOR-213 with respect to the anniversary of the primary vaccination trial means the duration of subject participation in the present trial will be different. Following inclusion in NOR-213 subjects will have yearly blood draws. Subjects from NOR-107 will enter this trial at the time of their 3rd year post-primary vaccination. For NOR-210 and 204, entry will correspond to their 2nd year post-primary vaccination.

Trial procedures will include a maximum of 4 visits over 3 years. At each visit, a blood sample, including peripheral blood mononuclear cell (PBMC) isolation (only for the subset of subjects initially included in NOR-107 and NOR-204 trials), CCI [redacted] At each contact with the subject, fatal and life threatening serious adverse events (SAEs), NoV vaccine-related SAEs, potential immune–mediated events of medical significance and any procedure-related medical occurrences will be recorded. An interim analysis (IA) is planned when all subjects have provided one blood sample corresponding to at least their first year of participation in NOR-213.

It is expected that up to 575 subjects who participated in the selected trials will be available for enrollment.

A schematic of the trial design is included as Figure 6.a. A schedule of trial procedures is provided in Section 2.1.

Figure 6.a Schematic of Trial Design



Primary Vaccination Trial	Age	Doses	GI.1/GII.4 VLP/MPL (µg)	Blood draws*
NOR-204:	18 to 49 and ≥60 years	1 or 2 doses (Day 1/Day 29)	15/50/0 or 15/50/15	Days 1, 8, 29, 36, 57, 211, 393
NOR-210:	18 to 49 years	1 dose (Day 1)	15/50/0	Days 1, 8, 15, 29
NOR-107:	18 to 64 years	1 (Day 1) or 2 doses (Day 1/Day 28)	11 compositions	Days 1, 28, 35, 56, 208, 393

*Samples taken during the primary vaccination trial may be re-tested in NOR-213

6.2 Justification for Trial Design, Dose, and Endpoints

Subjects who participated in trials NOR-107, NOR-210 and NOR-204 will have already reached 1 year or more post-primary vaccination with NoV vaccine at the time of trial NOR-213 start.

The endpoints defined for this trial aim to provide data on persistence of the immune response for up to 5 years following the administration of NoV vaccine.

Please refer to the IB [9].

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

The total estimated duration of trial participation is approximately 2 years for subjects who previously participated in NOR-107.

The total estimated duration of trial participation is approximately 3 years for subjects who previously participated in NOR-210 and NOR-204.

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:

- Significant deviation from GCP that compromises the ability to achieve the primary vaccination 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 Sites

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 need to be confirmed prior to performing any trial procedure.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. The subject is aged over 18 years.
2. Male and female subjects who previously received at least 1 dose of NoV vaccine in trials NOR-107, NOR-210 and NOR-204, have baseline and post-vaccination data, and completed the primary vaccination trial protocol as initially described.
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 B).
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. Participation in any clinical trial is allowed, on condition that no investigational product is administered within 30 days prior to blood sampling.
2. In the opinion of the investigator, the subject is not medically eligible to provide blood specimens.
3. 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.

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

7.3 Criteria for Delay of Blood Sampling

After enrollment, subjects may encounter clinical circumstances that warrant a delay in blood sampling.

1. Individuals who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to blood sampling.
2. In the event that a subject meets a criterion for delay of blood sampling, the subject may undergo this procedure once the window for delay has passed as long as the subject is otherwise eligible for trial participation.

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

Under some circumstances, a subject's trial participation may be terminated early. This means that no further trial procedures (including data collection) will be performed on that subject beyond the specific date of early termination. The primary reason for early termination of the subject from the trial should be recorded in the subject's electronic case report form (eCRF "end of study visit" page) using the following categories. For screen failure subjects, refer to Section 9.1.11.

1. Adverse Event (AE): The subject has experienced an AE (irrespective of being related/unrelated to the Trial Vaccine administered during the primary vaccination trial or trial-related procedures during NOR-213) that requires early termination because continued participation imposes an unacceptable risk to the subject's health and/or the subject is unwilling to continue participation because of the AE. If the subject is unwilling to continue because of the AE, the primary reason for early termination in this case will be 'withdrawal due to AE' and not 'withdrawal of consent', see below. Any ongoing AEs leading to early termination should be followed by the investigator until resolution or stabilization.
2. Lost to follow-up: The subject did not return to the clinic and at least 3 attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
3. Withdrawal of consent: The subject wishes to withdraw from the trial. The primary reason for early termination will be 'withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (ie, reason other than AE). The reason for withdrawal, if provided, should be recorded in the subject's 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.
4. Premature trial termination by the sponsor, a regulatory agency, the IRB/IEC, or any other authority.

   If the clinical trial is prematurely terminated by the sponsor, the investigator is to promptly inform the trial subjects and local IRB/IEC and should assure appropriate follow-up for the subjects according to Section 10.5.4. The primary reason for early termination in this case will be 'trial termination".
5. Subject's death during trial participation.
6. Other.

   Note: The specific reasons should be recorded in the "specify" field of the subject's eCRF.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

No trial vaccine will be administered during this trial.

8.1 Dosages Administered During the Primary Vaccination Trials

The NoV vaccine dosages administered during the selected primary vaccination trials are listed in the following sections. Details on manufacturing, packaging, labeling and storage are provided in the individual protocols.

8.1.1 NOR-107 [NCT 02038907]

Trial title: A phase 2, randomized, controlled, double-blind, dosage and adjuvant justification, safety and immunogenicity trial of IM NoV vaccine adjuvanted with aluminum as $Al(OH)_3$ and with or without MPL in adults.

Subjects aged 18 to 64 years inclusive (stratified as 18 to 49 years and 50 to 64 years) received either 1 dose of NoV vaccine or 2 doses of NoV vaccine by IM injection, 28 days apart. In order to remain blinded and to have the same trial time points with both dosing regimens, subjects randomized to the one-dose treatment arms received a dose of hepatitis A vaccine (Havrix®, manufactured by GSK) followed by a dose of NoV vaccine 28 days later (Table 8.a).

Table 8.a Identity of Trial Vaccines – NOR-107

Trial Vaccine/Arm	Vaccine Dose		MPL	Route of Administration	
	GI.1-VLP (µg)	GII.4 VLP (µg)		Route	Timing
NoV vaccine[(a)]/ Arm 1	15	15	50	IM	Day 28
NoV vaccine[(a)]/ Arm 2	15	50	50	IM	Day 28
NoV vaccine[(a)]/ Arm 3	50	50	50	IM	Day 28
NoV vaccine[(a)]/ Arm 4	15	15	15	IM	Day 28
NoV vaccine[(a)]/ Arm 5	15	50	15	IM	Day 28
NoV vaccine[(a)]/ Arm 6	50	50	15	IM	Day 28
NoV vaccine[(a)]/ Arm 7	15	15	0	IM	Day28
NoV vaccine[(a)]/ Arm 8	15	50	0	IM	Days 1, Day 28
NoV vaccine[(a)]/ Arm 9	50	50	0	IM	Day 28
NoV vaccine[(a)]/ Arm 10	50	150	0	IM	Days 1, Day 28
NoV vaccine[(a)]/ Arm 11	15	50	0	IM	Days 1, Day 28
One-dose groups	Havrix®		-	IM	Day 1 (1-dose arms)

(a) Investigational vaccine for formulation arms 1 to 10 contained 500 µg aluminum as $Al(OH)_3$. For formulation arm 11, the investigational vaccine contained approximately 1/3 the aluminum content of the other arms (167 µg). Havrix® was administered as the first dose for the 1-dose arms in order to maintain the blind.

8.1.2 NOR-210 [NCT 02475278]

Trial title: Phase 2, single arm, open-label trial for serologic assay validation, proficiency testing, safety and immunogenicity of the IM NoV vaccine.

Subjects aged 18 to 49 years provided a pre-vaccination blood sample (to evaluate baseline norovirus antibody titers) and were vaccinated with a single dose of the NoV vaccine occurred on Day 1 (Table 8.b).

Table 8.b Identity of Trial Vaccines – NOR-210

Trial Vaccine	Vaccine Dose			Route of Administration
	GI.1 NoV VLP	GII.4 NoV VLP	Aluminum as $Al(OH)_3$	
NoV Vaccine	15 µg	50 µg	500 µg	IM

NoV Vaccine = Norovirus vaccine.

8.1.3 NOR-204 [NCT 02661490]

Trial title: A phase 2, randomized, double-blind, safety and immunogenicity trial of NoV vaccine in healthy elderly adults.

Subjects aged 18 to 49 and ≥60 years received either 1 dose of saline (placebo) control on Day 1 and 1 dose of NoV vaccine (composition A or composition B) or 2 doses of NoV vaccine (composition A or composition B) by IM injection, 28 days apart. In order to remain blinded and to have the same trial time points with both dosing regimens, subjects randomized to the one-dose treatment arms received a dose of saline (placebo) control followed by a dose of NoV vaccine 28 days later (Table 8.c).

Table 8.c Identity of Trial Vaccines – NOR-204

Age groups (years)	Day 1	Day 29	Route of Administration
18–49	Saline Placebo	Composition A	IM
60–74	Saline Placebo	Composition A	IM
	Composition A	Composition A	IM
	Saline Placebo	Composition B	IM
	Composition B	Composition B	IM
75–84	Saline Placebo	Composition A	IM
	Composition A	Composition A	IM
	Saline Placebo	Composition B	IM
	Composition B	Composition B	IM
≥85	Saline Placebo	Composition A	IM
	Composition A	Composition A	IM
	Saline Placebo	Composition B	IM
	Composition B	Composition B	IM

Composition A: 15 µg of GI.1 norovirus VLP; 50 µg of GII.4 norovirus VLP, 500 µg $Al(OH)_3$.
Composition B: 15 µg of GI.1 norovirus VLP; 50 µg of GII.4 norovirus VLP, 500 µg $Al(OH)_3$, 15 µg of MPL.

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 ICF 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.

9.1.2 Documentation of Trial Entrance

Only subjects who have a signed ICF, meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the trial.

After informed consent is obtained, each subject will be identified with the same unique subject number allocated for the primary vaccination trial. There is no randomization. If all eligibility criteria are fulfilled, this subject number will be used throughout the trial. If a subject is found to be not eligible for the trial phase, the Investigator should record the primary reason for failure on the screening log and the subject number assigned to subjects who fail screening will not be reused, and the screen failure eCRF should be completed.

9.1.3 Demographics, Medical History and Prior Medications

Demographic information to be obtained includes age, sex and race/ethnicity.

Medical History will be collected at trial entry, 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.

Assess and record concomitant therapy (prescription medications ONLY) and vaccine history from 1 month prior to Day 1 in the subject's eCRF.

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 the ICF.

9.1.4 Physical Examination

Physical examination will not be performed during this trial.

9.1.5 Vital Signs

Vital signs will not be assessed during this trial.

9.1.6 Immunogenicity Assessments

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[redacted]

9.1.7 Processing, Labeling and Storage of Biological Samples

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

9.1.8 Safety Assessments

At every subject contact, fatal and life threatening SAEs, NoV vaccine-related SAEs, potential immune–mediated events of medical significance and any procedure-related medical occurrences will be collected throughout the trial.

Refer to Section 10.1 for safety definitions. Details on collection and reporting of AEs are in Section 10.5.

9.1.9 Contraception and Pregnancy Avoidance Procedure

Not applicable.

9.1.10 Pregnancy

Any pregnancy occurring during this trial should be reported immediately using a pregnancy notification form, to the contact listed in the Investigator Site File.

9.1.11 Documentation of Subjects who are not Randomized

Not applicable.

9.2 Monitoring Subject Treatment Compliance

Not applicable.

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 point(s).

9.3.1 Screening Visit (Day 1)

The following assessments are planned at the screening visit (coincides with trial entry visit):

1. Informed consent.
2. Eligibility criteria checked.
3. Demographics
4. Medical history/prior medications.
5. Concomitant medication.

9.3.2 Annual Visits

At each annual visit, confirm that the subject does not meet any criteria for delaying or cancelling additional trial procedures, as described in Section 7.3 and Section 7.4.

At every subject contact, fatal and life threatening SAEs, NoV vaccine-related SAEs, potential immune–mediated events of medical significance, any procedure-related medical occurrences and concomitant medication related to AEs and SAEs will be collected.

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The site should schedule the next trial visit and provide the subject with a written reminder of the visit date. 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 an important medical event. Site staff will instruct the subject on which medical conditions are considered important and in which situations they should immediately inform the site. (Section 10.1.4). The contact details of the investigator/trial site will be provided to the subject.

9.3.3 Final (End of Trial) Visit

The final visit will be performed up to 5 years post primary vaccination. If a subject terminates earlier, end of trial visit procedures should be performed if possible. The investigator must complete the end of trial eCRF page.

9.3.4 Post-Trial Care

No post-trial care will be provided.

9.4 Biological Sample Retention and Destruction

In this trial, specimens for immune response testing will be collected as described in Section 9.1.6. After blood draw and processing, the serum and PBMC samples will be preserved and retained at a central laboratory that was contracted by the sponsor for this purpose for up to but not longer than 20 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

Serum and PBMC samples will be used for the analyses defined in this protocol, but can also, with permission from the subject, be used to assess, improve or develop tests related to the norovirus AGE or the NoV vaccine under trial that will allow more reliable measurement of the response to the NoV vaccine.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

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.

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

Not applicable to this trial – no vaccine administered.

10.1.3 Adverse Events of Special Interest

Not collected.

10.1.4 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.

5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT in the offspring of a subject.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

10.2 Causality of AEs

Relatedness (causality) to vaccine will also be assessed by the investigator. The relationship of each AE, 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

Resolved with *sequelae*: As a result of the AE, the subject suffered persistent and significant disability/incapacity (eg, became blind, deaf or paralysed)

Fatal: The subject died due to the event. If the subject died due to other circumstances than the event, the outcome of the event per se should be stated otherwise (eg, Not Resolved or Resolving)

Unknown: If outcome is not known or not reported.

10.3 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.
- 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, signs or symptoms should be recorded appropriately as AEs.

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of ICF are not considered 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, whether or not considered related to the use of the trial vaccine administered during the primary vaccination trial or a trial procedure, must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. For this trial, recording of AEs in the subject's eCRF is limited to fatal and life threatening SAEs, NoV vaccine-related SAEs, potential immune–mediated events of medical significance and any procedure-related medical occurrences and must be recorded in the subject's source documents.

The following information will be documented for each event:

- 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 during the primary vaccination trial ("related" or "not related"),
- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure,
- Outcome of event.

10.4.2 Collection and Reporting of Solicited AEs

Not applicable to this trial – no vaccine administered.

10.4.3 Collection and Reporting of AESI

Not applicable.

10.4.4 Collection and Reporting of SAEs

Collection of SAEs will commence from the time that the subject enters trial NOR-213 (Day 1), following signature of the ICF. Routine collection of SAEs will continue until the end of the trial (Year 5).

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 administered during the primary vaccination trial.
- 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: (1) For this trial, 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. (2) For this trial, recording of SAEs in the subject's eCRF is limited to fatal and life threatening SAEs, NoV vaccine-related SAEs, potential immune–mediated events of medical significance and any procedure-related medical occurrences and must be recorded in the subject's source documents.

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. Ongoing SAEs could potentially be followed outside of this trial or in a planned extension trial.

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.

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, 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 SAE 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 administered during the primary vaccination trial must be reported to the sponsor. These SAEs will be processed by the sponsor's Pharmacovigilance Department. Instructions for how to submit these SAEs will be provided in a handout in the Investigator Site File.

11.0 TRIAL-SPECIFIC REQUIREMENTS

There are no trial-specific requirements or committees for this trial.

11.1 Data Monitoring Committee

An overall data monitoring committee is established to evaluate overall safety of the Takeda NoV vaccine program on an ongoing basis.

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, high level term, low level term, preferred term [PT], and their corresponding descriptive terms). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 Electronic CRFs

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

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 forms 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.

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.

eCRFs 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 the records stipulated in Section 12.0 and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records. 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, 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 Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study 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 database lock for the IA. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives and the handling of missing data.

13.1.1 Analysis Sets

The following analysis sets are defined for this trial:

Full Analysis Set (FAS): All subjects with data from at least 1 follow-up time point.

Per Protocol Set: All subjects in the FAS who do not have major protocol violations that potentially confound the primary endpoint.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics will be calculated for demographic and baseline characteristics (eg age, gender, race, etc) obtained during the primary vaccination trial.

13.1.3 Efficacy Analysis

Not applicable to this trial.

13.1.4 Immunogenicity Analysis

Immunogenicity measured by HBGA blocking assay and pan-Ig ELISA will be evaluated using point estimates of parameters such as $GMBT_{50}$ and GMT on a yearly basis. Immunogenicity measurements obtained at baseline and post-vaccination visits during the primary vaccination trial may be accessed from databases to contribute to designated summaries of immunogenicity endpoints over time following vaccination.

Time points to be considered will include relevant ones from the primary vaccination trial and this follow-up trial. Descriptive statistics, including 95% CIs, will be calculated for the subject subsets (ie groups) of interest. Analysis will be done by primary vaccination trial, however additional subject groupings may be explored such as pooling similar dose levels across studies including subject subsets with/without MPL to consider subjects administered a 1-dose or 2-dose regimen. Where data permit (eg, demographic characteristic etc), additional exploration of the data may be presented in the SAP. CCI [redacted]

13.1.5 Safety Analysis

The FAS will be used for all safety analyses.

Fatal and life threatening SAEs, NoV vaccine-related SAEs, potential immune–mediated events of medical significance and any procedure-related medical occurrences will be coded using the MedDRA and summarized by SOC and PT by each primary vaccination trial. Details for summarizing or listing these events will be provided in the SAP.

13.1.6 Other Analyses

Not applicable.

13.2 Interim Analysis and Criteria for Early Termination

An IA will be performed after all subjects have provided one blood sample corresponding to at least their first year of participation in NOR-213 and the data for that trial segment have been sufficiently reviewed for accuracy and correctness. An interim report will be developed based on these data. The final CSR will include the description of the immunogenicity results corresponding to up to 5 years post-primary vaccination as well as safety data. The sponsor may consider terminating or amending the trial after review of the IA.

13.3 Determination of Sample Size

This trial is descriptive and will only enroll subjects who previously received at least 1 dose of NoV vaccine, have baseline and post-vaccination data, and completed the primary vaccination trial according to protocol. Sample size will not be determined based on formal statistical power calculations.

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 contract research organization and by the IRB or IEC.

All aspects of the trial and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, subject medical records, ICF 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 [MHRA], the Pharmaceuticals and Medical Devices Agency [PMDA] 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-GCP guidelines. 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 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 IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject ICF must be obtained and submitted to the sponsor or designee before commencement of the trial (ie, before 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 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-GCP Guidelines 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 subject 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 informed consent 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 ICF in the subject's medical record and eCRF. Copies of the signed informed consent, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

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

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-GCP Guidelines 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, MHRA, PMDA), 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, admission and discharge summaries for hospital admissions occurring during a subject's trial participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the ICF process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's 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 proposed by the sponsor to the PIs, to be eventually agreed upon by all authors. 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 Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

1. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ Accessed 12 March 2018.
2. Guideline for good clinical practice. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf Accessed 12 March 2018.
3. Atmar RL and Estes MK. The epidemiologic and clinical importance of norovirus infection. Gastroenterol Clin North Am 2006;35(2):275-90, viii. doi: 0.1016/j.gtc.2006.03.001.
4. Ramani S, Atmar RL, Estes MK. Epidemiology of human noroviruses and updates on vaccine development. Curr Opin in Gastroenterol 2014:30(1):25-33. doi: 10.1097/MOG.0000000000000022.
5. Lopman B, Vennema H, Kohli E, Pothier P, Sanchez A, Negredo A et al. Increase in viral gastroenteritis outbreaks in Europe and epidemic spread of new norovirus variant. Lancet 2004;363(9410):682-88. doi: 10.1016/S0140-6736(04)15641-9.
6. Treanor JJ, Atmar RL, Frey SE, Gormley R, Chen WH, Ferreira J et al. A novel intramuscular bivalent norovirus virus-like particle vaccine candidate-reactogenicity, safety, and immunogenicity in a phase 1 trial in healthy adults. J Infect Dis 2014;210(11):1763-71. doi: 10.1093/infdis/jiu337.
7. Bernstein DI, Atmar RL, Lyon GM, Treanor JJ, Chen WH, Jiang X et al. Norovirus vaccine against experimental human GII.4 virus illness: a challenge study in healthy adults. J Infect Dis 2015;15;211(6):870-78. doi: 10.1093/infdis/jiu497.
8. Atmar RL, Baehner F, Cramer JP, Song E, Borkowski A and Mendelman PM; on behalf of the NOR-201 Study Group. Rapid Responses to 2 Virus-Like Particle Norovirus Vaccine Candidate Formulations in Healthy Adults: A Randomized Controlled Trial. J Infect Dis 2016;214(6):845-53. doi: 10.1093/infdis/jiw259.
9. Global Investigator's Brochure. Norovirus Bivalent VLP Vaccine. Edition 6.0, 22 November 2017.

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP guidelines 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 who 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 ICF 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 CSR.

Appendix B 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 description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
10. 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.
11. 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.
12. 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.
13. The anticipated prorated payment(s), if any, to the subject for participating in the trial.
14. The anticipated expenses, if any, to the subject for participating in the trial.
15. 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.
16. 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.
17. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

18. 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.
19. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
20. The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
21. 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 studies;
    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.
22. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information concerning the investigator, including his or her name, address, and other personally identifiable information. In addition, the 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 studies.
- 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 studies that may contain the same chemical compound present in the investigational vaccine administered to subjects during the primary vaccination trial.
- 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 the investigator's own country. The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

CCI [redacted]

Signature Page for NOR-213 Protocol Amendment 2, Version 3.0, 27 March 2018
Title: A Phase 2, Long-Term Immunogenicity Follow-up Trial of Adult and Elderly

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