TAKEDA VACCINES, INC.

STATISTICAL ANALYSIS PLAN
AMENDMENT 1

STUDY NUMBER: NOR-202

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

PHASE II

Version**:** Final

Date**:** 17 February 2017

1.0   APPROVAL SIGNATURES

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

Takeda Approvals:

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3.0   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
CMH	Cochran-Mantel-Haenszel
CMI	Cell-Mediated Immunity
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
ET	Early Termination
FAS	Full Analysis Set
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GSD	Geometric Mean Standard Deviation
HBGA	Histoblood Group Antigen
HIV	Human Immunodeficiency Virus
CCI	CCI
CCI	CCI
IM	Intramuscular
LLoQ	Lower Limit of Quantification
LS	Least Squares
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
NoV	Norovirus
OME	Otitis Media with Effusion
Pan-Ig	Pan Immunoglobulin
CCI	CCI
PPS	Per-Protocol Analysis Set
PT	Preferred Term
RCD	Reverse Cumulative Distribution
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
VLP	Virus-like Particles
WHO	World Health Organization

4.0   OBJECTIVES

4.1   Primary Objectives

To select the optimal formulation of the norovirus (NoV) bivalent virus-like particles (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 adverse events (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 serious adverse events (SAEs) throughout the trial.

4.2   Secondary Objectives

- To evaluate the geometric mean titers (GMT) and geometric mean fold rises (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.

4.3   Exploratory Objectives

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4.4 Study Design

This is a Phase II, randomized, double-blind, multi-site, dosage, safety and immunogenicity trial of the intramuscular (IM) NoV bivalent VLP vaccine combined with aluminum hydroxide (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 4.a

Figure 4.a   Schematic of Trial Design

* Recently manufactured clinical trial material lots

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A total of 840 healthy subjects will be randomized to the following cohorts, with stratification by country and group:

- Cohort 1, N=480 (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 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.

- 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 comprising 3 age ranges (Group 1: aged 4 to less than 9 years; Group 2 and Group 2a: both groups 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 Protocol Section 11.1.1).

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). 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 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).

Investigational Vaccine:

The investigational vaccine for each formulation arm contains 500 µg aluminum as $Al(OH)_3$.

- **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

Expected duration of trial participation for each subject is up to 210 days (Cohort 1) and 293 days (Cohort 2). 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 4.a and Table 4.b.

Table 4.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)

Procedure / Timing	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:
(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 (Protocol 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   , 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

Table 4.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:
(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 (Protocol 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 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.
(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 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.

Table 4.c **Schedule of Trial Procedures for Subjects Aged 6 Weeks to Less Than 6 Months (Cohort 2; N=360)**

Procedure \ Timing	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

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 (Protocol 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

5.0   ANALYSIS ENDPOINTS

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 $\geq$ 3 years, and HBGA binding assay to a panel of GI.1 and GII.4 not represented in the vaccine.

5.1   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.

- 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   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).

5.3   Exploratory Endpoints

CCI

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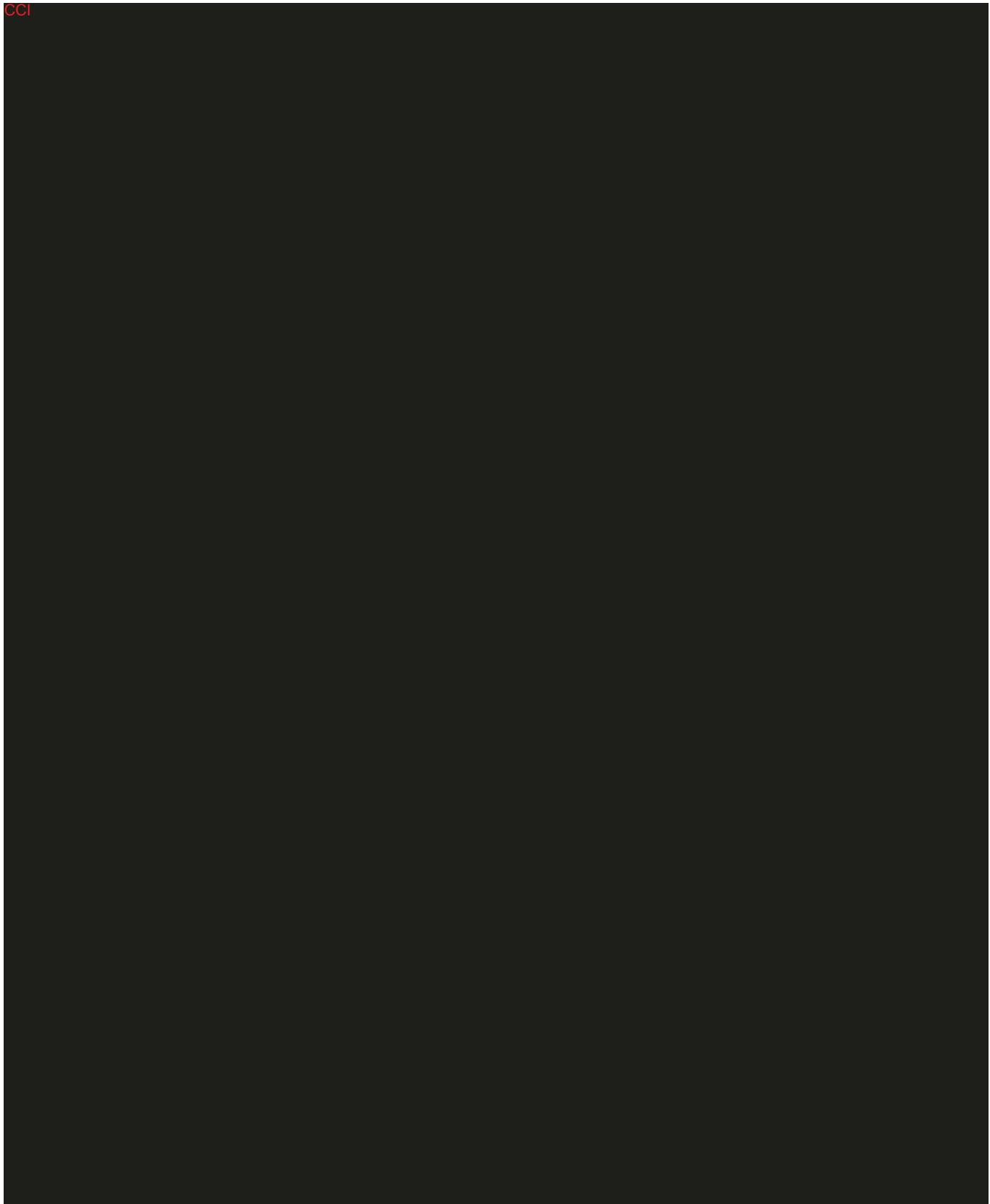
CCI

6.0   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 in Protocol Section 13.3

7.0   METHODS OF ANALYSIS AND PRESENTATION

7.1   General Considerations

This statistical analysis plan (SAP) is based on protocol Amendment 3, Version 4.0, dated 01 March 2016.

The purpose of this trial is to evaluate the immunogenicity and safety profile of 4 formulations under different dosing regimens in 4 pediatric age ranges. Two cohorts of subjects will be enrolled into the trial (Figure 4.a). Cohort 1 will consist of 4 age 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 4.4. The youngest age group (Cohort 2, 6 weeks to <6 months) will be the last to complete enrollment. Enrollment into each successive age group is initiated based on DMC recommendation. Hereafter the age groups (5 groups covering 4 age ranges) will be designated as 'group'. The factors under investigation for each group within each cohort 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.

Immunogenicity and safety endpoints will be summarized descriptively (frequency and percent for categorical data; and number of subjects with non-missing observations, mean [or geometric mean], standard deviation [SD] [or geometric standard deviation {GSD}], median, minimum, and maximum for continuous data, unless specified otherwise) at all relevant study visits, as appropriate. In summary tables for categorical data for which categories are defined on the electronic case report form (eCRF), all categories will be presented as specified, even if the subject count within that category is zero. For other categorical data (eg, AEs and medications), only categories with at least 1 subject will be presented. Unless otherwise specified, for each group summarized, category percentages will be based on the number of subjects in the group with non-missing data and the non-missing 'n' will be displayed for each count/percentage.

Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Means, geometric means, least squares means (LS Means), and medians will be presented to 1 more decimal place than the recorded data. SD and GSD will be presented to 2 more decimal places than the recorded data. The confidence interval (CI) about a parameter estimate will be presented using the same number of decimal places as the parameter estimate (ie, 1 more decimal place than the recorded data). Percentages will be presented to 1 decimal place (eg, 80.3%). All p-values will be rounded to 3 decimal places. If a p-value is less than 0.001, it will be reported as "<0.001"; if a p-value is greater than 0.999, it will be reported as ">0.999".

In general, summaries and analyses will be provided by formulation/dose combination (the 8 available combinations of the 4 formulations and 2 dose groups), by age group and by cohort. For the by-cohort summaries and analyses, those for Cohort 1 are pooled over the 3 age groups (ie, groups 1 – 3).

Unless otherwise specified, all data collected during the trial will be presented in the subject listings. For all listings where information on screen failure is collected, the screen failures data will be presented at the end of the listing.

All statistical analyses will be generated using SAS Version 9.2 or higher.

Handling of Missing Values

There will be no imputation of missing data with the exception of (1) missing or partial dates (ie, start dates of AEs), and (2) titer values measured as below the lower limit of quantification (LloQ) for the particular antigen and assay.

Missing or Partial Dates

Partial dates will be presented as recorded in the listings. Missing and partial AE start dates will be imputed to determine the relationship between the start date of the event and the dose dates of the double-blind vaccinations.

An adverse event should be temporally associated with the correct vaccination dose as far as possible. If an event has a missing or incomplete onset date, the date will be imputed using the following guidelines. If available date information indicates that the start of an event is between two vaccination dates, then the earliest of the vaccination dates will be used for imputation. For example, if Vaccination 1 is on 01 January 2015 and Vaccination 2 is on 02 March 2015 and the event has an incomplete onset date of February 2015, then the event would have an imputed date of 01 February 2015. If the available start date information is insufficient to distinguish between 1 or more vaccination dates, then the event end date will be used to determine the earliest possible imputed date relative to the latest vaccination. In the above example if an event is known to start in 2015 (day and month missing) and the end date is known as 20 March 2015, then an imputed onset date of 02 March (date of Vaccination 2) will be used. If an event is missing both onset and end date then the last vaccination date will be used as the imputed onset date. Similar logic will be used for partial dates of subjects in age group 4, who receive 3 doses.

The imputation of partial end dates for AEs will consider information such whether the AEs are ongoing by the end of study.

Titers measured below the LloQ

If a titer value, for either of the 2 vaccine VLPs or for exploratory endpoint non-vaccine antigens, is measured as below LloQ, it will be imputed as the half of the LloQ in summaries and analyses, but will be listed as reported in the raw serology data. For example, a serologic assay with LloQ = 30 generally reports values below LloQ as "<30". The data listings will present the values as "<30", while values of 15 (30/2) are to be used in the summaries and analyses.

Since the missing data resulting from dropouts in vaccine trials are typically classified as missing completely at random (MCAR) [1], a simple way of handling the missing data is to use a

"complete case analysis". That is, the subjects with missing data are to be excluded. Complete case analysis is essentially being done since the per-protocol analysis set (PPS) excludes subjects not receiving the full vaccine regimen or not having data at the primary endpoint times of Day 57 (Cohort 1) or Day 140 (Cohort 2). If more than 20% of the subjects have missing data for the primary immunogenicity endpoint, multiple imputation methods may be explored as a sensitivity analysis.

Handling of Temperature Measurements

If temperature data (whether collected by subject via memory aid, 30-minute in-clinic assessment, or as part of vitals collection at exam) contain a mixture of Fahrenheit and centigrade measurements, a temperature value in centigrade will be derived from the collected measurement as follows. If the original value was recorded in centigrade, the derived temperature value will be set equal to the recorded value; if the recorded value is in Fahrenheit, the derived temperature value will be the conversion to degrees Fahrenheit.

All summaries and analyses of temperature will be presented in centigrade. However, the 'temperature as recorded' will be retained in the analysis dataset. The 'temperature as recorded' and 'temperature in degrees centigrade' will both be presented in the relevant data listing.

Baseline Definition and Windowing Conventions

Study Day 1 is defined as the date of the first vaccination, as recorded on the eCRF vaccination page. Other study days are defined relative to Study Day 1, with Day -1 being the day prior to Day 1. In addition, day relative to vaccination will be derived for each vaccination dose. For example, day relative to the first dose will be equal to the Study Day. Day relative to the second dose will start with a value of 1 on the day of the second dose and so on for each vaccination given. Day relative to dose is of use for tables presenting summaries of events relative to dose.

For listings presenting observations or events by day, both the Study Day and Day Relative to Dose will be presented.

Baseline is defined as the last non-missing measurement taken before the first dose of vaccination (Day 1), unless otherwise defined for a particular endpoint parameter.

A windowing convention will be used to determine the analysis value for a given study visit for observed data analyses. The window definitions as outlined below in Table 7.a and Table 7.b will be used for the immunogenicity (serology and CMI) and vital signs, respectively. The window conventions are:

1. A window of +/- 7 days from the target day is applied to the following visits: Study Days 29 and 57 for cohort 1 and Study Days 56, 84, 112, and 140 for cohort 2;

2. A window of +/- 28 days from the target day is applied to the following visits: Study Day 210 for cohort 1 and Study Day 293 for cohort 2.

The windows for immunogenicity are constructed by dosing period relative to actual dosing day. Windows for vital signs are constructed relative to the actual study day.

One or more results for a particular immunogenicity or vital sign variable may be obtained in the same visit window (see study window definitions in Table 7.a and Table 7.b). In such an event, the result with the date closest to the expected visit date will be used. In the event that 2 observations are equidistant from the expected visit date, the later observation will be used.

Table 7.a   Visit Windows for Immunogenicity by Visit

Cohort	Period	Visit	Day Relative to Dose within the Period[b]	Visit Window (Study Day)	
				Serology	CMI and Avidity[c]
1	Period 1	Baseline[a]	≤1	≤1	≤1
	(Relative to Dose 1)	Day 29	29	22 – 36	22 – 36
	Period 2	Day 57	29	22 – 36	22 – 36
	(Relative to Dose 2)	Day 210	182	154 – 210	---
2	Period 1	Baseline[a]	≤1	≤1	≤1
	(Relative to Dose 1)	Day 56	56	49 – 63	49 – 63
	Period 2	Day 84	29	22 – 36	22 – 36
	(Relative to Dose 2)				
	Period 3	Day 140	29	22 – 36	22 – 36
	(Relative to Dose 3)	Day 293	182	154 – 210	---

(a) Where time is available, the time of the collection must be prior to the first dose of study drug. Day 1 observations taken after the first dose are considered post-baseline values.

(b) For each period, the administration of the study drug is designated as Study Day 1. For analyses within a period, the study day value is incremented by 1 for each date following the vaccine administration. Dates prior to the vaccine administration are decremented by 1, with the date preceding the vaccine administration designated as Study Day -1 (there is no Study Day 0).

(c) CMI is measured only for Cohort 1.

Table 7.b   Visit Windows for Vital Signs by Visit

Cohort	Visit	Visit Window (Study Day)
		Vital Signs
1	Baseline[a]	≤1
	Day 29	22 – 36
2	Baseline[a]	≤1
	Day 56	49 – 63
	Day 112	105 - 119

(a) Where time is available, the time of the collection must be prior to the first dose of study drug. Day 1 observations taken after the first dose are considered post-baseline values.

In-Clinic Reactogenicity Assessments and Diary Data

On vaccination days, at 30 minutes following the dose, in-clinic assessments of reactogenicity (solicited local and systemic AEs) and temperatures are collected onto the eCRF. These data are only collected on vaccination days so visit window rules do not apply.

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In addition, solicited local and systemic Aes and body temperature are recorded daily (by diary) by the subject's legal guardian for 7 days following each dose (day of dose plus 6 additional days). These data are collected at the study visit following the dose and contain entries by day within that interval. Visit window rules will not be applied to the diary data; they will be summarized by diary day (and within specified diary day intervals, eg, 1-7, 1-3, 4-7) following vaccination.

7.2   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. A major protocol violation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity results of the subject. All major protocol violations will be identified prior to unblinding from review of study monitoring deviation logs and through programmatic review of blinded data, based on pre-specified criteria. Clinical judgment from Takeda will be necessary to classify each deviation as a "major" violation or not. The major protocol violation criteria will be finalized as part of the blind data review prior to the interim analysis (Day 57 for Cohort 1 and Day 140 in Cohort 2) and may include:

1) Not meeting entry criteria, based on selected inclusion/exclusion criteria (exclusion criteria #6 and #7) defined in protocol sections 7.1 and 7.2;

   Exclusion criterion #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) 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.

  Exclusion criterion #7: Abnormalities of splenic or thymic function.

2) Receiving wrong treatment.

3) Receiving prohibited therapies in the following categories (also specified in protocol Section 9.1.2):

- Parenteral immunoglobulin preparation, blood products, and/or plasma derivatives 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.

4) Significant deviation from protocol-specified dosing and/or sample collection regimen as subject to pre-lock blinded medical review.

5) Not receiving all planned doses of the investigational vaccine.

6) Did not have evaluable blood sample at Baseline and Day 57 (for subjects from Cohort 1) and Baseline and Day 140 (for subjects from Cohort 2).

7) Other major violations, which may be identified during blinded data review prior to the interim analysis (Day 57 for Cohort 1 and Day 140 in Cohort 2) and study completion (Day 210 in Cohort 1 and Day 293 in Cohort 2).

The primary population for immunogenicity analyses will be based on the PPS. Supportive immunogenicity analyses on the primary and key secondary endpoints will also be performed using FAS. All safety analyses will be based on the Safety Analysis Set. Subjects excluded from any of the analysis datasets will be listed with the reason for exclusion in the final clinical study report. Major violations resulting in exclusion from the PPS will also be summarized by reason for exclusion.

7.3 Disposition of Subjects

Disposition of all screened subjects will be summarized descriptively, including a summary of the number of screened subjects and the number of randomized subjects by group. The primary reasons for ineligibility for randomization will be summarized by group. The number of randomized patients by treatment arm and center, and analysis populations by group and formulation/dose combination will also be presented.

Disposition for all randomized subjects will be summarized by the 8 formulation/dose combinations within each group and cohort. Disposition categories include:

- Number of randomized subjects and number of randomized subjects but not dosed;

- Number of subjects completing the vaccine regimen/study visits;

- Number of subjects who prematurely discontinued the vaccine regimen/study visits;

- Primary reason for premature discontinuation of the vaccine regimen/study visits.

Primary reason for premature discontinuation of the vaccine regimen/study visits will be summarized. For interim analysis, a subject is to be assumed ongoing unless he/she completed the end of study eCRF page for Day 210 (cohort 1) or Day 293 (cohort 2), indicating either completion or early termination.

Protocol deviations pertaining to study conduct are routinely collected and reviewed as part of study monitoring. These deviation logs are maintained by study management. Non-minor deviations will be transferred to the clinical data base and presented in the subject data listings. As described in Section 7.2 (under PPS), deviations will also reviewed as part of blinded data review prior to interim and final data locks to determine if any deviation constitutes a major protocol violation.

7.4   Demographic and Baseline Characteristics

Age, gender, race, and other baseline characteristics will be summarized descriptively by formulation arm and dose group, overall and separately for each of the groups in the cohorts, for randomized subjects and subjects in the PPS. Baseline characteristics will include the numbers and percentages of subjects with Baseline (pre-vaccination) values of antibody titers below the LLoQ for each assay (Pan-Ig, HBGA, and IgA) for each VLP antigen (GI.1 and GII.4). In addition the number and percentage of subjects with values below the LLoQ for all assays and antigens will be provided.

7.5   Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, Version 17.0 or later) coding system.

Frequencies and percentages of subjects by medical history and concurrent medical conditions will be summarized by system organ class (SOC) and preferred term (PT) for the safety population and by age group, dose group and formulation arm. Multiple entries for an individual patient under the same SOC/PT will only be counted once

7.6   Medication History and Concomitant Medications

Medication history and concomitant medications will be coded using the World Health Organization DRUG dictionary (WHODrug, 01MAR2014 version or later).

Medication history includes all medication that was taken but ended at informed consent or within 3 months prior to the time of informed consent. Concomitant medications include medications taken from informed consent through post-study follow-up.

Frequencies and percentages of subjects by medication history and concomitant medications will be summarized by preferred medication name for the safety population and by group, dose group and formulation arm. Subjects with multiple uses of a medication history or concomitant medication will be counted once for a given preferred medication name.

A glossary of medication history and concurrent medications by preferred medication name will be presented.

7.7   Duration of Follow up and Vaccine Regimen Compliance

Compliance rate will be summarized by the 8 formulation/dose combinations for each group, by presenting the number and percentage of subjects receiving each vaccine dose. The vaccination date/time information will be listed for each subject. The duration of follow-up will be summarized as a continuous variable, and also as a frequency and percentage of subjects in the following categories: (1.1) 1 – 29 days, (1.2) 30 - 57 days, (1.3) > 57 days for cohort 1 and (2.1) 1 - 56 days, (2.2) 57 - 112 days, (2.3) 113 - 140 days, (2.4) >140 days for cohort 2. The duration of follow-up is defined as the number of days from the first vaccination to the date of last contact specified on the End of Study Visits form. This will generally be the date of the last clinic visit but could be a phone contact. For interim analyses, if the End of Study Visits form is not available, the date of data cutoff will be used for calculation

7.8   Immunogenicity Analysis

General Methodology

The primary population for immunogenicity analyses will be the PPS. Supportive immunogenicity analyses on primary and key secondary endpoints will also be performed using FAS.

Descriptive statistics for the primary, secondary, and exploratory endpoints will be computed for all available assays at all relevant time points and include the following:

- Titer values (eg, GMT, BT50, GMFR): geometric mean, GSD, 95% CIs, minimum, and maximum;

- Other continuous endpoints: mean, SD, median, minimum, and maximum;

- Categorical variable (eg, seroresponse rate): number and percentage of subjects, and 95% CIs in specified categories. The 95% CI of seroresponse rate will be calculated using exact (Clopper-Pearson) method.

Cohorts will be analyzed separately due to different number of doses (1 or 2 in Cohort 1; 2 or 3 in Cohort 2).

Analysis of covariance (ANCOVA) will be conducted for continuous outcome parameters (eg, GMT, GMFR), examining the effect of formulation/dose combination using log-transformed values of the endpoint as the dependent variable and the corresponding log-transformed baseline (pre-vaccination) value as a continuous covariate. 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 as follows. If the interaction term p-value is <= 0.05, the term will remain in the model. If the p-value is >0.05 it will be removed. For Cohort 1, the model will include estimates for treatment (formulation/dose combination) effect within each group, and at the cohort level across groups. A factor for country will be included in all models.

For binomial outcomes the Cochran-Mantel-Haenszel (CMH) method [2] for difference in proportions will be conducted, stratified by group (Cohort 1).

All pairwise comparisons (with the lower level as a reference group) will be presented, without adjustments for multiplicity.

Pre-specified comparisons of interest will be tested. The pre-specified comparisons of interest are the following:

- "A: 15/15, 1 Dose" vs. "A: 15/15, 2 Dose"
- "A: 15/15, 1 Dose" vs. "B: 15/50, 2 Dose"
- "B: 15/50, 1 Dose" vs. "C: 50/50, 1 Dose"
- "B: 15/50, 1 Dose" vs. "B: 15/50, 2 Dose"
- "C: 50/50, 1 Dose" vs. "B: 15/50, 2 Dose"
- "C: 50/50, 1 Dose" vs. "C: 50/50, 2 Dose"
- "C: 50/50, 1 Dose" vs. "D: 50/150, 2 Dose"
- "D: 50/150, 1 Dose" vs. "D: 50/150, 2 Dose"
- "A: 15/15, 2 Dose" vs. "B: 15/50, 2 Dose"
- "A: 15/15, 2 Dose" vs. "C: 50/50, 2 Dose"
- "A: 15/15, 2 Dose" vs. "D: 50/150, 2 Dose"
- "B: 15/50, 2 Dose" vs. "C: 50/50, 2 Dose"
- "B: 15/50, 2 Dose" vs. "D: 50/150, 2 Dose"
- "C: 50/50, 2 Dose" vs. "D: 50/150, 2 Dose".

Subjects with baseline values below the LLoQ for all assays (Pan-Ig, HGBA, and IgA) and VLP antigens (GI.1 and GII.4) will be identified. If warranted, selected immunogenicity summaries may be prepared for subsets of interest.

7.8.1   Primary Immunogenicity Endpoint(s)

The primary immunogenicity endpoint for this trial is seroresponse rate, defined as the 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). The primary analyses will be based on the PPS data but will also be provided using the FAS.

The seroresponse rates and 95% CIs will be summarized (as described in the General Methodology of Section 7.9) for each of the 8 formulation/dose combinations (4 formulation arms; 1 and 2 [or 2 and 3] doses), by group. These summaries will also be provided at the cohort level (pooling subjects across groups in Cohort 1). The 95% CI of seroresponse rate will be

calculated using the exact (Clopper-Pearson) method. These summaries will be provided for the subjects in the PPS and FAS.

Statistical analyses of the primary endpoint will be performed at the cohort level using the CMH method stratified by group to assess the effect of formulation/dose schedule. Common risk differences and corresponding 95% CIs will be provided for all pairwise comparisons of interest, without adjustments for multiplicity. The 14 comparisons of interest (listed in the *General Methodology* of Section 7.8 above) will be tested.

7.8.2   Secondary and Exploratory Immunogenicity Endpoint(s)

The secondary and exploratory immunogenicity endpoints for this trial are listed in Sections 5.2 and 5.3, respectively. Secondary endpoints include seroresponse rates, GMT or BT50 and GMFR for Pan-Ig and HBGA assays at Day 57 (Cohort 1) and Day 140 (Cohort 2). CCI

However, for summaries and analyses (as applicable) of secondary and exploratory endpoints for a particular assay, all time points will be presented together in the table.

As a reference for summary purposes, secondary and exploratory parameters are listed with all collection time points, separately according to whether continuous or binomial, in the two subsections below.

Secondary and Exploratory Binomial Immunogenicity Endpoints

The binomial secondary and exploratory seroresponse rate endpoints are listed below:

- CCI

- CCI

-

-

-

Rates of seroresponse to both NoV GI.1 VLP and GII.4 VLP will be summarized and analyzed similarly to the primary immunogenicity endpoint, for both the PPS and FAS.

Seroresponse rate to each VLP (GI.1 VLP or GII.4 VLP antibody titers) will be summarized similarly to the primary immunogenicity endpoint for the PPS only.

Graphics may be prepared to present seroresponse over time and to concisely illustrate the effects of formulation and number of doses within groups.

Secondary and Exploratory Continuous Immunogenicity Endpoints

The secondary and exploratory continuous immunogenicity endpoints are listed below:

- CCI

-

-

-

-

-

-

GMT, BT50 and GMFR will be summarized descriptively, as described in the General Methodology of Section 7.9, for each of the 8 formulation/dose combinations (4 formulation arms; 1 and 2 [or 2 and 3] doses), by group, at each scheduled time point. These summaries will

also be provided at the cohort level, ie, by pooling subjects across the relevant groups. These summaries will be provided for the subjects in the PPS and FAS.

The GMT and BT50 will be calculated as the anti-logarithm of $\sum$(log transformed titer/n), ie, as the anti-logarithm transformation of the mean of the log-transformed titer, where n is the number of subjects with titer information. The GSD for GMT and BT50 will be calculated as the anti-logarithm transformation of the standard deviation of the log-transformed titer. The 95% CI will be calculated as the anti-logarithm transformation of the upper and lower limits for a two-sided CI for the mean of the log-transformed titers.

GMFR will be calculated as anti-logarithm of $\sum$ (log transformed (post-vaccination titer/ pre-vaccination titer)/n). The GSD and 95% CIs for GMFR will be calculated similarly to those for GMT and BT50.

GMT, BT50 and GMFR will be analyzed with an ANCOVA model 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. The ANCOVA models will include group as a factor for analyses of Cohort 1 with agroup by formulation/dose combination interaction term included if appropriate, as follows. If the interaction term p-value is <= 0.05, the term will remain in the model. If the p-value is >0.05 it will be removed. For Cohort 1, the model will include estimates for treatment (formulation/dose combination) effect within each group, and at the cohort level across groups. A factor for country will be included. All the applicable pairwise comparisons will be provided with lower levels as the reference groups, with no adjustments for multiplicity. The 14 comparisons of interest listed in the *General Methodology* of Section 7.8 will be tested. The analyses will be based on the PPS.

Box plots and/or reverse cumulative distribution (RCD) curves will be provided for comparisons of interest. Other graph formats may be included for illustration purposes.

7.8.3   Additional Immunogenicity Endpoint(s)

CCI
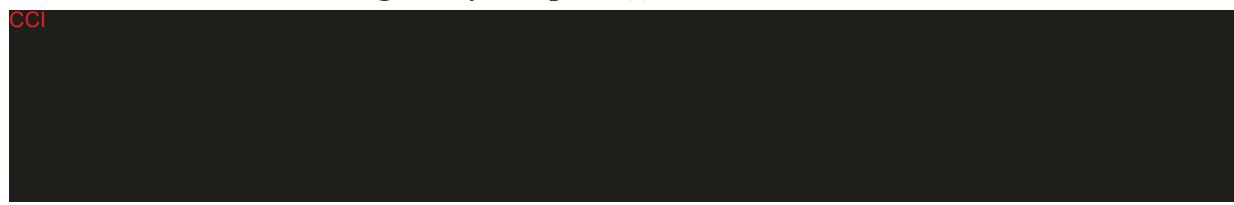
7.9   Pharmacokinetic/Pharmacodynamic Analysis

{Not applicable}

7.10   Other Outcomes

{Not applicable}

7.11   Safety Analysis

All summaries and analyses of safety data are based on subjects in the Safety Analysis Set. Unless otherwise specified, the safety data will be summarized according to the treatment arms,

(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.

7.11.1 Adverse Events

In-Clinic Assessments of Reactogenicity

In-clinic 30-minutes post-vaccination assessments of reactogenicity AEs include local events (injection site pain, erythema/redness, induration, and swelling) and systemic events (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). Severity of injection site pain and of the systemic events is assessed in-clinic as mild, moderate or severe according to Protocol Tables 9a (age 4 – 9 years) and 9b (age 6 weeks to <4 years). Measurements of the largest diameter for injection site erythema/redness, swelling, and induration are collected. These measurements will be used to derive severity grades based on the criteria included in Appendix A and Appendix B. Temperature measurements are also collected and a systemic event of 'fever' will be derived as Yes/No based on temperatures >= 38 degrees centigrade [3]. Temperature levels will also be categorized in 0.5 degree intervals (centigrade). Number and percent of subjects with reactogenicity events 30-minutes post vaccination will be summarized for each vaccine administered, for each local and systemic event, and by severity.

Subjects' Legal Guardian Assessments of Reactogenicity via Subject's Diary

Reactogenicity is also assessed by the subject's legal guardian for 7 days following each vaccination (day of vaccination and the following 6 days) via diary collection of solicited AEs. These include local events (injection site pain, erythema/redness, 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. Measurements of the largest diameter for injection site erythema/redness, swelling, and induration are collected. These measurements will be used to derive severity grades based on the criteria presented in Appendix A and Appendix B. Temperature measurements are also collected and a systemic event of 'fever' will be derived as Yes/No based on temperature >= 38 degrees centigrade. Temperature levels will also be categorized in 0.5 degree intervals (centigrade). Severity categories for each solicited AE are defined in Protocol Section 9.1.7. In addition, the relationship of solicited systemic symptoms occurring within 7 days after each vaccination is assessed by the investigator during diary review.

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 within the 7 days following vaccination. In addition, summaries will be provided for the intervals of Days 1 to 3 and Days 4 to 7 following each vaccination. For subjects with more than 1 episode of the

same event within an interval (overall within the 7 days following vaccination, days 1-3, and days 4-7), the maximum severity will be used for tabulations.

The relationship of solicited systemic symptoms occurring within 7 days after each vaccination will also be tabulated. If a subject reported more than one episode of the same event, then the strongest relationship will be included in the summaries.

A summary of the day of first onset of each event with intensity grade mild or higher and the number of days subjects reported experiencing each event with intensity grade mild or higher will also be provided for each vaccination. The number of days a subject reported experiencing a symptom is calculated as the total of all days the subject reported the symptom, regardless of whether the symptom was reported on consecutive days (eg, a headache reported on Day 1, Day 3, and Day 4 would be included with a duration of 3 days).

For all summaries by each vaccination, summaries after any vaccination will also be included.

Unsolicited AEs

Unsolicited AEs will be coded using the MedDRA, Version 17.0 or later.

All unsolicited AEs will be collected for 28 days following each vaccination. To attain 28 full days, all AEs with onset on the day of vaccination (day 1 relative to the given vaccination day) through day 29 relative to the given vaccination day will be included. SAEs and AEs leading to subject withdrawal from the trial will be collected throughout the trial.

Unsolicited AEs will be assigned to vaccine dose (1st, 2nd or 3rd, if applicable). All summaries described in this Section will be generated by vaccine dose number. Summaries by each vaccination will also include summaries after any vaccination

The incidence of AEs will be summarized by SOC and PT by presenting the number and percentage of subjects with an AE. A subject will be counted only once within each SOC and within each PT, or the overall category. Separate summaries will be provided for AEs by maximum severity (mild, moderate, severe) and relationship (not related, related) to study vaccine. If a subject reported more than one AE within a SOC or PT, then the AE with the highest known severity or strongest relationship within each SOC and each PT will be included in the summaries by severity or relationship, respectively. These summaries will generally be presented 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.

In addition, the incidence of AEs will be summarized by SOC and by PT separately. Vaccine-related AEs and vaccine-related AEs by maximum intensity will be summarized by SOC and PT. These summaries will be provided for events occurring up to 28 days after each vaccination.

In addition, for each group, *most frequent* unsolicited AEs (with frequency of preferred term greater than 5% and with a minimum of two subjects in any of the 8 formulation/dose combination groups) will be summarized (number/percent of subjects with the event) up to 28 days after either vaccination by SOC and PT. This summary will also be done for *most frequent* non-serious events (presenting both number of events and number/percent of subjects with the

event). The number of most frequent non-serious events will also be presented. Note that the summaries of most frequent non-serious events are being prepared only for trial results disclosure requirements and will not necessarily be addressed in the clinical study report (CSR).

The incidence of AEs leading to investigational vaccine withdrawal will be summarized by SOC and PT after each vaccination and for the entire study duration (including all events leading to withdrawal with onset after the first vaccination dose through the end of the study).

The number of SAEs and number/percent of subjects experiencing SAEs will be summarized by SOC and PT after each vaccination and for the entire study duration (including all reported SAEs with onset after the first vaccination dose).

In addition to the overall AE listing, separate listings for SAEs, AEs leading to subject withdrawal from the trial, AEs resulting in death will be provided

7.11.2 Clinical Laboratory Evaluations

{Not applicable. Not a routine procedure in the protocol}.

7.11.3 Vital Signs

Vital signs are collected during the scheduled physical examinations. Heart rate, body temperature, height, and weight will be summarized descriptively at each scheduled visit. The change from baseline to each scheduled post-baseline visit will also be presented. Measurement parameters will be sorted alphabetically

7.11.4 12-Lead ECGs

{Not Applicable. Not a routine procedure in the protocol}

7.11.5 Other Observations Related to Safety

{Not applicable}

7.12   Interim Analysis

Interim analyses are planned in this study: Day 57 for Cohort 1 and Day 140 for Cohort 2 (primary analysis time point). The Day 57 interim for Cohort 1 will be provided initially for Groups 1 and 2, which 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. Interim analyses will be finalized after the primary safety and immunogenicity data for the group are available, ie, after all subjects from Cohort 1 have completed Day 57 or terminated early and after all subjects from Cohort 2 have completed Day 140 or terminated early.

The interim analyses will be performed by a separate group of unblinded statisticians and programmers at Quintiles who will have access to individual treatment assignments, but will not 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).

The interim results will be shared with limited personnel at Takeda and will include only aggregate group unblinded reports. Individual results will not be shared with any Takeda personnel or the Quintiles blinded team. The list of team members from the study who are given access to the group results will be documented in an unblinding plan. Statistical Methodology for interim analyses will be the same as for final study analysis, described in previous sections, but may be a subset of the analyses to be performed at the end of the study.

Data listings containing subject-level unblinding information will not be generated for either the Day 57 or Day 140 analyses for Cohort 1 and Cohort 2, respectively.

Complete clinical database subject listings will be provided only at final analysis (ie, Day 210 for Cohort 1 and Day 393 for Cohort 2) after the database is locked

7.13   Changes in the Statistical Analysis Plan

Changes from the Analyses Planned in Protocol Version 3.0, 1 March 2016

Section 13.1.4 of the Protocol (Version 3.1) referred to exclusion of biologically implausible measurements. Large or implausible outlying values may be identified by medical reviewers during blind data review and queried before database lock. However, no criteria to identify implausible measurements will be defined in this SAP. Due to the age range of the subjects and the multi-regional settings in this trial, a reliable and consistent cut-off for implausible measurements cannot be developed. Hence all values in the database at time of database lock will be included in the analyses.

Section 6.1 in the study protocol indicated that two interim analyses are to be performed after the primary safety and immunogenicity data are available (ie, Day 57 for Cohort 1 and Day 140 for Cohort 2). Cohort 1 consists of 3 age groups enrolled in age step-down fashion. However due to delay in availability of investigational product, enrollment of Group 3 has been delayed. Therefore, the Day 57 interim analysis of Cohort 1 will proceed on schedule but will initially include only age groups 1 and 2. After study enrollment resumes, Day 57 interim analyses of Group 3 will be provided at a later time.

Description of the Amendment 1 changes to the initial Statistical Analysis Plan

The initial NOR-202 SAP (11 February 2016) has been amended to address changes to the NOR-202 study design effected in Protocol Version 4.0, (Amendment 3) 01 March 2016 [4]. A description of those changes follows. Unless otherwise stated, the reason for each of the changes is to align with Protocol Version 4.0 by updating statistical methodology text to reflect the addition of Group 2a to the study.

Section 4.4, Figure 4.a

Prior Text:

Figure 1   **Schematic of Trial Design**
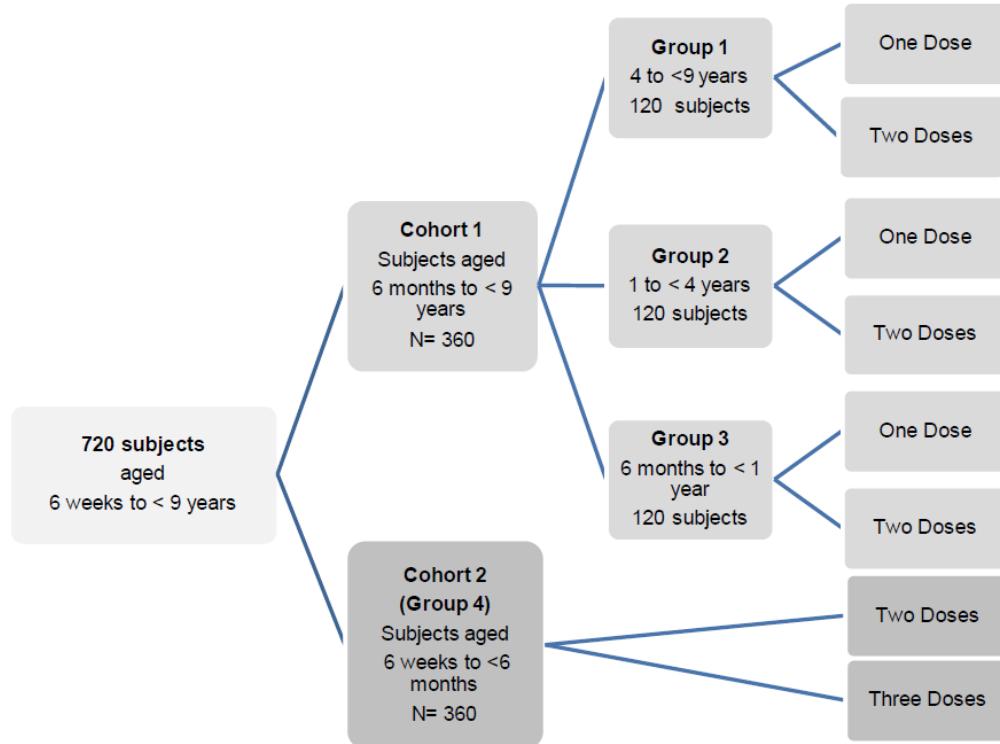
Amended Text:

Figure 4.a   Schematic of Trial Design
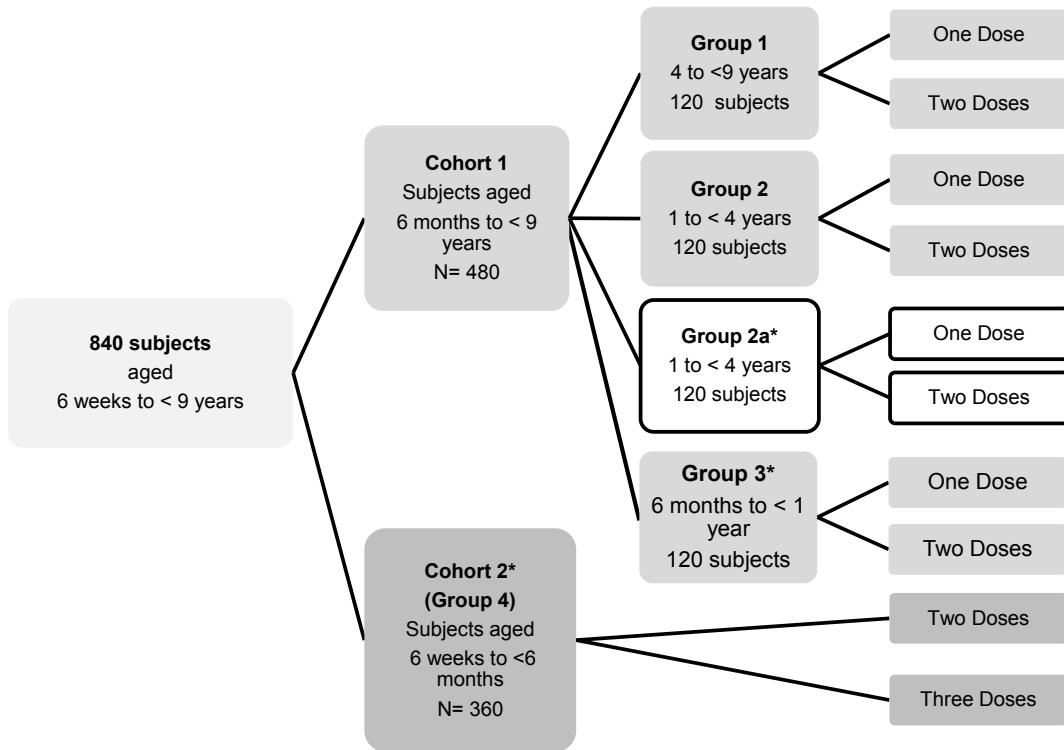
* Recently manufactured clinical trial material lots

Reason for Change:

Reflect the addition of Group 2a to the study.

Section 4.4, Figure 4.a description

Prior Text:

A total of *720* healthy subjects will be randomized to the following cohorts, with stratification by country and group:

- Cohort 1, N=*360* (Group 1: aged 4 to less than 9 years; Group 2: 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). Each of the combinations will consist of approximately 15 subjects per age group.

- Cohort 2 (Group 4: aged 6 weeks to less than 6 months): 360 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 2 or 3 doses). Each of the combinations will consist of approximately 45 subjects.

Amended Text:

A total of **840** healthy subjects will be randomized to the following cohorts, with stratification by country and group:

- Cohort 1, N=**480** (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 will consist of 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 45 subjects.

Reason for Change:

Reflect the addition of Group 2a to the study.

Section 4.4, second paragraph following figure description bullets

Prior Text:

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 age* groups **(**Group 1: aged 4 to less than 9 years; Group 2: aged 1 to less than 4 years; 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.

Amended Text:

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 comprising 3 age ranges (**Group 1: aged 4 to less than 9 years; Group 2 **and Group 2a**: **each group** 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.

Reason for Change:

Reflect the addition of Group 2a to the study and make it clear that the additional group (2a) is enrolled in the dame age range as group 2.

Section 4.4, fourth paragraph following figure description bullets

Prior Text:

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). The interim analyses will be performed by a separate *group* of unblinded statisticians and programmers at Quintiles who will have access to individual treatment assignments but will *not be involved* in subsequent study conduct.

Amended Text:

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). 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 Quintiles who will have access to individual treatment assignments but will not be **otherwise** involved in subsequent study conduct.

Reason for Change:

Update the description of interim analysis strategy to align with the protocol description, amended to accommodate the addition of Group 2a and the delayed enrolment of Group 3.

Section 4.4, Investigational Vaccine:

Prior text:

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, and 3* (Cohort 1) and for the 2 dose group in Group 4 (Cohort 2).

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, *and 260* for Cohort 2.

Revised Text:

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).

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.

Reason for Change:

Reflect the addition of Group 2a and make a correction to the telephone contact schedule for Cohort 2.

Section 4.4, Duration of Trial:

Prior Text:

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.

Amended Text:

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

Reason for Change:

Clarify the total expected study duration for each subject.

Section 4.4, Schedules of Protocol Procedures in Table 4.a, Table 4.b and Table 4.c.

Prior Text:

Table 1   Schedule of Trial Procedures for Subjects Aged 6 Months to Less Than 9 Years (*Cohort 1*)

{Table body and footnotes a-g}

h. CMI will be analyzed in *children* aged ≥ 3 years at selected sites. For these subjects, 3 mL of whole blood will be obtained for whole blood method assays immediately prior to and approximately 28 days after each dose (eg, Days 1, 29, and 57) for a subtotal of 9 mL. Thus, for those children in the CMI subset, a total of 17 mL/subject will be obtained for the entire study period.

Amended Text:

Table 4.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)

{Table body and footnotes a-g}

h. CMI will be analyzed in **a subset** of children aged ≥ 3 years at selected sites. For these subjects, 3 mL of whole blood will be obtained for whole blood method assays immediately prior to and approximately 28 days after each dose (eg, Days 1, 29, and 57) for a subtotal of 9 mL. Thus, for those children in the CMI subset, a total of 17 mL/subject will be obtained for the entire study period

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

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:
(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 (Protocol Sections 9.35 and 9.36).
(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 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.
(e) AEs will be categorized by the investigator by severity (mild, moderate, or severe) and causality (related or not related to vaccine).

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(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 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 for IgA, Avidity, 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.

Reason for Change:

Separate the schedule of study procedures for Cohort 1 (formerly Table 1) into 2 tables (Table 4.a and Table 4.b) to reflect the differences in study procedures for Group 2a and those for Groups 1 and 2, and to clarify that samples for CMI are only collected in a subset of groups 1 and 2.

Prior Text:

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

Amended Text**:**

Table 4.c   Schedule of Trial Procedures for Subjects Aged 6 Weeks to Less Than 6 Months (Cohort 2; N=360)

Reason for Change:

Renumber former Table 2 to Table 4.c. to follow current tables 4.a and 4.b.

Section 5.0, Analysis endpoints, first paragraph:

Prior Text:

Endpoints apply to Cohorts 1 and 2 unless otherwise stated.

Amended Text:

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**

Reason for Change:

Include a general summary of the differences in endpoints between groups 1, 2 and 2a.

Section 5.3, Exploratory Endpoints (selected as shown):

CCI

Reason for Change:

Explicitly indicate which endpoints will not apply to Group 2a.

Section 7.0 Methods of Analysis and Presentation:

Prior Text:

 The phrase "*age group*" used within subsections 7.1, 7.3, 7.4, 7.6, 7.8, and 7.11

Amended text:

Removed the adjective '**age**' from all applicable 'age group' phrases

Reason for Change:

Group 2a was added to the study design in Protocol Version 4 (Amendment 3) and enrolls subjects in the same age range as Group 2. Changing text to refer to "group" rather than to "age group" clarifies that study group (4 groups [groups 2 and 2a with same age range]), not age range per se, is the factor of interest in the statistical model for Cohort 1.

Section 7.1 Methods of Analysis and Presentation, General Considerations:

Prior Text:

This statistical analysis plan (SAP) is based on protocol Amendment 2, Version 3.1, dated April 1st, 2015.

The purpose of this trial is to evaluate the immunogenicity and safety profile of 4 formulations under different dosing regimens in 4 pediatric age *groups*. Two cohorts of subjects will be

enrolled into the trial Figure 4.a). Cohort 1 will *enroll 3 age* groups, *oldest group to youngest group,* in a step-down fashion. The youngest age group (Cohort 2) will be *enrolled last*. Enrollment into each successive *age* group *(oldest to youngest)* is initiated based on DMC recommendation. The factors under investigation for each *age* group within each cohort include: formulation (4 formulation arms within each *age* group); and number of doses (2 levels for each formulation within each *age* group). For *age groups1-3* (in Cohort 1), the number of active doses will be 1 or 2 doses. For *age* 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 *age* group as a stratification factor.

Amended Text:

This statistical analysis plan (SAP) is based on protocol Amendment **3**, Version **4.0**, dated **01 March 2016**.

The purpose of this trial is to evaluate the immunogenicity and safety profile of 4 formulations under different dosing regimens in 4 pediatric age **ranges**. Two cohorts of subjects will be enrolled into the trial (Figure 4.a). 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 4.4**. The youngest age group (Cohort 2, 6 weeks to <6 months) will be **the last to complete enrollment**. Enrollment into each successive group is initiated based on DMC recommendation. **Hereafter the age groups (5 groups covering 4 age ranges) will be designated as 'group'.** The factors under investigation for each group within each cohort 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**.

Reason for Change:

Reflect the addition of Group 2a to the study.

Section 7.1 Methods of Analysis and Presentation, Handling of Missing Values, Titers measured below the LLoQ

Prior Text:

If a *titer value is measured* as below LLoQ, it will be imputed as the half of the LLoQ in summaries and analyses, but will be listed as reported in the raw serology data.

Amended Text:

If a titer value, **for either of the 2 vaccine VLPs or for exploratory endpoint non-vaccine antigens**, is measured as below LLoQ, it will be imputed as the half of the LLoQ in summaries and analyses, but will be listed as reported in the raw serology data.

Reason for Change:

Clarify handling of assay titer values below the LLoQ.

Section 7.4 Demographic and Baseline Characteristics

Prior Text:

Age, gender, race, and other baseline characteristics will be summarized descriptively by formulation arm and dose group, *separately* for each of the groups in the cohorts, for randomized subjects and subjects in the PPS.

Amended Text:

Age, gender, race, and other baseline characteristics will be summarized descriptively by formulation arm and dose group, **overall and separately** for each of the groups in the cohorts, for randomized subjects and subjects in the PPS.

Reason for Change:

Correct omission.

Section 7.7, Study Drug Exposure and Compliance, section header

Prior Text:

7.7 *Study Drug Exposure and* Compliance

Amended Text:

7.7 **Duration of Follow-up and Vaccine Regimen** Compliance

Reason for Change:

In vaccine studies there is no continuous dosing. Therefore study duration is summarized along with vaccination regimen compliance.

Section 7.8, Immunogenicity Analysis, General Methodology

Prior Text:

Analysis of covariance (ANCOVA) will be conducted for continuous outcome *parameters,* examining the effect of formulation/dose combination using log-transformed values of the endpoint as the dependent variable and the corresponding log-transformed baseline (pre-vaccination) value as a continuous covariate. The ANCOVA models will *also* include *age* group as a factor for analyses of Cohort 1 with *an age group* by formulation/dose combination interaction *term as follows*. If the interaction term p-value is <= 0.05, the term will remain in the

model. If the p-value is >0.05 it will be removed. For Cohort 1, the model will include estimates for treatment (formulation/dose combination) effect within each age group, and at the cohort level across *age* groups. A factor for country will be included.

Amended Text:

Analysis of covariance (ANCOVA) will be conducted for continuous outcome parameters **(eg, GMT, GMFR)**, examining the effect of formulation/dose combination using log-transformed values of the endpoint as the dependent variable and the corresponding log-transformed baseline (pre-vaccination) value as a continuous covariate. 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 as follows. If the interaction term p-value is <= 0.05, the term will remain in the model. If the p-value is >0.05 it will be removed. For Cohort 1, the model will include estimates for treatment (formulation/dose combination) effect within each group, and at the cohort level **across groups**. A factor for country will be included **in all models**.

Reason for Change:

(1) clarify that country will be included as a factor in all models (2) change text to refer to group rather than age group, to clarify that group (4 groups [groups 2 and 2a with same age range]), not age range per se, is the factor of interest in the statistical model for Cohort 1 and (3) provide examples of continuous parameters

Section 7.8, Immunogenicity Analysis, *comparisons of interest*

Prior Text:

Subjects with baseline values below the LLoQ for all assays (Pan-Ig, HGBA, and IgA) and VLP antigens (GI.1 and GII.4) will be identified. If warranted, selected immunogenicity summaries may be prepared *by for this subset.*

Amended Text:

Subjects with baseline values below the LLoQ for all assays (Pan-Ig, HGBA, and IgA) and VLP antigens (GI.1 and GII.4) will be identified. If warranted, selected immunogenicity summaries may be prepared **for subsets of interest.**

Reason for Change:

Correction of typo and clarification of phrase.

Section 7.8.1 Immunogenicity Analysis, Secondary and Exploratory Continuous Immunogenicity Endpoints

Prior Text:

GMT, BT50 and GMFR will be analyzed with an ANCOVA model 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. The ANCOVA models will include

age group as a factor for analyses of Cohort 1 with *an age* group by formulation/dose combination interaction *term included as follows*. If the interaction term p-value is <= 0.05, the term will remain in the model. If the p-value is >0.05 it will be removed. For Cohort 1, the model will include estimates for treatment (formulation/dose combination) effect within each *age* group, and at the cohort level across *age* groups. A factor for country will be included. All the applicable pairwise comparisons will be provided with lower levels as the reference groups, with no adjustments for multiplicity. The 14 comparisons of interest listed in the *General Methodology* of section 7.8 will be tested. The analyses will be based on the PPS.

Box plots and/or reverse cumulative distribution (RCD) curves will be provided for comparisons of interest.

Amended Text:

GMT, BT50 and GMFR will be analyzed with an ANCOVA model 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. The ANCOVA models will **include group** as a factor for analyses of Cohort 1 **with a group** by formulation/dose combination interaction term included **if appropriate,** as follows. If the interaction term p-value is <= 0.05, the term will remain in the model. If the p-value is >0.05 it will be removed. For Cohort 1, the model will include estimates for treatment (formulation/dose combination) effect **within each group,** and at the cohort level **across groups**. A factor for country will be included. All the applicable pairwise comparisons will be provided with lower levels as the reference groups, with no adjustments for multiplicity. The 14 comparisons of interest listed in the *General Methodology* of section 7.8 will be tested. The analyses will be based on the PPS.

Box plots and/or reverse cumulative distribution (RCD) curves will be provided for comparisons of interest. **Other graph formats may be included for illustration purpose**

Reason for Change:

Change text to (1) refer to group rather than age group, to clarify that group (4 groups [groups 2 and 2a with same age range]), not age range per se, is the factor of interest in the statistical model for Cohort 1; (2) clarify method for inclusion of interaction term in final model.

Section 7.12, Interim Analysis

Prior Text:

Interim analyses are planned in this study: Day 57 for Cohort 1 and Day 140 for Cohort 2 (primary analysis time point). The Day 57 interim for Cohort 1 will be provided initially for Groups 1 and 2, which will complete Day 57 substantially earlier *than Group 3. Group 3 Day 57 interim analyses* will be provided at a later *time. Interim* analyses will be performed after the primary safety and immunogenicity *data are* available, ie, after all subjects from Cohort 1 have completed Day 57 or terminated early and after all subjects from Cohort 2 have completed Day 140 or terminated early.

Amended Text:

Interim analyses are planned in this study: Day 57 for Cohort 1 and Day 140 for Cohort 2 (primary analysis time point). The Day 57 interim for Cohort 1 will be provided initially for Groups 1 and 2, which 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.** Interim analyses will be finalized after the primary safety and immunogenicity data **for the group** are available, ie, after all subjects from Cohort 1 have completed Day 57 or terminated early and after all subjects from Cohort 2 have completed Day 140 or terminated early.

Reason for Change:

Update the description of interim analysis strategy to align with the protocol description, amended to accommodate the addition of Group 2a and the delayed enrolment of Group 3.

Section 7.13, Changes in the Statistical Analysis Plan

Updated to provide a change history in this document (SAP Amendment 1) relative to the NOR-202 SAP (11 February 2016).

8.0   REFERENCES

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2. Ge M, Durham LK, Meyer RD, Xie W, and Thomas N. Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences, Therapeutic Innovation & Regulatory Science, July 2011, vol. 45 no. 4, 481-493.

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4. A Phase II, Randomized, Double-Blind, Dosage and Adjuvant Justification, Safety and Immunogenicity Trial of Intramuscular Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine combined with Aluminum Hydroxide, with and without Monophosphoryl Lipid A Adjuvant in Children, Toddlers, and Infants, Takeda Vaccines, Inc., Protocol No. NOR-202, Version 4.0 (Amendment 3) dated 01 March, 2016.

Appendix A   Severity Grading Scale for Solicited Local AEs 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	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Swelling at injection site	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Induration at injection site	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm

Source: Protocol Version 4.0, Table 9.a.

Appendix B   Severity Grading Scale for Solicited Local AEs in Children Aged 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	0	<10 mm
	1	Mild: ≥10 – ≤20 mm
	2	Moderate: >20 – ≤40 mm
	3	Severe: >40 mm
Swelling at injection site	0	<10 mm
	1	Mild: ≥10 – ≤20 mm
	2	Moderate: >20 – ≤40 mm
	3	Severe: >40 mm
Induration at injection site	0	<10 mm
	1	Mild: ≥10 – ≤20 mm
	2	Moderate: >20 – ≤40 mm
	3	Severe: >40 mm

Source: Takeda Vaccines Pharmacovigilance.

Signature Page for NOR-202 Statistical Analysis Plan Amendment 1, 17 February 20

Title:

Approval	PPD
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Approval	PPD

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