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

NCT Number: NCT02661490

SAP Approve Date: 02 February 2017

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: NOR-204

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

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

PHASE II

Version: Final 1.0

Date: 02 February 2017

Prepared by:

PPD

Based on:

Protocol Version: 2.0

Protocol Date: 16 November 2015

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1.1 Approval Signatures

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

Approvals:

PPD

02-Feb-2017
Date

02 Feb 2017
Date

03 Feb 2017
Date

02-Feb-2017
Date

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2.0 TABLE OF CONTENTS

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LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

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3.0 LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
Al(OH)3	Aluminum Hydroxide, Alhydrogel®
ANCOVA	Analysis of Covariance
anti-NoV	anti-norovirus
BMI	Body Mass Index
BT_{50}	Blocking Titers 50
CI	Confidence Interval
CCI	[redacted]
CRO	Contract Research Organization
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
E.T.	Early Termination
FAS	Full Analysis Set
$GMBT_{50}$	Geometric Mean Blocking Titer 50
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GI	Genogroup I
GII	Genogroup II
GI.1	Genogroup I, Genotype 1
GII.4	Genogroup II, Genotype 4
GSD	Geometric Standard Deviation
HBGA	Histoblood Group Antigen
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFNγ	Interferon Gamma
Ig	Immunoglobulin
IL-2	Interleukin 2
IL-21	Interleukin 21
IM	Intramuscular
IWRS	Interactive Web Response System
LLoQ	Lower Limit of Quantification
LS Ms	Least Square Means
MCAR	Missing Completely At Random
MedDRA	Medical Dictionary for Regulatory Activities

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MPL	Monophosphoryl Lipid A
NoV	Norovirus
NoVs	Noroviruses
Pan-Ig	Pan Immunoglobulin
PBMC	Peripheral Blood Mononuclear Cell
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TNF-α	Tumor Necrosis Factor-alpha
ULoQ	Upper Limit of Quantification
VLP	Virus-like Particles
WHODrug	World Health Organization Drug Dictionary

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4.0 OBJECTIVES

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

4.1 Primary Objectives

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

4.2 Secondary Objectives

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

4.3 Exploratory Objectives

CCI

[redacted]

4.4 Study Design

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

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vaccine administrations. The 18–49 year old subjects will receive only one NoV G.1/GII.4 Bivalent VLP Vaccine dose (Formulation A).

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

Planned number of Arms.

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

All subjects will receive trial vaccination on Day 1 and Day 29 as shown in Table 1. If Dose 2 is not given on Day 29, subsequent visits should be calculated from the actual Day given (e.g., if Dose 2 is given on trial Day 31, the next visit should be scheduled for trial Day 38).

Table 1 Subject Distribution for Trial NOR-204

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

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

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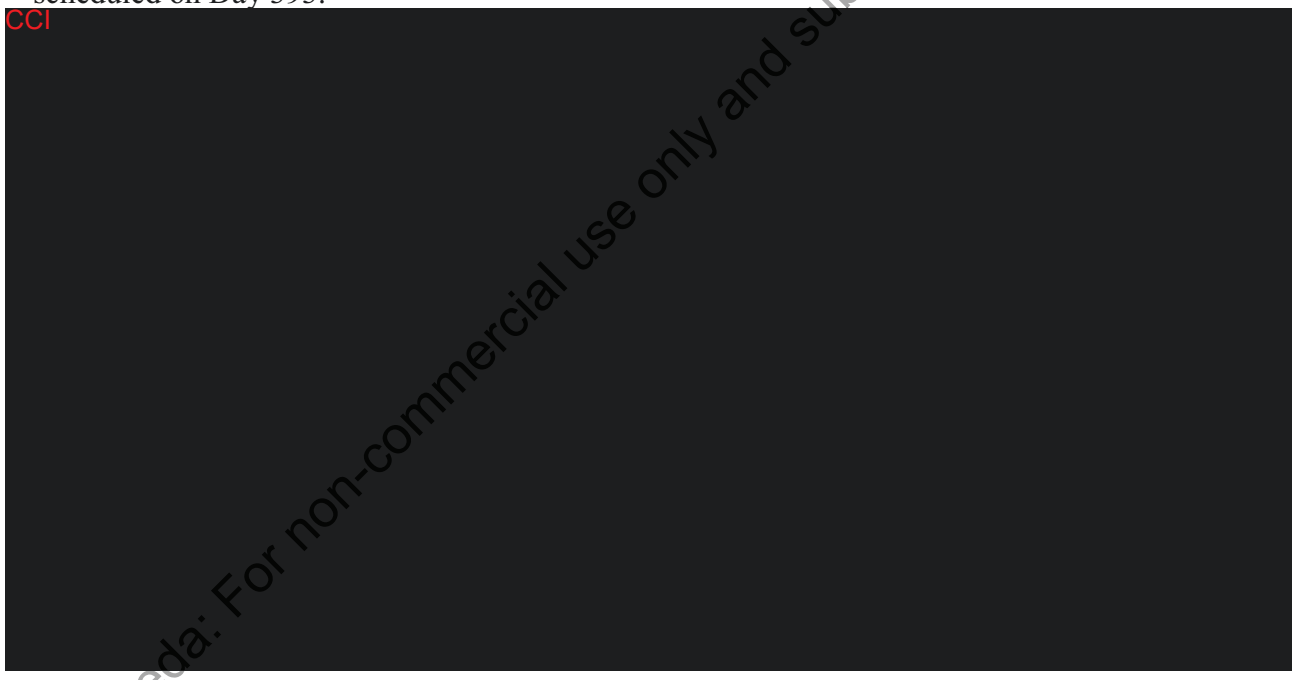
Trial Arms 1, 2, 3 and 4 will include subjects aged ≥60 years distributed into three age groups including: 60-74 years, 75-84 and ≥85 years. Trial Arm 5 will include subjects aged 18–49 years.

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

CCI



A review of safety data will be performed by the Data Monitoring Committee (DMC) as soon as the first approximately 100 subjects have completed the Day 36 Visit (8 days after last vaccination). Refer to Section 7.12.

An interim analysis on safety and immunogenicity data is planned when all subjects have completed the Day 57 Visit (28 days after last vaccination). Refer to Section 7.12. The final Clinical Study Report (CSR) will include analyses of all safety and immunogenicity data through Day 393 as well as individual subject data (including data listings and subject treatment assignments).

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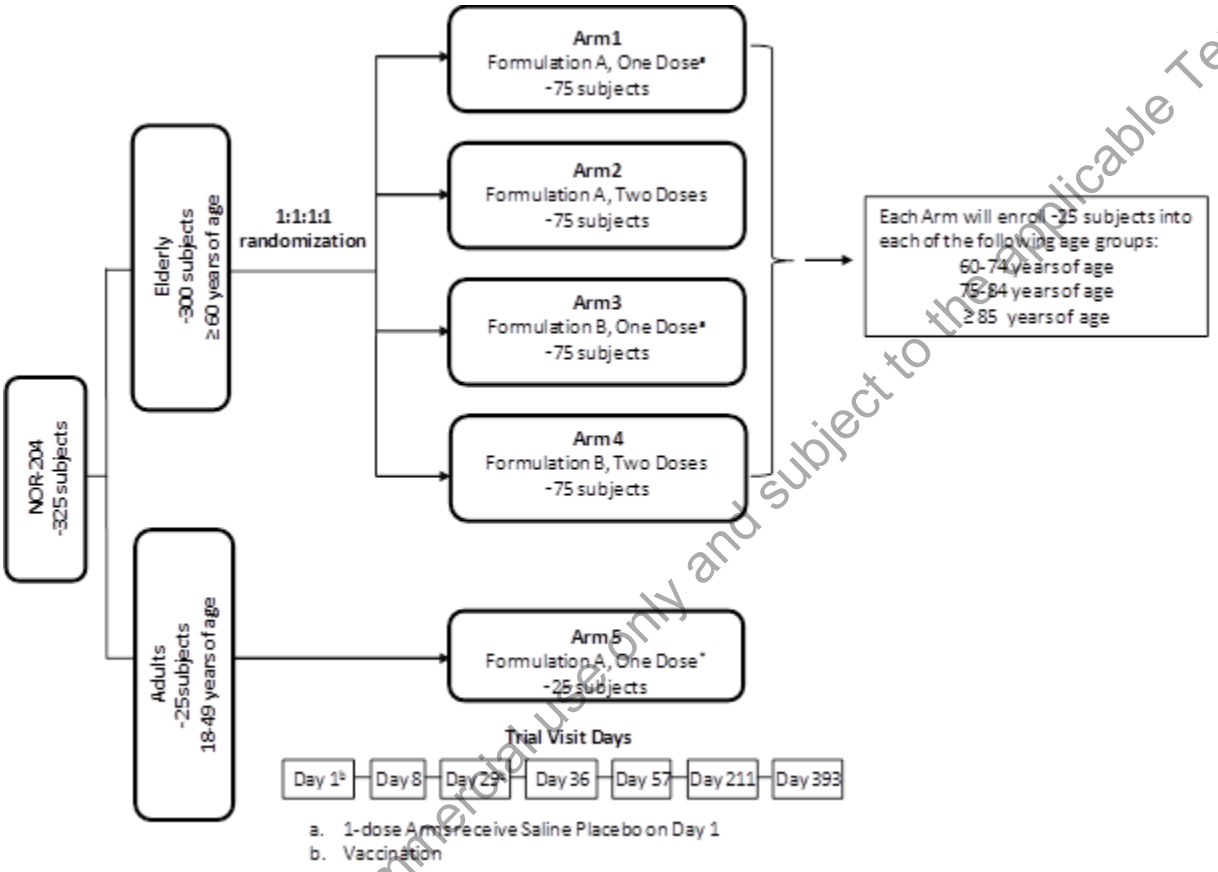
A schematic of the trial design is included as Figure 1.

Figure 1 Schematic of Trial NOR-204 Design



Trial Vaccines:

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

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

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

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

Visit Schedule

Clinical trial visits will be performed on Days 1, 8, 29, 36, 57, 211 and 393 for subjects in all five treatment arms.

Duration of Trial

Subjects will be enrolled for approximately 393 days; that is to capture safety information 365 days after the last trial dose. Short term follow-up for AEs, SAEs, concomitant medications and AESI will be 28 days following each dose (Dose 1: through Day 28, collected on Day 29 and Dose 2: through Day 56, collected on Day 57). Final follow-up for SAEs and AESI will be performed 365 days following the last vaccination (i.e., on Day 393).

A schedule of procedures is listed in Table 2.

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Table 2 Schedule of Trial Procedures

Procedure		Day 1	Day 8	Day 29	Day 36	Day 57	Day 211	Day 393/E.T.[1]
Visit Number		1	2	3	4	5	6	7
Visit Windows			+4 days	+4 days	+4 days	+4 days	+7 days	+14 days
Procedures								
Signed informed consent		X						
Pregnancy test[a]		X		X				
Assessment of eligibility criteria[b]		X		X				
Demographics		X						
Medical history		X						
Medication history		X						
Concomitant medications		X	X	X	X	X	X	X
Physical Examination	Complete[c]	X						
	Symptom Directed		(X)	(X)	(X)	(X)	(X)	(X)
Vital Signs		X	X	X	X	X	X	X
Height, weight and Body Mass Index (BMI)		X						
Randomization		X						
Investigational vaccine administration		X		X				
Post vaccination assessment[d]		X		X				
Diary card[e] training and hand out to the subject		Days 1-7	Days 8-28	Days 29-35	Days 36-56			
Diary card[e] review with the subject and collection			Days 1-7	Days 8-28	Days 29-35	Days 36-56		
Solicited Adverse Events (AEs)		X		X				
Unsolicited AEs[f]		X	X	X	X	X		
Serious Adverse Events (SAEs)[g]		X	X	X	X	X	X	X
Adverse Events of Special Interest (AESI)		X	X	X	X	X	X	X
Blood Draw for Immunogenicity (~ 10 mL)[h]		X[i]	X	X[i]	X	X	X	X
CCI								
CCI								

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

Footnotes:

a. In female subjects of childbearing potential, urine pregnancy tests will be performed before each vaccination. Subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the trial procedures.
b. Continuing eligibility (by review of relevant inclusion/exclusion criteria) will be documented before each vaccination.
c. A complete physical examination is performed on Day 1. At other visits, subjects may undergo a brief symptom-directed physical examination and, if performed, should assess clinically significant changes from baseline.
d. After vaccination on Day 1 and Day 29, the subject will be observed for at least 30 minutes including observation for solicited AEs, unsolicited AEs, and body temperature measurement.
e. Diary cards will be completed from Day 1 through Day 56. Daily diary of solicited AEs from Day 1 through Day 7 and Day 29 through Day 35 (the day of vaccination and for 6 days following each vaccination). Information about unsolicited AEs and medications will be collected from Day 1 through Day 56.
f. AEs including solicited local and systemic events and unsolicited AEs will be collected with the help of the diary card and by interview and categorized by the Investigator as mild, moderate or severe and relatedness to vaccine.
g. SAEs will be reported to the Sponsor or their designee within 24 hours of the Investigator becoming aware of the event throughout the trial. Note: For this trial, SAE reporting will be done by use of the electronic Case Report Form (eCRF). If the Electronic Data Capture (EDC) system is unavailable, a paper Sponsor SAE form/paper CRF should be completed and the event must be entered into the EDC once access is available.
h. Blood draw for immunogenicity includes anti-norovirus (anti-NoV) specific GI.1 and GII.4 Histoblood Group Antigen (HBGA) blocking assays, Pan Immunoglobulin Enzyme-linked Immunosorbent Assay (Pan-Ig ELISA) on Day 1 (prior to vaccination), Day 8, Day 29 (prior to vaccination), Day 36, Day 57, Day 211 and Day 393; IgA ELISA on Day 1 (prior to vaccination), Day 8, Day 29 (prior to vaccination), Day 36, Day 57, Day 211, Day 393 and HBGA blocking assay using a panel of NoV strains not represented in the vaccine on Day 1 (prior to vaccination), Day 36, Day 57 and Day 393. Geometric Mean Titer (GMT), Geometric Mean Blocking Titer 50 ($GMBT_{50}$), Geometric Mean Fold Rise (GMFR), and percentage of subjects with ≥4-fold antibody rise from baseline will be determined for all available subjects in each age group. CCI [redacted]
i. Samples will be taken prior to vaccination.
j. CCI [redacted]
k. CCI [redacted]
l. Day 393/E.T. Early Termination. In case of Early Termination same safety procedures will apply. Refer to Sections 7.5 and 9.3.8 of the protocol [1,2].

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5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

Immunogenicity

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

Safety

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

5.2 Secondary Endpoints

Immunogenicity

<u>HBGA blocking assay</u>

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

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

Pan-Ig Enzyme-linked Immunosorbent Assay (ELISA)

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

Safety

- Percentage of subjects with AESI throughout the trial;
- Percentage of subjects with any AE leading to subject's withdrawal throughout the trial.

5.3 Exploratory Endpoints

CCI

[redacted]

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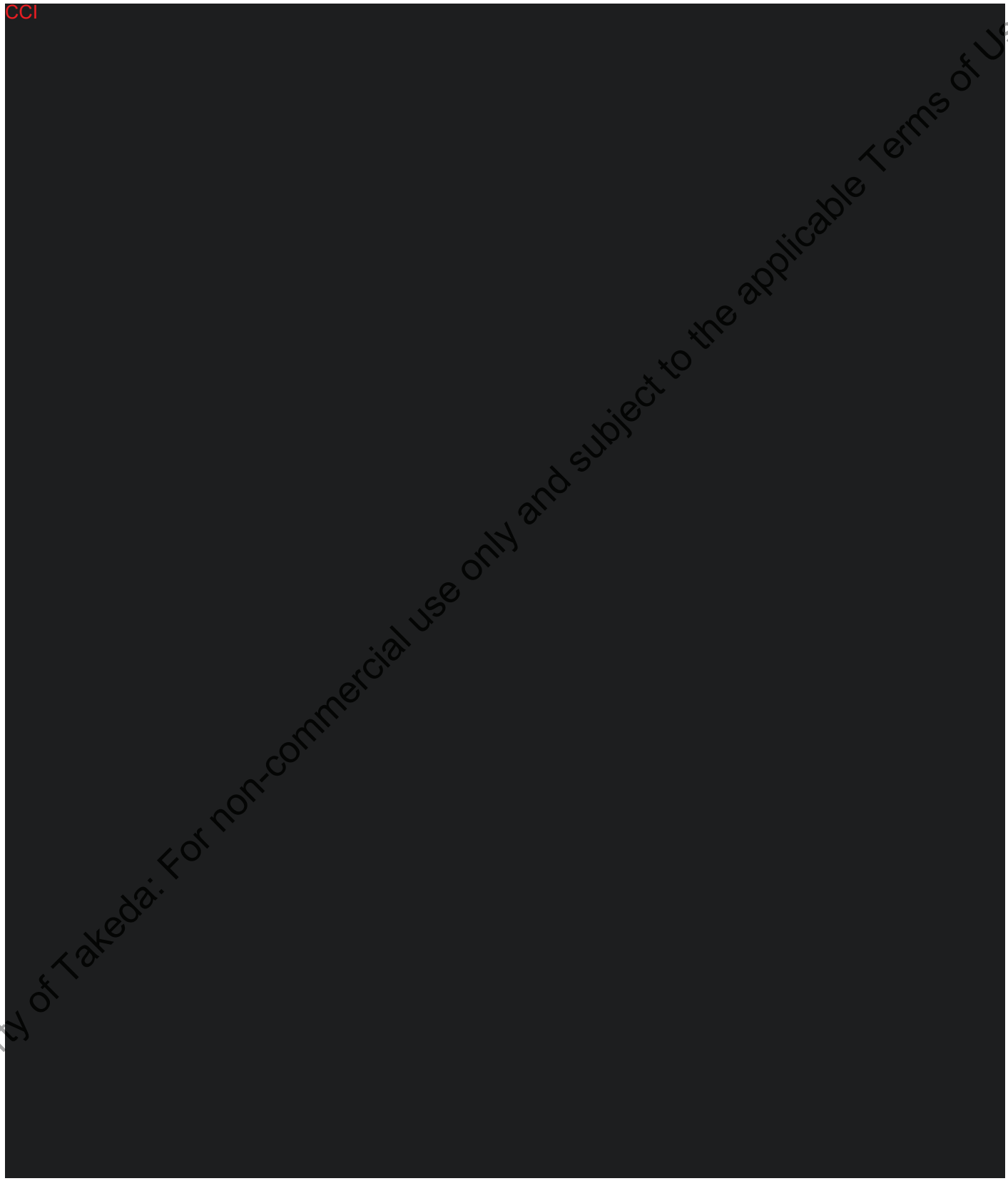
CCI



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6.0 DETERMINATION OF SAMPLE SIZE

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

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7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

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

Immunogenicity and safety endpoints will be summarized descriptively (frequency and percent for categorical data; and number of subjects with non-missing observation, mean, standard deviation (SD), median, minimum and maximum for continuous data) by all relevant study visits, as appropriate. In summary tables for categorical data for which categories are defined on the eCRF, all categories will be presented as specified, even if the subject count within that category is zero. For other categorical data (e.g. adverse events and medications), only categories with at least 1 subject will be presented.

In general, summaries and analyses are to be provided by treatment arm and by age group. The following terminology and conventions will be used as applicable.

Presentation of results by treatment, and by treatment within each age group (60–74, 75–84, and ≥85 years), will be provided for:

- **A1: Arm 1:** NoV GI.1/GII.4 Bivalent VLP Vaccine, Formulation A, 1-dose regimen (subjects ≥60 years).
- **A2: Arm 2:** NoV GI.1/GII.4 Bivalent VLP Vaccine, Formulation A, 2-dose regimen (subjects ≥60 years).
- **A3: Arm 3:** NoV GI.1/GII.4 Bivalent VLP Vaccine, Formulation B, 1-dose regimen (subjects ≥60 years).
- **A4: Arm 4:** NoV GI.1/GII.4 Bivalent VLP Vaccine, Formulation B, 2-dose regimen (subjects ≥60 years).
- **A5: Arm 5:** NoV GI.1/GII.4 Bivalent VLP Vaccine, Formulation A, 1-dose regimen (Subjects 18–49 years).

When applicable, summaries of all subjects (treatment arms **A1, A2, A3, A4** and **A5** combined), and/or summaries of all elderly subjects (treatment arms **A1, A2, A3,** and **A4** combined), will be provided.

Unless otherwise stated the conventions below will be used in reporting results. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Means, the least squares means (LS Means), and medians will be presented to 1 more decimal place than the recorded data. Standard deviations (SD) will be presented to 2 more decimal places than the recorded data. The 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 (e.g., 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".

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts.

Baseline is defined as the last non-missing measurement taken before the first dose of vaccination including the screening value or a value from an unscheduled visit, if necessary.

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7.1.1 Study Day and Analysis Window Definitions

Definition of Study Days

Study Day 1 is defined to be the date of the first vaccination, as recorded on the CRF vaccination page. Study days will be defined relative to Day 1. In addition the study period will be broken down into two periods. For period one, study days following the first vaccination up until the date of the second vaccination inclusive, are defined relative to study Day 1. For period two, study days following the second vaccination up until the end of study visit are defined relative to the date of the second vaccination.

Definition of Study Visit Windows

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 3 will be used for the immunogenicity (CCI [redacted]) and vital signs, respectively. The windows for immunogenicity and vital signs are constructed relative to actual dosing day. The window conventions are:

1) A window of +/- 4 days from the target day are applied to Study Visits 2 and 4;
2) A window of +/- 7 days from the target day are applied to Study Visits 3 and 5;
3) A window of +/- 28 days from the target day are applied to Study Visits 6 and 7.

Table 3 CCI [redacted] and Safety Analyses

				Visit Window (Study Day)		
Period	**Visit Number**	**Visit Name**	**Day Relative to Dose within the Period[b]**	**Serology**	**CCI [redacted]**	**Vital Signs**
Period 1 (Relative to Dose 1)	1	Baseline[a]	1	1	1	1
	2	Day 8	8	4 – 12	n/a	4 – 12
	3	Day 29	29	22 – 36	n/a	22 – 36
Period 2 (Relative to Dose 2)	4	Day 36	8	4 – 12	4 – 12	4 – 12
	5	Day 57	29	22 – 36	22 – 36	22 – 36
	6	Day 211	183	155 – 211	n/a	155 – 211
	7	Day 393	365	337 – 393	337 – 393	337 – 393

Footnotes:
(a) Where time is available, the time of the collection needs to be prior to the first dose of vaccination. Day 1 observations taken after the first dose are considered post-baseline values.
(b) For each period, the administration of the vaccination 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.

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 3). In such an event, the result with

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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.

In addition the following rules will be utilized to identify the relevant record to be used for immunogenicity analysis of genotype parameters GI.1 VLP and GII.4 VLP. These rules are applicable to all immunogenicity endpoints described in Section 7.8, CCI [redacted] The rules are to be applied in the following order:

1. If the collection data at closest visit window have both GI.1 and GII.4 non missing measurements, use that collection data.
2. If the collection data at closest visit window have either GI.1 or GII.4 measurement missing, but data collected at other date/time within the same visit window have both GI.1 and GII.4 measurements non-missing, use the collection data with both GI.1 and GII.4 non-missing.
3. If none of data collected within a visit window have both GI.1 and GII.4 non-missing, pick the GI.1 and GII.4 non-missing measurement separately based on SAP selection rule. That is, the analysis flag assigned to GI.1 and GII.4 will have different collection date/time.
4. If only one of the genotype parameter has non-missing measurement(s) within a visit window, the analysis flag will only apply to the parameter (GI.1 or GII.4) with non-missing measurement(s).
5. Data selected in point 3 will be included in summary analysis of ">= 4 fold rise for both GI.1 and GII.4" endpoints.

Diary data, including reactogenicity and oral body temperature, are collected at the study visits, and will contain entries by date within the interval between the visits. Visit window rules will not be applied to the diary data, and will be summarized by the nominal days, as recorded on the CRF.

All data in the clinical database will be provided in the listings at final analysis (ie. Day 393 Analysis), including those collected beyond the cut-off (eg. data collected after Day 400 for Day 393 analysis).

7.1.2 Conventions for Handling Missing Values

There will be no imputation for missing data with the exception of (1) missing or partial dates (i.e., start dates of AEs), and (2) titer values measured below lower limit of quantification (LLoQ) or above upper limit of quantification (ULoQ).

Missing or partial AE dates

Partial dates will be presented as recorded in the listings. The partial dates of AEs will be imputed only to determine the relationship between the start date of those partial dates and the dose date of the most appropriate vaccination that the AE should be associated with (i.e. Vaccination 1 or Vaccination 2).

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An adverse event should be temporally associated with the correct vaccination dose as far as possible. If an event has a missing or incomplete start 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 possible date will be used for imputation. For example, if Vaccination 1 is on 01 January 2016 and Vaccination 2 is on 02 March 2016 and the event has an incomplete start date of February 2016, then the event would have an imputed date of 01 February 2016. If the available start date information is insufficient to distinguish between 1 or more vaccination dates, then the event end date will be assessed to determine the earliest possible imputed date relative to the latest vaccination. In the above example if an event is known to start in 2016 (day and month missing) and the end date is known as 20 March 2016, then an imputed start date of 02 March (date of Vaccination 2) will be used. If an event is missing both start and end date then the last vaccination date will be used as the imputed start date. When event end dates are missing or partially missing, information such as whether the AEs are ongoing by the end of study will be taken into consideration.

Titer measured below LLoQ or above ULoQ

For a titer value measured as having a value below LLoQ, it is to be imputed as the half of the LLoQ in summaries and analyses, and it will be listed as reported in the raw data. For example, if an assay has the level of LLoQ of 120, and a sample is reported to have "<120" as the titer level, a value of 60 (half of 120) is to be used for the statistical summaries.

For a titer value measured as having a value above ULoQ, a value of the level of ULoQ will be used for the summaries and analyses, and it will be listed as reported in the raw data. For example, if an assay has the level of ULoQ of 120, and a sample is reported to have ">120" as the titer level, a value of 120 is to be used for the statistical summaries.

7.2 Analysis Sets

The following analysis sets are defined for this study.

Randomized Set: all randomized subjects regardless of whether any study vaccine (NoV VLP vaccine or placebo) was received. Data will be analyzed according to treatment randomized. Note that subjects who were randomized in error (per IWRS) will be excluded from the Randomized Set.

Safety Analysis Set (SAF): all subjects who receive at least 1 dose of vaccine (NoV VLP vaccine or placebo). Data will be analyzed according to treatment received.

Full Analysis Set (FAS): all subjects who are randomized and have at least 1 dose of vaccine (NoV VLP vaccine or placebo). Data will be analyzed according to treatment randomized.

Per Protocol Set (PPS): All subjects in the FAS, who receive the planned vaccination (both doses of vaccine, i.e. NoV VLP vaccine or placebo), and do not have major protocol violations will be included in the PPS. The categories of major protocol violations include:

1) Not meeting entry criteria, based on selected inclusion/exclusion criteria (exclusion criteria #10 and #11) defined in protocol [1, 2] Sections 7.1 and 7.2;

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Exclusion criterion #10: Known or suspected impairment/alteration of immune function, including the following:

a. Chronic use of oral steroids (Equivalent to 20 mg/day prednisone ≥ 12 weeks / ≥ 2 mg/kg body weight / day prednisone ≥ 2 weeks) within 60 days prior to Day 1 (use of inhaled, intranasal, or topical corticosteroids is allowed).
b. Receipt of parenteral steroids (Equivalent to 20 mg/day prednisone ≥ 12 weeks / ≥ 2 mg/kg body weight / day prednisone ≥ 2 weeks) within 60 days prior to Day 1.
c. Receipt of immunosuppressive therapy within 3 months prior to Day 1.
d. Receipt of immunostimulants within 60 days prior to Day 1.
e. Receipt of parenteral, epidural or intra-articular immunoglobulin preparation, blood products, and/or plasma derivatives within 3 months prior to Day 1 or planned during the full length of the trial.
f. Human Immunodeficiency Virus (HIV) infection or HIV-related disease.
g. Genetic immunodeficiency.

Exclusion criterion #11: Abnormalities of splenic or thymic function.

2) Receiving wrong trial treatment;
3) Not receiving both doses of trial vaccine or receiving the second trial dose inadmissibly outside of the visit window;
4) Receiving prohibited therapies in the following categories (also specified in protocol [1, 2] Section 9.1.2):
   - Parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within 3 months of the first vaccination, or any time during the trial.
   - Immunosuppressive therapy within 6 months or systemic (eg, oral or parenteral) corticosteroid treatment within 60 days prior to vaccine administration.
   - Administration of other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to administration of study vaccine.
5) Other major violations that compromise the primary immunogenicity endpoint assessment.

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 protocol deviations will be identified prior to unblinding and a clinical judgment will be necessary to classify each deviation as a "major" violation or not. These violations and the judgment regarding their use will be listed and summarized in the final clinical study report. Refer to Section 7.3.2. The major protocol violation criteria will be finalized as part of the blind data review prior to the interim analysis planned after all subjects have completed the Day 57 Visit (28 days after last vaccination). Refer to Section 7.12.

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The safety analysis will be based on the Safety Analysis Set. The primary immunogenicity analyses will be based on the PPS, and additional immunogenicity analyses will be based on the FAS. CCI [redacted]

7.3 Disposition of Subjects

7.3.1 Disposition

The number of screen failures, their characteristics and the primary reasons for screen failure will be summarized overall.

Disposition of all screened subjects will be summarized descriptively, including a summary of the number of screened subjects, the number of randomized subjects and the number of non randomized subjects for each age group, all elderly subjects and all subjects overall.

The number of randomized subjects will also be presented by treatment arm, all elderly subjects and all subjects overall for each country/center and age group. In addition analysis populations will be summarized by treatment arm, all elderly subjects and all subjects overall, for all age groups and by treatment arm and all elderly subjects within age groups.

Disposition for all randomized subjects will be summarized by treatment arm, all elderly subjects and all subjects overall for all age groups and by treatment arm and all elderly subjects within age groups. 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.

Individual subject disposition data will be provided in listings.

For DMC and IA the number of ongoing subjects that have not yet completed the vaccine regimen/study visits will also be provided.

7.3.2 Protocol Violations

Major protocol violations leading to exclusion from PPS will be summarized by treatment arm, all elderly subjects and all subjects overall, for all age groups and by treatment arm and all elderly subjects within age groups based on FAS. All protocol deviations will be listed and those considered as significant protocol deviation and also major protocol violations will be identified in the listing. For definition of major protocol violations in relation to this study PPS please refer to Section 7.2.

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7.4 Demographic and Other Baseline Characteristics

Age, gender, race, weight, height, BMI and other baseline characteristics will be summarized descriptively by treatment arm and all elderly subjects, for all age groups combined and within age groups based on the set of all randomized subjects. This analysis will also be repeated for the PPS CCI [redacted].

These data will also be listed.

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 18.0, or higher) coding system.

Frequency and percentages of subjects by medical history and concurrent medical conditions will be summarized by system organ class (SOC), preferred term (PT) and by treatment arm and all elderly subjects, for all age groups and within age groups based on the SAF.

Medical history and concurrent medical condition data will also be listed.

7.6 Medication History and Concomitant Medications

Medication history and concomitant medications will be coded using the World Health Organization DRUG dictionary (WHODrug Version March 2015).

Frequency and percentages of subjects by medication history and concomitant medications will be summarized by preferred medication name (i.e. generic), by treatment arm and all elderly subjects, for all age groups combined and within age groups based on the SAF.

Listings for medication history and concomitant medications will also be produced.

7.7 Study Drug Exposure and Compliance

Compliance rate will be summarized by treatment arm and all elderly subjects, for all age groups combined and within age groups, by presenting the number and percentage of subjects receiving the first dose only, and the number and percentage of those receiving both doses of vaccination.

The duration of follow-up will be summarized as a continuous variable, and also according to the following categories:

- 1 – 28 days,
- 29 – 56 days,
- 57 – 210 days,
- 211 – 392 days,
- >= 393 days

The follow-up is defined as the number of days since the first vaccination to the end of study visit. For interim analysis and safety review, if the end of study visit dates are not reported, the subject-specific date of data cutoff will be used for calculation.

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The analyses described above will be based on SAF. All data will be presented in listings as well.

7.8 Immunogenicity Analysis

Immunogenicity analyses will be based primarily on PPS. Supportive immunogenicity analyses will be performed using FAS.

Immunogenicity results from the trial will be summarized by treatment (**A1**, **A2**, **A3**, **A4** and **A5**), and by treatment within each age group. Treatment arm **A5** will be presented as reference, in each age group level analysis. In addition, for primary and secondary immunogenicity endpoints only, results will be summarized by dosing regimen (over all age groups and within each age group), where '1-Dose' grouping will summarize results over treatments **A1** and **A3** (i.e. one dose regimen treatment arms) and '2-Dose' grouping will summarize results over treatments **A2** and **A4** (i.e. two dose regimen treatment arms). Finally, for primary and secondary immunogenicity endpoints only, results will be summarized by formulation type (over all age groups and within each age group), where 'MPL-' grouping will summarize results over treatments **A1** and **A2** (i.e. formulation A treatment arms) and 'MPL+' grouping will summarize results over treatments **A3** and **A4** (i.e. formulation B treatment arms).

Where comparisons between treatment groups are to be performed, the following pre-specified pairwise comparisons of interest will be presented:

a. A2 vs A1; A3 vs A1; A4 vs A1;
b. A3 vs A2; A4 vs A2; A4 vs A3;
c. A1 vs A5; A2 vs A5; A3 vs A5; A4 vs A5;
d. 1-Dose (A1 + A3) vs 2-Dose (A2 + A4).
e. MPL- (A1 + A2) vs MPL+ (A3 + A4).

7.8.1 Primary Efficacy Endpoint(s)

The primary immunogenicity endpoint is defined in Section 5.1.

The primary endpoint will be presented by treatment arms for all age groups and within each elderly age group level, as well as by dosing regimen, as described in Section 7.8, at Day 57 for the PPS.

For each subject (i) the fold rise (f_i) in titer value, at a specific post baseline time point is calculated as :

$$f_i = v_{post}/v_{pre}$$

where v_{post} is the post vaccination value of the titer at that specific time point and v_{pre} is the pre vaccination (baseline) value of the titer. Subjects with a 4-fold rise or greater (i.e $f_i >= 4$) in serum anti-NoV antibody titers for both GI.1 VLP and GII.4 VLP as measured by HBGA blocking assay on Day 57 (28 days after the last vaccination) will be counted within each treatment arm at the visit and rates and percentages will be provided based on the number of

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subjects with a non-missing value within the treatment arm at the visit as well as the corresponding 95% CI. The exact (Clopper-Pearson) method will be used to produce the 95% CI, i.e. no adjustment related to age stratification will be applied.

In addition, pairwise comparisons with lower level as a reference group, as defined in Section 7.8, will be presented for Day 57, without multiplicity adjustment.

Risk ratios, and corresponding 95% CIs and Fisher's exact test p-values, will be calculated as well as risk differences and associated confidence limits based on the Newcombe score method for pairwise comparisons (a, b, c and d) between treatment arms, within each elderly age group (60–74, 75–84, and ≥85 years).

For between treatment arms analyses for all elderly age groups combined (60–74, 75–84, and ≥85 years), pairwise comparisons (a, b, c and d) will be performed as well. For pairwise comparisons 'a', 'b', 'd' and 'e' only, a Cochran Mantel Haenzel (CMH) method stratified by age, will be used to provide the age adjusted risk ratios, the corresponding 95% CIs and p-values. In addition age adjusted risk differences and corresponding 95% Wald-type CIs will be provided (due to computational simplicity) using a CMH weighting strategy. For pairwise comparisons 'c', a simple non stratified approach will be followed similar to the one described in the previous paragraph. Since elderly population treatment arms **A1, A2, A3** and **A4** do not share the same age stratification as the younger adults treatment arm **A5**, crude estimates for rates and proportions for treatment arms **A1, A2, A3** and **A4** will be utilized when comparing these with treatment arm **A5**.

Since the missing data resulting from dropouts in vaccine trials are typically missing completely at random (MCAR) [4], a simple way of handling missing data is to use a "complete case analysis", i.e., to exclude subjects with missing data at baseline or at the endpoint visit. In the case when more than 20% of the subjects have missing data in primary immunogenicity endpoint, multiple imputation methods may be explored as a sensitivity analysis.

7.8.2 Secondary Efficacy Endpoint(s)

Secondary immunogenicity endpoints are listed in Section 5.2.

Endpoints listed below, corresponding to percentages of subjects with a 4-fold rise or greater of serum anti-NoV antibody titers for GI.1 VLP and GII.4 VLP separately or both GI.1 VLP and GII.4 VLP simultaneously as measured by HBGA blocking assay or Pan-Ig Enzyme-linked Immunosorbent Assay (ELISA), will be summarized for study visits Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393, following a similar approach to that described in Section 7.8.1 for the primary endpoint. Any pairwise comparisons, with lower level as a reference group, as defined in Section 7.8, are to be presented for Day 36, Day 57, Day 211, and Day 393 only.

In addition, percentages of subjects with a 4-fold rise or greater and corresponding 95% CI will be graphically summarized using bar charts, by treatment arms for all age groups and within each elderly age group level for Day 8, Day 29, Day 36, Day 57, Day 211 and Day 393.

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HBGA blocking assay

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

Pan-Ig Enzyme-linked Immunosorbent Assay (ELISA)

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

Continuous endpoints listed below, corresponding to values of serum anti-NOV antibody titers for GI.1 VLP or GII.4 VLP separately as measured by HBGA blocking assay or Pan-Ig Enzyme-linked Immunosorbent Assay (ELISA), will be summarized and provided in the following way. Geometric mean titers (GMT) and the corresponding geometric standard deviation (GSD), and 95% CIs for the GMT as well as the minimum and maximum titer value, will be presented at first instance by treatment, and by treatment within each elderly age group, as well as by dosing regimen. Treatment arm **A5** will be presented as reference, in each age group level analysis.

Similarly estimates of Geometric Mean Fold Rise (GMFR) and the corresponding geometric standard deviation (GSD), and 95% CIs for the GMFR as well as the minimum and maximum fold rise value, will be presented following the same approach as the GMT results.

In addition, Geometric Mean Anti-NoV Antibody Titers and Geometric Mean Fold Rise in Anti-Nov Antibody Titers will be graphically summarized using bar charts, by treatment arms for all age groups and within each elderly age group level for Day 1, Day 8, Day 29, Day 36, Day 57, Day 211 and Day 393 respectively.

HBGA blocking assay

- GMT of anti-NoV GI.1 VLP antibody titers as measured by HBGA blocking assay (Day 1, Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);

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

Pan-Ig Enzyme-linked Immunosorbent Assay (ELISA)

- GMT of anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA (Day 1, Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMT of anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA (Day 1, Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMFR of anti-NoV GI.1 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393);
- GMFR of anti-NoV GII.4 VLP antibody titers as measured by Pan-Ig ELISA (Day 8, Day 29, Day 36, Day 57, Day 211, and Day 393).

The GMT will be calculated as the anti-logarithm of the mean of the log-transformed titer values v_i, i.e., anti-logarithm of ∑(log transformed titer/n), where n is the number of subjects with non missing titer information. Similarly the GSD for GMT 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 the mean of the log-transformed fold rise (f_i) in titer values, at a specific post baseline time point defined as :

$$f_i = v_{post}/v_{pre}$$

where v_{post} is the post vaccination value of the titer at that specific post baseline time point and v_{pre} is the pre vaccination baseline value of the titer, i.e., anti-logarithm of ∑ (log transformed (post-vaccination titer/ pre-vaccination titer)/n), where n is the number of subjects with non missing titer information at both pre and post baseline visits. The GSD and 95% CIs for GMFR will be calculated similarly to those for GMT.

In addition, statistical analyses utilizing an ANCOVA model will be performed for the continuous endpoints listed above. An ANCOVA model will be run separately at each study visit corresponding to Day 36, Day 57, Day 211, and Day 393 only, within each elderly age group, and overall. The model will be used to perform pre-specified pairwise comparisons (a, b, c, d, e), including treatment arm as a fixed factor and baseline values as a covariate. Treatment arm **A5** will be included in the analysis model in order to serve as reference.

More formally the following model:

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$$\log(v_{ij\text{-}post}) = \beta_0 + \text{treatment}_j + \beta \log(v_{ij\text{-}pre}) + e_{ij}$$

where $\log(v_{ij\text{-}post})$ is the log transformed titer value at the specific post baseline study day and $\log(v_{ij\text{-}pre})$ is the log transformed titer value at baseline, for subject i in treatment arm j (1=A1, 2=A2, 3=A3, 4=A4 and 5=A5).

For between treatment arms analyses for all elderly age groups combined (60–74, 75–84, and ≥85 years), when performing pre-specified pairwise comparisons 'a', 'b', 'd' and 'e', an additional age group fixed factor with 3 levels (60–74, 75–84, and ≥85 years) will be added to the model to utilize the age stratification information present within treatment arms **A1**, **A2**, **A3** and **A4**. In this case the younger adults treatment arm **A5** will not be included as a level, since elderly population treatment arms **A1**, **A2**, **A3** and **A4** do not share the same age stratification as the younger adults treatment arm **A5.** When performing pre-specified pairwise comparisons 'c' a similar model as the one described in the previous paragraph will be used.

Using the model described above the GMT estimates for each treatment arm will be provided by transforming back to original scale by exponentiation of the least squares means (LSMs) for each treatment arm. In addition the geometric mean ratio (and associated 95% CI) of the corresponding pairwise comparison will be provided by transforming back to original scale by exponentiation of the least squares means (LSMs) of the treatment arm difference. Finally a p-value for the assessment of each pairwise comparison will be provided.

A similar model will also be used to perform pairwise comparison between treatment arms based on log-transformed fold rise (f_i) in titer values. In this case the GMFR estimates for each treatment arm will be provided by transforming back to original scale by exponentiation of the least squares means (LSMs) of each treatment arm. In addition the geometric mean ratio (and associated 95% CI) of the of the corresponding pairwise comparison will be provided by transforming back to original scale by exponentiation of the least squares means (LSMs) of the treatment arm difference. Finally a p-value for the assessment of each pairwise comparison will be provided.

7.8.3 Additional Immunogenicity Endpoint(s)

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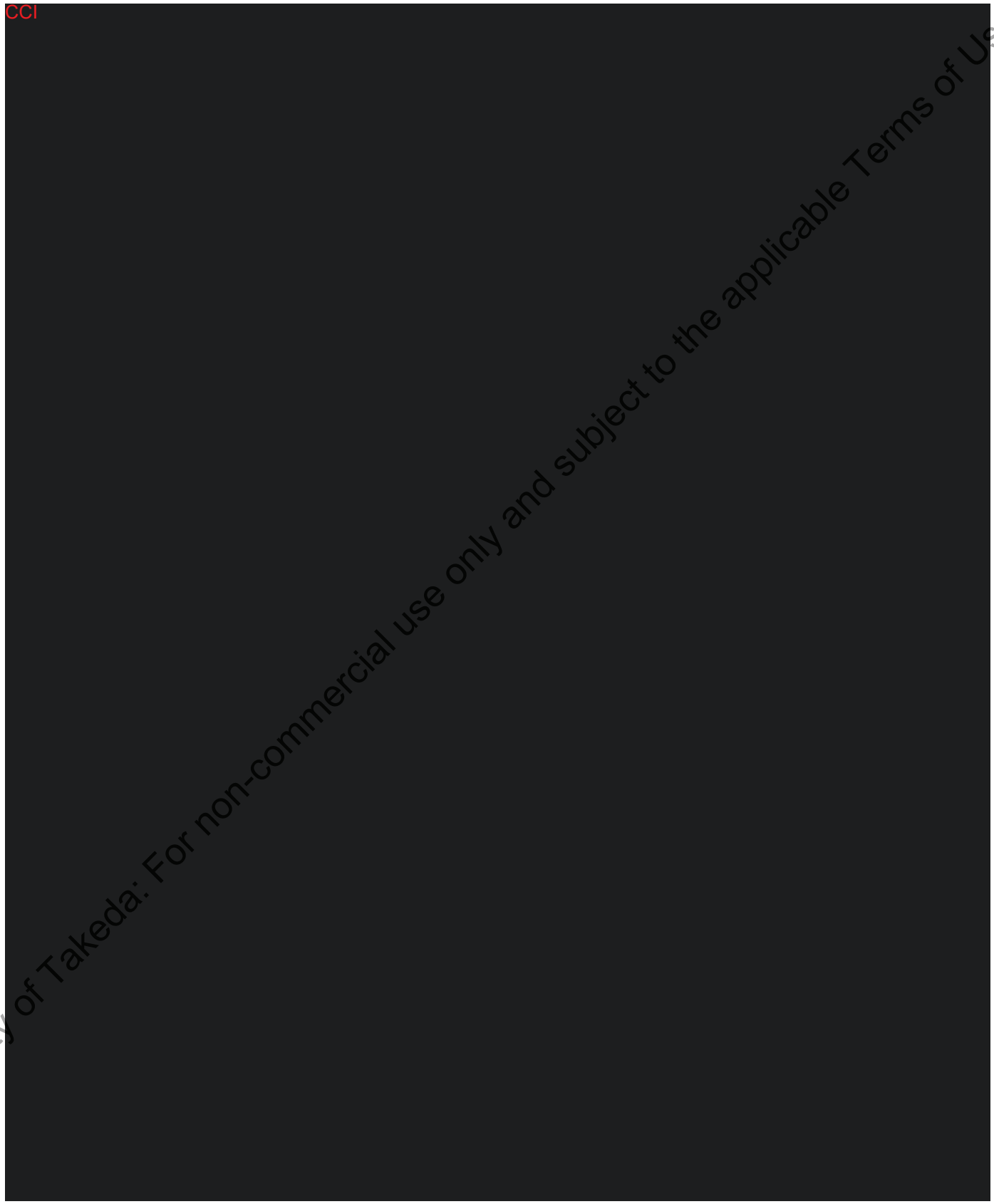
CCI



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7.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

7.9.1 Pharmacokinetic Analysis

Not applicable.

7.9.2 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 by treatment arm, all elderly subjects, for all age groups at first instance and by treatment arm and all elderly subjects within age groups as appropriate.

In general, data imputation will not be performed for any missing safety data. The biologically implausible measurements for body temperature and solicited local symptoms are provided in Table 4. Any measurements meeting those criteria will be excluded from the summaries and analyses, but included in the data listings.

Table 4 Definitions of implausible measurements

Parameters	Criteria
Body temperature (collected in diary data)	< 35°C or > 42°C
Erythema	>50.0 cm
Induration	>50.0 cm
Swelling	>50.0 cm

7.11.1 Adverse Events

Reactogenicity

After vaccination on Day 1 and Day 29, the subject will be assessed for reactogenicity by investigator/staff for at least 30 minutes including observation for solicited AEs, including local AEs (injection site: pain, erythema, induration and swelling) and systemic AEs (headache, fatigue, myalgia, arthralgia, vomiting, and diarrhea), as well as body temperature measurement. Furthermore reactogenicity will be assessed for 7 days following each vaccination (the day of vaccination and the following 6 days) via diary card completion and collection of solicited AEs, including local AEs (injection site: pain, erythema, induration and swelling) and systemic AEs (headache, fatigue, myalgia, arthralgia, vomiting, diarrhea, body temperature).

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The categories for each solicited AE are defined in Section 10.1.3 of the protocol [1, 2]. Pain is summarized as either none or any: where "any" will be broken down into the following categories: mild, moderate, and severe. Erythema, swelling and induration are recorded as yes or no, where the definition of "yes" is any area >= 25 mm; and "yes" will be further broken down into the following categories: >= 25 mm - <= 50 mm, > 50 mm - <= 100 mm, and > 100 mm. Severity categories for erythema, induration and swelling will be displayed in summary tables as: Mild: >=25-<=50 mm, Moderate: >50-<=100 mm, Severe: >100 mm, Any: >=25 mm, None: <25 mm.

Body temperature will be categorized as fever present (>= 100.4ºF, >=38ºC) or fever absent (< 100.4ºF, < 38ºC). For those subjects with fever present this will be further categorized as provided in Table 5.
Unless otherwise specified, the categories based on the Celsius (with 0.5 ºC increment) will be provided in the summary table. Conversion from Fahrenheit to Celsius as follows:

- Body Temperature in Celsius = (Body Temperature in Fahrenheit – 32) x (5/9)

Table 5 Fever Categorization[3]

Fever Present?	Body Temperatures ºC (ºF)
No	< 38.0ºC (< 100.4ºF)
Yes	38.0 ºC – <38.5 ºC (100.4 ºF – <101.2 ºF)
	38.5 ºC – <39 ºC (101.2 ºF – <102.1 ºF)
	39.0 ºC – <39.5 ºC (102.1 ºF – <103.1 ºF)
	39.5 ºC – <40.0 ºC (103.1 ºF – <104.0 ºF)
	>= 40.0 ºC (>= 104.0 ºF)

For each solicited (local and systemic) AE assessment 30 minutes after each vaccination the percentage of subjects reporting an event will be summarized by event severity and by vaccination (first dose or second dose) and overall (after any dose). Additionally, the relationship of solicited systemic symptoms 30 minutes after each vaccination will be tabulated.

The number and percentage of subjects without any solicited AE (Local, Systemic or Body Temperature) within 7 days following each vaccination (including the day of vaccination) will be summarized for each vaccination dose.

Furthermore, for each solicited AE collected via diary cards, the percentage of subjects will be summarized by event severity for each day from Day 1 to Day 7 following each 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. 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.

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

The occurrence of reactogenicity will also be summarized descriptively by the number of days subjects reported experiencing the symptom, by treatment group within each age group. The number of days a subject reported experiencing the symptom is the total of all days the subject reported the symptom within the first 7 days following each dose, regardless of whether the symptom was reported on consecutive days (e.g. a headache reported on Day 1 and on Days 3 and 4 would be included as 3 days). In the case when the event was ongoing at Day 7 post-vaccination, 1 day will be added to the total number of days, as it assumes the event is observed at least 1 day after Day 7 post-vaccination. This convention will not be applied for body temperature however, as the CRF does not include a question to establish whether fever was ongoing at Day 7 post-vaccination.

A summary of the day of first onset of each event will also be provided for each vaccination.

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

All tabular summaries of solicited AEs will be presented by treatment arm and by age group. Additionally, summaries of solicited adverse events within 7 days after vaccination will include summaries by formulation type (overall age groups and within age group), where 'MPL-' grouping will summarize results over the formulation A treatment arms (**A1** and **A2**) and 'MPL+' grouping will summarize results over the formulation B treatment arms (**A3** and **A4**).

Unsolicited AEs

Unsolicited AEs, SAEs and AESI will be coded using MedDRA dictionary.

Any unsolicited AEs are collected for 28 days following each vaccination (day of vaccination + 27 days). SAEs and AEs leading to subject withdrawal from the trial is collected throughout the trial from Day 1 through to Day 393.

AEs are also evaluated by the Investigator for the co-existence of AESI which are pre-defined AEs that are specifically highlighted to the Investigator. The list of AESI is summarized in Appendix A. AESI are collected by close monitoring from Day 1 up to Day 393 using the relevant AE CRF page.

Definition of unsolicited AEs, SAEs and AESI are provided in Sections 10.1.1, 10.1.3 and 10.1.4 of the protocol [1, 2] respectively.

Whilst the investigator's identification of AESI are present on the study database, for the purpose of reporting, AESI will be identified programmatically via a reference a list of relevant specific PTs provided by Takeda. AESI identified based on this process will be reported in the relevant tables and listings. Therefore, the investigator assignment of AESI (identified on the relevant AE CRF page file) will not be utilized for reporting purposes.

In general unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE) and by SOC and PT by presenting the number and percentage of subjects with an AE. Subjects reporting more than 1 occurrence for the term (level) being

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summarized will be counted only once. More specifically a subject will be counted only once within each SOC and within each PT, or the overall category.

Unless otherwise specified, unsolicited AEs will be summarized in the following 3 ways as needed:

1) overall up to 28 days after each vaccination (day of vaccination + 27 days),

2) with onset between 1 and 7 days after each vaccination (day of vaccination + 6 days), and

3) overall up to end of study

Unsolicited AEs will be summarized as follows:

- Overview (Unsolicited AEs, AESI, SAEs, Deaths) for 1, 2, 3;
- by SOC and PT for 1, 2;
- by SOC for 1;
- by PT for 1;
- by PT including events with frequency greater than 2%, of all subjects in each treatment arm, up to 28 days after either vaccination (day of vaccination + 27 days);
- by SOC and PT (Non-serious Unsolicited AEs) including events with frequency greater than 2%, of all subjects in each treatment arm, up to 28 days after either vaccination (day of vaccination + 27 days);
- by SOC, PT, and relationship (not related, related) to IMP for 1, 2;
- by SOC and PT (IMP-related Unsolicited AEs) for 1;
- by SOC, PT, and maximum severity (mild, moderate, severe) for 1, 2;
- by SOC, PT, and maximum severity (mild, moderate, severe) including only those events considered related to IMP for 1;

If a subject reported more than one AE within a SOC or PT, then the AE with the highest known severity or most closely related occurrence within each SOC and each PT will be included in the summaries by severity or relationship, respectively. If an AE with a start date at or after the first dose has a missing severity or relationship information, then this will be imputed using a worst case approach, i.e. missing severity will be imputed as 'severe' and missing relationship will be imputed as 'related'.

Unsolicited AEs will be assigned to vaccine dose (1^{st}, 2^{nd}). All summaries described in this section will be generated by vaccine dose number (except for those summaries reporting events with frequency greater than 2%). Summaries by vaccination will also include summaries after any vaccination.

In addition all AEs collected throughout the trial and identified as SAEs, AESI or AEs leading to study discontinuation will be summarized by SOC and PT after each vaccination and overall.

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All tabular summaries of AEs will be presented by treatment arm and by age group. Additionally, the Overview table described above, will include summaries by formulation type (overall age groups and within age group), where 'MPL-' grouping will summarize results over the formulation A treatment arms (**A1** and **A2**) and 'MPL+' grouping will summarize results over the formulation B treatment arms (**A3** and **A4**).

The listings for SAEs, AESI, AEs leading to study discontinuation, and AEs resulting in death will be provided.

7.11.2 Clinical Laboratory Evaluations

Not applicable (not as a routine procedure in the protocol [1, 2]).

7.11.3 Vital Signs

The vital signs collected in the trial include: systolic blood pressure, diastolic blood pressure, heart rate and body temperature. Vital signs will be summarized descriptively by treatment arm overall and within elderly age groups, at scheduled time points. The change from baseline to each scheduled post-baseline time point will also be presented. Measurement parameters will be presented alphabetically. All data will be listed as well.

7.11.4 12-Lead ECGs

Not applicable.

7.11.5 Other Observations Related to Safety

Complete physical examination will be performed on Day 1, the same day as the first vaccine administration. A detailed physical examination includes but is not limited to: height and weight, auscultation of heart and lungs, palpation of the abdomen, inspection of extremities (including skin over intended vaccination site), and a check of general appearance. Additional physical examinations may be performed if indicated by review of the subject's medical history. Symptom-directed physical examination may be performed during the trial visits if deemed necessary. All data will only be listed.

7.12 Interim Analysis

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

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An interim analysis on safety and immunogenicity data is planned when all subjects have completed the Day 57 Visit (28 days after last vaccination). This analysis will include group results but not individual subject information.

Each of the DMC safety review and interim analysis will be performed by a team of unblinded statisticians and programmers at PPD who will have access to individual treatment assignments but will not be involved in subsequent trial conduct. With exception of the unblinded pharmacist and unblinded administrator, the personnel involved in the conduct of the trial including those at the Sponsor site, at PPD, and the trial sites, will remain blinded to the individual subject data (including treatment assignment) until unblinding after database lock for data through Day 393.

The list of team members from the study who will gain access to unblinded treatment codes and outputs will be documented in an unblinding plan.

7.13 Changes in the Statistical Analysis Plan

Not applicable

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8.0 REFERENCES

1. A Phase II, Randomized, Controlled, Double-Blind, Safety and Immunogenicity Trial of Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine in Healthy Elderly Adults, Takeda Vaccines, Inc., Protocol No. NOR-204, dated 16 July, 2015.
2. A Phase II, Randomized, Controlled, Double-Blind, Safety and Immunogenicity Trial of Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine in Healthy Elderly Adults, Takeda Vaccines, Inc., Protocol No. NOR-204, dated 16 November, 2015.
3. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials
4. Li, X, Wang, W. Liu, G. and Chan, I, Handling Missing Data in Vaccine Clinical Trials for Immunogenicity and Safety Evaluation. Journal of Biopharmaceutical Statistics, 2011, 21(2), 294-310

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Appendix A Adverse Events of Special Interest (AESI)

Cardiac Disorders

- Endocarditis
- Myocarditis
- Pericarditis

Gastrointestinal Disorders

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

Immune System Disorders

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

Infections and Infestations

- Fever of Unknown Origin
- Sinusitis

Musculoskeletal and Connective Tissue Diseases

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

Neuroinflammatory Disorders

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

Renal and Urinary Disorders

- Glomerulonephritis
- Hematuria
- Nephritis
- Proteinuria
- Renal failure

Skin

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

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Thyroid Disorders

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

Vascular Disorders

- Pulmonary Embolism
- Raynaud's Phenomenon
- Vasculitis

Others

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

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Appendix B Data Monitoring Committee (DMC) Outputs

The following Tables and Listings will be provided during the DMC sessions. Treatment information for blinded and unblinded reports will be handled accordingly.

DMC ID	Full TLF Shell ID	Title	Analysis Set
Tables			
DMC Table 1	Table 15.1.5	Disposition of Subjects	All Randomized Subjects
DMC Table 2	Table 15.1.8.1	Demographics and Baseline Characteristics	All Randomized Subjects
DMC Table 3	Table 15.3.1.2.1	Summary of Subjects without Solicited Adverse Events (Local, Systemic or Body Temperature) within 7 Days After each Vaccination	Safety Analysis Set
DMC Table 4	Table 15.3.1.3.1	Summary of Solicited Local Adverse Events within 7 Days After each Vaccination	Safety Analysis Set
DMC Table 5	Table 15.3.1.3.2	Summary of Solicited Systemic Adverse Events within 7 Days After each Vaccination	Safety Analysis Set
DMC Table 6	Table 15.3.1.4.1	Summary (Daily) of Solicited Local Adverse Events Within 7 Days After each Vaccination	Safety Analysis Set
DMC Table 7	Table 15.3.1.4.2	Summary (Daily) of Solicited Systemic Adverse Events within 7 Days After each Vaccination	Safety Analysis Set
DMC Table 8	Table 15.3.2.2.1	Unsolicited Adverse Events Up to 28 Days After Vaccination by System Organ Class and Preferred Term	Safety Analysis Set
DMC Table 9	Table 15.3.2.7	Serious Adverse Events after each Vaccination by System Organ Class and Preferred Term	Safety Analysis Set
DMC Table 10	Table 15.3.2.8	Adverse Events of Special Interest After each Vaccination by System Organ Class and Preferred Term	Safety Analysis Set
Listings			
DMC Appendix 1	Appendix 16.2.1.2	Disposition – Vaccine Regimen	All Randomized Subjects
DMC Appendix 2	Appendix 16.2.1.3	Disposition – Study Visits	All Randomized Subjects
DMC Appendix 3	Appendix 16.2.4.1	Demographics and Baseline Characteristics	All Randomized Subjects
DMC Appendix 4	Appendix 16.2.5.1	Study Treatment Administration	Safety Analysis Set
DMC Appendix 5	Appendix 16.2.7.1	Solicited Local Adverse Events	Safety Analysis Set
DMC Appendix 6	Appendix 16.2.7.2	Solicited Systemic Adverse Events	Safety Analysis Set
DMC Appendix 7	Appendix 16.2.7.3	Diary Body Temperature	Safety Analysis Set
DMC Appendix 8	Appendix 16.2.7.4	Adverse Events	Safety Analysis Set
DMC Appendix 9	Appendix 16.2.7.6	Serious Adverse Events	Safety Analysis Set
DMC Appendix 10	Appendix 16.2.7.8	Adverse Events of Special Interest	Safety Analysis Set

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