



PROTOCOL

A Phase II, Randomized, Double-Blind, Dosage, Safety and Immunogenicity Trial of
Intramuscular Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine combined with
Aluminum Hydroxide adjuvant in Children, Toddlers, and Infants

NOR-202 Safety and Immunogenicity of Norovirus GI.1/GII.4 Bivalent VLP Vaccine in Children

Sponsor: Takeda Vaccines, Inc.
One Takeda Parkway
Deerfield, IL 60015
USA

Study Identifier: NOR-202

IND Number: 014421 **EudraCT Number:** 2014-000778-20

Vaccine Name: Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine combined
with Aluminum Hydroxide

Date: 1 March 2016

Version: 4.0

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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 emergency medical contact information cards to be carried by each subject's legally authorized representative.

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

Table 1-a Contact Information

Issue	Contact
Serious adverse event	PPD
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	
Responsible Medical Officer (carries overall responsibility for the conduct of the trial)	

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

PPD



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1.3 Protocol Amendment N° 3.0

This document describes the changes in reference to the Protocol incorporating Amendment N° 3.0.

The primary purposes of this amendment are: 1) to enroll an additional 120 children (1 to < 4 years; designated Group 2a), to assess the safety and immunogenicity of the recently manufactured NoV vaccine in a similar age group to Group 2; and 2) to perform the Day 57 IA for Groups 1 and 2 of Cohort 1, who will complete Day 57 substantially earlier than Groups 2a and 3. The Day 57 IA for Groups 2a and 3 combined will be performed at a later time. The Day 140 IA for Group 4 does not change.

The trial vaccine, originally manufactured for trial NOR-202, was not available for clinical use after 30 November 2015, due to expiration at 36 months after manufacture. Several factors affected the enrolment timeline in trial NOR-202: (1) Takeda's decision to not initiate enrollment until after agreement from the Pediatric Committee of the EMA on the Pediatric Investigational Plan (PIP) of the NoV vaccine; (2) and the regulatory, logistical, and operational study requirements for implementation of the two prior protocol amendments.

Per protocol, all children in Groups 1 (4 to < 9 years) and 2 (1 to < 4 years) were enrolled, randomized and received one of the four NoV vaccine formulations as a one or two dose trial vaccine regimen within the vaccine expiry dating period. Notably, children in Groups 3 (1 or 2 doses) and 4 (2 or 3 doses) were not enrolled due to expiration of the trial vaccine. Takeda has paused this study until additional trial vaccine is manufactured and released for clinical use.

Takeda has recently produced VLPs at a different manufacturer with increased capacity for manufacturing on a larger scale. To date, the NoV vaccine with these recently produced VLPs has been manufactured and released for clinical use in two studies in adults; trial NOR-204 in 350 adults aged 18 to > 85 years and trial NOR-211 in ~ 2800 adults aged 18 to 49 years.

To understand the safety and immunogenicity of the recently manufactured vaccine in a similar age group to Group 2, an additional 120 children designated Group 2a, will be enrolled in trial NOR-202, prior to enrolling children in Groups 3 and 4. Specifically, the safety data from Group 2a will be provided to the Data Monitoring Committee (DMC) for review prior to enrollment of the children in Groups 3 and 4.

Although the VLP manufacturer has changed, the vaccine dosages and regimens with the four vaccine formulations evaluated in Groups 1 and 2 will also be evaluated in children in Groups 2a, 3, and 4. However, only children in Groups 2a, 3, and 4, will receive the recently manufactured vaccine.

Enrollment in Group 2a will be initiated after all four vaccine formulations of the recently manufactured vaccine are released for clinical use.

Full details of changes to the text are given below. The following is a list of the sections modified in the amendment:

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- Trial summary Adapted to reflect the changes in the body of the protocol.
- Section 2.1 Added Table of procedures for Cohort 1 Group 2a as Table 2.b and retitled former Table 2.b for Cohort 2 (Group 4) to Table 2.c for Cohort 2.
- Section 4.2 Rationale for the trial and the Amendment 3.0 (version 4.0).
- Section 5.1.3 Clarification of the group-applicable exploratory objectives.
- Section 5.2 Clarification of group-applicable endpoints.
- Section 5.2.3 Clarification of the Cohort and group-applicable exploratory endpoints.
- Section 6.1 Schematic of trial design and text updated to include Group 2a. Additional phone contact at Day 200 for Cohort 2 (Group 4).
- Section 6.2 Addition of Group 2a.
- Section 7.1 Legally acceptable representative corrected to legally authorized representative and replaced by the abbreviation 'LAR' where applicable throughout.
- Section 8.2 Addition of Group 2a.
- Section 8.3 Clarification concerning the groups (deletion of 'age').
- Section 9.1.6 CCI [REDACTED]
- Section 9.1.7 Tables 9-a and 9-b clarified body temperature measurements in footnotes and for local injection reactions of erythema, swelling, and induration, added the number of millimeters (mm) to clarify the intensity grades.
- Section 9.3.5 Additional phone contact for safety collection at Day 200 for Cohort 2 (Group 4).
- Section 13.1 Description of the statistical and analytical plans.
- Section 13.1.1 Addition of Group 2a to analysis sets.
- Section 13.1.3 Addition of Group 2a to immunogenicity analysis.
- Section 13.2 Clarification concerning the timing of the D57 interim analyses for Cohort 1.
- Section 13.3 Table 13a adapted to include calculations for a sample size of 480 for probability of observing one or more adverse events.

1.3.1 Amendment History

Date	Amendment Number	Protocol Version	Amendment Type	Region
10 March 2014	Not applicable	1.0	Not applicable	Global
7 November 2014	1.0	2.0	Substantial	Global
26 March 2015	2.0	3.0	Substantial	Global
1 April 2015	2.1	3.1	Non-substantial	Global
1 March 2016	3.0	4.0	Substantial	Global

1.3.2 Summary of Changes

Summary of Protocol Amendment 1 dated 7 November 2014 to Protocol Version 1.0 dated 10 March 2014

Rationale for the Amendment:

Takeda has decided to revise the study design as follows:

- The age stratification has been modified.
- The number of blood draws for Cohort 1 has been reduced from 5 to 4 and for Cohort 2 has been reduced from 7 to 5.
- The number of formulation arms has been reduced from 11 to 8 based on data from the adult trial, NOR-107.
- CCI [REDACTED].

A licensed benefit vaccine may be offered to all subjects after trial exit.

Section	Description of change
Trial Summary	Adapted to reflect the changes in the body of the protocol (trial design, number of subjects, main criteria for evaluation and analyses, statistical considerations)
2.1	Blood draw for serology at Day 208 removed for Cohort 1 in Table 2.a. Blood draw for serology at Days 112 and 292 removed for Cohort 2 in Table 2.b.
5.1	Exploratory Objective added.
5.2.3	Blood draw time point at assay Day 208 removed for Cohort 1 and blood draw time points at assay Days 112 and 292 removed for Cohort 2.
6.1	Schematic adapted to show four age groups (previously five) for the age stratification. The number of subjects and description of the age stratification has changed.
6.1	Subject numbers and group definition changed.
6.2	Updated group naming
7.4	Criterion 5 deleted.
8.1.1.1	Investigational Vaccines description.
8.1.2	Temperature deviations must be reported to the sponsor; see the Pharmacy Manual for instructions.
8.1.3	Dose and Regimen (Table updated).
8.2	Updated group naming
8.3	Updated age stratification description.

9.1.5	Physical examination re-defined.
9.1.6	Blood volumes corrected in light of the Day 208 blood draw in Cohort 1 and Days 112 and 292 blood draws in Cohort 2 being removed.
9.1.7	Editing in and to label of Tables 9a. and 9b.
9.1.8	Updated text for CMI testing.
9.1.9	Editing.
9.3.1	Diary card text moved to section 9.3.3.
9.3.3	Diary card use explanation clarified. Minor editing.
9.3.7	Benefit Vaccine text added
13.1.1	Subject number updated.
13.1.3	Number of formulation arms updated.
13.1.4	Subject age updated.
13.3	Sample size calculation modified.
Other	Minor formatting.

Amendment N° 2.0 dated 26 March 2015 to Protocol Version 2.0 dated 7 November 2014

Rationale for the Amendment:

This amendment describes the changes in reference to the protocol Amendment N° 2.0. The primary purpose of this amendment is to change the trial design with regard to the down-selection of formulations based on additional data from the adult trial NOR-107. Specifically, the new antibody data from trial NOR-107 resulted in similar immunogenicity and safety in adults administered the NoV vaccine both with and without the MPL adjuvant when combined with Al(OH)₃ adjuvant. Therefore, the decision was made to evaluate the NoV vaccine with the Al(OH)₃ adjuvant alone in subjects enrolled in trial NOR-202. Therefore, the number of formulation arms in this study has been further reduced from eight to four.

Section	Description of change
Title	Removal of MPL from the title.
Trial Summary	Adapted to reflect the changes in the body of the protocol.
Section 2.1	Updated trial procedures table.
Sections 4.1 and 4.2	Update of the rationale to reflect the non-inclusion of MPL in the NoV vaccine.
Section 5.1.2	Update of the secondary objectives.
Section 5.1.3	Update of the exploratory objectives.
Section 5.2.1	Update of the primary endpoints.
Section 5.2.2	Update of the secondary endpoints.
Section 5.2.3	Update of the exploratory endpoints.
Section 6.1	Figure 6a updated to reflect the new sample size and subject distribution in the two cohorts.
Section 6.2	Update to the rationale for the number of treatment arms.
Section 6.3	Update on the expected duration of participation.

Section 7.3	Definition of the window for delay of vaccination.
Section 8.1.1	Deletion of MPL text from the description of the investigational vaccine.
Section 8.4	Deletion of MPL text.
Section 8.5	Update of timing of safety follow-up.
Section 9.1.6	Update of timings for the final immunogenicity assessments.
Section 9.1.7	Deleted text referring to AESIs and updated the duration of the safety assessments. Text updated to correspond to Table 9a.
Section 9.3.1	Specified blood for CMI testing will be provided by a subset of children.
Section 9.3.3	Update of diary card instructions.
Section 9.3.4	Update of clinic visits.
Section 9.3.5	Update of phone contacts and deletion of reference to AESIs.
Sections 9.3.7, 10.1.4, 10.2.1.1, 10.2.2	Update to timing of the final visit.
Sections 10.1.1, 10.2.1.2, 10.3.2, 12.0	Deletion of text referring to AESIs.
Section 13.1	Update to timing of the final visit.
Section 13.1.1	Update of the statistical analyses.
Section 13.1.3	Update to immunogenicity analyses.
Section 13.1.4	Update to safety analyses.
Section 13.2	Update to the timing of the final analysis.
Section 13.3	Update to the sample size justification.
Section 16.0	New reference added.
Appendix D	Deleted appendix (AESIs).

Amendment N° 2.1 dated 1 April 2015 to Protocol Version 3.0 dated 26 March 2015	
Rationale for the Amendment:	
This amendment corrects inconsistencies identified in V3.0 and is purely administrative.	
Section	Description of change.
Trial Summary	Title aligned with first page (inclusion of 'adjuvant').
Section 2.1	Table 2a: Optional physical examination added on Day 210.
Section 2.1	Table 2b: diary card dispensing added on Days 1 and 56.
Section 6.1	Inclusion of 'safety' in the first sentence.
Section 7.3	Formatting.
Section 9.3.7	Benefit vaccine provision is optional.
Section 13.1.4	Correction for AEs: collection is daily through day 7.

Amendment N° 3.0 dated 1 March 2016 to Protocol Version 3.1 dated 1 April 2015	
Rationale for Amendment N° 3.0: The primary purposes of this amendment are: 1) to enroll an additional 120 children (1 to < 4 years; designated Group 2a), to assess the safety and immunogenicity of the recently manufactured NoV vaccine in a similar age group to Group 2; and 2) to perform the Day 57 interim analysis (IA) for Groups 1 and 2 of Cohort 1, who will complete Day 57 substantially earlier than Groups 2a and 3. The Day 57 IA for Groups 2a and 3 combined will be performed at a later time. The Day 140 IA for Group 4 does not change	
Section	Description of change.
Trial Summary	Adapted to reflect the changes in the body of the protocol.
Section 2.1	Added Table of procedures for Cohort 1 Group 2a as Table 2.b and retitled former Table 2.b for Cohort 2 (Group 4) to Table 2.c for Cohort 2.
Section 4.1	<p>The safety of the NoV GI.1/GII.4 bivalent VLP vaccine adjuvanted with MPL and Al(OH)₃ has been evaluated in 2 studies conducted by Takeda (formerly LigoCyte): Studies LV03-104 (1 year follow-up is complete) and LV03-105 (1 year follow-up is complete). Preliminary results of healthy adults enrolled in Trial LV03-104 show that no allergic reactions, neurologic adverse events (AEs), or serious adverse events (SAEs) related to investigational vaccine were reported. In Cohort A, a dosage escalation cohort (5/5, 15/15, 50/50, and 150/150 µg of NoV GI.1/GII.4 antigens), the observed rates of solicited AEs were comparable across the formulation arms. No increase in severity or frequency of events was observed with the increased VLP concentration. The observed rates were similar following Dose 1 and Dose 2 of investigational vaccine. In Trial LV03-105, the 50/50 µg NoV adjuvanted vaccine dosage was evaluated and the preliminary results showed similar rates of solicited AEs as were seen in Trial LV03-104 and no SAEs related to investigational vaccine have been reported. In both studies, an adjuvanted formulation was investigated: VLPs were adjuvanted with both Al(OH)₃ and MPL and delivered by the intramuscular (IM) route of administration. The combination of Al(OH)₃ and MPL corresponds to GlaxoSmithKline's Adjuvant System 04 [31]. The selection of MPL in the investigational vaccine was to emulate the high and sustained antigen-specific neutralizing antibody responses that have been observed with GlaxoSmithKline's Cervarix vaccine [32]. Published data concerning the use of this form of adjuvant (Al(OH)₃ and MPL) supports an acceptable safety profile observed in clinical studies [13]. The Al(OH)₃ component is used as an adjuvant in many licensed vaccines at dosages ranging from 0.17 mg to 0.85 mg aluminum, and clinical studies have demonstrated that aluminum enhances the antigenicity of vaccines such as diphtheria and tetanus toxoids together with a demonstrated safety profile of over 6 decades [12].</p>

	<p>Additional text:</p> <p><i>Prior safety and immunogenicity data for the NoV vaccine given by the IM route are available from approximately 1000 adult subjects, evaluated in five Takeda clinical trials (LV03-104, LV03-105, NOR-107, NOR-201, and NOR-210). The NoV vaccine evaluated in these trials either contained both Al(OH)₃ plus monophosphoryl lipid A (MPL) adjuvants combined or the Al(OH)₃ adjuvant alone. Trial NOR-107 conducted in adults aged 18-64 years, a Phase II dosage, adjuvant justification, safety, and immunogenicity trial, evaluated 11 vaccine formulations, and showed that the NoV VLP vaccine adjuvanted with aluminum as Al(OH)₃ adjuvant was as immunogenic as the NoV VLP vaccine adjuvanted with Al(OH)₃ and MPL combined.</i></p> <p><i>Refer to the current Investigator Brochure of Takeda's NoV GI.1/GII.4 bivalent VLP vaccine for additional product information and a more detailed review of pre-clinical and clinical studies [31].</i></p>
Section 4.2	<p>Rationale for the Proposed Trial</p> <p>Additional text to paragraph 4:</p> <p>Norovirus strains drift from year to year and both GI and GII genogroups cause disease in all age groups. Although numerous types are reported, the GII.4 type remains dominant and is currently responsible for the majority of outbreaks worldwide. The rationale for developing a bivalent vaccine is based on NoV epidemiology and the lack of natural protection between genogroups. In trial LV03-104, the first NoV bivalent VLP vaccine was given IM, and compared equally balanced (1:1) dosages of the GI.1 and GII.4 VLPs in adults. For each of the 4 vaccine dosages evaluated (5/5, 15/15, 50/50, and 150/150 µg of NoV VLPs), the seroresponse rates (percent of subjects with at least a 4-fold rise in antibody levels) and geometric mean fold rises (GMFRs) were lower for the GII.4 VLP than for the GI.1 VLP at equivalent antigen dosages. Likewise, similar post-vaccination immunogenicity data were observed in adults in trial LV03-105, the GII.4 challenge trial that evaluated a 50/50 µg balanced 1:1 VLP dosage of vaccine. Separately the factorial design trial NOR-107 was initiated in subjects ages 18 to 64, to evaluate multiple vaccine formulations containing different (balanced and unbalanced) ratios of the antigenic VLP components of the bivalent vaccine (GI.1/GII.4) with Al(OH)₃ adjuvant both with and without MPL adjuvant. <i>Prior safety and immunogenicity data for the NoV vaccine given by the IM route are available from approximately 1000 adult subjects, evaluated in five Takeda clinical trials (LV03-104, LV03-105, NOR-107, NOR-201, and NOR-210). The NoV vaccine evaluated in these trials either contained both Al(OH)₃ plus monophosphoryl lipid A (MPL) adjuvants combined or the Al(OH)₃ adjuvant alone. Trial NOR-107 conducted in adults aged 18-64 years, a Phase II dosage, adjuvant justification, safety, and immunogenicity trial, evaluated 11 vaccine</i></p>

	<p><i>formulations, and showed that the NoV VLP vaccine adjuvanted with aluminum as Al(OH)₃ adjuvant was as immunogenic as the NoV VLP vaccine adjuvanted with Al(OH)₃ and MPL combined. Refer to the current Investigator Brochure of Takeda's NoV GI.1/GII.4 bivalent VLP vaccine for additional product information and a more detailed review of pre-clinical and clinical studies [31].</i></p>
	<p>Additional text: <u>Rationale for the Amendment N° 3.0:</u> <i>The primary purposes of this amendment are: 1) to enroll an additional 120 children (1 to < 4 years; designated Group 2a), to assess the safety and immunogenicity of the recently manufactured NoV vaccine in a similar age group to Group 2; and 2) to perform the Day 57 interim analysis (IA) for Groups 1 and 2 of Cohort 1, who will complete Day 57 substantially earlier than Groups 2a and 3. The Day 57 IA for Groups 2a and 3 combined will be performed at a later time. The Day 140 IA for Group 4 does not change.</i> <i>The trial vaccine, originally manufactured for trial NOR-202, was not available for clinical use after 30 November 2015, due to expiration at 36 months after manufacture. Several factors affected the enrolment timeline in trial NOR-202: (1) Takeda's decision to not initiate enrollment until after agreement from the Pediatric Committee of the EMA on the Pediatric Investigational Plan (PIP) of the NoV vaccine; (2) and the regulatory, logistical, and operational study requirements for implementation of the two prior protocol amendments.</i> <i>Per protocol, all children in Groups 1 (4 to < 9 years) and 2 (1 to < 4 years) were enrolled, randomized and received one of the four NoV vaccine formulations as a one or two dose trial vaccine regimen within the vaccine expiry dating period. Notably, children in Groups 3 (1 or 2 doses) and 4 (2 or 3 doses) were not enrolled due to expiration of the trial vaccine. Takeda has paused this study until additional trial vaccine is manufactured and released for clinical use.</i> <i>Takeda has recently produced VLPs at a different manufacturer with increased capacity for manufacturing on a larger scale. To date, the NoV vaccine with these recently produced VLPs has been manufactured and released for clinical use in two studies in adults; trial NOR-204 in 350 adults aged 18 to > 85 years and trial NOR-211 in ~ 2800 adults aged 18 to 49 years.</i> <i>To understand the safety and immunogenicity of the recently manufactured vaccine in a similar age group to Group 2, an additional 120 children designated Group 2a, will be enrolled in trial NOR-202, prior to enrolling children in Groups 3 and 4. Specifically, the safety data from Group 2a will be provided to the Data Monitoring Committee (DMC) for review prior to</i></p>

	<p><i>enrollment of the children in Groups 3 and 4.</i></p> <p><i>Although the VLP manufacturer has changed, the vaccine dosages and regimens with the four vaccine formulations evaluated in Groups 1 and 2 will also be evaluated in children in Groups 2a, 3, and 4. However, only children in Groups 2a, 3, and 4, will receive the recently manufactured vaccine.</i></p> <p><i>Enrollment in Group 2a will be initiated after all four vaccine formulations of the recently manufactured vaccine are released for clinical use.</i></p>
Section 5.1.3	<ul style="list-style-type: none">• CCI [REDACTED]• CCI [REDACTED]• To evaluate BT50, seroresponse rate, and GMFR of serum anti-NoV antibody titers of a panel of GI.1 and GII.4 not represented in the vaccine as measured by the HBGA binding assay (<i>not applicable to Group 2a</i>).• CCI [REDACTED]• CCI [REDACTED]• CCI [REDACTED]• CCI [REDACTED]• CCI [REDACTED]

Section 5.2	Endpoints apply to Cohorts 1 and 2 unless otherwise stated. <i>For subjects in Group 2a, the serologic assays to the vaccine VLPs for the Pan-Ig ELISA and for the HBGA binding assays will each be performed. Notably, the following endpoints will not be performed for Group 2a: Avidity, IgA ELISA, CMI for those aged ≥ 3 years, and HBGA binding assay to a panel of GI.1 and GII.4 not represented in the vaccine.</i>
Section 5.2.3	<ul style="list-style-type: none"> BT50, seroresponse rate, and GMFR of anti-NoV antibody titers to a panel of GI.1 and GII.4 strains not represented in the vaccine as measured by HBGA binding assay on Days 29, 57, and 210 (Cohort 1, <i>not applicable to Group 2a</i>) and Days 56, 84, 140, and 293 (Cohort 2).
	CCI [REDACTED]
	CCI [REDACTED]
	CCI [REDACTED]
Section 6.1	Schematic of Trial design and text updated to include Group 2a.
	<p>A total of 720 840 healthy subjects will be <i>enrolled within two cohorts and randomized to vaccine regimen across two Cohorts</i> as follows to the following cohorts:</p> <ul style="list-style-type: none"> Cohort 1, N= 360 480, <i>consisting of</i> Group 1: aged 4 to less than 9 years; Group 2: aged 1 to less than 4 years; Group 2a: aged 1 to less than 4 years; Group 3: aged 6 months to less than 1 year (N= 120 each): subjects will be randomized with equal probabilities to 1 of the 8 unique combinations of formulation arms and dose groups (ie, 4 formulation arms and 1 or 2 doses). <i>The additional 120 children, designated as Group 2a, are being included to evaluate the recently manufactured NoV bivalent VLP vaccine formulations prior to enrolling children in Groups 3 and 4.</i> Each of the combinations <i>in Groups 1, 2, 2a, and 3</i> will consist of <i>approximately 15</i> subjects per age group. <i>Thus Cohort 1 consists of 480 subjects in Groups 1, 2, 2a, and 3 combined.</i> Cohort 2 (Group 4: aged 6 weeks to less than 6 months): 360 subjects will be randomized <i>to receive the recently manufactured NoV bivalent VLP vaccine</i> with equal probabilities to 1 of the 8 unique combinations of formulation arms and dose groups (ie, 4 formulation arms and 2 or 3 doses). Each of the combinations will consist of <i>approximately 45</i> subjects.

	<p>Primary evaluation of the trial objectives is planned at 28 days after the final (second) vaccination in subjects aged 6 months to less than 9 years (Cohort 1) and 28 days after the final (third) vaccination in subjects aged 6 weeks to less than 6 months (Cohort 2). In order to maintain the blind and to have the same trial time points and dosing regimens, subjects in Cohort 1 (Groups 1, 2, 2a and 3) who are randomized to the 1 dose group will receive a dose of the NoV bivalent VLP vaccine on Day 1 followed by a placebo injection of saline 28 days later (Day 29) and subjects in the 2 dose group will receive 2 doses of NoV VLP vaccine approximately 28 days apart (Days 1 and 29). Likewise, subjects in Cohort 2 (Group 4) who are randomized to the 2 dose group will receive 2 doses of NoV bivalent VLP vaccine on Days 1 and 56, followed by a placebo injection of saline approximately 56 days later (Day 112), and subjects in the 3 dose group will receive 3 doses of NoV VLP vaccine approximately 56 days apart (Days 1, 56, and 112), independent of the infant routine vaccinations by approximately 28 days. This is a double-blind trial; investigators, subjects, data collectors, and data evaluators are blinded to the specific formulation arms and the dosing groups.</p>
	<p>Subjects 6 months to less than 9 years of age (inclusive, Cohort 1) will receive either 1 or 2 doses by IM injection, at least 28 days apart (Days 1 and 29), in 3 4 age-groups in 3 age ranges (Group 1: aged 4 to less than 9 years; Group 2 and Group 2a: aged 1 to less than 4 years; and Group 3: aged 6 months to less than 1 year). Infants 6 weeks to less than 6 months of age (Group 4/Cohort 2) will receive 2 or 3 doses by IM injection given approximately 56 days apart (Days 1, 56, and 112). Routine child and infant vaccinations will be given on schedule per the national guidelines approximately 28 days apart from the investigational vaccine in each age group.</p>
	<p>Two Interim analyses (IA) will be performed after the primary safety and immunogenicity data are available (ie, Day 57 for Cohort 1 and Day 140 for Cohort 2) (primary analysis time point). Day 57 IA for Cohort 1 will be provided initially for Groups 1 and 2, who will complete Day 57 substantially earlier than Groups 2a and 3. The Day 57 IA for Groups 2a and 3 combined will be provided at a later time. Thus, the Day 57 IA will be conducted in two parts to be followed by the Day 140 IA in Group 4. The All interim analyses will be performed by a separate set of unblinded statisticians and programmers at the contract research organization (CRO), Quintiles, who will have access to individual treatment assignments but will not otherwise be involved in subsequent study conduct. The rest of the personnel involved in the conduct of the study, including those at Takeda, Quintiles, and the study sites, will remain blinded to the individual subject data (including treatment assignments) until unblinding after database lock (Day 210 for Cohort 1 and Day 293 for Cohort 2). More details on the analyses will be provided in the statistical analysis plan</p>

	(SAP).
	<p><u>Placebo Control:</u></p> <p>Saline will be administered as a single control injection (as the final dose) in order to maintain the trial blind for the 1 dose groups in Groups 1, 2, 2a and 3 (Cohort 1) and for the 2 dose group in Group 4 (Cohort 2). Subjects in the 1 dose groups in Cohort 1 receive NoV vaccine on Day 1 and a saline placebo injection on Day 29. Subjects in the 2 dose group in Cohort 2 receive NoV vaccine on Days 1 and 56 and a saline placebo injection on Day 112.</p>
	<p><u>Visit Schedule</u></p> <p>Clinical trial visits will be performed on Days 1, 8, 29, 36, 57, and 210 for Cohort 1 and Days 1, 8, 29, 56, 63, 84, 112, 119, 140, and 293 for Cohort 2. Telephone contacts will be performed on Days 3, 32, and 134 for Cohort 1 and Days 3, 59, 115, 200 and 260 for Cohort 2.</p>
Section 6.2	<p>The trial design is consistent with the evaluation of dose finding studies for vaccines. The formulations for NOR-202 are selected based on the initial and additional results obtained from the factorial design study NOR-107 in adults. Based on additional NOR-107 results, the number of formulation arms has been further reduced from 8 in Amendment 1 of the protocol to 4 in this amended protocol. The descriptive design of trial NOR-202 in early childhood is justified to initially define the dose and dosing regimen for young children at high risk of norovirus disease. <i>An additional group designated Group 2a of 120 children aged 1 to less than 4 years, has been added within Cohort 1, to allow evaluation of the recently manufactured vaccine prior to dosing younger children in Groups 3 and 4. Safety in Group 2a will be reviewed by the DMC, prior to enrolling in Groups 3 and 4. Immunogenicity will be reviewed as available.</i></p>
	<p>A single saline placebo injection will be administered as a placebo control (as a final dose on Day 29) in order to maintain the trial blind in subjects in the 1 dose groups in Groups 1, 2, 2a and 3, (Cohort 1) and in the 2 dose group in Group 4 (as a final dose on Day 112 in Cohort 2).</p>
Section 7.2	<p>Abbreviation corrected and edited throughout:</p> <p><u>Bullet 3:</u></p> <p>The subject's legally acceptable authorized representative (LAR) signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements (Appendix C). An assent will also be obtained according to age appropriate country-specific regulations.</p>

Section 8.2	<p><u>Paragraph 4</u></p> <p>The vaccines will be administered IM in the anterolateral thigh for children aged ≤ 12 months; for children aged > 12 months, the vaccines will be administered in the anterolateral thigh or the deltoid muscle of the subject's arm per national guidelines. Expired vaccines must not be administered. The vaccine and placebo are visually distinguishable and the blind must be maintained. The vaccination will be prepared and administered by the unblinded designee according to the instructions in the Pharmacy Manual. Cohort 1 will receive either 1 or 2 doses at least 28 days apart and Cohort 2 will receive 2 or 3 doses approximately 56 days apart. In order to maintain the blind and to have the same trial time points and dosing regimens, subjects in Cohort 1 (Groups 1, 2, 2a, and 3) who are randomized to the 1 dose group will receive a dose of the NoV bivalent VLP vaccine on Day 1 followed by a placebo injection of saline 28 days later (Day 29). Subjects in the 2 dose group will receive 2 doses of NoV VLP vaccine approximately 28 days apart (Days 1 and 29). Likewise, subjects in Cohort 2 (Group 4) who are randomized to the 2 dose group will receive 2 doses of NoV bivalent VLP vaccine on Days 1 and 56, followed by a placebo injection of saline 56 days later (Day 112), and subjects in the 3 dose group will receive 3 doses of NoV VLP vaccine approximately 56 days apart (Days 1, 56, and 112), independent of the infant routine vaccinations by at least 28 days.</p>
Section 8.3	<p>Randomization will be stratified by country and age group: Group 1 (age 4 to less than 9 years); Groups 2 and 2a (age 1 to less than 4 years); Group 3 (age 6 months to less than 12 months); and Group 4 (age 6 weeks to less than 6 months). On Day 1, qualified subjects will be randomized using the IWRS to a formulation arm and number of doses depending on their age at the time of enrollment.</p>
Section 9.1.6	<p>Subjects in Cohort 1 in all vaccine arms will undergo blood sampling for serological immunogenicity testing on Day 1 (prior to the first vaccination), Day 29 (prior to the second vaccination), Day 57 (28 days after the second vaccination), and Day 210; Subjects in Cohort 2 will undergo blood sampling for serological testing on Day 1 (prior to the first vaccination), Day 56 (prior to the second vaccination), Day 84 (28 days after the second and 28 days prior to the third vaccination), Day 140 (28 days after the third vaccination), and Day 293. To alleviate the pain associated with blood sampling in this pediatric population, blood collection will be performed by experienced, trained personnel who routinely obtain blood from infants and children, under the supervision of the Principal Investigator after optional application of EMLA cream/patch and using pediatric size needles. All blood samples will be collected in accordance with acceptable laboratory procedures. For serology in all subjects, the volume of blood taken at any single visit is approximately 2</p>

	<p>mL. ^{CCI}</p> <p>[REDACTED]</p> <p>. To clarify, for the youngest infants, those in Cohort 2 (Group 4), a total of 10 mL per subject will be obtained for the entire study period. All blood samples will be processed and stored at the trial site according to the Laboratory Guidelines as provided in the Procedures Manual.</p>
Section 9.1.7	Tables 9a and 9b clarified body temperature measurements in footnotes and for local injection reactions of erythema, swelling, and induration, added the number of millimeters (mm) to clarify the intensity grades.
Section 9.3.5	<p>Title:</p> <p>Phone Contacts – Safety Data Collection (Day 134 [Cohort 1] and Days 200 and 260 [Cohort 2])</p>
	<p>Safety calls will be performed on Day 134 for subjects in Cohort 1 and on Days 200 and 260 for subjects in Cohort 2. Safety calls are calls made to the subject by a trained healthcare provider. These calls will follow a script which will facilitate the collection of relevant safety information. The subject's legally authorized representative LAR will be interviewed according to the script, and information relating to SAEs, and concomitant medications or vaccinations associated with those events must be written down. All safety information described by the subject must be written down in a designated location within the source documents and not written on the script used for the telephone call. The site should schedule the next safety call or clinic visit with the subject's legally authorized representative LAR. The subject or the subject's legally authorized representative LAR will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.</p>
Section 13.1	<p>A SAP will be prepared and finalized prior to the interim analyses (Day 57 in Cohort 1 and Day 140 in Cohort 2). This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives. <i>Unless otherwise stated, the statistical methods described in the following subsections apply to all groups.</i></p>

	<p>A blinded data review will be conducted by the blinded trial team prior to the interim analyses and the analysis at study completion (Day 210 in Cohort 1 and Day 293 in Cohort 2). Limited blinded data review (of protocol deviations and subject evaluability) will also be done prior to the interim analyses. These reviews will assess the accuracy and completeness of the trial database and subject evaluability.</p>
Section 13.1.1	<p>The trial, within each age stratum in both cohorts, is to will evaluate the immunogenicity and safety of four formulations (A—D), under two different dosing regimens in 4 pediatric age ranges. Two cohorts of subjects will be enrolled into the trial. Cohort 1 will consist of 4 groups (4 to <9 years, 1 to <4 years [2 groups] and 6 months to <1 year), enrolled in age-step down fashion as described in Section 6.1. The youngest age group (Cohort 2, 6 weeks to <6 months) will be the last to complete enrollment (ie, 1 or 2 doses in Cohort 1 and 2 or 3 doses in Cohort 2). The age groups are used as a stratification factor during randomization. The trial factors under investigation, overall, and for each group include: formulation (4 formulation arms within each group); and number of doses (2 levels for each formulation within each group). For groups 1, 2, 2a, and 3 (in Cohort 1) the number of active doses will be 1 or 2 doses. For group 4 (Cohort 2), the number of active doses will be 2 or 3. Within each cohort, subjects are randomized to 1 of 8 trial arms (2 dose levels for 4 formulations), with group as a stratification factor. formulation arms (4), number of doses (2 levels within each group), and age groups (4 age groups with Groups 2 and 2a in the same age range). For summary purposes, there are 8 arms in the trial within each age group, which are defined by the combination of formulation arm and number of doses. The purpose of Group 2a is to evaluate the safety and selected immunogenicity endpoints in subjects in the same age range as Group 2, but who receive the recently manufactured NoV bivalent VLP vaccine. Statistical methods described in the following sections will be essentially the same, but will be done only for the endpoints indicated in Section 5.2.</p> <p>In general, the results (both safety and immunogenicity) from the trial will be summarized separately for each age group, by formulation/dose arm. For immunogenicity results, additional summaries and/analyses by treatment group for Cohort 1 will be provided, by pooling subjects in Aage groups 1–3. Other summaries based on different groups may be provided, with details provided in the SAP.</p>
Section 13.1.3	<p>The trial will evaluate the immunogenicity and safety of four formulations under different dosing regimens in 4 pediatric age ranges. Two cohorts of subjects will be enrolled into the trial. Cohort 1 will consist of 4 groups (4 to <9 years, 1 to <4 years [2 groups] and 6 months to <1 year), enrolled in age-step down fashion as described in Section 6.1. The youngest age group</p>

	<i>(Cohort 2, 6 weeks to <6 months) will be the last to complete enrollment. The factors under investigation, overall, and for each group include: formulation (4 formulation arms within each group); and number of doses (2 levels for each formulation within each group). For groups 1, 2, 2a, and 3 (in Cohort 1) the number of active doses will be 1 or 2 doses. For group 4 (Cohort 2), the number of active doses will be 2 or 3. Within each cohort, subjects are randomized to 1 of 8 trial arms (2 dose levels for 4 formulations), with group as a stratification factor.</i>
	Descriptive statistics for the primary, secondary and exploratory endpoints including estimates of seroresponse (≥ 4 -fold rises), and 95% confidence intervals (CI) will be provided. Summaries will be provided by formulation arm (ie. combination of formulation arms and number of doses) and age group (4 age ranges with Groups 2 and 2a in the same age range). Additional summaries will be provided at the cohort level, by pooling subjects across the relevant age groups in Cohort 1 , if as applicable.
	Furthermore, a Additional analyses will also be provided at the cohort level (pooling groups in Cohort 1). Statistical analyses of the primary endpoint will be performed for each cohort using the CMH method [36] stratified by age group (in Cohort 1) to assess the effects of formulation/ dose combination arms . Risk differences and corresponding 95% CIs will be provided for all pairwise comparisons of interest, without adjustments for multiplicity. The primary analyses will be based on the PPS.
	Continuous secondary endpoints, such as GMT and GMFR, will be summarized descriptively by group for each of the 8 formulation arms (ie. for each of the formulation/ dose combinations arm , separately for the 1 and 2 (or 2 and 3) dose groups), by age groups.
	Statistical analyses of selected continuous variables will be performed using analysis of covariance (ANCOVA) to assess the effects of formulation arms. For example, to assess the effect of formulation on GMT, an ANCOVA model of log-transformed GMT will be used with a fixed effect for formulation arm (ie. combination of formulation arms and number of doses), and, age stratum as a factors, and baseline (pre-vaccination) value as a covariate. Analysis of covariance (ANCOVA) will be conducted for selected continuous endpoints (such as GMT and GMFR), examining the effect of formulation/dose combination using the log-transformed value as the dependent variable and the corresponding log-transformed baseline value as a covariate. Cohorts will be analyzed separately due to different number of doses (1 or 2 in Cohort 1; 2 or 3 in Cohort 2). For Cohort 1, the model will include estimates for treatment effect (formulation/dose combination) within each group, and at the cohort level across groups. The ANCOVA models will include group as a factor for analyses of Cohort 1 with a group by formulation/dose combination interaction term if appropriate. The pre-specified rule for

	<i>inclusion of the interaction term will be described in the SAP. A factor for country will be included.</i>
	CC Details regarding exploratory endpoints will be provided in the SAP.
Section 13.2	Two interim analyses will be performed after the primary safety and immunogenicity data are available (ie, Day 57 for Cohort 1 and Day 140 for Cohort 2) (primary analysis time point). <i>Day 57 IA for Cohort 1 will be provided initially for Groups 1 and 2, who will complete Day 57 substantially earlier than Groups 2a and 3. The Day 57 IA for Groups 2a and 3 combined will be provided at a later time. Thus, the Day 57 IA will be conducted in two parts to be followed by the Day 140 IA in Group 4.</i> The All interim analyses will be performed by a separate set of unblinded statisticians and programmers at the contract research organization (CRO), Quintiles, who will have access to individual treatment assignments but will not <i>otherwise</i> be involved in subsequent study conduct. The rest of the personnel involved in the conduct of the study, including those at Takeda, Quintiles, and the study sites, will remain blinded to the individual subject data (including treatment assignments) until unblinding after database lock (Day 210 for Cohort 1 and Day 293 for Cohort 2). More details on the analyses will be provided in the statistical analysis plan (SAP).
Section 13.3	Table 13a adapted to include calculations for a sample size of 480.
Section 16	<ol style="list-style-type: none"> Garçon N, Morel S, Didierlaurent A, Descamps D, Wettendorff M, Van Mechelen M. Development of an AS04-adjuvanted HPV vaccine with the adjuvant system approach. BioDrugs. 2011;25:217-26. Garçon N, Wettendorff M, Van Mechelen M. Role of AS04 in human papillomavirus vaccine: mode of action and clinical profile. Expert Opin Biol Ther. 2011;11:667-77.

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 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 B](#) of this protocol.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

Location of Facility (Country)

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2.0 TRIAL SUMMARY

Name of Sponsor(s): Takeda Vaccines, Inc. One Takeda Parkway Deerfield, IL 60015 USA		Product Name: Norovirus Bivalent GI.1/GII.4 VLP Vaccine	
Trial Title: A Phase II, Randomized, Double-Blind, Dosage, Safety and Immunogenicity Trial of Intramuscular Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine combined with Aluminum Hydroxide Adjuvant in Children, Toddlers, and Infants			
IND No.: 014421		EudraCT No.: 2014-000778-20	
Study Identifier: NOR-202	Phase: II	Trial Blinding Scheme: Double Blind	
<p>Background and Rationale:</p> <p>Noroviruses (NoV) 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 immunocompromized individuals. Noroviruses cause acute debilitating illness characterized by vomiting, diarrhea, and abdominal pain. There are no substantial differences in clinical presentation between adults and children, although children less than 1 year of age present more frequently with diarrhea and less frequently with vomiting than other age groups. The duration of the diarrhea is also longer in this age group with a median duration of 6 days compared to 1 to 3 days in other age groups [1]. In the European Union (EU), for children under 5 years of age, it is estimated that each year there are 5,600,000 cases of NoV gastroenteritis [2], resulting in 380,000 outpatient and 147,000 emergency room visits (population adjusted from Hall, 2011[3]), 30,000 to 47,000 hospitalizations (population adjusted from Phillips, 2010 [2]) and as many as 200 deaths (assumes ratio of deaths to hospitalizations is the same as rotavirus in the pre-vaccine era). For children below the age of 5 years in high income countries, an estimated figure of 64,000 episodes of NoV disease occur requiring hospitalization [4]. Whereas mortality due to NoV disease in the pediatric population is rare in industrialized countries, it is frequent in developing countries. In developing countries, mortality from NoV disease in children below the age of 5 years is approximately 200,000 deaths per year [4, 5]. Although potentially a cause for hospitalization in infants, there are fewer deaths than expected possibly due to the protection offered by maternal antibodies during the first 6 months of life. A study in Finland found that 68% of infants less than 6 months old had immunoglobulin G (IgG) antibodies against GII.4 NoV with high avidity, which likely reflects acquired maternal IgG antibodies (from transplacental transfer), compared to the antibodies found in infants aged 7 to 12 months. However, the presence of immunoglobulin A (IgA) antibodies in 20% of these children suggests that maternal antibodies do not offer full protection [6]. Vaccination of young infants with a NoV vaccine during the first 6 months of life may provide protection thereafter, when infants and young children are at highest risk of acquiring NoV disease.</p> <p>In addition to the inherent morbidity and mortality problem, NoV infections exact a significant socioeconomic toll on businesses, hospitals, schools, and other closed settings dealing with outbreaks [7]. As the burden of rotavirus in children decreases through the childhood rotavirus vaccination programs, NoV infections and disease are likely to increase with consequences extending beyond this population [8]. A prophylactic approach could counter this.</p> <p>The vaccine in this trial is based on NoV virus-like particles (VLPs) as the antigens. Norovirus VLPs are non-infectious because they do not contain viral genomic ribonucleic acid (RNA) and are immunogenic because they preserve particulate antigen conformation and structure that mimic functional interactions of the virus with cellular receptors. The vaccine also contains the single Al(OH)₃ adjuvant.</p> <p>Aluminum hydroxide [Al(OH)₃] has been shown to enhance the antigenicity and immunogenicity of vaccines. The rationale for an Al(OH)₃ adjuvanted intramuscular (IM) NoV VLP vaccine is based on the low immune responses previously observed in healthy adults after oral administration of Norwalk Virus VLP vaccine [9, 10, 11]. Aluminum adjuvant has a demonstrated safety profile of over 6 decades [12]). The aluminum concentration per dose was selected</p>			

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empirically from data that demonstrated that this amount of aluminum enhanced the antigenicity and immunogenicity of the vaccine.

Norovirus strains drift from year to year and both GI and GII genogroups cause disease in all age groups. Although numerous types are reported, the GII.4 type remains dominant and is currently responsible for the majority of outbreaks worldwide. The rationale for developing a bivalent vaccine is based on NoV epidemiology and the lack of natural protection between genogroups. In trial LV03-104, the first NoV bivalent VLP vaccine was given IM, and compared equally balanced (1:1) dosages of the GI.1 and GII.4 VLPs in adults. For each of the 4 vaccine dosages evaluated (5/5, 15/15, 50/50, and 150/150 µg of NoV VLPs), the seroresponse rates (percent of subjects with at least a 4-fold rise in antibody levels) and geometric mean fold rises (GMFRs) were lower for the GII.4 VLP than for the GI.1 VLP at equivalent antigen dosages. Likewise, similar post-vaccination immunogenicity data were observed in adults in trial LV03-105, the GII.4 challenge trial that evaluated a 50/50 µg balanced 1:1 VLP dosage of vaccine. Separately the factorial design trial NOR-107 was initiated in subjects ages 18 to 64, to evaluate multiple vaccine formulations containing different (balanced and unbalanced) ratios of the antigenic VLP components of the bivalent vaccine (GI.1/GII.4) with Al(OH)₃ adjuvant both with and without MPL adjuvant. Prior safety and immunogenicity data for the NoV vaccine given by the IM route are available from approximately 1000 adult subjects, evaluated in five Takeda clinical trials (LV03-104, LV03-105, NOR-107, NOR-201, and NOR-210). The NoV vaccine evaluated in these trials either contained both Al(OH)₃ plus monophosphoryl lipid A (MPL) adjuvants combined or the Al(OH)₃ adjuvant alone. Trial NOR-107 conducted in adults aged 18-64 years, a Phase II dosage, adjuvant justification, safety, and immunogenicity trial, evaluated 11 vaccine formulations, and showed that the NoV VLP vaccine adjuvanted with aluminum as Al(OH)₃ adjuvant was as immunogenic as the NoV VLP vaccine adjuvanted with Al(OH)₃ and MPL combined.

This trial NOR-202 in children aged 6 weeks to less than 9 years will evaluate the safety and immunogenicity of multiple formulations with different ratios of the antigenic VLP components of the bivalent vaccine. The formulations for NOR-202 are selected based on the initial and additional results obtained from the factorial design study NOR-107 in adults. Based on the additional NOR-107 results, the number of formulation arms is reduced from 8 in amendment N° 1.0 of the original protocol to 4 in this amended protocol.

The upper age cut-off for the NOR-202 trial was selected based on the assumption that the immune response in older children and adolescents aged 9 to <18 years is similar to the immune response observed in those aged ≥18 years. Therefore subjects aged 9 to <18 years are not included in trial NOR-202.

The primary goals of this clinical trial are therefore to evaluate the immunogenicity and safety of 1 to 2 doses in children 6 months to less than 9 years of age and 2 to 3 doses in infants 6 weeks to less than 6 months of age with the IM NoV bivalent VLP vaccine using different dosages of the VLPs to obtain confirmation of dosage and schedule, in these age groups. In order to maintain the trial blind, a single injection of saline placebo will be administered as the final dose for the 1 dose group in Cohort 1 and for the 2 dose group in Cohort 2.

Background and Rationale for Amendment Number 3.0:

The primary purposes of this amendment are: 1) to enroll an additional 120 children (1 to < 4 years; designated Group 2a), to assess the safety and immunogenicity of the recently manufactured NoV vaccine in a similar age group to Group 2; and 2) to perform the Day 57 interim analysis (IA) for Groups 1 and 2 of Cohort 1, who will complete Day 57 substantially earlier than Groups 2a and 3. The Day 57 IA for Groups 2a and 3 combined will be performed at a later time. The Day 140 IA for Group 4 does not change.

The trial vaccine, originally manufactured for trial NOR-202, was not available for clinical use after 30 November 2015, due to expiration at 36 months after manufacture. Several factors affected the enrolment timeline in trial NOR-202: (1) Takeda's decision to not initiate enrollment until after agreement from the Pediatric Committee of the EMA on the Pediatric Investigational Plan (PIP) of the NoV vaccine; (2) and the regulatory, logistical, and operational study requirements for implementation of the two prior protocol amendments.

Per protocol, all children in Groups 1 (4 to < 9 years) and 2 (1 to < 4 years) were enrolled, randomized and received one of the four NoV vaccine formulations as a one or two dose trial vaccine regimen within the vaccine expiry dating period. Notably, children in Groups 3 (1 or 2 doses) and 4 (2 or 3 doses) were not enrolled due to expiration of the trial

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vaccine. Takeda has paused this study until additional trial vaccine is manufactured and released for clinical use.

Takeda has recently produced VLPs at a different manufacturer with increased capacity for manufacturing on a larger scale. To date, the NoV vaccine with these recently produced VLPs has been manufactured and released for clinical use in two studies in adults; trial NOR-204 in 350 adults aged 18 to > 85 years and trial NOR-211 in ~ 2800 adults aged 18 to 49 years.

To understand the safety and immunogenicity of the recently manufactured vaccine in a similar age group to Group 2, an additional 120 children designated Group 2a, will be enrolled in trial NOR-202, prior to enrolling children in Groups 3 and 4. Specifically, the safety data from Group 2a will be provided to the Data Monitoring Committee (DMC) for review prior to enrollment of the children in Groups 3 and 4.

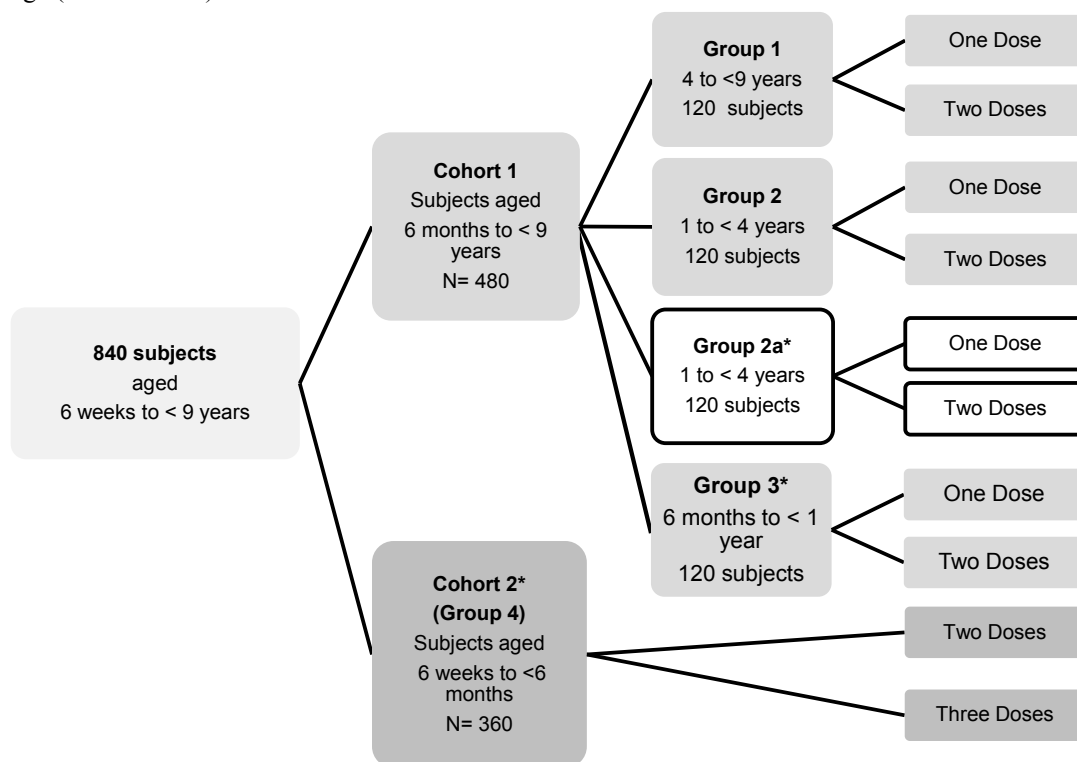
Although the VLP manufacturer has changed, the vaccine dosages and regimens with the four vaccine formulations evaluated in Groups 1 and 2 will also be evaluated in children in Groups 2a, 3, and 4. However, only children in Groups 2a, 3, and 4, will receive the recently manufactured vaccine.

Enrollment in Group 2a will be initiated after all four vaccine formulations of the recently manufactured vaccine are released for clinical use.

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

Trial Design:

This is a Phase II, randomized, double-blind, multi-site, dosage, safety, and immunogenicity trial of the IM NoV bivalent VLP vaccine combined with Al(OH)₃. Subjects randomized in the trial will be placed into 1 of 2 cohorts based on age (shown below).



* Recently manufactured clinical trial material lots

Subjects 6 months to less than 9 years of age (inclusive, Cohort 1) will receive either 1 or 2 doses by IM injection, at least 28 days apart (Days 1 and 29), in 4 groups in 3 age ranges (Group 1: aged 4 to less than 9 years; Group 2 and Group 2a: aged 1 to less than 4 years; and Group 3: aged 6 months to less than 1 year). Infants 6 weeks to less than 6 months of age (Group 4/Cohort 2) will receive 2 or 3 doses by IM injection, approximately 56 days apart (Days 1, 56, and 112). Routine child and infant vaccinations will be given on schedule per the national guidelines approximately 28 days apart from the investigational vaccine in each age group.

Primary evaluation of the trial objectives is planned at 28 days after the final (second) vaccination in subjects aged 6 months to less than 9 years (Cohort 1) and 28 days after the final (third) vaccination in subjects aged 6 weeks to less than 6 months (Cohort 2). In order to maintain the blind and to have the same trial time points and dosing regimens, subjects in Cohort 1 (Groups 1, 2, 2a and 3) who are randomized to the 1 dose group will receive a dose of the NoV bivalent VLP vaccine on Day 1 followed by a placebo injection of saline 28 days later (Day 29) and subjects in the 2 dose group will receive 2 doses of NoV VLP vaccine approximately 28 days apart (Days 1 and 29). Likewise, subjects in Cohort 2 (Group 4) who are randomized to the 2 dose group will receive 2 doses of NoV bivalent VLP vaccine on Days 1 and 56, followed by a placebo injection of saline approximately 56 days later (Day 112), and subjects in the 3 dose group will receive 3 doses of NoV VLP vaccine approximately 56 days apart (Days 1, 56, and 112), independent of the infant routine vaccinations by approximately 28 days. This is a double-blind trial; investigators, subjects, data collectors, and data evaluators are blinded to the specific formulation and the dosing groups.

This study plans to assess the immunogenicity and safety of the NoV bivalent VLP vaccine in children when given independently of the routine pediatric vaccines but, importantly, never to interfere with routine vaccine administration of children in each of the countries planned for evaluation. National pediatric vaccine regimens in children 6 weeks to less than 6 months of age vary by country (eg, routine pediatric vaccines may be given at 2, 3, and 4 months of age; at 2, 4, and 6 months of age; or at 3, 5, and 12 months).

An independent program level Data Monitoring Committee (DMC) has been established to assess safety data on an ongoing basis. The DMC will also have study level responsibilities to review data and make recommendations about the sequential enrollment of various groups and formulation arms in this study (see Section 11.1.1).

A licensed benefit vaccine may be offered to all subjects after trial exit.

Interim analyses (IA) will be performed after the primary safety and immunogenicity data are available (ie, Day 57 for Cohort 1 and Day 140 for Cohort 2) (primary analysis time point). The Day 57 IA for Cohort 1 will be provided initially for Groups 1 and 2, who will complete Day 57 substantially earlier than Groups 2a and 3. The Day 57 interim analyses for Groups 2a and 3 combined will be provided at a later time. Thus, the Day 57 IA will be conducted in two parts to be followed by the Day 140 IA in Group 4. All interim analyses will be performed by a separate set of unblinded statisticians and programmers at the contract research organization (CRO), Quintiles, who will have access to individual treatment assignments but will not otherwise be involved in study conduct. The rest of the personnel involved in the conduct of the study, including those at Takeda, Quintiles, and the study sites, will remain blinded to the individual subject data (including treatment assignments) until unblinding after database lock (Day 210 for Cohort 1 and Day 293 for Cohort 2).

More details on the analyses will be provided in the statistical analysis plan (SAP).

Primary Objectives:

To select the optimal formulation of the NoV bivalent VLP vaccine from different dosages of VLP for further development:

- By assessing the seroresponse rate (percentage of subjects with ≥ 4 -fold rises) in serum anti-NoV GI.1 VLP and GII.4 VLP antibody titers by Pan immunoglobulin (Pan-Ig) enzyme-linked immunosorbent assay (ELISA).
- By assessing the safety profile of different formulations of the NoV bivalent VLP vaccine as measured by solicited local and systemic adverse events (AEs) for the period of 7 days after each vaccination and as measured by the occurrence of unsolicited AEs 28 days after each vaccination, and serious adverse events (SAEs) throughout the trial.

Secondary Objectives:

- To evaluate the geometric mean titers (GMT) and GMFRs of anti-NoV GI.1 VLP and GII.4 VLP antibody titers as measured by Pan-Ig ELISA.
- To evaluate the seroresponse rate in serum anti-NoV GI.1 VLP and/or GII.4 VLP antibody blocking titers as measured by histoblood group antigen (HBGA) binding assay.
- To evaluate Geometric Mean Blocking Titers (BT50) and GMFR of serum anti-NoV antibody titers for GI.1 VLP and GII.4 VLP as measured by the HBGA binding assay.
- To assess safety by the incidence of AEs leading to subject's withdrawal from the trial.

Exploratory Objectives:

CCI

Subject Population:

Healthy Subjects: Yes

Planned Minimum Age: 6 weeks

Planned Maximum Age: less than 9 years

Planned Number of Subjects: 840

Number of Subjects:

A total of 840 healthy subjects will be enrolled within two cohorts and randomized to vaccine regimen as follows:

- Cohort 1, N=480, consisting of Group 1: aged 4 to less than 9 years; Group 2: aged 1 to less than 4 years; Group 2a: aged 1 to less than 4 years; Group 3: aged 6 months to less than 1 year (N= 120 each): subjects will be randomized with equal probabilities to 1 of the 8 unique combinations of formulation arms and dose groups (ie, 4 formulation arms and 1 or 2 doses). The additional 120 children, designated as Group 2a, are being included to evaluate the recently manufactured NoV bivalent VLP vaccine formulations prior to enrolling children in Groups 3 and 4. Each of the combinations in Groups 1, 2, 2a, and 3 will consist of approximately 15 subjects per group. Thus Cohort 1 consists of 480 subjects in Groups 1, 2, 2a, and 3 combined.
- Cohort 2 (Group 4: aged 6 weeks to less than 6 months): 360 subjects will be randomized to receive the recently manufactured NoV bivalent VLP vaccine with equal probabilities to 1 of the 8 unique combinations of formulation arms and dose groups (ie, 4 formulation arms and 2 or 3 doses). Each of the combinations will consist

of approximately 45 subjects.	
<p>Planned Number of Formulation Arms: 4</p> <p><u>Investigational vaccine:</u> Doses of the antigen component of each investigational vaccine are outlined below. Investigational vaccines (Arms A, B, C, and D) are manufactured by Althea Technologies, San Diego (CA), United States. Presented formulations are an approximation (within a defined specification) of the respective antigen/adjuvant concentrations.</p> <ul style="list-style-type: none"> • Arm A: GI.1/GII.4 (15 µg/15 µg) • Arm B: GI.1/GII.4 (15 µg/50 µg) • Arm C: GI.1/GII.4 (50 µg/50 µg) • Arm D: GI.1/GII.4 (50 µg/150 µg) <p>The investigational vaccine for each arm contains 500 µg alum.</p> <p>Subjects aged 6 months to less than 9 years will receive either 1 dose of investigational vaccine on Day 1 and 1 dose of saline placebo on Day 29 or 2 doses of investigational vaccine at least 28 days apart (on Day 1 and Day 29). Infants aged 6 weeks to less than 6 months will receive 2 doses of investigational vaccine, approximately 56 days apart (on Day 1 and Day 56) and 1 dose of saline placebo on Day 112 or 3 doses of investigational vaccine, approximately 56 days apart (on Days 1, 56, and 112).</p> <p><u>Placebo Control:</u> Saline will be administered as a control injection in order to maintain the trial blind for the 1 dose groups in Groups 1, 2, 2a and 3, (Cohort 1) and for the 2 dose group in Group 4 (Cohort 2). Subjects in the 1 dose groups in Cohort 1 receive NoV vaccine on Day 1 and a saline placebo injection on Day 29. Subjects in the 2 dose group in Cohort 2 receive NoV vaccine on Days 1 and 56 and a saline placebo injection on Day 112.</p> <p><u>Route of Administration:</u> IM (anterolateral thigh for children aged ≤12 months; anterolateral thigh or deltoid muscle of the arm for children aged >12 months [per national guidelines]).</p>	
<p>Main Criteria for Inclusion:</p> <ul style="list-style-type: none"> • Male and female subjects aged between 6 weeks and less than 9 years at the time of enrollment. • Subjects who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator. • The subject's legally authorized representative (LAR) 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. An assent will also be obtained according to age appropriate country-specific regulations. • Individuals who can comply with trial procedures and are available for the duration of the trial. 	
<p>Main Criteria for Exclusion:</p> <ul style="list-style-type: none"> • Known hypersensitivity to any of the vaccine components. • Subjects with known or suspected impairment/alteration of immune function. 	
<p>Duration of the Trial:</p> <p>Six months after last administration of investigational vaccine.</p>	<p>Period of Evaluation:</p> <p>210 or 293 days.</p>
<p>Main Criteria for Evaluation and Analyses:</p> <p>Endpoints apply to Cohorts 1 and 2 unless otherwise stated. For subjects in Group 2a, the serologic assays to the vaccine VLPs for the Pan-Ig ELISA and for the HBGA binding assays will each be performed. Notably, the following endpoints will not be performed for Group 2a: Avidity, IgA ELISA, CMI for those aged ≥ 3 years, and HBGA binding assay to a panel of GI.1 and GII.4 not represented in the vaccine.</p> <p><u>The primary endpoints for this trial are:</u></p> <p>Immunogenicity</p> <ul style="list-style-type: none"> • Seroresponse rate (defined as percentage of subjects with a 4-fold rise or greater) in serum anti-NoV antibody titers for both GI.1 VLP and GII.4 VLP as measured by Pan-Ig ELISA at Day 57 (Cohort 1) and Day 140 	

(Cohort 2).

Safety

- Percentage of subjects with solicited local AEs of injection site: pain, erythema, induration, and swelling on the day of vaccination and then daily through Day 7 after each vaccination.
- Percentage of subjects with solicited systemic AEs of headache, fatigue, myalgia, arthralgia, vomiting (number per day/intensity), and diarrhea (number per day/consistency) for children aged 4 to <9 years; and irritability/fussiness, drowsiness, loss of appetite, vomiting (number per day/intensity), and diarrhea (number per day/consistency) for children aged 6 weeks to <4 years on the day of vaccination and daily through Day 7 after each vaccination.
- Body temperature on the day of vaccination (approximately 30 minutes and 6 hours later); then daily through Day 7 after each vaccination.
- Percentage of subjects with unsolicited AEs for 28 days after each vaccination.
- Percentage of subjects with SAEs throughout the trial.

The secondary endpoints for this trial are:

Immunogenicity

Pan-Ig ELISA

- Seroresponse rate in serum anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- Seroresponse rate in serum anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- GMT of anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- GMT of anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- GMFR of anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- GMFR of anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).

HBGA Binding Assay

- Seroresponse rate in serum anti-NoV GI.1 VLP and GII.4 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- Seroresponse rate in serum anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- Seroresponse rate in serum anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- BT50 of anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- BT50 of anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- GMFR of anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- GMFR of anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).

Safety

- Percentage of subjects with any AE leading to subject's withdrawal from the trial - from the day of vaccination

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through Day 210 (Cohort 1) and Day 293 (Cohort 2).

The exploratory endpoints for this trial are:

CCI



CCI

Statistical Considerations:

This trial, within each age stratum in both cohorts, is to evaluate the immunogenicity and safety of four formulations (A – D), under two different dosing regimens (ie, 1 or 2 doses in Cohort 1 and 2 or 3 doses in Cohort 2). The age groups are used as a stratification factor during randomization. The trial factors under investigation include: formulation arms (4), number of doses (2 levels within each group), and age (4 age groups with Groups 2 and 2a in the same age range). For summary purpose, there are 8 formulation arms in the study within each age group, which is defined by the combination of formulation arm and number of doses.

Analysis of Demographics and Other Baseline Characteristics

Summaries of age, gender, race, and other baseline characteristics will be presented by formulation arm for each age group.

Immunogenicity Analysis

Descriptive statistics for the primary, secondary and exploratory endpoints, including estimates of seroresponse (≥ 4 -fold rises), and 95% confidence intervals (CI) will be provided. Summaries will be provided by formulation arm (ie. combination of formulation arms and number of doses), and age group. Additional summaries will be provided at the cohort level, by pooling subjects across the relevant age groups, if applicable.

CCI

Safety Analysis

Reactogenicity will be assessed for 7 days following each vaccination via collection of solicited AEs, including local events (injection site: pain, erythema, induration, and swelling) and systemic reactions of headache, fatigue, myalgia, arthralgia, vomiting (number per day/intensity), and diarrhea (number per day/consistency) for children aged 4 to <9 years; and irritability/fussiness, drowsiness, loss of appetite, vomiting (number per day/intensity), and diarrhea (number per day/consistency) for children aged 6 weeks to <4 years daily through Day 7 after each vaccination. In addition, other indicators of reactogenicity will be collected (body temperature). Solicited reactogenicity data will be captured daily on the day of vaccination and the following 6 days.

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

Unsolicited AEs, and SAEs, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for each formulation arm. AEs leading to subject's withdrawal from the trial will also be summarized.

Sample Size Justification:

This trial is designed to be descriptive and is not based on testing formal null hypotheses, and therefore the sample size was not determined based on formal statistical power calculations.

Interim Analysis:

Interim analyses will be performed after the primary safety and immunogenicity data (28 days after last dose) are available (ie, Day 57 for Cohort 1 and Day 140 for Cohort 2) (primary analysis time point). Day 57 IA for Cohort 1 will be provided initially for Groups 1 and 2, who will complete Day 57 substantially earlier than Groups 2a and 3. The Day 57 IA for Groups 2a and 3 combined will be provided at a later time. Thus, the Day 57 IA will be conducted in two parts to be followed by the Day 140 IA in Group 4. All interim analyses will be performed by a separate set of unblinded statisticians and programmers at the CRO, Quintiles, who will have access to individual treatment assignments but will not otherwise be involved in study conduct. The rest of the personnel involved in the conduct of the study, including those at Takeda, Quintiles, and the study sites, will remain blinded to the individual subject data (including treatment assignments) until unblinding after database lock (Day 210 for Cohort 1 and Day 293 for Cohort 2).

More details on the analyses will be provided in the SAP.

Data Monitoring Committee:

An independent program level DMC will assess safety data on an ongoing basis. The DMC will also have study level responsibilities to review data and make recommendations about the sequential enrollment of various groups and formulation arms in this study.

Enrollment in this study will be initiated sequentially based on age groups and formulation arms, with ongoing DMC review.

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2.1 Schedule of Trial Procedures

Table 2-a Schedule of Trial Procedures for Subjects Aged 6 Months to Less Than 9 Years (Cohort 1 for Groups 1, 2 and 3; N=360)

Timing Procedure	Day 1	Day 3	Day 8	Day 29	Day 32	Day 36	Day 57	Day 134	Day 210 ^a
Visits	X		X	X		X	X		X
Phone Contacts ^b		X			X			X	
Visit Window (days)	-	-1/+2	+3	+3	-1/+2	+3	+3	±7	+7
Signed Informed Consent	X								
Physical Examination ^c	X		(X)	X		(X)	(X)		(X)
Trial Vaccine Administration	X ^d			X ^d					
Diary Card Dispensing	X			X					
Diary Card Delivery			X	X		X	X		
AEs ^e	Day 1-28			Day 28-56					
SAEs ^f	X	X	X	X	X	X	X	X	X
Blood Draw for Serology (2 mL) ^g	X			X			X		X
CCI ^h	X			X			X		

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Use of (X) indicates that samples or procedures that generally will not be performed but may be performed to investigate an AE, previous laboratory abnormality, or at the time of premature discontinuation.

Footnotes:

- a. **Day 210 is the 6-month end of study visit.**
- b. Phone contacts are only reminder calls on Days 3 and 32; phone contact on Day 134 is for safety data collection (Sections 9.3.5 and 9.3.6).
- c. Complete at the first visit (Day 1), brief physical exam at each vaccination, and symptom-directed thereafter. If a subject early terminates (ET), Day 210 procedures should be performed.
- d. All subjects receive NoV vaccine at Day 1; subjects in the 1 dose groups in Cohort 1 receive a saline placebo injection at Day 29 whereas subjects in the 2 dose groups in Cohort 1 receive NoV vaccine at Day 1 and Day 29.
- e. AEs will be categorized by the investigator by severity (mild, moderate, or severe) and causality (related or not related to vaccine).
- f. SAEs will be reported to the sponsor within 24 hours of the investigator becoming aware of the event.
- g. Blood draw for serology at 4 visits (all subjects); 2 mL per time point for a total of 8 mL. Anti-NoV specific GI.1 and GII.4 VLP antibodies by Pan-Ig ELISA, CCI [REDACTED] and HBGA antibody assays; GMT, GMFR, and seroresponse rate (≥ 4 -fold rise from baseline) will be determined for all available subjects in each formulation group. Serum NoV IgG antibody avidity will be determined pre- and post-vaccination on Days 1, 29, and 57 as available with remaining sera.
- h. CCI [REDACTED]

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Table 2-b Schedule of Trial Procedures for Subjects Aged 1 to Less Than 4 Years (Cohort 1 for Group 2a; N=120)

Timing Procedure	Day 1	Day 3	Day 8	Day 29	Day 32	Day 36	Day 57	Day 134	Day 210 ^a
Visits	X		X	X		X	X		X
Phone Contacts ^b		X			X			X	
Visit Window (days)	-	-1/+2	+3	+3	-1/+2	+3	+3	±7	+7
Signed Informed Consent	X								
Physical Examination ^c	X		(X)	X		(X)	(X)		(X)
Trial Vaccine Administration	X ^d			X ^d					
Diary Card Dispensing	X			X					
Diary Card Delivery			X	X		X	X		
AEs ^e	Day 1-28			Day 28-56					
SAEs ^f	X	X	X	X	X	X	X	X	X
Blood Draw for Serology (2 mL) ^g	X			X			X		X

Use of (X) indicates that samples or procedures that generally will not be performed but may be performed to investigate an AE, previous laboratory abnormality, or at the time of premature discontinuation.

Footnotes:

- Day 210 is the 6-month end of study visit.**
- Phone contacts are only reminder calls on Days 3 and 32; phone contact on Day 134 is for safety data collection (Sections 9.3.5 and 9.3.6).
- Complete at the first visit (Day 1), brief physical exam at each vaccination, and symptom-directed thereafter. If a subject early terminates (ET), Day 210 procedures should be performed.
- All subjects receive NoV vaccine at Day 1; subjects in the 1 dose groups in Cohort 1 Group 2a receive a saline placebo injection at Day 29 whereas subjects in the 2 dose groups in Cohort 1 Group 2a receive NoV vaccine at Day 1 and Day 29.
- AEs will be categorized by the investigator by severity (mild, moderate, or severe) and causality (related or not related to vaccine).
- SAEs will be reported to the sponsor within 24 hours of the investigator becoming aware of the event.
- Blood draw for serology at 4 visits (all subjects); 2 mL per time point for a total of 8 mL. Anti-NoV specific GI.1 and GII.4 VLP antibodies by Pan-Ig ELISA and HBGA antibody assays; GMT, GMFR, and seroresponse rate (≥4-fold rise from baseline) will be determined for all available subjects in each formulation group. CCI, and HBGA for a panel of GI.1 and GII.4 strains not represented in the vaccine will not be evaluated for Group 2a subjects. CMI will not be evaluated for Group 2a subjects.

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Table 2-c Schedule of Trial Procedures For Subjects Aged 6 Weeks to Less Than 6 Months (Cohort 2; N=360)

Timing Procedure	Day 1	Day 3	Day 8	Day 29	Day 56	Day 59	Day 63	Day 84	Day 112	Day 115	Day 119	Day 140	Day 200	Day 260	Day 293^a
Visits	X		X	X	X		X	X	X		X	X			X
Phone Contacts ^b		X				X				X			X	X	
Visit Window (days)	-	-1/+2	+3	+3	+3	-1/+2	+3	+3	+3	-1/+2	+3	+7	+7	+7	+7
Signed Informed Consent	X														
Physical Examination ^c	X		(X)	(X)	X		(X)	(X)	X		(X)	(X)			(X)
Trial Vaccine Administration	X ^d				X ^d				X ^d						
Diary Card Dispensing	X				X				X						
Diary Card Delivery			X	X			X	X			X	X			
AEs ^e	Day 1-28				Day 56-84				Day 112-140						
SAEs ^f	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Draw for Serology (2 mL) ^g	X				X			X				X			X

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Use of (X) indicates that samples or procedures that generally will not be performed but may be performed to investigate an AE, previous laboratory abnormality, or at the time of premature discontinuation.

Footnotes:

- a. Day 293 is the 6-month end of study visit.
- b. Phone contacts are only reminder calls on Days 3, 59, and 115; phone contact on Days 200 and 260 are for safety data collection (Sections 9.3.5 and 9.3.6).
- c. Complete at the first visit (Day 1), brief physical examination at each vaccination, and symptom-directed thereafter. If a subject early terminates (ET), Day 293 procedures should be performed.
- d. Investigational study doses will be given at least 28 days before and/or after routine pediatric vaccines given per the national vaccine program. NoV bivalent VLP study doses for the 3 dose groups are given at Days 1, 56, and 112. NoV bivalent VLP vaccine for the 2 dose groups are given at Days 1 and 56 with a saline placebo injection given on Day 112.
- e. AEs will be categorized by the investigator by severity (mild, moderate, or severe) and causality (related or not related to vaccine).
- f. SAEs will be reported to the sponsor within 24 hours of the investigator becoming aware of the event.
- g. Blood draw for serology at 5 visits (all subjects); **2 mL per time point for total of 10 mL**. Anti-NoV specific GI.1 and GII.4 VLP antibodies by Pan-Ig ELISA, **CCI**, and HBGA antibody assays; GMT, GMFR, and seroresponse rate (≥ 4 -fold rise from baseline) will be determined for all available subjects in each formulation group. Serum NoV IgG antibody avidity will be determined pre- and post-vaccination on Days 1, 56, 84, and 140 as available with remaining sera

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3.0 TRIAL REFERENCE INFORMATION

3.1 Trial-Related Responsibilities

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

3.3 List of Abbreviations

AE	Adverse Event
Al(OH) ₃	Aluminum Hydroxide
ANCOVA	Analysis of Covariance
AOM	Acute Otitis Media
BT50	Blocking Titers 50
CI	Confidence Interval
CMI	Cell-Mediated Immunity
CRO	Contract Research Organization
DMC	Data Monitoring Committee
EC	European Community
eCRF	electronic Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
HBGA	Histoblood Group Antigen
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
CCI	CCI
CCI	CCI
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
LAR	Legally Authorized Representative
MedDRA	Medical Dictionary for Regulatory Activities

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MPL	Monophosphoryl Lipid A
NoV	Norovirus
OME	Otitis Media with Effusion
Pan-Ig	Pan Immunoglobulin
CCI	CCI
PPS	Per-Protocol Analysis Set
PT	Preferred Term
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
USP	United States Pharmacopeia
VLP	Virus-like Particles
WHO	World Health Organization

3.4 Corporate Identification

TV Takeda Vaccines, Inc.

4.0 INTRODUCTION

4.1 Background

Noroviruses (NoV) are non-cultivable human caliciviruses that have emerged as the single most significant cause of epidemic outbreaks of nonbacterial gastroenteritis worldwide [14]. These outbreaks commonly result in significant morbidity and mortality. Norovirus outbreaks are common in all countries in Europe; however, the number of epidemics being reported in recent years has been increasing in England, Wales, Germany, the Netherlands, and other countries [15]. The reason for this increase is unclear, but this may be due to the improved recognition of NoV as an infectious agent responsible for acute gastroenteritis [16, 17, 18, 19]. In addition, surveillance systems have shown an increase in NoV activity globally during late 2012 due to the emergence of a new NoV GII.4 variant, termed Sydney 2012 [20, 21].

Although NoVs affect people of all ages, those most at risk are elderly, very young, and immunocompromized individuals [15]. Following an incubation period of 1 to 2 days, gastric symptoms including nausea, diarrhea, vomiting, and abdominal pain appear [22]. These symptoms may be accompanied by mild fever, muscle, and joint pain [23]. Illness is generally mild and lasts a few days on average. Although usually self-limiting, the disease may become chronic, particularly in immunocompromized individuals [17]. Norovirus-infected people may continue to shed virus for several weeks following the resolution of the symptoms [14], and some cases may be asymptomatic [24]. Norovirus is highly infectious, with 18 to 1000 viral particles estimated to be sufficient for infection [25]. More than 50 million cases of illness per year are thought to occur in Europe and the United States; many of these cases require medical attention or admission to hospitals. There is also a substantial burden of illness in developing countries, where over 200,000 deaths per year of children under 5 years of age are attributed to NoV [4]. In addition to the inherent morbidity and mortality problem, NoV infections exact significant socioeconomic toll on businesses, hospitals, schools, and other settings [26].

The clinical significance of NoVs was underappreciated prior to the development of molecular diagnostic assays that could detect these enteric viruses. The cloning of the prototype genogroup I Norwalk virus genome and the production of virus-like particles (VLPs) from a recombinant Baculovirus expression system led to the development of sensitive assays that revealed that infections due to NoVs are widespread [27, 28, 29]. The investigational vaccine in this trial (ie, NoV GI.1/GII.4 bivalent VLP vaccine adjuvanted with aluminum hydroxide [Al(OH)₃] [NoV GI.1/GII.4 bivalent VLP vaccine]) contains NoV VLPs as the antigens. Norovirus VLPs are noninfectious because they do not contain viral genomic ribonucleic acid (RNA) and are immunogenic because they preserve particulate antigen conformation and structure that mimic functional interactions of the virus with cellular receptors.

Human NoV cannot be grown in cell culture, and no small animal model of human infection is available. Consequently, knowledge of the pathogenesis of NoV, as well as demonstration of proof-of-concept for candidate vaccines, has been derived primarily from studies in human volunteers who have been experimentally infected with stool filtrates obtained from naturally infected human donors or from epidemiologic studies of natural infection [30].

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Prior safety and immunogenicity data for the NoV vaccine given by the IM route are available from approximately 1000 adult subjects, evaluated in five Takeda clinical trials (LV03-104, LV03-105, NOR-107, NOR-201, and NOR-210). The NoV vaccine evaluated in these trials either contained both Al(OH)₃ plus monophosphoryl lipid A (MPL) adjuvants combined or the Al(OH)₃ adjuvant alone. Trial NOR-107 conducted in adults aged 18-64 years, a Phase II dosage, adjuvant justification, safety, and immunogenicity trial, evaluated 11 vaccine formulations, and showed that the NoV VLP vaccine adjuvanted with aluminum as Al(OH)₃ adjuvant was as immunogenic as the NoV VLP vaccine adjuvanted with Al(OH)₃ and MPL combined.

Refer to the current Investigator Brochure of Takeda's NoV GI.1/GII.4 bivalent VLP vaccine for additional product information and a more detailed review of pre-clinical and clinical studies [31].

4.2 Rationale for the Proposed Trial

Noroviruses have emerged as the single most significant cause of epidemic outbreaks of nonbacterial gastroenteritis worldwide. These outbreaks commonly result in significant morbidity and mortality in almost all age groups, though elderly, very young, and immunocompromized individuals are most at risk.

The vaccine in this trial is based on NoV VLPs as the antigens. Norovirus VLPs are non-infectious because they do not contain viral genomic RNA and are immunogenic because they preserve particulate antigen conformation and structure that mimic functional interactions of the virus with cellular receptors. The vaccine also contains **the single Al(OH)₃** adjuvant.

Al(OH)₃ has been shown to enhance the antigenicity and immunogenicity of vaccines. The rationale for an **Al(OH)₃** adjuvanted IM NoV VLP vaccine is based on the low immune responses previously observed in healthy adults after oral administration of Norwalk Virus VLP vaccine [9, 10, 11]. Aluminum adjuvant has a demonstrated safety profile of over 6 decades [12]. The aluminum concentration per dose was selected empirically from data that demonstrated that this amount of aluminum enhanced the antigenicity and immunogenicity of the NoV GI.1/GII.4 bivalent VLP vaccine.

Norovirus strains drift from year to year and both GI and GII genogroups cause disease in all age groups. Although numerous types are reported, the GII.4 type remains dominant and is currently responsible for the majority of outbreaks worldwide. The rationale for developing a bivalent vaccine is based on NoV epidemiology and the lack of natural protection between genogroups. In trial LV03-104, the first NoV bivalent VLP vaccine was given IM, and compared equally balanced (1:1) dosages of the GI.1 and GII.4 VLPs in adults. For each of the 4 vaccine dosages evaluated (5/5, 15/15, 50/50, and 150/150 µg of NoV VLPs), the seroresponse rates (percent of subjects with at least a 4-fold rise in antibody levels) and geometric mean fold rises (GMFRs) were lower for the GII.4 VLP than for the GI.1 VLP at equivalent antigen dosages. Likewise, similar post-vaccination immunogenicity data were observed in adults in trial LV03-105, the GII.4 challenge trial that evaluated a 50/50 µg balanced 1:1 VLP dosage of vaccine. Separately the factorial design trial NOR-107 was initiated in subjects ages 18 to 64, to evaluate multiple vaccine formulations containing different (balanced and unbalanced) ratios of the antigenic VLP components of the

bivalent vaccine (GI.1/GII.4) with Al(OH)₃ adjuvant both with and without MPL adjuvant. Prior safety and immunogenicity data for the NoV vaccine given by the IM route are available from approximately 1000 adult subjects, evaluated in five Takeda clinical trials (LV03-104, LV03-105, NOR-107, NOR-201, and NOR-210). The NoV vaccine evaluated in these trials either contained both Al(OH)₃ plus monophosphoryl lipid A (MPL) adjuvants combined or the Al(OH)₃ adjuvant alone. Trial NOR-107 conducted in adults aged 18-64 years, a Phase II dosage, adjuvant justification, safety, and immunogenicity trial, evaluated 11 vaccine formulations, and showed that the NoV VLP vaccine adjuvanted with aluminum as Al(OH)₃ adjuvant was as immunogenic as the NoV VLP vaccine adjuvanted with Al(OH)₃ and MPL combined.

This trial NOR-202 in children aged 6 weeks to less than 9 years will evaluate the safety and immunogenicity of multiple formulations with different ratios of the antigenic VLP components of the bivalent vaccine. The formulations for NOR-202 are selected based on the initial and additional results obtained from the factorial design study NOR-107 in adults. Based on the additional NOR-107 results, the number of formulation arms is reduced from 8 in amendment N° 1.0 of the original protocol to 4 in this amended protocol.

The upper age cut-off for the NOR-202 trial was selected based on the assumption that the immune response in older children and adolescents aged 9 to <18 years is similar to the immune response observed in those aged 18 years and over. Therefore subjects aged 9 to ≥18 years, are not included in trial NOR-202.

The primary goals of this clinical trial are therefore to evaluate the immunogenicity and safety of 1 to 2 doses in children 6 months to less than 9 years of age and 2 to 3 doses in infants 6 weeks to less than 6 months of age with the IM NoV bivalent VLP vaccine using different dosages of the VLPs to obtain confirmation of dosage, and schedule in these age groups. In order to maintain the trial blind, a single injection of saline placebo will be administered as the final dose for the 1 dose group in Cohort 1 and for the 2 dose group in Cohort 2.

Rationale for the Amendment N° 3:

The primary purposes of this amendment are: 1) to enroll an additional 120 children (1 to < 4 years; designated Group 2a), to assess the safety and immunogenicity of the recently manufactured NoV vaccine in a similar age group to Group 2; and 2) to perform the Day 57 interim analysis (IA) for Groups 1 and 2 of Cohort 1, who will complete Day 57 substantially earlier than Groups 2a and 3. The Day 57 IA for Groups 2a and 3 combined will be performed at a later time. The Day 140 IA for Group 4 does not change.

The trial vaccine, originally manufactured for trial NOR-202, was not available for clinical use after 30 November 2015, due to expiration at 36 months after manufacture. Several factors affected the enrolment timeline in trial NOR-202: (1) Takeda's decision to not initiate enrollment until after agreement from the Pediatric Committee of the EMA on the Pediatric Investigational Plan (PIP) of the NoV vaccine; (2) and the regulatory, logistical, and operational study requirements for implementation of the two prior protocol amendments.

Per protocol, all children in Groups 1 (4 to < 9 years) and 2 (1 to < 4 years) were enrolled, randomized and received one of the four NoV vaccine formulations as a one or two dose trial vaccine regimen within the vaccine expiry dating period. Notably, children in Groups 3 (1 or 2 doses) and 4 (2 or 3 doses) were not enrolled due to expiration of the trial vaccine. Takeda has paused this study until additional trial vaccine is manufactured and released for clinical use.

Takeda has recently produced VLPs at a different manufacturer with increased capacity for manufacturing on a larger scale. To date, the NoV vaccine with these recently produced VLPs has been manufactured and released for clinical use in two studies in adults; trial NOR-204 in 350 adults aged 18 to > 85 years and trial NOR-211 in ~ 2800 adults aged 18 to 49 years.

To understand the safety and immunogenicity of the recently manufactured vaccine in a similar age group to Group 2, an additional 120 children designated Group 2a, will be enrolled in trial NOR-202, prior to enrolling children in Groups 3 and 4. Specifically, the safety data from Group 2a will be provided to the Data Monitoring Committee (DMC) for review prior to enrollment of the children in Groups 3 and 4.

Although the VLP manufacturer has changed, the vaccine dosages and regimens with the four vaccine formulations evaluated in Groups 1 and 2 will also be evaluated in children in Groups 2a, 3, and 4. However, only children in Groups 2a, 3, and 4, will receive the recently manufactured vaccine.

Enrollment in Group 2a will be initiated after all four vaccine formulations of the recently manufactured vaccine are released for clinical use.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

The primary, secondary, and exploratory objectives of this trial are:

5.1.1 Primary Objectives

To select the optimal formulation of the NoV bivalent VLP vaccine from different dosages of VLP for further development in children:

- By assessing the seroresponse rate (percentage of subjects with ≥ 4 -fold rises) in serum anti-NoV GI.1 VLP and GII.4 VLP antibody titers by Pan immunoglobulin (Pan-Ig) enzyme-linked immunosorbent assay (ELISA).
- By assessing the safety profile of different formulations of the NoV bivalent VLP vaccine as measured by solicited local and systemic AEs for the period of 7 days after each vaccination (including the day of vaccination) and as measured by the occurrence of unsolicited AEs 28 days after each vaccination and SAEs throughout the trial.

5.1.2 Secondary Objectives

- To evaluate the geometric mean titers (GMT) and GMFRs of anti-NoV GI.1 VLP and GII.4 VLP antibody titers as measured by Pan-Ig ELISA.
- To evaluate the seroresponse rate in serum anti-NoV GI.1 VLP and/or GII.4 VLP antibody blocking titers as measured by histoblood group antigen (HBGA) binding assay.
- To evaluate Geometric Mean Blocking Titers (BT50) and GMFR of serum anti-NoV antibody titers for GI.1 VLP and/or GII.4 VLP as measured by the HBGA binding assay.
- To assess safety by the incidence of AEs leading to subject's withdrawal from the trial throughout the trial.

5.1.3 Exploratory Objectives

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Endpoints apply to Cohorts 1 and 2 unless otherwise stated. For subjects in Group 2a, the serologic assays to the vaccine VLPs for the Pan-Ig ELISA and for the HBGA binding assays will each be performed. Notably, the following endpoints will not be performed for Group 2a: Avidity, IgA ELISA, CMI for those aged ≥ 3 years, and HBGA binding assay to a panel of GI.1 and GII.4 not represented in the vaccine.

5.2.1 Primary Endpoints

Immunogenicity

- Seroresponse rate (defined as percentage of subjects with a 4-fold rise or greater) in serum anti-NoV antibody titers for both GI.1 VLP and GII.4 VLP as measured by Pan-Ig ELISA at Day 57 (Cohort 1) and Day 140 (Cohort 2).

Safety

- Percentage of subjects with solicited local AEs of injection site pain, erythema, induration, and swelling on the day of vaccination and then daily through Day 7 after each vaccination (including the day of vaccination).
- Percentage of subjects with solicited systemic AEs of headache, fatigue, myalgia, arthralgia, vomiting (number per day/intensity), and diarrhea (number per day/consistency) for children aged 4 to <9 years; and irritability/fussiness, drowsiness, loss of appetite, vomiting (number per day/intensity), and diarrhea (number per day/consistency) for children aged 6 weeks to <4 years on the day of vaccination and daily through Day 7 after each vaccination.

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- Body temperature on the day of vaccination (approximately 30 minutes and 6 hours later); then daily through Day 7 after each vaccination.
- Percentage of subjects with unsolicited AEs for 28 days after each vaccination.
- Percentage of subjects with SAEs throughout the trial.

5.2.2 Secondary Endpoints

Immunogenicity

Pan-Ig ELISA

- Seroresponse rate in serum anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- Seroresponse rate in serum anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- GMT of anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- GMT of anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- GMFR of anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- GMFR of anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA on Day 57 (Cohort 1) and Day 140 (Cohort 2).

HBGA Binding Assay

- Seroresponse rate in serum anti-NoV GI.1 VLP and GII.4 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- Seroresponse rate in serum anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- Seroresponse rate in serum anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- BT50 of anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- BT50 of anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).
- GMFR of anti-NoV GI.1 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).

- GMFR of anti-NoV GII.4 VLP antibody titers as measured by HBGA binding assay on Day 57 (Cohort 1) and Day 140 (Cohort 2).

Safety

- Percentage of subjects with any AE leading to subject's withdrawal from the trial - from the day of vaccination through Day 210 (Cohort 1) and Day 293 (Cohort 2).

5.2.3 Exploratory Endpoints

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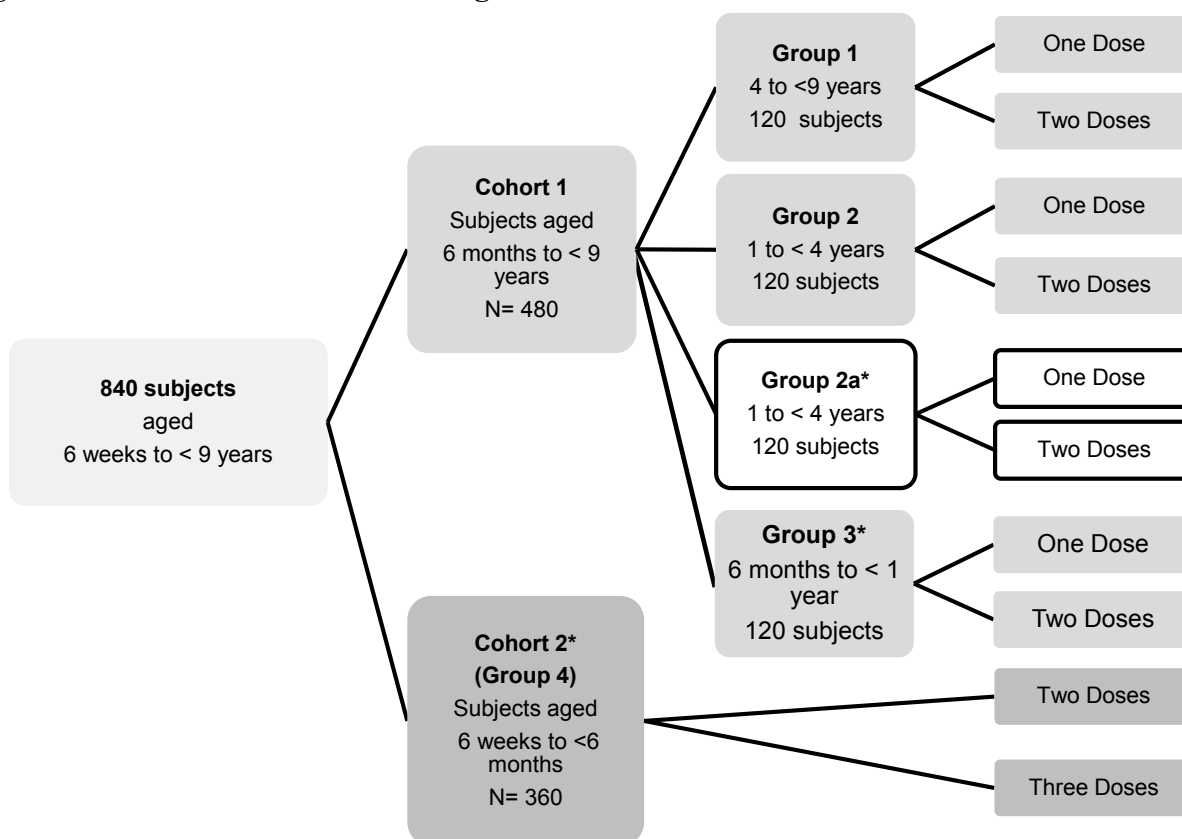
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6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a Phase II, randomized, double-blind, multi-site, dosage, safety and immunogenicity trial of the IM NoV bivalent VLP vaccine combined with Al(OH)₃ adjuvant. Subjects randomized into the trial will be placed into 1 of 2 cohorts based on age. A schematic of the trial design is included as Figure 6-a.

Figure 6-a Schematic of Trial Design



* Recently manufactured clinical trial material lots

A total of 840 healthy subjects will be enrolled within two cohorts and randomized to vaccine regimen as follows:

- Cohort 1, N= 480, consisting of Group 1: aged 4 to less than 9 years; Group 2: aged 1 to less than 4 years; Group 2a: aged 1 to less than 4 years; Group 3: aged 6 months to less than 1 year (N= 120 each): subjects will be randomized with equal probabilities to 1 of the 8 unique combinations of formulation arms and dose groups (ie, 4 formulation arms and 1 or 2 doses). The additional 120 children, designated as Group 2a, are being included to evaluate the

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recently manufactured NoV bivalent VLP vaccine formulations prior to enrolling children in Groups 3 and 4. Each of the combinations in Groups 1, 2, 2a, and 3 will consist of approximately **15** subjects per group. Thus Cohort 1 consists of 480 subjects in Groups 1, 2, 2a, and 3 combined.

- Cohort 2 (Group 4: aged 6 weeks to less than 6 months): 360 subjects will be randomized to receive the recently manufactured NoV bivalent VLP vaccine with equal probabilities to 1 of the 8 unique combinations of formulation arms and dose groups (ie, 4 formulation arms and 2 or 3 doses). Each of the combinations will consist of approximately 45 subjects.

Primary evaluation of the trial objectives is planned at 28 days after the final (second) vaccination in subjects aged 6 months to less than 9 years (Cohort 1) and 28 days after the final (third) vaccination in subjects aged 6 weeks to less than 6 months (Cohort 2). In order to maintain the blind and to have the same trial time points and dosing regimens, subjects in Cohort 1 (Groups 1, 2, 2a and 3) who are randomized to the 1 dose group will receive a dose of the NoV bivalent VLP vaccine on Day 1 followed by a placebo injection of saline 28 days later (Day 29) and subjects in the 2 dose group will receive 2 doses of NoV VLP vaccine approximately 28 days apart (Days 1 and 29). Likewise, subjects in Cohort 2 (Group 4) who are randomized to the 2 dose group will receive 2 doses of NoV bivalent VLP vaccine on Days 1 and 56, followed by a placebo injection of saline approximately 56 days later (Day 112), and subjects in the 3 dose group will receive 3 doses of NoV VLP vaccine approximately 56 days apart (Days 1, 56, and 112), independent of the infant routine vaccinations by approximately 28 days. This is a double-blind trial; investigators, subjects, data collectors, and data evaluators are blinded to the specific formulation arms and the dosing groups.

This study plans to assess the immunogenicity and safety of the NoV bivalent VLP vaccine in children when given independently of the routine pediatric vaccines but, importantly, never to interfere with routine vaccine administration of children in each of the countries planned for evaluation. National pediatric vaccine regimens in children 6 weeks to 6 months of age vary by country (eg, routine pediatric vaccines may be given at 2, 3, and 4 months of age; 2, 4, and 6 months of age; or at 3, 5, and 12 months of age).

Subjects 6 months to less than 9 years of age (inclusive, Cohort 1) will receive either 1 or 2 doses by IM injection, at least 28 days apart (Days 1 and 29), in 4 groups in 3 age ranges (Group 1: aged 4 to less than 9 years; Group 2 and Group 2a: aged 1 to less than 4 years; and Group 3: aged 6 months to less than 1 year). Infants 6 weeks to less than 6 months of age (Group 4/Cohort 2) will receive 2 or 3 doses by IM injection given approximately 56 days apart (Days 1, 56, and 112). Routine child and infant vaccinations will be given on schedule per the national guidelines approximately 28 days apart from the investigational vaccine in each age group.

An independent program level Data Monitoring Committee (DMC) has been established to assess safety data on an ongoing basis. The DMC will also have study level responsibilities to review data and make recommendations about the sequential enrollment of various groups and formulation arms in this study (see Section 11.1.1).

Interim analyses will be performed after the primary safety and immunogenicity data are available

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(ie, Day 57 for Cohort 1 and Day 140 for Cohort 2) (primary analysis time point). The Day 57 IA for Cohort 1 will be provided initially for Groups 1 and 2, who will complete Day 57 substantially earlier than Groups 2a and 3. The Day 57 IA for Groups 2a and 3 combined will be provided at a later time. Thus, the Day 57 IA will be conducted in two parts to be followed by the Day 140 IA in Group 4. All interim analyses will be performed by a separate set of unblinded statisticians and programmers at the contract research organization (CRO), Quintiles, who will have access to individual treatment assignments but will not otherwise be involved in study conduct. The rest of the personnel involved in the conduct of the study, including those at Takeda, Quintiles, and the study sites, will remain blinded to the individual subject data (including treatment assignments) until unblinding after database lock (Day 210 for Cohort 1 and Day 293 for Cohort 2). More details on the analyses will be provided in the statistical analysis plan (SAP).

Investigational Vaccine:

The investigational vaccine for each arm contains 500 µg alum.

- **Arm A:** GI.1/GII.4 (15 µg/15 µg)
- **Arm B:** GI.1/GII.4 (15 µg/50 µg)
- **Arm C:** GI.1/GII.4 (50 µg/50 µg)
- **Arm D:** GI.1/GII.4 (50 µg/150 µg)

Placebo Control:

Saline will be administered as a single control injection (as the final dose) in order to maintain the trial blind for the 1 dose groups in Groups 1, 2, 2a and 3 (Cohort 1) and for the 2 dose group in Group 4 (Cohort 2). Subjects in the 1 dose groups in Cohort 1 receive NoV vaccine on Day 1 and a saline placebo injection on Day 29. Subjects in the 2 dose group in Cohort 2 receive NoV vaccine on Days 1 and 56 and a saline placebo injection on Day 112.

Visit Schedule

Clinical trial visits will be performed on Days 1, 8, 29, 36, 57, and 210 for Cohort 1 and Days 1, 8, 29, 56, 63, 84, 112, 119, 140, and 293 for Cohort 2. Telephone contacts will be performed on Days 3, 32, and 134 for Cohort 1 and Days 3, 59, 115, 200 and 260 for Cohort 2.

Duration of the Trial

Subjects will be followed for SAEs for 180 days after the last trial dose. Safety follow-up for other unsolicited AEs, and concomitant medications will be for 28 days following each trial dose.

Schedules of procedures by cohort are listed in [Table 2-a](#) and [Table 2-c](#).

6.2 Justification for Trial Design, Dose, and Endpoints

The trial design is consistent with the evaluation of dose finding studies for vaccines. The formulations for NOR-202 are selected based on the initial and additional results obtained from the factorial design study NOR-107 in adults. Based on additional NOR-107 results, the number of

formulation arms has been further reduced from 8 in Amendment 1 of the protocol to 4 in this amended protocol. **The** descriptive design of trial NOR-202 in early childhood is justified to initially define the dose and dosing regimen for young children at high risk of norovirus disease. An additional group designated Group 2a of 120 children aged 1 to less than 4 years, has been added within Cohort 1, to allow evaluation of the recently manufactured vaccine prior to dosing younger children in Groups 3 and 4. Safety in Group 2a will be reviewed by the DMC, prior to enrolling in Groups 3 and 4. Immunogenicity will be reviewed as available.

The collection of solicited symptoms and AEs following vaccination are consistent with vaccine evaluation studies.

For this trial, the collection of blood at the given time points, the selection of assays for the assessment of antibody response to vaccination and the selected formulations are based on experience from previous studies with the investigational vaccine and will assist in the determination of the antigen dosage, the need for multiple doses of investigational vaccine in the non-adjuvanted arms, and dosage of adjuvant if needed.

Please refer to the Investigator's Brochure [31] for further details.

A single saline placebo injection will be administered as a placebo control (as a final dose on Day 29) in order to maintain the trial blind in subjects in the 1 dose groups in Groups 1, 2, 2a and 3, (Cohort 1) and in the 2 dose group in Group 4 (as a final dose on Day 112 in Cohort 2).

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

Expected duration of trial participation for each subject is up to 210 days (Cohort 1) and 293 days (Cohort 2).

6.4 Premature Termination or Suspension of Trial or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Trial

The trial will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the trial.

- New information or other evaluation regarding the safety or efficacy of the investigational vaccine that indicates a change in the known risk/benefit profile, such that the risk/benefit is no longer acceptable for subjects participating in the trial.
- The DMC recommends that the trial should be suspended or terminated.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary trial objectives or compromises subject safety.

6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or trial suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. Male and female subjects aged between 6 weeks and less than 9 years at the time of enrollment.
2. Subjects who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator.
3. The subject's legally authorized representative (LAR) signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements ([Appendix C](#)). An assent will also be obtained according to age appropriate country-specific regulations.
4. Individuals who can comply with trial procedures and are available for the duration of the trial.

7.2 Exclusion Criteria

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

1. Subjects with a clinically significant active infection (as assessed by the investigator) or body temperature 38.0°C (100.4°F) or higher within 3 days of the intended date of vaccination.
2. Subjects who have received antipyretic/analgesic medications within 24 hours prior to the intended vaccine administration.
3. Known hypersensitivity or allergy to investigational vaccine (including excipients of the investigational vaccines as summarized in protocol Section [8.1](#)).
4. Subjects with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the subject's ability to participate in the trial.
5. Subjects with a history of any progressive or severe neurologic disorder, seizure disorder, or neuroinflammatory disease (eg, Guillain-Barré syndrome).
6. Known or suspected impairment/alteration of immune function, including the following:
 - a. Children <18 months of age with history of repeated episodes of acute otitis media (AOM) [[32](#)] in the first 6 months of life (AOM defined as a bulging tympanic membrane) and not to be confused with otitis media with effusion (OME).

- b. Chronic use of oral steroids (equivalent to 20 mg/day prednisone for ≥ 12 weeks/ ≥ 2 mg/kg body weight/day for ≥ 2 weeks) within 60 days prior to Day 1 (use of inhaled, intranasal, or topical corticosteroids is allowed).
 - c. Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥ 12 weeks/ ≥ 2 mg/kg body weight/day for ≥ 2 weeks) within 60 days prior to Day 1.
 - d. Receipt of immunostimulants within 60 days prior to Day 1.
 - e. Receipt of parenteral, epidural, or intra-articular immunoglobulin preparation, blood products, and/or plasma derivatives within 3 months prior to Day 1 or planned during the full length of the trial.
 - f. Receipt of immunosuppressive therapy within 6 months prior to Day 1.
 - g. Human immunodeficiency virus (HIV) infection or HIV-related disease.
 - h. Chronic Hepatitis B or C infection.
 - i. Heritable immunodeficiency.
- 7. Abnormalities of splenic or thymic function.
 - 8. Subjects with a known bleeding diathesis or any condition that may be associated with a prolonged bleeding time.
 - 9. Subjects with any serious chronic or progressive disease according to judgment of the investigator (eg, neoplasm, insulin dependent diabetes, cardiac, renal, or hepatic disease).
 - 10. Subjects participating in any clinical trial with another investigational product 30 days prior to first trial visit or intent to participate in another clinical trial at any time during the conduct of this trial.
 - 11. Subjects who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial.
 - 12. Subjects who are first degree relatives of individuals involved in trial conduct.
 - 13. Subjects with a history of autoimmune disease.
 - 14. There may be instances when individuals meet all entry criteria except one that relates to transient clinical circumstances (eg, body temperature elevation or recent use of excluded medication or vaccine). Under these circumstances, a subject may be considered eligible for trial enrollment if the appropriate window for delay has passed, inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

7.3 Criteria for Delay of Vaccination and Blood Sampling

After enrollment, subjects may encounter clinical circumstances that warrant a delay in subsequent trial vaccination. These situations are listed below:

- Subjects with a body temperature 38.0°C (100.4°F) or higher within 3 days of intended trial vaccination.
- Subjects who have received antipyretics/analgesic medications within 24 hours prior to the intended vaccine administration.
- Subjects who have received blood, blood products, and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 3 months (prior to initial vaccination).

If the subject cannot be randomized and vaccinated on Day 1 due to a temporary contraindication and must return at a later time, the same identification number (screening number) should be kept. If the subject randomization visit is re-scheduled for more than 15 days after the screening, then a new ICF should be obtained.

For subsequent vaccination visits, it is strongly recommended to schedule them as early in the visit window as possible, in case these visits need to be re-scheduled due to a vaccination and/or blood sampling temporary contraindication.

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

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the trial should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.9.

1. Protocol violation: The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety, or rights.
2. Adverse event: The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject (or subject's LAR) is unwilling to continue because of the AE. For safety reasons, the subject should be followed-up after withdrawal.
3. Lost to follow-up: The subject did not return to the clinic and attempts to contact the subject's LAR were unsuccessful.
4. Withdrawal by subject: The subject (or subject's LAR) wishes to withdraw from the trial. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

5. Study terminated by sponsor.
6. Other.

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Note: The specific reasons should be recorded in the “specify” field of the eCRF.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may terminate a subject’s trial participation at any time during the trial when the subject meets the trial termination criteria described in Section 7.4. In addition, a subject (or subject’s LAR) may discontinue his or her participation without giving a reason at any time during the trial. Should a subject’s participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures scheduled for the final visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Investigational Vaccine(s) and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

This trial will involve the use of the following vaccines for IM administration. Althea Technologies, San Diego (CA), United States, manufactures the investigational vaccine.

8.1.1.1 Sponsor-Supplied Vaccines

All vaccines described in this protocol will be supplied by the sponsor. The prefilled vials will be supplied in tamper-evident, single dose cartons. Some kits may also contain diluent vial(s). Each vial and carton will contain a label that includes pertinent trial information and caution statements. The label text will either be in English or the specific country language, depending on local requirements. The vaccine to be used will be identifiable by a unique identification number and managed by the interactive web response system (IWRS).

• Investigational Vaccines

The investigational vaccine is presented in a labeled, single-use, 2 mL glass vial with a FluroTec-coated butyl rubber stopper and flip-top aluminum overseal that contains a single 0.5 mL liquid dose for IM injection. Each vial contains additional volume (fill specification, 0.9 ± 0.05 mL) to facilitate withdrawal of 0.5 mL. Each 0.5 mL dose delivers either 15 or 50 μ g of GI.1 NV-VLP; 15, 50, or 150 μ g of GII.4 C-VLP; all of which are adsorbed to $\text{Al}(\text{OH})_3$ adjuvant. The doses should be prepared at the time of administration by the unblinded administrator (or pharmacist). Before mixing, the vial contents may appear biphasic with a clear upper layer and a white precipitate on the bottom of the vial. After the vial contents have been mixed, a uniformly turbid suspension should be observed.

The investigational vaccine also contains the following excipients (per 0.5 mL dose): approximately 4.38 mg sodium chloride (150 mM), approximately 1.55 mg L-histidine (20 mM), HCl to adjust pH, 1.83 mg sucrose and water for injection. The investigational vaccine does not contain a preservative. Investigational vaccine for each of the trial arms (A, B, C and D) contains 500 μ g $\text{Al}(\text{OH})_3$ adjuvant.

- **Investigational vaccine for Arm A:** GI.1/GII.4 (15 μ g/15 μ g)
- **Investigational vaccine for Arm B:** GI.1/GII.4 (15 μ g/50 μ g)
- **Investigational vaccine for Arm C:** GI.1/GII.4 (50 μ g/50 μ g)
- **Investigational vaccine for Arm D:** GI.1/GII.4 (50 μ g/150 μ g)
- **Placebo Control:** Saline (0.9% sodium chloride for injection, USP); 0.5 mL dose; administered in same manner as investigational vaccine (Section 8.2).

8.1.2 Storage

Vaccines will be shipped in refrigerated containers. From receipt and prior to use, vaccines must be protected from light and stored at 2°C to 8°C in a refrigerator with controlled access available only to authorized trial personnel. The vaccines must not be frozen. Vaccines are single use only.

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. All sponsor-supplied vaccines must be stored under the conditions specified on the label, and remain in the original container until administered. A daily temperature log of the vaccine storage area must be maintained every working day.

Temperature deviations must be reported to the sponsor; see the Pharmacy Manual for instructions.

8.1.3 Dose and Regimen

The formulations for the sponsor-supplied investigational vaccine are presented in [Table 8-a](#).

Presented formulations are an approximation (within a defined specification) of the respective antigen/adjuvant concentrations. The number of subjects in each dose group will be equally distributed across the formulation arms.

Table 8-a Sponsor-Supplied Investigational Vaccine

	VLP 15 µg/15 µg	VLP 15 µg/50 µg	VLP 50 µg/50 µg	VLP 50 µg/150 µg
GI.1/GII.4 [and 500 µg of Al(OH) ₃]	Arm A	Arm B	Arm C	Arm D

8.2 Investigational Vaccine Assignment and Dispensing Procedures

The investigator or investigator's designee will access the IWRS on Day 1 to obtain the subject number.

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

The vaccine identification number of the kit to be administered will be assigned by the IWRS.

The vaccines will be administered IM in the anterolateral thigh for children aged ≤12 months; for children aged >12 months, the vaccines will be administered in the anterolateral thigh or the deltoid muscle of the subject's arm per national guidelines. Expired vaccines must not be administered. The vaccine and placebo are visually distinguishable and the blind must be maintained. The vaccination will be prepared and administered by the unblinded designee according to the instructions in the Pharmacy Manual. Cohort 1 will receive either 1 or 2 doses at least 28 days apart and Cohort 2 will receive 2 or 3 doses approximately 56 days apart. In order to

maintain the blind and to have the same trial time points and dosing regimens, subjects in Cohort 1 (Groups 1, 2, 2a and 3) who are randomized to the 1 dose group will receive a dose of the NoV bivalent VLP vaccine on Day 1 followed by a placebo injection of saline 28 days later (Day 29). Subjects in the 2 dose group will receive 2 doses of NoV VLP vaccine approximately 28 days apart (Days 1 and 29). Likewise, subjects in Cohort 2 (Group 4) who are randomized to the 2 dose group will receive 2 doses of NoV bivalent VLP vaccine on Days 1 and 56, followed by a placebo injection of saline 56 days later (Day 112), and subjects in the 3 dose group will receive 3 doses of NoV VLP vaccine approximately 56 days apart (Days 1, 56, and 112), independent of the infant routine vaccinations by at least 28 days.

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

If sponsor-supplied vaccine is lost or damaged, the site can request a replacement from the IWRS (refer to IWRS manual supplied separately). At subsequent vaccine-dispensing visits, the investigator or designee will again contact the IWRS to request additional investigational vaccine for a subject.

8.2.1 Precautions to be Observed in Administering the Investigational Vaccine

Prior to vaccination, subjects must be determined to be eligible for trial vaccination, and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first vaccine administration is determined by evaluating the entry criteria outlined in this protocol (Sections 7.1 and 7.2).

Eligibility for subsequent trial vaccination is determined by following the criteria outlined in Sections 7.1, 7.2, and 7.3.

Investigational vaccines should not be administered to subjects with known hypersensitivity to any component of the vaccines.

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

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

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. Randomization information will be stored in a secured area, accessible only by authorized personnel.

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Randomization will be stratified by country and group: Group 1 (age 4 to less than 9 years); Groups 2 and 2a (age 1 to less than 4 years); Group 3 (age 6 months to less than 12 months); and Group 4 (age 6 weeks to less than 6 months). On Day 1, qualified subjects will be randomized using the IWRS to a formulation arm and number of doses depending on their age at the time of enrollment.

Randomization into groups and formulation arms will be restricted during various stages of the study as described previously in the protocol (section 6.1) based on DMC review of data from certain groups/arms prior to opening enrollment to other groups (see Section 11.1.1).

8.4 Investigational Vaccine Blind Maintenance

This is a double-blind trial; investigators, subjects, data collectors (eg, investigator), and data evaluators (eg, trial statisticians) are blinded to the specific formulation arm (ie, GI.1/GII.4 VLP). The investigational vaccine blind will be maintained by the unblinded designee.

8.5 Unblinding Procedure

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

For unblinding a subject, the investigational vaccine blind can be obtained by the investigator by accessing the IWRS.

The sponsor's Pharmacovigilance Department and their designee must be notified as soon as possible if the investigational vaccine blind is broken by the investigator for the purposes of a medical emergency, and if appropriate a completed SAE form must be sent within 24 hours. The date, time, and reason the blind was broken must be recorded in the source document and the same information (except the time) must be recorded on the eCRF.

In the event of accidental unblinding of the investigational vaccine, the sponsor shall be immediately contacted for further decision about the subject's eligibility to continue in the trial. Regardless of the sponsor's decision, the subject should be followed for safety through Day 210 (Cohort 1) or Day 293 (Cohort 2).

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

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

The investigator or designee must ensure that the sponsor-supplied vaccine is used in accordance with the approved protocol and is administered only to subjects randomized into the trial. To document appropriate use of sponsor-supplied vaccine, the investigator must maintain records of

all sponsor-supplied vaccine delivery to the site, site inventory, dispensation, and use by each subject, and return to the sponsor or designee as noted below.

Upon receipt of sponsor-supplied vaccine, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the medication is received within the labeled storage conditions, and the medication is in good condition. If the quantity and conditions are acceptable, the investigator or designee will acknowledge receipt of the shipment by recording it in the IWRS.

If there are any discrepancies between the packing list and the actual product received, the sponsor must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

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

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

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

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

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

Prior to site closure or at appropriate intervals throughout the trial, before any clinical trial materials are returned to the sponsor or its designee for destruction, a representative from the sponsor or its designee will perform clinical trial material accountability and reconciliation. The investigator will retain a copy of the documentation regarding clinical trial material accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

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

9.0 TRIAL PLAN

9.1 Trial Procedures

The following sections describe the trial procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Trial Procedures is located in Section 2.1.

9.1.1 Informed Consent Procedure

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

Informed consent must be obtained prior to the subject entering into the trial, and before any protocol-directed procedures are performed. An assent will also be obtained according to age appropriate country-specific regulations.

After informed consent is obtained, a unique identification number (screening number) will be assigned to each subject by the IWRS. If all eligibility criteria are fulfilled, this will become the definitive subject number to be used throughout the trial. Subject numbers assigned to subjects who fail screening should not be reused (Section 9.1.9).

9.1.2 Demographics, Medical History and Medication History Procedure

Demographic information to be obtained will include age, sex, race as described by the subject or subject's legal guardian.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for trial participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during trial participation, if it represents an exacerbation of an underlying disease/pre-existing problem. Adverse medical occurrences that occur after the ICF and assent form (where applicable) have been signed, but before administration of the vaccine, will be documented in the Medical History eCRF.

All prescription medications, vaccines and blood products taken or received by the subjects within 3 months prior to the start of the trial are to be recorded on the Prior and Concomitant Medications eCRF. The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source documents or the eCRF. Trial vaccination should be delayed if subjects have used antipyretics/analgesic medications within 24 hours prior to vaccine administration.

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

Assess and record concomitant therapy (prescription medications ONLY) and vaccine history from 3 months prior to Day 1 in the subject's source document.

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Prohibited Therapies (see also Section 7.2):

- Parenteral immunoglobulin preparation, blood products, and/or plasma derivatives administered within 3 months of the first vaccination.
- Immunosuppressive therapy within 6 months or systemic (eg, oral or parenteral) corticosteroid treatment within 60 days prior to vaccine administration or planned during the trial period.
- Administration of other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial.

These data must be written in the source documents.

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

9.1.3 Documentation of Trial Entrance/Randomization

Only subjects whose legal representative(s) have signed the ICF and, where required, have signed assent, meet all of the inclusion criteria and none of the exclusion criteria are eligible for enrollment/randomization into the vaccination phase. The list of randomization assignments is produced by IWRS.

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

9.1.4 Physical Examination Procedure

Physical examinations must be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Site Responsibility Delegation Log. A complete physical exam will be performed on Day 1. A detailed physical examination includes, but is not limited to: auscultation of heart and lungs, palpation of the abdomen, inspection of extremities (including skin over intended vaccination sites), and a check of general appearance. Additional physical examination procedures may be performed if indicated by review of the subject's medical history. The findings will be documented in the subject's source document.

Physical examinations (type) will be performed at clinic visits on Day 1 (complete) and Day 29 (brief) for Cohort 1 and Day 1 (complete), Day 56 (brief), and Day 112 (brief) for Cohort 2. Subjects may undergo a brief symptom-directed physical examination at any other clinic visit.

9.1.5 Vital Signs

During the physical examination, a subject should have their vital signs measured. These may include heart rate, body temperature, height, and weight. Refer to the Procedures Manual.

9.1.6 Immunogenicity Assessments

Subjects in Cohort 1 in all vaccine arms will undergo blood sampling for serological immunogenicity testing on Day 1 (prior to the first vaccination), Day 29 (prior to the second vaccination), Day 57 (28 days after the second vaccination), and Day 210; Subjects in Cohort 2 will undergo blood sampling for serological testing on Day 1 (prior to the first vaccination), Day 56 (prior to the second vaccination), Day 84 (28 days after the second and 28 days prior to the third vaccination), Day 140 (28 days after the third vaccination), and Day 293. To alleviate the pain associated with blood sampling in this pediatric population, blood collection will be performed by experienced, trained personnel who routinely obtain blood from infants and children, under the supervision of the Principal Investigator after optional application of EMLA cream/patch and using pediatric size needles. All blood samples will be collected in accordance with acceptable laboratory procedures. For serology in all subjects, the volume of blood taken at any single visit is approximately 2 mL. For subjects (without CMI testing), the approximate total volume of blood in the trial is 8 mL for Cohort 1 subjects in Groups 1, 2, 2a, and 3 (4 blood draws) and 10 mL for Cohort 2 subjects in Group 4 (5 blood draws). For those subjects with CMI, a subset of the subjects aged ≥ 3 years at selected sites in Groups 1 and 2 only, an additional volume of 3 mL of blood at each of three time points will be drawn immediately prior to and approximately 28 days after each vaccination (Days 1, 29, and 57) for a subtotal of approximately 9 mL. To clarify, for those children aged 3 years and older selected to be in the CMI subset in Groups 1 and 2 only, a total of 17 mL per subject will be obtained for the entire study period. Because subjects in Group 2a will not participate in CMI testing, the total volume of blood for Group 2a subjects is 8 mL. Likewise, the total volume of blood for Group 3 subjects remains at 8 mL. To clarify, for the youngest infants, those in Cohort 2 (Group 4), a total of 10 mL per subject will be obtained for the entire study period. All blood samples will be processed and stored at the trial site according to the Laboratory Guidelines as provided in the Procedures Manual.

9.1.7 Safety Assessments

The occurrence of selected indicators of reactogenicity (listed below), which by definition can occur only up to 7 days after vaccination (including the day of vaccination), will be collected during site visits or remotely via diary cards and will be recorded on the “Local and Systemic Reactions” eCRF as applicable. These will be summarized in the final report under the category “solicited AEs” to differentiate them from other AEs that were unsolicited. Any solicited local or systemic AE observed as continuing on the 8th day after the last administered vaccination (including day of vaccination) will be recorded as an AE on the Adverse Event eCRF.

Local AEs (injection site):

- Pain.
- Erythema.
- Induration.
- Swelling.

- Erythema, induration, and swelling will be measured with a millimeter ruler provided to each parent at screening visit.

Systemic AEs (children aged 4 to <9 years):

- Headache.
- Fatigue.
- Myalgia.
- Arthralgia.
- Vomiting.
- Diarrhea.

Systemic AEs (children aged 6 weeks to <4 years):

- Irritability/fussiness.
- Drowsiness.
- Loss of appetite.
- Vomiting.
- Diarrhea (number of loose/liquid stools per day and consistency).

Other indicators of reactogenicity:

- Body temperature.

SAEs will be collected through Day 210 (Cohort 1) or Day 293 (Cohort 2). Any unsolicited AEs will be collected for 28 days following each study dose. AEs leading to subject's withdrawal will be collected from Day 1 through Day 210 (Cohort 1) or Day 293 (Cohort 2).

Solicited Safety Parameters

Safety parameters will be collected during site visits or remotely via diary cards. The grading scale for children 4 to < 9 years of age and older is shown in [Table 9-a](#); the grading scale for children younger than 6 weeks to < 4 years is shown in [Table 9-b](#).

Table 9-a Solicited Safety Parameters in Children Aged 4 to <9 Years

Adverse Event	Intensity grade	Severity/Intensity
Pain at injection site	0	None
	1	Mild: Does not interfere with play and daily activities
	2	Moderate: Interferes with play and daily activities with or without treatment
	3	Severe: Prevents daily activities with or without treatment
Erythema at injection site ^(a)	0	<25 mm
	1	Mild: 25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Swelling at injection site ^(a)	0	<25 mm
	1	Mild: 25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Induration at injection site ^(a)	0	<25 mm
	1	Mild: 25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Body temperature*	Record temperature in °C/°F	
Headache	0	No headache
	1	Mild: No interference with activity
	2	Moderate: Some interference with activity with or without treatment
	3	Severe: Prevents daily activity with or without treatment
Fatigue	0	None
	1	Mild: No interference with activity
	2	Moderate: Some interference with activity
	3	Severe: Significant; prevents daily activity
Muscle aches/ Myalgia	0	None
	1	Mild: No interference with activity
	2	Moderate: Some interference with activity
	3	Severe: Significant; prevents daily activity
Joint aches/ Arthralgia	0	None
	1	Mild: No interference with activity
	2	Moderate: Some interference with activity
	3	Severe: Significant; prevents daily activity
Vomiting	0	None
	1	Mild: No interference with activity
	2	Moderate: Some interference with activity
	3	Severe: Prevents daily activity
Diarrhea	0	None
	1	Mild: No interference with activity
	2	Moderate: Some interference with activity
	3	Severe: Prevents daily activity

* = Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method used [33]. Body temperature will be collected and recorded, preferably using the same method throughout the trial for a subject. The site staff will record the actual temperature route taken on the CRF. Note that identification of fever, as a solicited AE will be accomplished in the study database, based on actual temperature measurements. (a) Record greatest surface diameter in mm in the Diary.

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Table 9-b Solicited Safety Parameters in Children Aged 6 Weeks to <4 Years)

Adverse Event	Intensity grade	Severity/Intensity
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Erythema at injection site ^(a)	0	<10 mm
	1	Mild: >10 – ≤ 20 mm
	2	Moderate: > 20 – ≤ 40 mm
	3	Severe: > 40 mm
Swelling at injection site ^(a)	0	<10 mm
	1	Mild: >10 – ≤ 20 mm
	2	Moderate: > 20 – ≤ 40 mm
	3	Severe: > 40 mm
Induration at injection site ^(a)	0	<10 mm
	1	Mild: >10 – ≤ 20 mm
	2	Moderate: > 20 – ≤ 40 mm
	3	Severe: > 40 mm
Body temperature*	Record temperature in °C/°F	
Irritability/Fussiness	0	Behaviour as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behaviour as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all
Vomiting	0	None
	1	Mild: No interference with activity or 1 – 2 episodes/24 hours
	2	Moderate: Some interference with activity or >2 episodes/24 hours
	3	Severe: Prevents daily activity, requires outpatient intravenous (IV) hydration
Diarrhea	0	None
	1	Mild: 2 – 3 loose stools/24 hours
	2	Moderate: 4 – 5 loose stools/24 hours
	3	Severe: ≥6 watery stools/24 hours or requires outpatient IV hydration

* = Fever is defined as greater than or equal to 38.0°C (100.4°F) regardless of method taken [33]. Body temperature will be collected and recorded, preferably using the same method throughout the trial for a subject. The site staff will record the actual temperature route taken on the CRF. Note that identification of fever, as a solicited AE will be accomplished in the study database, based on actual temperature measurements. (a) Record greatest surface diameter in mm in the Diary.

9.1.8 Processing, Labeling and Storage of Peripheral Blood Mononuclear Cell Samples

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9.1.9 Documentation of Subjects who are not Randomized

Investigators must account for all subjects whose LAR signs an informed consent. If the subject is found to be not eligible, the investigator should complete the eCRF. The IWRS should be contacted as a notification of non-randomization.

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

- Adverse event.
- Screen failure (did not meet inclusion criteria or did meet exclusion criteria).
- Withdrawal by subject.
- Study terminated by sponsor.
- Other (the specific reasons should be recorded in the “specify” field of the eCRF).

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

9.2 Monitoring Subject Treatment Compliance

The investigator records all injections of investigational vaccine given to the subject in the eCRF.

9.3 Schedule of Observations and Procedures

The schedule for all trial-related procedures for all evaluations is shown in Section 2.1. Assessments should be completed at the designated visit/time point(s).

9.3.1 Pre-vaccination Procedures (Day 1 and Day 29 [Cohort 1] and Day 1, Day 56, and Day 112 [Cohort 2])

a. Informed consent (refer to Section 9.1.1 for details) – on Day 1 only.

Demographics: refer to Section 9.1.2 for details – on Day 1 only.

- a. Prior and concomitant medication (refer to Section 9.1.2 for details).
- b. Medical history: refer to Section 9.1.2 for details.

Review of organ systems: Review of organ systems is a structured interview that queries the subject or the subject's LAR as to any complaints the subject has experienced across each organ system.

"General" physical examination and body temperature: refer to Section 9.1.4 for details.

Vital signs: refer to Section 9.1.5 for details.

Review of eligibility criteria: refer to Sections 7.1 and 7.2 for details.

Enrollment: refer to Section 9.1.1 – Day 1 only.

Randomization: refer to Section 9.1.3 – Day 1 only

Blood sampling: Prior to administering the trial vaccination, blood will be drawn from all subjects for serologic immunogenicity testing and from the subset of subjects selected for the CMI testing (children aged ≥ 3 years at selected sites). Details regarding the volume of blood and testing to be performed are specified in Sections 9.1.6 and 9.1.8.

9.3.2 Vaccination Procedures (Day 1 and Day 29 [Cohort 1] and Day 1, Day 56, and Day 112 [Cohort 2])

After confirming eligibility (and enrolling the subject on Day 1), vaccination will be performed according to the assigned investigational vaccine and according to the procedures described in Section 8.2. At later clinic visits that involve vaccination (Day 29 [Cohort 1] and Day 56 and Day 112 [Cohort 2]), it will be confirmed that the subject does not meet any criteria for delaying or cancelling additional trial vaccination, as described in Section 7.3.

9.3.3 Post-vaccination Procedures (Day 1 and Day 29 [Cohort 1] and Day 1, Day 56, and Day 112 [Cohort 2])

The following post-vaccination procedures will be performed on Day 1 and Day 29 (Cohort 1), and Day 1, Day 56, and Day 112 (Cohort 2).

- Careful training of the subject's LAR on how to measure local AEs and body temperature, how to complete the diary card, and how often to complete the diary card. Training should be directed at the individual(s) who will perform the measurements of local AEs and those who will enter the information into the diary card. This individual may or may not be the subject's LAR, but if a person other than the subject's LAR enters information into the diary card, this person's identity must be documented in the trial file and this person must receive training on the diary card. Training of the subject's LAR on how to measure an injection site reaction should be performed while the subject is under observation after vaccination.

Diary card instructions must include the following:

- The subject's LAR must understand that timely completion of the diary card on a daily basis is a critical component of trial participation. The subject's LAR should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card that are

performed by the person completing the diary card should include a single strikethrough line with a brief explanation for any change and be initialed and dated.

Please note:

Diary cards will be the only source document allowed for remote collection of solicited local and systemic AEs (including body temperature measurements). The following additional rules apply to the documentation of safety information collected by diary card:

- The Diary Card should be reviewed with the subject's LAR.
- No corrections or additions to the diary card will be allowed after it is reviewed with the investigator/designee.
- Any data that is identified as implausible or incorrect, and confirmed by the subject's LAR to be a transcription error should be corrected by the subject's LAR on the diary card (the correction should include a single strikethrough line and should be initialed and dated by the subject's LAR).
- Any blank or illegible fields on the diary card not otherwise corrected as above will be missing in the eCRF.
- The site must enter all readable entries on the diary card into the eCRF.
- Any newly described solicited safety information should be added to the diary card by the subject's LAR or by the person who is authorized by the subject's LAR to complete the diary, then initialed and dated. Any new unsolicited safety information such as a verbally reported event, should also be recorded in the subject medical chart (as recorded on the diary card/source document) and captured as an AE and recorded in the AE eCRF.
- Starting on the day of vaccination, the subject's LAR will check for specific types of events at the injection site (solicited local AEs), any specific generalized symptoms (solicited systemic AEs), body temperature (any method), any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals). These solicited AEs and body temperature will be recorded in the diary. Assessments should preferably take place in the evening at day's end.
- Temperature measurement is to be performed using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject's LAR should check their temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the diary card.
- The measurement of solicited local AEs (erythema, swelling, and induration) is to be performed using the ruler provided by the site.
- The collection on the diary card of body temperature, solicited local AEs, and solicited systemic AEs will continue for a total of 7 days following vaccine administration. The collection on the diary card of unsolicited AEs and medications will continue for 28 days following vaccine administration.

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After vaccination, the subject will be observed for at least 30 minutes, including observation for unsolicited AEs, solicited AEs, and body temperature measurement. The investigator or delegate will take the opportunity to remind the subject's LAR how to measure solicited reactions and body temperature as part of this observation period. All safety data will be collected in the subject's source documents.

The site should schedule the post-vaccination reminder calls (Days 3, and 32 for Cohort 1, and Days 3, 59, and 115 for Cohort 2).

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

9.3.4 Clinic Visits after Vaccination

Clinic visits that do NOT include a vaccination will be performed on Day 8, Day 36, Day 57, and Day 210 (Cohort 1) and Day 8, Day 29, Day 63, Day 84, Day 119, Day 140, and Day 293 (Cohort 2).

At each visit a brief symptom-directed physical assessment may be performed, including (but not limited to) the measurement of vital signs. Corresponding information will be documented in the source documents and eCRFs.

Blood should be taken from the subject using an aseptic venipuncture technique for serological immunogenicity testing as described in Sections 9.1.6 and 9.1.8. Refer to the detailed collection and handling procedures outlined in the Procedures Manual.

The site should schedule the next trial activity clinic visit with the subject's LAR.

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

9.3.5 Phone Contacts – Safety Data Collection (Day 134 [Cohort 1] and Days 200 and 260 [Cohort 2])

Safety calls will be performed on Day 134 for subjects in Cohort 1 and on Days 200 and 260 for subjects in Cohort 2. Safety calls are calls made to the subject by a trained healthcare provider. These calls will follow a script which will facilitate the collection of relevant safety information. The subject's LAR will be interviewed according to the script, and information relating to SAEs, and concomitant medications or vaccinations associated with those events must be written down. All safety information described by the subject must be written down in a designated location within the source documents and not written on the script used for the telephone call. The site should schedule the next safety call or clinic visit with the subject's LAR. The subject or the

subject's LAR will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

9.3.6 Phone Contacts - Reminder Calls (Day 3 and Day 32 [Cohort 1] and Day 3, Day 59, and Day 115 [Cohort 2])

Post-vaccination reminder phone calls will be performed on Day 3 and Day 32 (Cohort 1) and on Day 3, Day 59, and Day 115 (Cohort 2). The purpose is to remind the subject or the subject's LAR about completion of the diary card. It is a conversation that follows the reminder telephone call script provided to the site (refer to the Procedures Manual), and it is not intended to be a call for collection of safety data. If the subject or the subject's LAR wishes to describe safety information, this information should only be collected by a trained healthcare professional at the site, and the safety data described must be written down in source documents. The subject or the subject's LAR should be reminded to write the information down in the diary card and to contact the site via the telephone number provided in the informed consent to discuss medical questions.

9.3.7 Final Visit

The final visit will be performed on Day 210 for Cohort 1, and Day 293 for Cohort 2. If a subject terminates earlier, standard visit procedures should be performed if possible (ie, Day 210 procedures for Cohort 1, and Day 293 for Cohort 2). For all subjects receiving an investigational vaccine, the investigator must complete the End-of-Trial eCRF page.

After trial exit and outside the context of this trial, a licensed benefit vaccine may be offered to all enrolled subjects. The choice of this vaccine will be discussed between the sponsor and the investigator, and will need to be approved by the appropriate ethics committee. This licensed benefit vaccine would only be administered according to the labelling approved in the country.

9.3.8 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 Sections [9.1.6](#) and [9.1.8](#). After blood draw and serum processing, the serum samples will be preserved and retained at a central laboratory that was contracted by the sponsor for this purpose for up to but not longer than 20 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

10.0 AEs

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a vaccine. Adverse medical occurrences that occur after the ICF and assent form (where applicable) have been signed but before administration of the vaccine are documented in the Medical History. An AE does not necessarily have a causal relationship with investigational vaccine administration.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease whether or not it is considered related to the investigational vaccine.

AEs will be graded by the investigator using the following categorical descriptors:

Mild (Grade 1)	Awareness of symptoms that are easily tolerated, cause minimal discomfort, and do not interfere with everyday activities.
Moderate (Grade 2)	Sufficient discomfort is present to cause interference with normal activity.
Severe (Grade 3)	Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

Relatedness to vaccine will also be assessed by the investigator. SAEs will be reported to the sponsor within 24 hours of the investigator becoming aware of the event.

Please note: any solicited AE that meets any of the following criteria must also be entered as an AE on the Adverse Event eCRF.

- Solicited local or systemic AEs that lead the subject to withdraw from the trial.
- Solicited local or systemic AEs lasting beyond 7 days after vaccination (including day of vaccination).
- Solicited local and systemic AEs that lead to the subject being withdrawn from the trial by the investigator.
- Solicited local and systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.5).

10.1.2 Causality of AEs

Relatedness to vaccine will also be assessed by the investigator. The relationship of each AE to investigational vaccine(s) will be assessed using the following categories:

- Related: An AE that follows a reasonable temporal sequence from administration of an investigational vaccine, and for which reasonable possible involvement of the investigational vaccine can be argued, although factors other than the investigational vaccine, such as underlying diseases, complications and concomitant drugs, may also be responsible.
- Not Related: An AE that does not follow a reasonable temporal sequence from administration of an investigational vaccine and/or that can reasonably be explained by other factors, such as underlying diseases, complications, and concomitant drugs.

10.1.3 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.”

10.1.4 Additional Points to Consider for AEs

An untoward occurrence generally may:

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

Diagnoses versus signs and symptoms:

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

Worsening of AEs:

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

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Changes in severity of AEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs (but will be recorded in the subject's medical history). 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.

Follow Up:

- All AEs will be monitored until resolution or a stable status is reached or until a formal diagnosis can be made. AEs will not be monitored beyond Day 210(Cohort 1) or Day 293 (Cohort 2), unless deemed necessary by the sponsor.

10.1.5 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

a. Results in DEATH.

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.

Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.

Results in persistent or significant DISABILITY/INCAPACITY.

Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:

- May require intervention to prevent items 1 through 4 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 Procedures

10.2.1 Collection and Reporting of AEs

Please refer to Section [10.2.2](#) for Collection and Reporting of SAEs.

10.2.1.1 AE Reporting

All subjects experiencing AEs within 28 days of each study dose, whether considered causally related with the use of the investigational vaccine or not, must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an Adverse Event eCRF and on the SAE form, if applicable (see Section 10.2.2), which is part of the Investigator Site File. All findings in subjects experiencing AEs must also be reported in the subject's medical records. AE reporting beyond Day 57 (Cohort 1) or Day 140 (Cohort 2) will be spontaneous, at safety calls, or retrospectively at Day 210 (Cohort 1) or Day 293 (Cohort 2).

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 investigational vaccine(s) ("related" or "not related").
- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure.
- Action taken with study treatment (investigational vaccine).
- Outcome of event.

10.2.2 Collection and Reporting of SAEs

Collection of SAEs will commence from the time that the subject is administered the first study dose (Day 1). Routine collection of SAEs will continue until the end of the trial (All subjects experiencing AEs within 28 days of each study dose, whether considered causally related with the use of the investigational vaccine or not, must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an Adverse Event eCRF and on the SAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must also be reported in the subject's medical records. AE reporting beyond Day 57 (Cohort 1) or Day 140 (Cohort 2) will be spontaneous, at safety calls, or retrospectively at Day 210 (Cohort 1) and Day 293 (Cohort 2).

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 investigational vaccine(s) –in a blinded way in blinded trials.
- 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.

10.3 Follow-up of 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, and 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.

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), the Food and Drug Administration (FDA), 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 investigational 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.

10.3.2 Post-Trial Events

Any related SAEs that occur outside of the protocol-specified observation period or after the end of the trial must be reported to the sponsor. These AEs will be processed by the sponsor's

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

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11.0 TRIAL-SPECIFIC REQUIREMENT(S)

11.1 Trial-Specific Committees

An independent DMC will be used for this trial as described in Section [11.1.1](#).

11.1.1 Independent DMC

An independent program level DMC will assess safety data on an ongoing basis. The DMC will also have study level responsibilities to review data and make recommendations about the sequential enrollment of various groups and formulation arms in this study.

Enrollment in this study will be initiated sequentially based on age groups and formulation arms, with ongoing DMC review.

The DMC will be composed at a minimum of 2 members with pediatric infectious disease and/or vaccine expertise, and a clinician and statistician. The DMC will monitor safety during the study and can meet ad hoc, as necessary. The roles and responsibilities of the DMC will be described in the DMC charter.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the DMC can conduct additional analyses of the safety data.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. Unsolicited and solicited AEs, SAEs, and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) codes (system organ class [SOC], High-level Group Terms, High-level Terms, Lower-level Terms, preferred terms [PTs]) and their corresponding descriptive terms. Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject whose LAR consented to the subject's participation and signed an ICF for the minor child.

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. Reasons for significant corrections should additionally be included.

The 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 12.1 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 (which should be copied and certified), source worksheets, all original signed and dated ICFs and assent forms (where applicable), subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of vaccine disposition to enable evaluations or audits from regulatory authorities,

the sponsor or its designees. Furthermore, International Conference on Harmonization (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified vaccine indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical 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 SAP will be prepared and finalized prior to the interim analyses (Day 57 in Cohort 1 and Day 140 in Cohort 2). This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives. Unless otherwise stated, the statistical methods described in the following subsections apply to all groups.

A blinded data review will be conducted by the blinded trial team prior to the analysis at study completion (Day 210 in Cohort 1 and Day 293 in Cohort 2). Limited blinded data review (of protocol deviations and subject evaluability) will also be done prior to the interim analyses. These reviews will assess the accuracy and completeness of the trial database and subject evaluability.

13.1.1 Analysis Sets

The analyses sets are defined as follows:

Safety Analysis Set: all subjects who receive at least 1 dose of vaccine (NoV GI.1/GII.4 bivalent VLP vaccine or control vaccine).

Full Analysis Set (FAS): all subjects who are randomized and have at least 1 NoV GI.1/GII.4 bivalent VLP vaccine injection.

Per-Protocol Analysis Set (PPS): all subjects who receive the planned vaccination and do not have major protocol violations will be included in the PPS. The major protocol violation criteria will be finalized as part of the blinded data review prior to the IA (Day 57 for Cohort 1 and Day 140 in Cohort 2).

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

The trial will evaluate the immunogenicity and safety of four formulations under different dosing regimens in 4 pediatric age ranges. Two cohorts of subjects will be enrolled into the trial. Cohort 1 will consist of 4 groups (4 to <9 years, 1 to <4 years [2 groups] and 6 months to <1 year), enrolled in age-step down fashion as described in Section 6.1. The youngest age group (Cohort 2, 6 weeks to <6 months) will be the last to complete enrollment. The factors under investigation, overall, and for each group include: formulation (4 formulation arms within each group); and number of doses (2 levels for each formulation within each group). For groups 1, 2, 2a, and 3 (in Cohort 1) the number of active doses will be 1 or 2 doses. For group 4 (Cohort 2), the number of active doses will be 2 or 3. Within each cohort, subjects are randomized to 1 of 8 trial arms (2 dose levels for 4 formulations), with group as a stratification factor. The purpose of Group 2a is to evaluate the safety and selected immunogenicity endpoints in subjects in the same age range as Group 2, but who receive the recently manufactured NoV bivalent VLP vaccine. Statistical methods described in the following sections will be essentially the same, but will be done only for the endpoints indicated in Section 5.2.

In general, the results (both safety and immunogenicity) from the trial will be summarized separately for each group, by formulation/dose arm. For immunogenicity results, additional summaries and/analyses by treatment group for Cohort 1 will be provided, by pooling subjects in age groups. Other summaries based on different groups may be provided, with details provided in the SAP.

Unless otherwise specified, descriptive summary statistics include mean, SD, median, minimum, and maximum values for continuous variables, and the number and percentage of subjects in specified categories for categorical variables.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Age, gender, race, and other baseline characteristics will be summarized descriptively by formulation arm, separately for each of the age groups in the cohorts.

13.1.3 Immunogenicity Analysis

The trial will evaluate the immunogenicity and safety of four formulations under different dosing regimens in 4 pediatric age ranges. Two cohorts of subjects will be enrolled into the trial. Cohort 1 will consist of 4 groups (4 to <9 years, 1 to <4 years [2 groups] and 6 months to <1 year), enrolled in age-step down fashion as described in Section 6.1. The youngest age group (Cohort 2, 6 weeks to <6 months) will be the last to complete enrollment. The factors under investigation, overall, and for each group include: formulation (4 formulation arms within each group); and number of doses (2 levels for each formulation within each group). For groups 1, 2, 2a, and 3 (in Cohort 1) the number of active doses will be 1 or 2 doses. For group 4 (Cohort 2), the number of active doses will be 2 or 3. Within each cohort, subjects are randomized to 1 of 8 trial arms (2 dose levels for 4 formulations), with group as a stratification factor.

Descriptive statistics for the primary, secondary and exploratory endpoints including estimates of seroresponse (≥ 4 -fold rises), and 95% confidence intervals (CI) will be provided. Summaries will be provided by formulation arm (ie. combination of formulation arms and number of doses) and group (4 age ranges with Groups 2 and 2a in the same age range). Additional summaries will be provided at the cohort level, by pooling subjects across the relevant age groups in Cohort 1, as applicable.

Additional analyses will also be provided at the cohort level (pooling groups in Cohort 1). Statistical analyses of the primary endpoint will be performed for each cohort using the CMH method [36] stratified by group (in Cohort 1) to assess the effects of formulation/dose combination. Risk differences and corresponding 95% CIs will be provided for all pairwise comparisons of interest, without adjustments for multiplicity. The primary analyses will be based on the PPS.

Continuous secondary endpoints, such as GMT and GMFR, will be summarized descriptively by group for each of the 8 formulation/dose combinations.

Analysis of covariance (ANCOVA) will be conducted for selected continuous endpoints (such as GMT and GMFR), examining the effect of formulation/dose combination using the

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log-transformed value as the dependent variable and the corresponding log-transformed baseline value as a covariate. Cohorts will be analyzed separately due to different number of doses (1 or 2 in Cohort 1; 2 or 3 in Cohort 2). For Cohort 1, the model will include estimates for treatment effect (formulation/dose combination) within each group, and at the cohort level across groups. The ANCOVA models will include group as a factor for analyses of Cohort 1 with a group by formulation/dose combination interaction term if appropriate. The pre-specified rule for inclusion of the interaction term will be described in the SAP. A factor for country will be included.

Pairwise comparisons of interest will be made in the framework of the ANCOVA model, without adjustments for multiplicity. The primary analyses will be based on the PPS.

Additional secondary and exploratory endpoints will be summarized descriptively, and selected endpoints will be analyzed using ANCOVA for continuous variables or the CMH method [36] stratified by age for dichotomous variables as described previously. Box plots and/or reverse cumulative distribution [RCD] curves will be provided for comparisons of interest.

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

CCI . Details regarding exploratory endpoints will be provided in the SAP.

13.1.4 Safety Analysis

All summaries and analyses of safety data are based on subjects in the Safety Analysis Set. Unless otherwise specified, the safety data will be summarized by formulation arm, (ie. according to the formulation arms, separately for the 1 and 2 (or 2 and 3) dose groups), for each age stratum and overall within each cohort. Further grouping or subgrouping may be investigated as appropriate.

In general, data imputation will not be performed for any missing safety data. The criteria for biologically implausible measurements are defined in the SAP, and any measurements meeting those criteria (eg, body temperature $>42^{\circ}\text{C}$) will be excluded from the summaries and analyses.

Reactogenicity

Reactogenicity will be assessed for 7 days following each vaccination (including the day of vaccination) via collection of solicited AEs, including local (injection site: pain, erythema, induration, and swelling) and systemic events of headache, fatigue, myalgia, arthralgia, vomiting (number per day/intensity), and diarrhea (number per day/consistency) for children aged 4 to <9 years; and irritability/fussiness, drowsiness, loss of appetite, vomiting (number per day/intensity), and diarrhea (number per day/consistency) for children aged 6 weeks to <4 years daily through Day 7 after each vaccination. In addition, other indicators of reactogenicity will be collected (body temperature). The categories for each solicited AE are defined in Section 9.1.7. Solicited reactogenicity data will be captured daily on the day of vaccination and the following 6 days.

For each solicited AE, the percentage of subjects will be summarized by event severity for each day for the 7 days following vaccination (including the day of vaccination), and overall. In addition, summaries will be provided for the intervals of Days 1 to 3 and Days 4 to 7 following

each vaccination. A summary of the day of first onset of each event and the number of days subjects reported experiencing each event will also be provided. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs

Unsolicited AEs, and SAEs, will be MedDRA coded and summarized by system organ class (SOC) and preferred term (PT) for each formulation arm in each cohort. AEs leading to subject's withdrawal from the trial will also be summarized.

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

In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subjects with at least 1 AE) and by SOC and PT. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. Unsolicited AEs will be summarized as follows: by PT by SOC and PT, including events with frequency greater than 5% (and as above for subjects with at least 1 AE); by SOC, PT, and severity; and by SOC, PT, and relationship to the investigational vaccine. Unless otherwise specified, unsolicited AEs will be summarized in the following 3 ways: 1) overall up to 28 days after each vaccination, 2) with onset between 1 and 7 days after each vaccination, and 3) with onset between 8 and 28 days after each vaccination.

13.2 Interim Analysis and Criteria for Early Termination

Interim analyses will be performed after the primary safety and immunogenicity data are available (ie, Day 57 for Cohort 1 and Day 140 for Cohort 2) (primary analysis time point). Day 57 interim analyses (IA) for Cohort 1 will be provided initially for Groups 1 and 2, which will complete Day 57 substantially earlier than Group 2a and 3. The Day 57 IA for Groups 2a and 3 combined will be provided at a later time. Thus, the Day 57 IA will be conducted in two parts to be followed by the Day 140 IA. All interim analyses will be performed by a separate set of unblinded statisticians and programmers at the contract research organization (CRO), Quintiles, who will have access to individual treatment assignments but will not otherwise be involved in study conduct. The rest of the personnel involved in the conduct of the study, including those at Takeda, Quintiles, and the study sites, will remain blinded to the individual subject data (including treatment assignments) until unblinding after database lock (Day 210 for Cohort 1 and Day 293 for Cohort 2). More details on the analyses will be provided in the statistical analysis plan (SAP).

13.3 Determination of Sample Size

This trial is designed to be descriptive and is not based on testing formal null hypotheses, and therefore the sample size was not determined based on formal statistical power calculations. However, for illustrative purposes, the probabilities of detecting 1 or more AEs in this design for various scenarios are provided.

Safety: Including all randomized subjects, [Table 13-a](#) illustrates the probability of observing 1 or more events (eg, any specific type of AE related to study vaccine) for a range of assumed true but

unknown event rates in the range of 0.33% to 5.00% (without considering the background incidence).

Table 13-a Probability of Observing 1 or More Events for Assumed “True” Event Rate and Given Samples

“True” Unknown Event Rate	Sample Size			
	N=480	N=360	N=240	N=120
0.33%	79.5%	69.6%	54.8%	32.7%
0.50%	91.0%	83.5%	70.0%	45.2%
1.00%	99.2%	97.3%	91.0%	70.1%
2.00%	>99.9%	99.9%	99.2%	91.1%
3.00%	>99.9%	>99.9%	99.9%	97.4%
4.00%	>99.9%	>99.9%	>99.9%	99.2%
5.00%	>99.9%	>99.9%	>99.9%	99.8%

Therefore, even with an event rate as low as 0.33%, there is a 80% chance that at least 1 such event will be observed in Cohort 1 of the trial. Restricting to one age group in Cohort 1 (N=120) there is still a 91% chance of observing 1 or more events when the true rate is 2.00%.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Trial-Site Monitoring Visits

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

All aspects of the trial and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, investigational vaccine, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other trial personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the vaccine is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the trial site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all trial documents as described in Section [14.1](#).

15.0 ETHICAL ASPECTS OF THE TRIAL

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

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable 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.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol’s review and approval. This protocol, the Investigator’s Brochure [31], a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB’s or IEC’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the trial (ie, before shipment of the sponsor-supplied vaccine or trial-specific screening activity). The IRB or IEC approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from 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 Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, assent form (where applicable), subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the trial. The ICF and the subject information sheet (if applicable) further explain the nature of the trial, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's LAR may provide such consent for the subject in accordance with applicable laws and regulations.

The subject or the subject's LAR 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 or the subject's LAR determines he or she will participate in the trial, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's LAR, at the time of consent and prior to the subject entering into the trial. The subject or the subject's LAR should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to subject entering into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's LAR in the same manner as the original informed consent. The date the revised consent was obtained

should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this trial, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, electrocardiogram reports, admission and discharge summaries for hospital admissions occurring during a subject's trial participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, the sponsor will, at a minimum register all clinical trials conducted in patients 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.

In line with European Community (EC) Regulation N° 1901/2006, the sponsor will submit the pediatric studies within 6 months of their completion and irrespective of whether it is part of a Pediatric Investigation Plan (completed or not yet completed) or not, or whether it is intended for submission later on as part of a variation, extension or new stand-alone marketing-authorization application or not [35].

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.

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Appendix A Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. Ensure that trial-related procedures, including trial specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
5. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conform to 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 ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the trial, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's LAR.
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.

Appendix B Investigator Consent to Use of Personal Information

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

- The sponsor, 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 the sponsor 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.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within the sponsor, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting investigator site contact information, trial details, and results on publicly accessible clinical trial registries, databases, and websites.

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

Appendix C Elements of the Subject Informed Consent

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

- 1 A statement that the trial involves research.
- 2 An explanation of the purposes of the research.
- 3 The expected duration of the subject's participation.
- 4 A description of the procedures to be followed, including invasive procedures.
- 5 The identification of any procedures that are experimental.
- 6 The estimated number of subjects involved in the trial.
- 7 A description of the subject's responsibilities.
- 8 A description of the conduct of the trial.
- 9 A statement describing the vaccination(s) and the probability for random assignment to each treatment.
- 10 A description of the possible side effects following vaccine administration that the subject may receive.
- 11 A description of any reasonably foreseeable risks or discomforts to the subject.
- 12 A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- 13 Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
- 14 A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject or the subject's LAR is authorizing such access.
- 15 For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
- 16 The anticipated prorated payment(s), if any, to the subject for participating in the trial.
- 17 The anticipated expenses, if any, to the subject for participating in the trial.

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- 18 An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
- 19 A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- 20 The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- 21 A statement that the subject or the subject's LAR will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- 22 A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
- 23 The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
- 24 A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the trial. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
 - a. that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) the sponsor, its affiliates, and licensing partners; (2) business partners assisting the sponsor, 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, the sponsor 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 the sponsor'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.
- 25 A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.