Title: Phase 2b, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Immunogenicity of the Intramuscular Norovirus GI.1/GII.4 Bivalent Virus-like Particle Vaccine in Healthy Adults Aged 18 - 49 Years

NCT Number: NCT02669121

SAP Approve Date: 14 June 2018

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

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

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

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: NOR-211

Phase IIb, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Immunogenicity of Intramuscular Norovirus GI.1/GII.4 Bivalent Virus-like Particle Vaccine in Healthy Adults Aged 18 - 49 Years

NOR-211 Efficacy and Immunogenicity of Norovirus GI.1/GII.4 Bivalent Virus-like Particle Vaccine in Adults

PHASE IIB

Version**:** 2.0

Date**:** 14 June 2018

Prepared by:

PPD

Based on:

Protocol Version: 2.0 (Amendment 1)

Protocol Date: 9 February 2016

1.1 Approval Signatures

Study Title: NOR-211 Efficacy and Immunogenicity of Norovirus GI.1/GII.4 Bivalent Virus-like Particle Vaccine in Adults

Approvals:

PPD

Date

Date

Date

Date

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

AGE	Acute Gastroenteritis
AE	Adverse Event
$Al(OH)_3$	Aluminum Hydroxide
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
CCI	[redacted]
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GSD	Geometric Standard Deviation
HAI	Hemagglutination-inhibition
HBGA	Histoblood Group Antigen
IA	Interim Analysis
IAP	Interim Analysis Plan
IM	Intramuscular
IMP	Investigational Medicinal Product
IWRS/IVRS	Interactive Web/Voice Response system
LLoQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NHRC	Naval Health Research Center
NoV	Norovirus
Pan-Ig	Pan-Immunoglobulin
PH	Cox Proportional Hazard
PPS	Per Protocol Set
PT	Preferred Term
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBA	Serum Bactericidal Assay
SD	Standard Deviation

SOC	System Organ Class
ULoQ	Upper Limit of Quantification
U.S.	United States
VE	Vaccine Efficacy
VLP	Virus-like Particles
VPDI	Vaccine Preventable Disease Incidence
WHO-DDE	World Health Organization Drug Dictionary Enhanced

4.0 OBJECTIVES

4.1 Primary Objectives

- To evaluate the efficacy of a single dose of the norovirus (NoV) bivalent virus-like particles (VLP) vaccine compared with placebo against first confirmed cases **of moderate or severe** acute gastroenteritis (AGE) occurring > 7 days after dosing due to **genotype-specific** (GI.1 or GII.4) NoV strains represented in the vaccine (**excluding co-infection** with *Salmonella, Shigella,* or *Campylobacter)*.

4.2 Secondary Objectives

Secondary Efficacy Objectives:

- To evaluate the efficacy of a single dose of the NoV bivalent VLP vaccine compared with placebo against first confirmed cases **of moderate or severe** AGE occurring > 7 days after dosing due to **any** NoV strain (**including co-infection** *with Salmonella, Shigella, or Campylobacter*).
- To evaluate the efficacy of a single dose of the NoV bivalent VLP vaccine compared with placebo against first confirmed cases **of moderate or severe** AGE occurring > 7 days after dosing due to **genotype-specific** (GI.1 or GII.4) NoV strains represented in the vaccine (**including co-infection** with *Salmonella, Shigella,* or Campylobacter).
- To evaluate the efficacy of a single dose of the NoV vaccine compared with placebo against first confirmed cases of **moderate or severe** AGE occurring > 7 days after dosing due to **any** NoV strain (**excluding co-infection** with *Salmonella*, *Shigella*, or *Campylobacter*).

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4.4 Study Design

This is a Phase IIb, double-blind, randomized, multi-site, placebo-controlled, efficacy trial of a single dose of the intramuscular (IM) NoV vaccine combined with aluminum hydroxide (Al(OH)3) adjuvant compared to a single dose of placebo (saline) control. Subjects will be randomized in a 1:1 ratio. The estimated sample size for the trial is 2800-8700 healthy subjects aged 18 to 49 years who will be recruited from the United States (U.S.) military training installations.

This trial has a case-driven design, with the primary analysis planned after ~ 30 cases of moderate or severe AGE due to infection with genotype-specific (GI.1 or GII.4) NoV strains represented in the vaccine have been confirmed (excluding co-infection with any of three bacterial pathogens: Salmonella, Shigella, or Campylobacter). If there are < 30 cases (as defined above) at the end of the first season, the trial may be continued beyond the end of the first season, may be stopped, or may be continued for a second season. For all enrolled subjects, accrual of additional AGE cases due to NoV will continue until the end of the respective active AGE surveillance period. Thereafter, further enrollment of new subjects will be stopped.

Informed consent, blood draw, randomization and vaccination will occur in the first few days after subjects enter the recruit training facilities, specifically within 7 days prior to vaccination or on Day 1. Subjects who have signed the informed consent form, and meet eligibility criteria will subsequently have blood drawn and be randomized (1:1) by using the interactive web/voice response system (IWRS/IVRS), to receive either a single dose of NoV vaccine or saline placebo. On Day 1, subjects would receive the study dose they were randomized to receive, after receipt of the routine immunizations required by the U.S. military. The licensed routinely required vaccines administered on Day 1, may include meningococcal, diphtheria-tetanus-acellular pertussis, influenza, adenovirus 4/7, hepatitis A, B, or A/B, measles-mumps-rubella (MMR), and/or varicella, vaccines per the site requirements.

In addition, subjects may be assigned to a Subset as follows:

- Subset A: First 200 subjects randomized in the trial.
- Subset B: Safety subset of approximately 200 subjects randomly selected at the same time as the double-blind randomization.
- CCI [redacted]

Subjects from Subsets A and B are mutually exclusive. CCI [redacted]

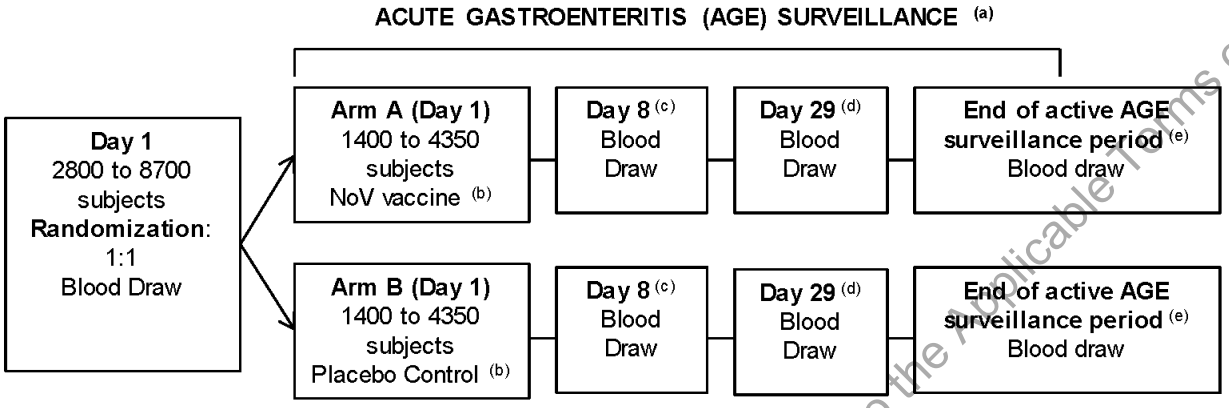
All enrolled subjects will have sera collected four times during the trial: once within 7 days prior to vaccination or on Day 1, and once on each of Days 8, 29, and end of AGE surveillance period, which is also the end of study (EOS). Immunogenicity to the NoV vaccine will be evaluated for the subjects from Subsets ACCI CCI [redacted] In addition, a saliva specimen will be collected once during the trial (at any time pre- or post-vaccination) restricted to 200 subjects in Subset A for assessment of histoblood group antigen (HBGA) secretor status, i.e., negative or positive for FUT-2 gene status.

Subjects from Subsets A and B will be evaluated for solicited AEs for 7 days after dosing using diary cards returned on or after Day 8 and for unsolicited AEs for 28 days after dosing by interview on or after Day 29. All enrolled subjects will be evaluated for SAEs and any AEs that lead to trial withdrawal throughout the active AGE surveillance period.

For those subjects ill with AGE who meet case criteria (see definition further below in this section), a fresh stool sample and *vomitus* sample (if available) will initially be obtained and processed to define AGE due to NoV by RT-PCR assay. To assess duration of NoV shedding by RT-PCR assay of the stool, three additional stool samples will optionally be obtained (as available); once between 7 to 14 days, once between 21 to 29 days and once at EOS. CCI [redacted]

A schematic of the trial design is included as Figure 4.a. A schedule of trial procedures is provided in Appendix A: Table 8.a, Table 8.b and Table 8.c.

Figure 4.a Schematic of Trial Design



(a) Fresh stool and/or *vomitus* specimens will be obtained for each new onset AGE disease episode and a convalescent serum will be obtained once 7-14 days thereafter. As available, a 2nd and 3rd stool specimen will be obtained once 7-14 days, and once 21-28 days thereafter and EOS.
(b) Subjects will also receive their routine immunizations required by the U.S. military.
(c) All subjects will have a blood draw for serology. Subjects in subsets A and B will have diary card collection and review.
(d) All subjects will have a blood draw for serology. Subjects in subset A and B will have safety assessment by interview.
(e) All subjects will have a blood draw for serology. Day 45 for Navy subjects, Day 53 for Air Force subjects, and Day 72 for Marine subjects. Safety follow-up will continue up to the end of the AGE surveillance study period.

Surveillance for AGE:

Each enrolled subject will have surveillance for AGE performed from Day 1 until the end of the active AGE surveillance period (e.g., Day 45 for U.S. Navy subjects). Each enrolled participant will be given an AGE symptom log at trial entry (Day 1) and instructed to record any AGE symptoms and report to the medical clinic as soon as possible after onset of AGE symptoms. The subjects will record on the AGE symptom log the onset time of vomiting and/or diarrhea, number of episodes of each, and the stop time of vomiting and/or diarrhea to calculate duration of AGE. Other symptoms associated with the AGE episode will also be recorded.

Work-up for AGE in Ill Subjects:

At the medical clinic, the subject will be assessed to determine if they have an AGE that meets the following work-up definition:

- 1 or more episodes of vomiting within 24 hours judged by the investigator as not related to the training AND/OR;
- Any diarrhea episode of 3 or greater severity of diarrhea on a 5-point scale† within 24 hours.

† *Grade 1: fully formed (normal); Grade 2: soft (normal); Grade 3: thick liquid (diarrheal); Grade 4: opaque watery (diarrheal); or Grade 5: Rice-water (diarrheal).*

Subjects who meet the work-up definition will provide a fresh stool specimen (not rectal swabs), and *vomitus* specimen (if available) for processing and later detection of NoV by RT-PCR and be assessed for disease severity. Subjects will receive standard of care treatment for AGE disease from the site clinic and additional AGE disease symptom logs will be given to record further AGE symptoms until resolution. Subjects will be instructed to return all subsequent AGE symptom logs to the trial staff at the next trial visit.

NoV AGE Case Definition in Ill Subjects:

- A case of NoV AGE is defined as one occurring > 7 days after immunization until the end of the active AGE surveillance period.
- A NoV AGE case is defined as meeting the work-up definition plus a NoV positive stool sample or *vomitus* sample confirmed by RT-PCR. In circumstances where both stool and *vomitus* samples are obtained, the subject will be considered NoV positive if either specimen is confirmed NoV positive by RT-PCR.

Severity of AGE is defined as follows:

Mild:	• 1 to 2 episodes of vomiting* within 24 hours AND/OR
	• 3 unformed stools** within 24 hours
Moderate:	• 3 to 5 episodes of vomiting* within 24 hours AND/OR
	• 4 to 5 unformed stools** within 24 hours
Severe:	• 6 or more episodes of vomiting* within 24 hours AND/OR
	• 6 or more unformed stools** within 24 hours AND/OR
	• Hospital admission and/or intravenous rehydration for mild or greater AGE.

*Judged by the investigator as not due to the training; uses the Common Terminology Criteria for AEs (CTCAE) for vomiting episodes.

**For definition purposes, unformed stools are those meeting a 3 or greater severity of diarrhea on a 5-point scale ([†]noted above).

Notes:

− "Within 24 hours" refers to a rolling time period. That is, the criteria will be considered to have been met if occurring during any 24-hour period between the onset and end of AGE symptoms.

− A new episode of vomiting is defined as one that occurs at least 5 minutes after the previous one.

− A new episode of diarrhea is defined as 'a trip to the toilet'.

Identification of Co-pathogens in Stool of Each Subject with New Onset AGE:

The initial stool specimen obtained from each subject with new onset of AGE will be evaluated for the following enteric pathogens: Salmonella, Shigella, and Campylobacter. Because the true cause of AGE may be difficult to determine in cases where both NoV and these enteric pathogen(s) are detected; cases including and excluding these co-pathogen(s) will be analyzed.

Investigational Trial Dose:

The investigational NoV vaccine dose is presented in a labeled, single-use prefilled syringe that contains a single 0.5 mL liquid dose for IM injection. Each dose (0.5 mL) delivers 15 µg of GI.1 NoV VLP, 50 µg of GII.4 NoV VLP (consensus of 3 strains), and 500 µg of aluminum as Al(OH)3.

Placebo (Saline) Control:

The placebo (saline) dose is presented in a labeled, single-use prefilled syringe that contains a single 0.5 mL liquid dose for IM injection to closely match the NoV vaccine.

Duration of Subject's Expected Participation in the Entire Trial

Trial participation is expected to be from enrollment through EOS.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

- **Moderate or severe** AGE occurring > 7 days after dosing due to **genotype-specific** (GI.1 or GII.4) NoV strains represented in the vaccine (**excluding co-infection** with *Salmonella, Shigella,* or *Campylobacter*).

5.2 Secondary Endpoints

Efficacy Secondary Endpoints:

- **Moderate or severe** AGE occurring > 7 days after dosing due to **any** NoV strains (**including co-infection** with *Salmonella, Shigella, or Campylobacter*).
- **Moderate or severe** AGE occurring > 7 days after dosing due to **genotype-specific** (GI.1 or GII.4) NoV strains represented in the vaccine (**including co-infection** with *Salmonella, Shigella,* or *Campylobacter*).
- **Moderate or severe** AGE occurring > 7 days after dosing due to **any** NoV strains (**excluding co-infection** with *Salmonella, Shigella,* or *Campylobacter*).

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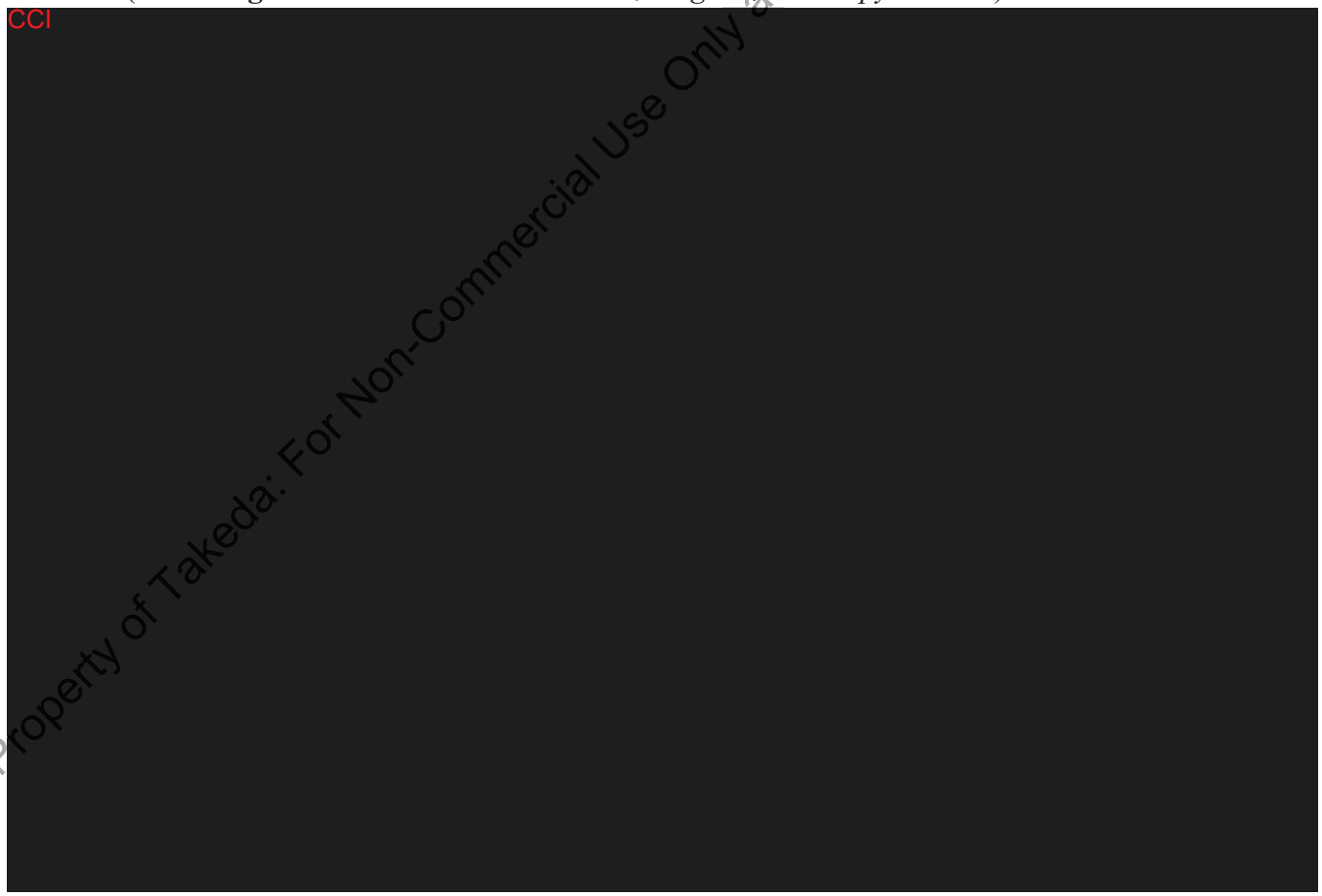

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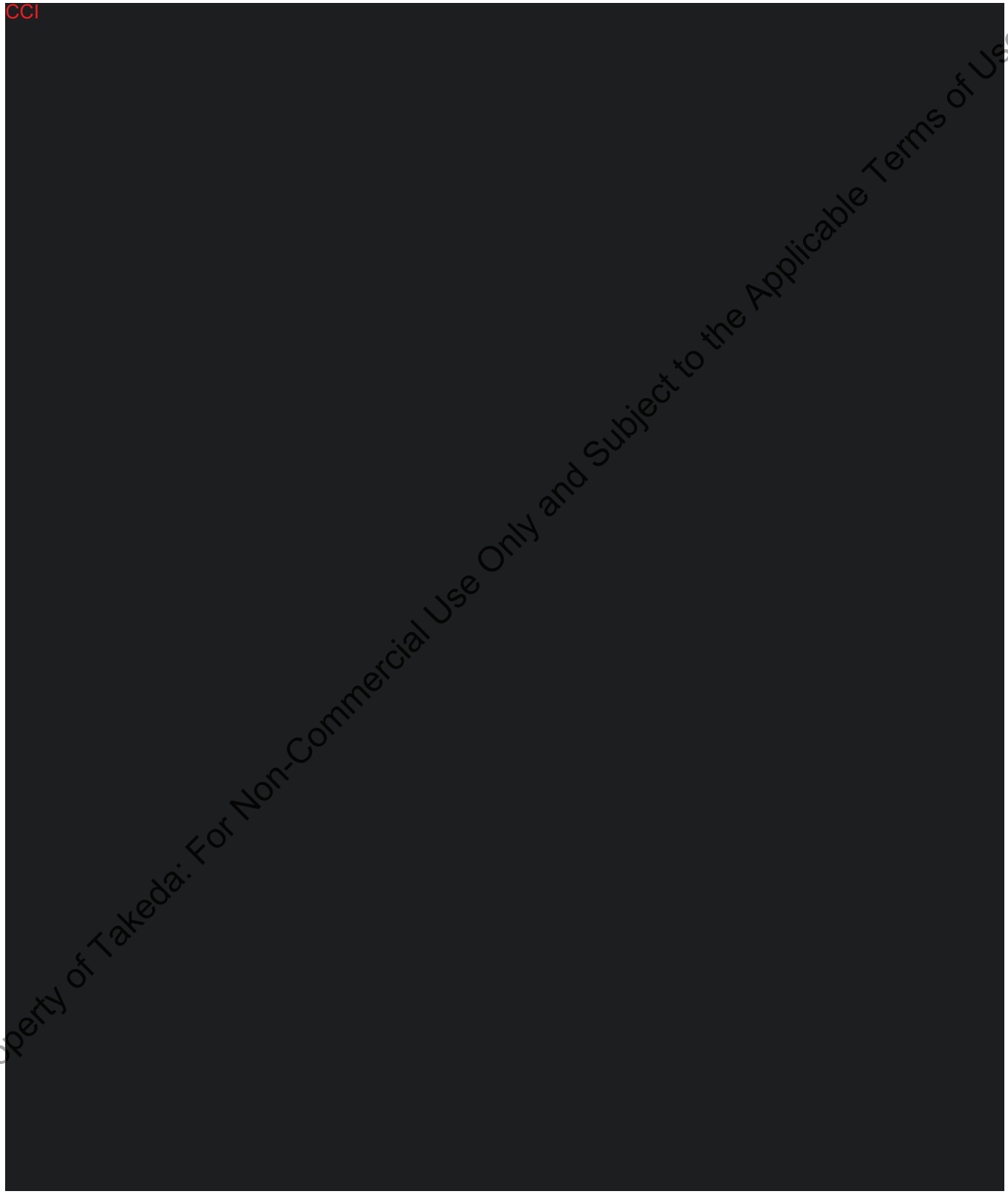

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6.0 DETERMINATION OF SAMPLE SIZE

Assuming true vaccine efficacy (VE) of 70% and a 1:1 randomization ratio to either NoV vaccine or saline placebo, a total of 30 cases of first confirmed moderate or severe AGE due to NoV infection (based on the case definition, due to genotype-specific [GI.1 and GII.4] NoV strains represented in the vaccine, excluding co-infection) would provide about 80% power to rule out a null hypothesis of no treatment effect.

The average weekly incidence (as percentage of recruits on the base) over the winter NoV high seasons (October-May) and summer low seasons (June-September) of consultation at the medical stations for symptoms of AGE were evaluated for the period from September 2011 to September 2014. The expected background rate of NoV GI.1/GII.4 was calculated using three assumptions. The incidence of NoV over the winter high season is the excess of AGE in the winter (first panel in Table 13-1 of the protocol) compared to the summer (second panel in Table 13-1 of the protocol) and can thus be calculated as the average weekly AGE incidence during the winter season minus the average weekly AGE incidence during the corresponding summer season. This has been calculated in the last panel in Table 13-1 of the Protocol. The second assumption is that 50% of the NoV cases are due to GI.1/GII.4 that is compatible with the overall breakdown of the Naval Health Research Center (NHRC) genotype analysis and the NoV genotypes identified by the Centers for Disease Control and Prevention (CDC) as the cause of NoV outbreaks reported to CDC over the same 2011-2014-time period. The weekly incidence rates are then multiplied by 7.6 (average length of training) to obtain the incidence rate over training and thus during the trial. There is a further assumption that all subjects reporting to the medical station are moderate or severe AGE cases.

The background incidence rate of moderate or severe NoV AGE due to genotype-specific (GI.1 and GII.4) NoV strains represented in the vaccine (excluding co-infection with *Salmonella*, *Shigella*, or *Campylobacter*) is assumed to be 0.5-1.7% per subject-training period of observation based on NHRC AGE NoV surveillance data at the planned trial sites. Under such attack rate assumptions, approximately 2800-8700 subjects, randomized in 1:1 ratio to NoV vaccine and saline placebo, would be needed to reach 30 cases of moderate or severe AGE due to NoV infection by genotype-specific (GI.1 or GII.4) NoV strains. As this is a case-driven trial, subjects will continue to be enrolled and followed through the entire active AGE surveillance period until ~ 30 cases of moderate or severe AGE due to genotype-specific (GI.1or GII.4) NoV strains, excluding co-infection are confirmed. Thereafter, the trial will be closed to further enrollment.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

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 (e.g., AEs), only categories with at least one subject will be presented.

Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Means, geometric 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, with possible exceptions made for derived data. The confidence interval (CI) about a parameter estimate will be presented using the same number of decimal places as the parameter estimate (i.e., 1 more decimal place than the recorded data). Percentages will be presented to 1 decimal place (e.g., 80.3%).

Unless otherwise specified, all data collected during the trial will be presented in the subject listings.

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

Handling of Missing Values

There will only be limited imputation of missing data as described here: (1) missing or partial dates (i.e., start dates of AEs), (2) missing intensity (i.e., severity) for unsolicited AEs and missing relatedness for solicited and unsolicited AEs, (3) missing measurements for solicited adverse events, and (4) titer values measured as below (or above) the lower (or upper) limit of quantification (LLoQ/ULoQ) for the particular antigen and assay.

Unsolicited Adverse Events Missing or Partial Dates

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

The following methods will be used to impute missing or partial dates of AE start dates:

- AE start date month/year available and day missing:
    - If the month and year are the same as those in the first dose date, the first dose date is to be used to impute the AE start date.
    - If the month and year are different from those in the first dose date, the first day of the month will be used for the start date.

- AE start date year available and month/day missing:
    - If the year is the same as the year of the first dose, the first dose date is to be used to impute the AE start date.
    - If the year is not the same as the year of the first dose date, set the start date as January 1.
- AE start date completely missing:
    - The first dose date is to be used to impute the AE start date.

Missing intensity for unsolicited AEs and missing relatedness for solicited and unsolicited AEs

Unsolicited AE tables presenting AE intensity (mild, moderate, severe) or solicited/unsolicited AE tables presenting AE relationship to vaccine administration (related, not related) will handle all cases of missing intensity or relatedness by evaluating the AE using "worst case", that is severe for intensity and related for relatedness.

Missing Solicited Adverse Event Measurements

On the solicited AE diary card, subjects are instructed to enter a measurement for erythema/redness, swelling, and induration, an intensity grade for pain, headache, fatigue, myalgia, arthralgia, vomiting, and diarrhea and the highest daily temperature. As much as possible, there should not be a missing value for the measurements or intensity grades of any of these solicited AEs. It is understood that this study population is on a demanding schedule and it is a possibility subjects are unable to find the time to perform the necessary measurements or report the intensity grades to complete the recording of these data. Therefore, from the eCRF completion guidelines, sites were instructed to enter a value of 999 if the event was present, but a measurement or intensity grade wasn't obtained on the diary. Subjects with a measurement or intensity grade value of 999 will be counted in the overall tally, but will not be counted in either of the severity categories (e.g., mild, moderate, and severe). For these a category of "Present, not measured" will be tallied. The eCRF completion guidelines were also amended to permit an entry of 888 to indicate the subject failed to complete the measurement or include the intensity grade, i.e., true missing data. Subjects with values of 888 will not be included as evaluable subjects for the associated analysis.

Titers Measured Below (or Above) the LLoQ (or ULoQ)

The following will be used for all CCI [redacted]. A titer value measured below LLoQ will be imputed to a value that is 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.
CCI [redacted].

Titer values measured as above ULoQ will be imputed at the ULoQ value.

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.

Baseline is defined as the last non-missing measurement taken before the first dose of vaccination. For immunogenicity parameters, if the time is not available, then the last assessment prior to or on the day of vaccination is considered as baseline.

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 will be used for the immunogenicity (serology).

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

Table 7.a Analysis Visit Windows for Immunogenicity by Visit

Visit	Scheduled Study Day	Visit Window (Study Day)
Baseline	≤1	≤1
Day 8	8	7 – 14
Day 29	29	21-35
EOS	45	>35

Diary Data

In Study Subsets A and B, solicited local and solicited systemic AEs and body temperature are recorded daily (by diary) by the subject for 7 days following vaccination (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, e.g., 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 received the trial dose (NoV GI.1/GII.4 bivalent VLP vaccine or saline placebo). Subjects in this set will be included under the study dose she/he received.

Full Analysis Set (FAS): all subjects who are randomized and received the trial dose. Subjects in this set will be included under the study dose she/he was randomized to receive.

Per-Protocol Set (PPS): all subjects in the FAS who have no major protocol violations will be included in the PPS. All protocol violations will be identified prior to unblinding and clinical judgment from Takeda will be necessary to classify each deviation as "major" or not. These violations and the judgment regarding their use will be listed and summarized in the final clinical study report. The major protocol violation criteria will be finalized as part of the blind data review at study completion and may include:

1. Selected entry criteria (not meeting inclusion criteria 1 and 4, and meeting exclusion criteria 4, 5, 8, 9, and 13) defined in protocol sections 7.1 and 7.2;
2. Receiving wrong treatment;
3. Receiving prohibited therapies in the following categories (also specified in protocol section 9.1.4):
    - Parenteral immunoglobulin (Ig) preparation, blood products, and/or plasma derivatives within 3 months of trial vaccination;
    - Immunosuppressive therapy within 3 months or systemic (e.g., oral or parenteral) corticosteroid treatment within 60 days prior to trial dose administration;

1) Other major violations, which may be identified during blinded data reviews at study completion.

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7.3 Disposition of Subjects

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 primary reason for ineligibility for randomization. In addition, the number and percentage of randomized subjects by study arm will be provided.

Disposition for all randomized subjects will be summarized by study arm. This summary will also be repeated for subjects from subsets A, B, C [redacted] and A and B. Disposition categories include:

CI

- Number of randomized subjects, number of randomized subjects but not vaccinated, and number of vaccinated subjects but not randomized;
- Number of subjects completing the study through the end of active AGE surveillance period;
- Number of subjects who did not complete the study through the end of active AGE surveillance period;
- Primary reason for early discontinuation.

7.4 Demographic and Other Baseline Characteristics

Age, gender, ethnicity, race and branch of the military will be summarized descriptively by study arm for all randomized subjects. This summary will be repeated for subjects from subset A, B, A and B, [redacted]

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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 18.1 or later) coding system.

A medical history is defined as any significant condition/disease that stopped at or prior to the time of study dose administration and a concurrent medical condition is defined as any significant condition/disease that is ongoing at the time of study dose administration.

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 by study arm. Multiple entries for an individual patient under the same SOC/PT will only be counted once. These summaries may be repeated by study subset if data suggests a need.

7.6 Medication History and Concomitant Medications

Medication history and concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE, 01MAR2015 version or later).

Medication history includes all medication that was taken but ended before trial vaccination or within 3 months prior to the time of informed consent. Concomitant medications include medications taken from trial vaccination through the end of study.

Frequencies and percentages of subjects by medication history and concomitant medications will be summarized by preferred medication name for the safety population by study arm. Subjects with multiple uses of a medication history or concomitant medication will be counted once for a given preferred medication name. These summaries may be repeated by study subset if data suggests a need.

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

Concomitant licensed vaccine administration will be provided in data listings.

7.7 Study Drug Exposure and Compliance

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 – 8 days, (2) 9 – 29 days and (3) > 29 days. The duration of follow-up is defined as the number of days from 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. The vaccination date/time information will be listed for each subject.

7.8 Efficacy Analysis

This analysis plan is being amended at the end of the second norovirus season at which time it is known that an insufficient number of primary endpoint cases will be obtained. Therefore, this amended analysis plan establishes the intent to formally test the primary endpoint using a significance level of $\alpha = 0.0001$; if the null hypothesis for the primary endpoint is rejected, the significance level for the secondary endpoint - moderate or severe AGE occurring > 7 days after dosing due to any NoV strains (excluding co-infection with Salmonella, Shigella, or Campylobacter) – will be $\alpha=0.05$, otherwise it will be $\alpha=0.0499$. The corresponding confidence intervals for the primary and the above secondary endpoints are 99.99% and either 95% or 95.01%, respectively. All other endpoints, secondary CCI will use 95% CIs.

Calculation of AGE Severity

As stated in section 4.4, severity of AGE is defined as follows:

Mild:	• 1 to 2 episodes of vomiting* within 24 hours AND/OR
	• 3 unformed stools** within 24 hours
Moderate:	• 3 to 5 episodes of vomiting* within 24 hours AND/OR
	• 4 to 5 unformed stools** within 24 hours
Severe:	• 6 or more episodes of vomiting* within 24 hours AND/OR
	• 6 or more unformed stools** within 24 hours AND/OR
	• Hospital admission and/or intravenous rehydration for mild or greater AGE.

* Judged by the investigator as not due to the training; uses the Common Terminology Criteria for AEs (CTCAE) for vomiting episodes.

**For definition purposes, unformed stools are those meeting a 3 or greater severity of diarrhea on a 5-point scale ([†]as noted in section 4.2).

Notes:

- *"Within 24 hours" refers to a rolling time period. That is, the criteria will be considered to have been met if occurring during any 24-hour period between the onset and end of AGE symptoms.*
- *A new episode of vomiting is defined as one that occurs at least 5 minutes after the previous one.*
- *A new episode of diarrhea is defined as 'a trip to the toilet'.*

AGE severity will be derived based the number of diarrhea and vomiting episodes entered onto the subjects' AGE log and based on information on hospital admission and/or intravenous rehydration entered onto the eCRF. Since only AGE cases that meet the work-up definition (see section 4.4) are entered into the electronic data capture (EDC), the following assumptions are made on the diarrhea and vomiting episodes:

- All diarrhea episodes entered into the AGE log and transferred into EDC are assumed to meet a 3 or greater severity of diarrhea on a 5-point scale (where the scale is defined in section 4.4). Subjects are instructed that a new episode of diarrhea is defined as 'a trip to the toilet'.
- All vomiting episodes entered into the AGE log and transferred into EDC are assumed not related to training. Subjects are instructed that a new episode of vomiting is defined as one that occurs at least 5 minutes after the previous one.

In the AGE log, subjects are instructed to enter the number of vomiting and/or diarrhea episodes at the intervals (1) '00:01 – 08:00', (2) '08:01 – 16:00', and (3) '16:01 – 24:00' for each day of illness. Since AGE severity is contingent on the number of vomiting or diarrhea episodes within

a rolling 24-hour period of time, the number of diarrhea and vomiting episodes will be calculated for each possible 24-hour interval within the duration of the AGE event. That is, the number of vomiting (and separately diarrhea) episodes will first be calculated by adding the number of episodes that occurred at the intervals (1), (2) and (3) of the first day of illness. Then the number of vomiting (and separately diarrhea) episodes will be calculated by adding the number of episodes that occurred at the intervals (2) and (3) of the first day of illness and interval (1) of the second day of illness, and so on. The rolling 24-hour interval with the greatest number of vomiting episodes or the rolling 24 hour interval with the greatest number of diarrhea episodes will be used to determine the severity of the AGE event.

All data from the AGE logs and clinical site assessment of AGE will be included in data listings. The duration of the AGE event will also be calculated and included in data listings.

7.8.1 Primary Efficacy Endpoint(s)

The primary endpoint is moderate or severe AGE occurring > 7 days after dosing due to genotype-specific (GI.1 or GII.4) NoV strains represented in the vaccine (excluding co-infection with *Salmonella, Shigella,* or *Campylobacter*).

For the primary endpoint, the primary analysis method will be based on the FAS and a Cox proportional hazard (PH) model. To perform this analysis, subjects will be identified as having the event (AGE meeting the endpoint definition) or censored (subject did not have AGE meeting the endpoint criteria). Time to event, i.e., the duration in days since study dose to event or censoring (i.e., EOS visit), will be fit using the PH model with treatment as a factor. Hazards ratios for each study arm will be obtained from the PH model and VE will be estimated along with a two-sided XX% CI (see section 7.8 for confidence level). The number of subjects with primary endpoint and the number of censored subjects will also be provided. The primary efficacy objective is met if the lower bound of the CI for the VE is above 0%, where VE is defined as $1 - (\lambda_v/\lambda_c)$, where λ_v and λ_c denote the hazard rates for the NoV vaccine and saline placebo arms, respectively. The XX% CI for the VE is obtained by taking one (1) minus the XX% CI of the hazard ratio from the PH model. The proportional hazard assumptions will be examined and a sensitivity analysis may be conducted if appropriate.

A first sensitivity analysis of the primary endpoint is an analysis based on exact XX% CIs based on the FAS [1] and omits time as a covariate. In this sensitivity analysis, the VE is defined as $1 - (AR_v/AR_c)$, where AR_v and AR_c denote the attack rates for the NoV vaccine and saline placebo arms, respectively, and the attack rate is estimated by the number of ill cases occurring during the surveillance period, divided by the total number of initially illness-free subjects.

A second sensitivity analysis will be based on the PPS using the same PH model as in the primary analysis.

7.8.2 Secondary Efficacy Endpoints

The secondary endpoints are:

a) Moderate or severe AGE occurring > 7 days after dosing due to any NoV strains (including co-infection with *Salmonella, Shigella, or Campylobacter*).

b) Moderate or severe AGE occurring > 7 days after dosing due to genotype-specific (GI.1 or GII.4) NoV strains represented in the vaccine (including co-infection with *Salmonella, Shigella,* or *Campylobacter*).

c) Moderate or severe AGE occurring > 7 days after dosing due to any NoV strains (excluding co-infection with *Salmonella, Shigella,* or *Campylobacter*).

The above secondary endpoints will be analyzed using the same methodology applied to the primary endpoint; including estimation of the point estimate and XX% CI for VE based on the FAS and sensitivity analyses. The confidence level for secondary endpoints (a) and (b) will be 95%, and for (c) the level will be either 95% or 95.01% per the strategy explained in Section 7.8.

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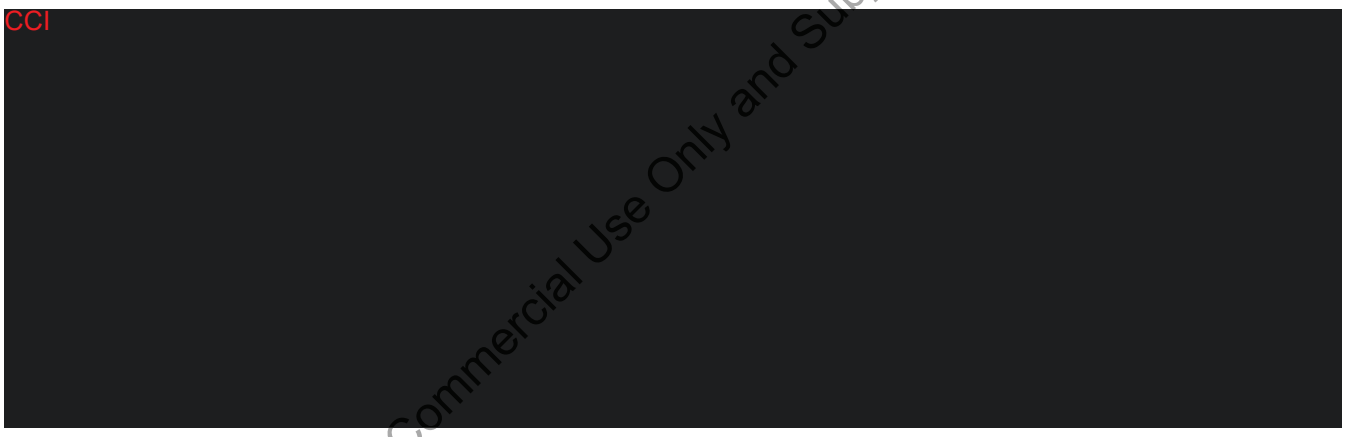

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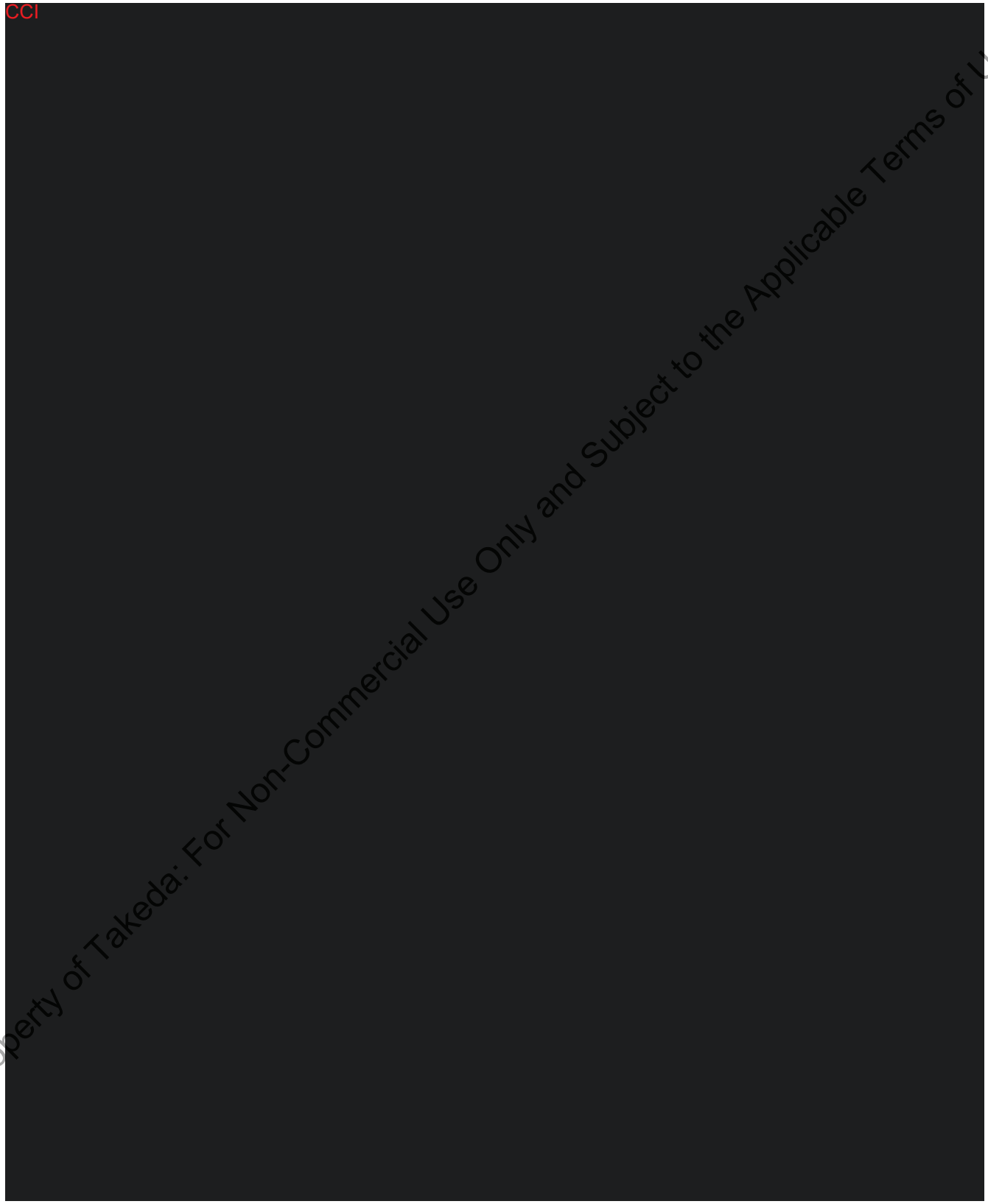

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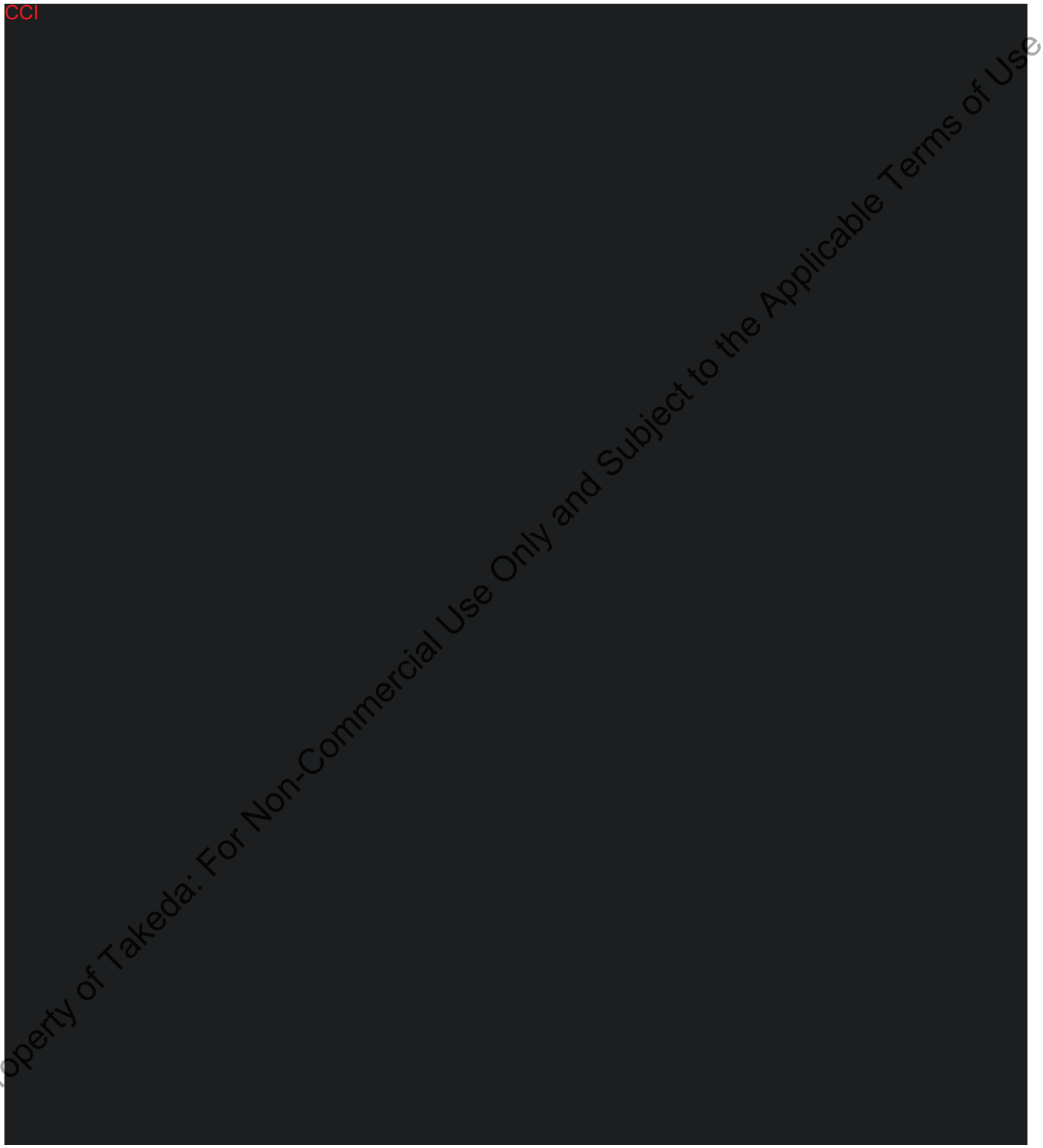

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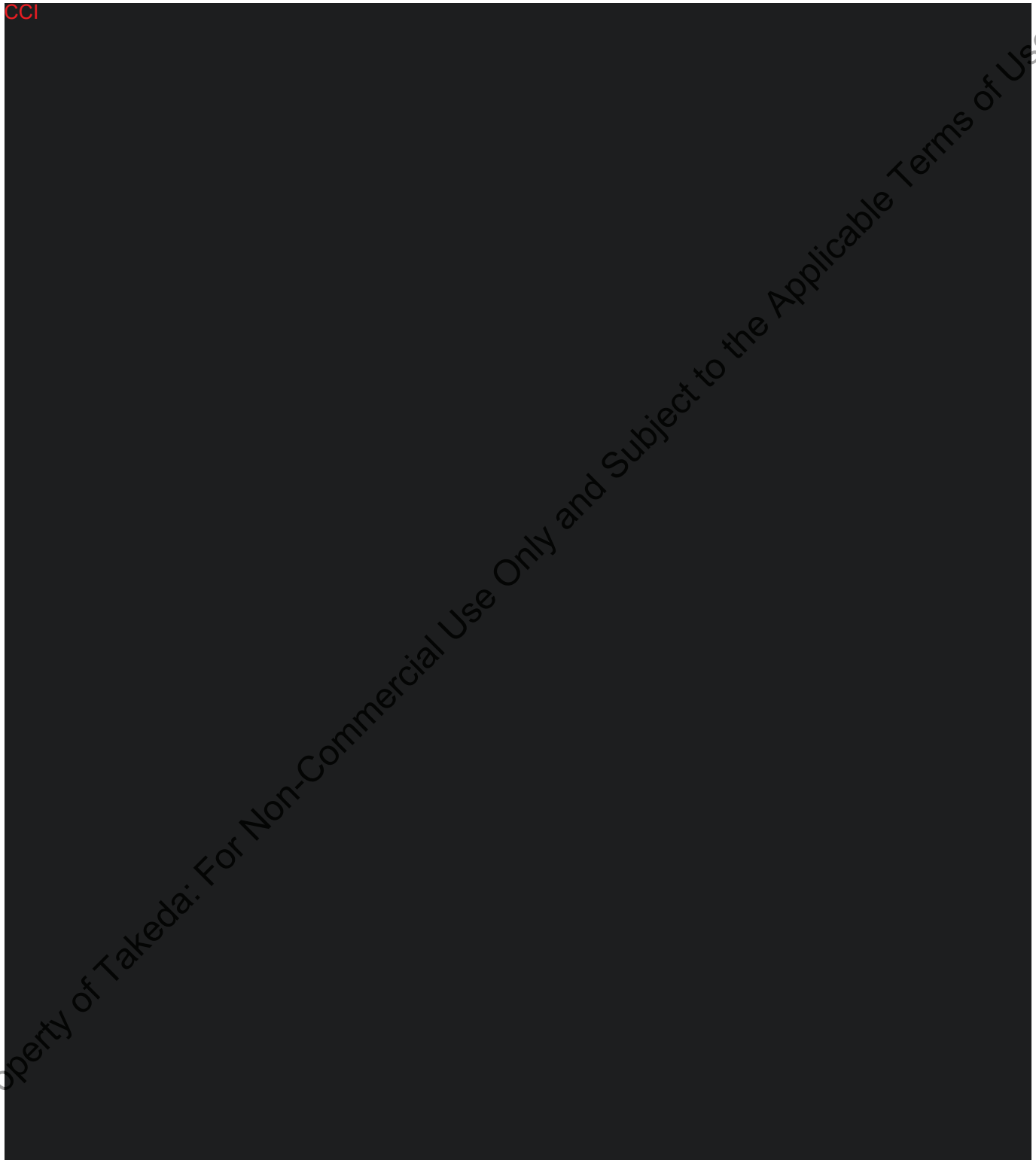

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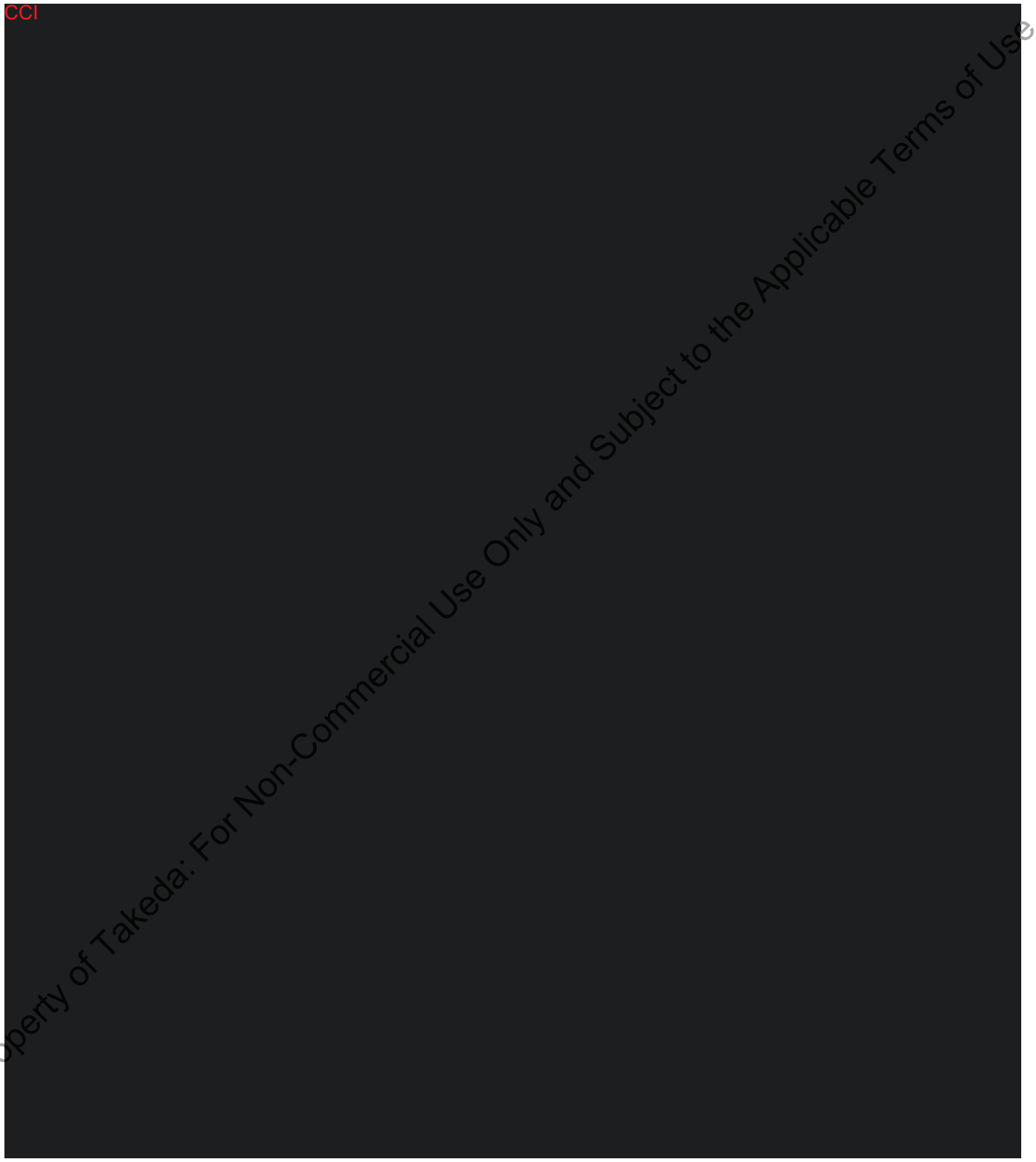

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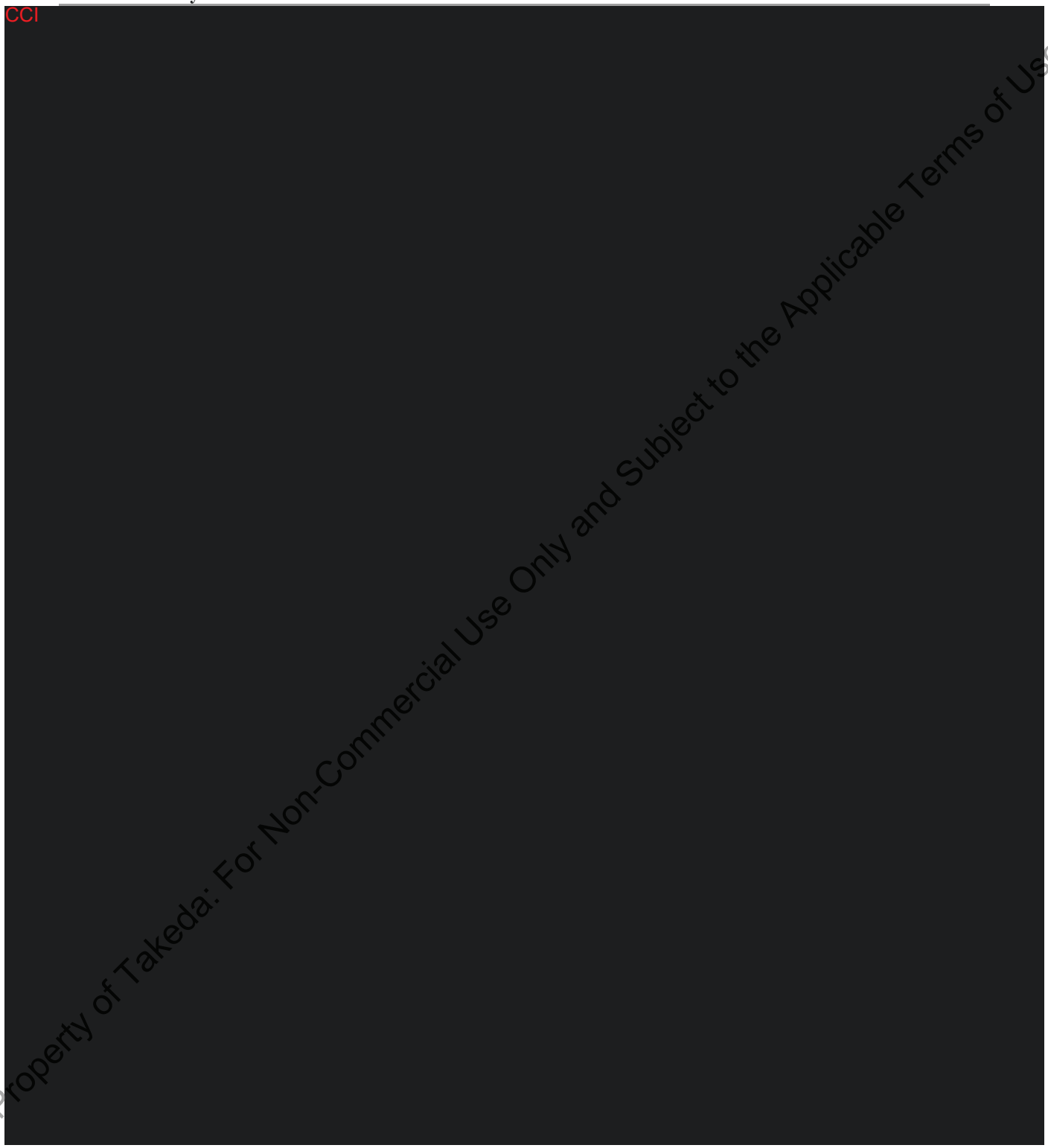

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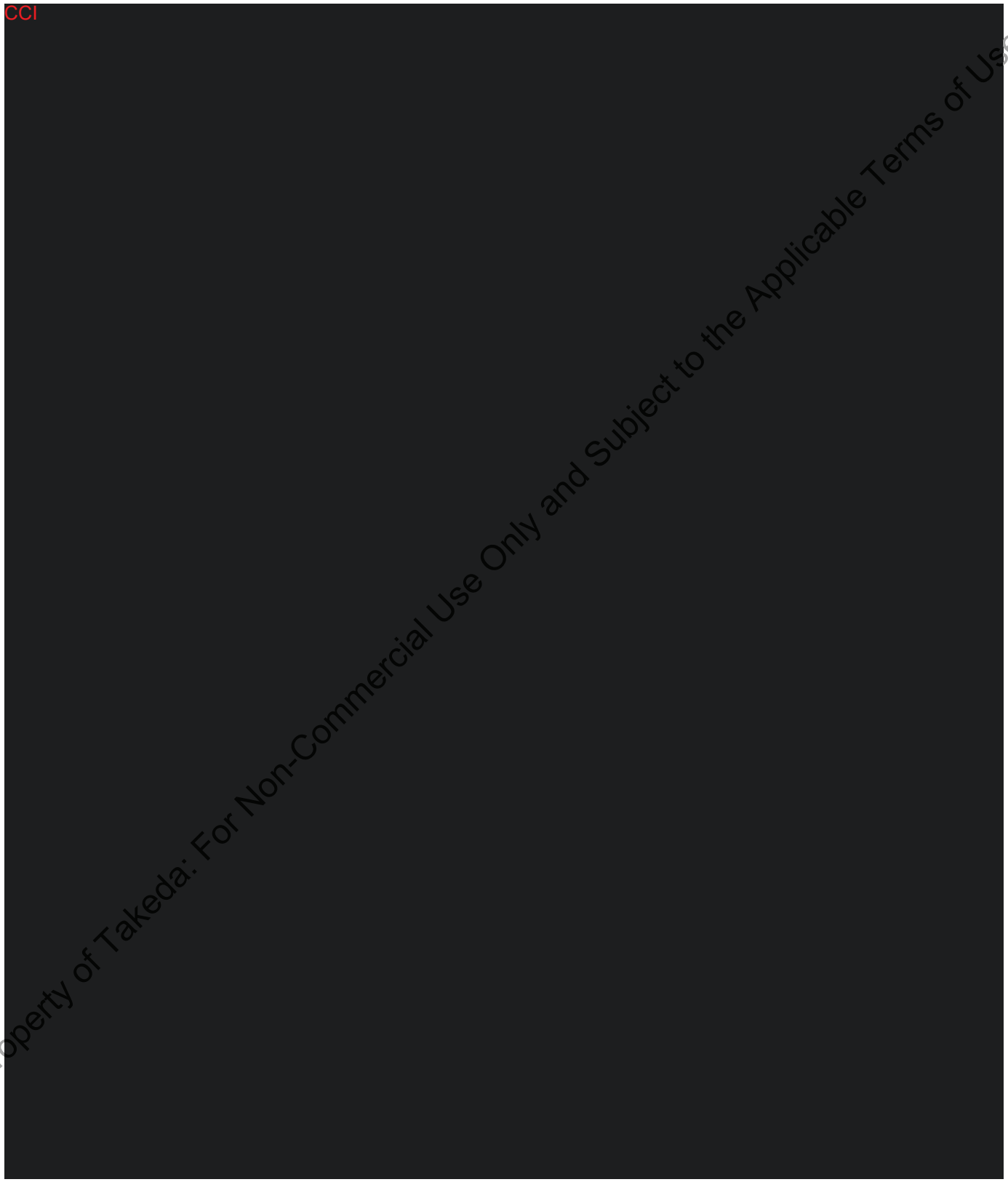

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7.9 Pharmacokinetic/Pharmacodynamic Analysis

{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 study arm. For endpoints that are evaluated for subjects from both subsets A and B, summaries will be repeated by subset.

7.11.1 Adverse Events

Subjects from subsets A and B will be evaluated for solicited local and solicited systemic AEs for 7 days after dosing and for unsolicited AEs for 28 days after dosing. All subjects will be assessed for all SAEs and for all AEs leading to withdrawal from the trial for the entire AGE surveillance period.

Solicited AEs

For subjects in Subsets A and B, safety will be assessed daily for 7 days after vaccination (day of vaccination and the following 6 days) via diary collection of solicited AEs. These include four local events (injection site pain, erythema/redness, induration, and swelling) and seven systemic events (headache, fatigue, myalgia, arthralgia, vomiting, diarrhea, and fever). Measurements of the largest diameter for each of the injection site reactions (erythema/redness, swelling, and induration) are collected, and if not present a value of 0 mm would be recorded. These measurements will be used to derive severity grades based on the criteria presented in

Appendix C. Body temperature is also collected and a systemic event of 'fever' defined as temperatures ≥ 38°C will be summarized by the actual route taken (as recorded on the eCRF) with no adjustments or conversion for route of measurement. The subjects are informed that the recommended route to take their temperature is oral and are instructed to use this route. Severity categories for systemic solicited AE are defined in Appendix D. In addition to severity, the relationship of solicited systemic symptoms, occurring within 7 days after vaccination will be assessed by the investigator during diary review. Missing solicited local and systemic AE measurements (refer to section 7.1) will be evaluated as follows:

1. Subjects with an entry of 999 in the eCRF (i.e., a solicited AE present, but subject failed to record a measurement on the diary) will have their AE evaluated as being present, but the specific severity will be summarized as "Present, not measured";
2. Subjects with an entry of 888 in the eCRF (i.e., solicited AE not present and therefore not measured, hence truly missing) will not be included as an evaluable subject for the associated analysis of the solicited AE.

Each solicited AE will be summarized at the following time intervals: Days 1-7, Days 1-3, Days 4-7, and Days 1-7 (individually). For each time interval, the count and percentage of subjects will be determined for each of the following categories: subjects evaluated, subjects without any events, subjects with any event, mild events, moderate events, and severe events, and where applicable "Present, not measured" (999). Subjects should not be double counted; therefore the event of greatest severity will be used for subjects with more than 1 episode of the same event. Similar counts and percentages will be presented for solicited local AEs "Overall" and solicited systemic AEs "Overall".

The relationship of the administered investigational medicinal product (IMP) to the solicited systemic AE will be tabulated for the time interval Days 1-7. If a subject reported more than one episode of the same event, then the strongest relationship will be included in the summaries. Additionally, the previously described summary by severity (see earlier paragraph) will be repeated on the interval Days 1-7 by relationship to IMP status.

A summary of the day of first onset of each event and the number of days subjects reported experiencing each event will be presented. The number of days a subject reported experiencing an event is calculated as the total of all days the subject reported the event, regardless of whether the symptom was reported on consecutive days (e.g., a headache reported on Day 1, Day 3, and Day 4 would be included with a duration of 3 days). If a subject's 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.

Unsolicited AEs

Unsolicited AEs will be coded using the MedDRA, Version 18.1 or later.

All unsolicited AEs will be collected for 28 days following vaccination for subjects from Subsets A and B. SAEs and AEs leading to subject withdrawal from the trial will be collected throughout the trial for all subjects.

The incidence of AEs will be summarized by SOC and PT for each study arm 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 (i.e., subjects with at least one AE). Separate summaries will be provided for AEs by maximum severity (mild, moderate, and 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 vaccination, 2) with onset between 1 and 7 days after vaccination, and 3) with onset between 8 and 28 days after vaccination. For summaries 1 and 3, SAEs and AEs leading to study discontinuation that occurred after 28 days following vaccination will also be included.

In addition, the incidence of AEs will be summarized by SOC and by PT separately. IMP-related (or not related) AEs and IMP-related (or not 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.

The number and percentage of subjects with *most frequent* unsolicited AEs (i.e., events with frequency of preferred term greater than 2% within all study arms combined) will be summarized overall up to 28 days after vaccination by SOC and PT. This summary will also be done for *most frequent* non-serious events by presenting both number of events and number/percent of subjects with the event.

The incidence of AEs leading to study withdrawal and SAEs will be summarized by SOC and PT for the entire duration active AGE surveillance period. The number of SAEs will also be presented.

In addition to the overall AE listing, separate listings for SAEs, AEs leading to subject withdrawal from the trial, and AEs resulting in death will be provided. An AE listing for subjects with AGE will also be provided.

7.11.2 Clinical Laboratory Evaluations

{Not applicable}

7.11.3 Vital Signs

{Not applicable}

7.11.4 12-Lead ECGs

{Not applicable}

7.11.5 Other Observations Related to Safety

{Not applicable}

7.12 Interim Analysis

An IA will be performed on the first 200 subjects (Subset A). Details of the statistical methods that will be applied to the planned IA for study NOR-211, and the process for protecting the study blind are described in the IA plan (IAP), version 1.0, dated 03 August 2016. This IA is concerned with data in the areas of safety and immunogenicity, both for norovirus and co-administered vaccines. Unblinded IA results will be provided to the data monitoring committee (DMC) and treatment group unblinded results will be distributed to Takeda according to the unblinding plan contained in Appendix D of the IAP.

If the accrual of cases for the primary endpoint is slower than expected, a second IA may be performed when approximately 30 cases of moderate or severe AGE due to any NoV strain have been accrued. Details about this analysis, including criteria for terminating the trial for futility, will be documented separately.

If there is a considerable lag in time between the 30th NoV AGE event and the final visit of the last enrolled subject, descriptive statistics on the efficacy data may be produced prior to the final/primary analysis without any α spending. These results would be group wise only and would be protected as in other interim analyses.

7.13 Changes in the Statistical Analysis Plan

Changes from the Analyses Planned in the Protocol

Section 13.1.5 of the Protocol (Version 2.0) 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. Hence all values in the database at time of database lock will be included in the analyses.

SAP Amendment 1 changes (excluding editorial) are identified below.

Section 7.1 in Table 7.a, the EOS window was changed from **≥35** to **>35.**

CCI [redacted]

Section 7.3, removed clinical site as by variable in the disposition summary, since study only enrolled at the one site.

Section 7.8, originally contained the following.

At the time of the writing of the SAP, there is no definitive plan to perform an interim analysis (IA) of the primary endpoint. However, due to the rarity of the norovirus illness, Takeda has not ruled out the possibility of a futility analysis. Absent of a futility analyses, the final efficacy analyses will be performed using 95% confidence intervals and 5% significance levels. However, if a futility analysis is performed, see section 7.12, a significance level of α = 0.0001 will be

reserved for the futility analysis. As a result, the final analysis will use a significance level of α= 0.0499 and confidence intervals of 95.01%. For simplicity, the same significance level used in the primary analysis will be carried forward to all efficacy analyses. Confidence intervals outside efficacy endpoints, for example immunology point estimates, will be strictly 95%, regardless of any test of futility on the efficacy endpoints.

Another provision is as follows since a considerable lag in time may be present between the 30th NoV AGE event and the final visit of the last enrolled subject. Descriptive statistics on the efficacy data may be produced prior to the final/primary analysis without any α spending. These results would be group wise only and would be protected as in other IAs.

Amendment Change

his analysis plan is being amended at the end of the second norovirus season at which time it is known that an insufficient number of primary endpoint cases will be obtained. Therefore, this amended analysis plan establishes the intent to formally test the primary endpoint using a significance level of α = 0.0001; if the null hypothesis for the primary endpoint is rejected, the significance level for the secondary endpoint - moderate or severe AGE occurring > 7 days after dosing due to any NoV strains (excluding co-infection with Salmonella, Shigella, or Campylobacter) – will be α=0.05, otherwise it will be α=0.0499. The corresponding confidence intervals for the primary and the above secondary endpoints are 99.99% and either 95% or 95.01%, respectively. All other endpoints, secondary and exploratory, will use 95% CIs.

Section 7.8.1 originally contained the following

Time to event, i.e., the duration in days since study dose to event or censoring (i.e., EOS visit), will be fit using the PH model with treatment as a factor**, adjusted for gender and age**. Hazards ratios for each study arm will be obtained from the PH model and VE will be estimated along with a two-sided 95% CI. The number of subjects with primary endpoint and the number of censored subjects will also be provided. The primary efficacy objective is met if the lower bound of the CI for the VE is above 0%, where VE is defined as $1 - (\lambda_v/\lambda_c)$, where λ_v and λ_c denote the hazard rates for the NoV vaccine and saline placebo arms, respectively. The 95% CI for the VE is obtained by taking one (1) minus the 95% CI of the hazard ratio from the PH model. The proportional hazard assumptions will be examined and a sensitivity analysis may be conducted if appropriate.

A first sensitivity analysis of the primary endpoint is an analysis based on exact 95% CIs based on the FAS [1]. In this sensitivity analysis, the VE is defined as $1 - (AR_v/AR_c)$, where AR_v and AR_c denote the attack rates for the NoV vaccine and saline placebo arms, respectively, and the attack rate is estimated by the number of ill cases occurring during the surveillance period, divided by the total number of initially illness-free subjects. A Cochran-Mantel-Haenszel procedure will be used to estimate the relative risk (i.e., AR_v/AR_c) from which the 95% CI for the VE will be obtained by taking one (1) minus the 95% CI of the relative risk of illness.

Amendment Change

Time to event, i.e., the duration in days since study dose to event or censoring (i.e., EOS visit), will be fit using the PH model with treatment as a factor. Hazards ratios for each study arm will be obtained from the PH model and VE will be estimated along with a two-sided **XX% CI (see section 7.8 for confidence level)**. The number of subjects with primary endpoint and the number of censored subjects will also be provided. The primary efficacy objective is met if the lower bound of the CI for the VE is above 0%, where VE is defined as $1 - (\lambda_v/\lambda_c)$, where λ_v and λ_c denote the hazard rates for the NoV vaccine and saline placebo arms, respectively. The **XX**% CI for the VE is obtained by taking one (1) minus the **XX**% CI of the hazard ratio from the PH model. The proportional hazard assumptions will be examined and a sensitivity analysis may be conducted if appropriate.

A first sensitivity analysis of the primary endpoint is an analysis based on exact **XX**% CIs based on the FAS [1] **and omits time as a covariate**. In this sensitivity analysis, the VE is defined as $1 - (AR_v/AR_c)$, where AR_v and AR_c denote the attack rates for the NoV vaccine and saline placebo arms, respectively, and the attack rate is estimated by the number of ill cases occurring during the surveillance period, divided by the total number of initially illness-free subjects. ~~A Cochran-Mantel-Haenszel procedure will be used to estimate the relative risk (i.e., AR_v/AR_c) from which the XX% CI for the VE will be obtained by taking one (1) minus the 95% CI of the relative risk of illness.~~

Section 7.8.2 original contained the following

The above secondary endpoints will be analyzed using the same methodology applied to the primary endpoint; including estimation of the point estimate and 95% CI for VE based on the FAS and sensitivity analyses, i.e., (1) based on the Cochran-Mantel-Haenszel procedure using the FAS and (2) based on PPS using the same model as in the primary analysis.

Amendment Change

The above secondary endpoints will be analyzed using the same methodology applied to the primary endpoint; including estimation of the point estimate and XX% CI for VE based on the FAS and sensitivity analyses~~, i.e., (1) based on the Cochran-Mantel-Haenszel procedure using the FAS and (2) based on PPS using the same model as in the primary analysis.~~ **The confidence level for secondary endpoints (a) and (b) will be 95%, and for (c) the level will be either 95% or 95.01% per the strategy explained in Section 7.8.**

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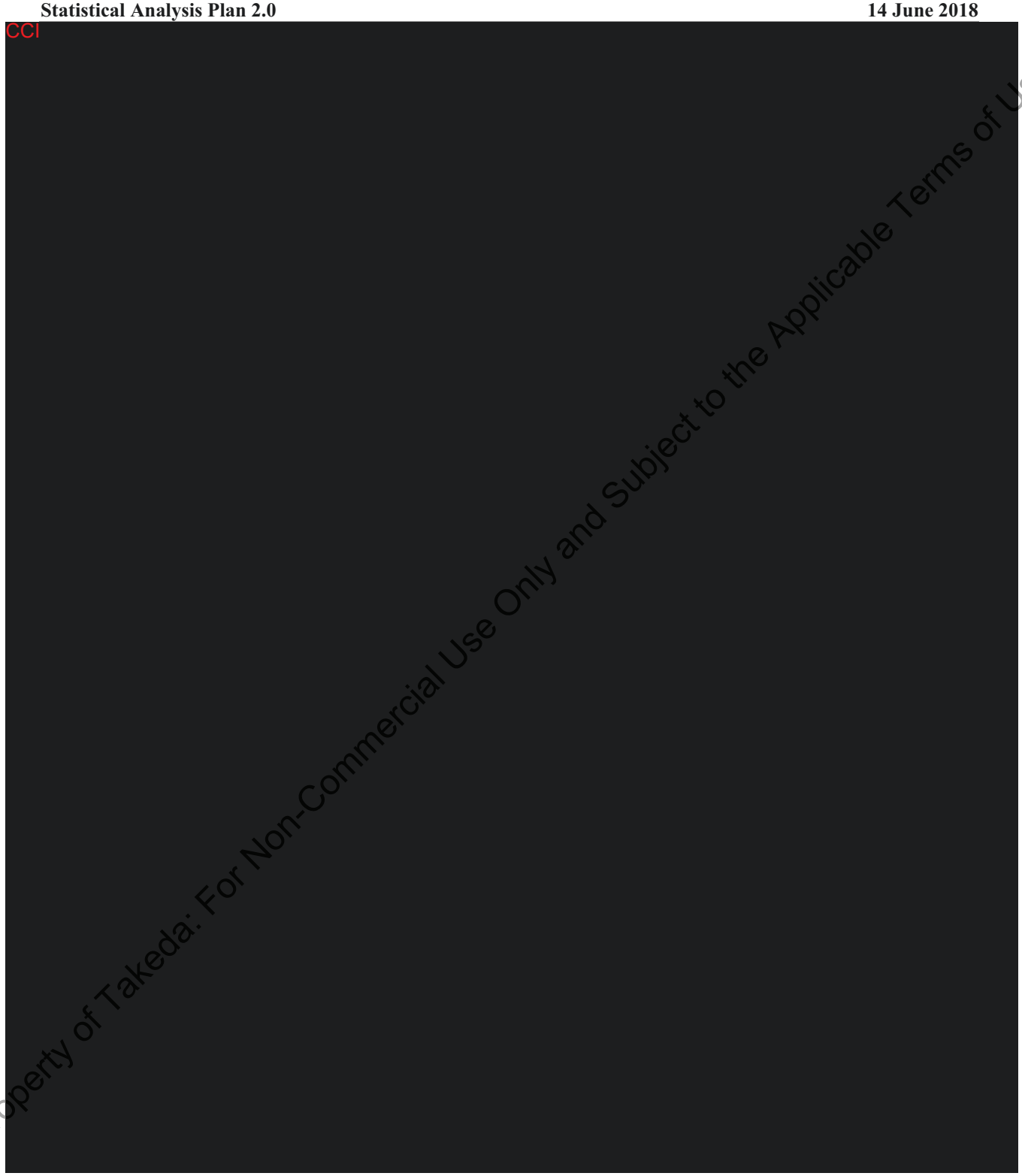

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Appendix A Schedule of Trial Procedures

Table 8.a Schedule of Trial Procedures for all Subjects (2800-8700 subjects)

Procedure	Screening	Day 1	Day 8	Day 29	End of active AGE surveillance period[a] (Day 45 / Day 53 / Day 72) / ET
Visit window	-7 days		+ 7 days	+ 7 days	+/- 4 days
Visits	X	X	X	X	X
Screening interview	X				
Signed Informed Consent	X				
Assessment of eligibility criteria[b]	X	X			
Demographics	X				
Medical history	X				
Prior medications	X				
Concomitant medications & vaccinations		X			
Pregnancy screening[c]		X			
Randomization[d]		X			
Trial treatment[d]		X			
SAEs[e]		X	X	X	X
Blood draw (10-15 mL)[f]	X		X	X	X

Source: Protocol Version 2.0, Table 2-1.
Note: ET: early termination

(a) Trial personnel will follow U.S. Navy subjects through Day 45, U.S. Air Force subjects through Day 53, and U.S. Marine subjects through Day 72. If a subject early terminates (ET), Day 45, Day 53 or Day 72 procedures, as applicable, should be performed.

(b) Eligibility by review of inclusion/exclusion criteria will be documented before randomization and before vaccination. Eligibility criteria can be assessed initially within 7 days prior to Day 1 procedures and/or on Day 1.

(c) Pregnancy testing by serum or urine must be done within 72 hours before vaccination. Results must be confirmed and documented as negative prior to trial dose administration. If more than 72 hours have elapsed since pregnancy test was performed, the serum or urine pregnancy test must be repeated within 72 hours prior to trial dose administration by either method.

(d) After written informed consent is obtained within 7 days prior to vaccination or on Day 1, subsequent study procedures including blood draw and randomization may be done. Subjects will be randomized 1:1 to receive NoV GI.1/GII.4 bivalent VLP vaccine or placebo (saline). On Day 1, the subject will receive the study dose he/she was randomized to receive. The study dose will be administered IM in the middle 1/3 of the deltoid muscle. After vaccination, the subject will be observed for at least 15 minutes. Those concomitant required vaccines administered on Day 1 (the same day as the NoV GI.1/GII.4 bivalent VLP vaccine or placebo) will be recorded on the subject's source documents (by manufacturer, lot number, expiry date) and subsequently recorded in the electronic case report form (eCRF).

(e) SAEs and AEs leading to trial withdrawal will be collected and recorded in the eCRF for all subjects by actively monitoring at each visit from Day 1 through to the end of the active AGE surveillance period. SAEs will be reported to the sponsor within 24 hours of the investigator becoming aware of the event.

(f) Blood will be collected on all subjects once within 7 days prior to vaccination or on Day 1, and once post vaccination on each of Days 8 and 29 and at EOS in order to explore a level of protection. The EOS sera will also provide information on asymptomatic NoV illness for those subjects who develop a 4-fold or greater rise in anti-NoV antibodies between Day 29 and EOS.

Table 8.b Schedule of Additional Trial Procedures and Analyses for the Subjects Meeting Work-up and AGE Case Definitions

Procedure	AGE onset	Once Day 7 - 14	Once Day 21- 29	End of active AGE surveillance period[(a)] (Day 45 / Day 53 /Day 72) / ET
Visit window		+ 7 days	+ 7 days	+/- 4 days
AGE symptom log [(a)]	X			
Stool sample collection [(b)]	X	X	X	X
Vomitus sample collection [(b)]	X			
Convalescent blood draw (5-10 mL)[(c)]		X		

Source: Protocol Version 2.0, Table 2-2.
In case of AGE:

(a) During the AGE surveillance period (Day 1 through Day 45 for U.S. Navy, Day 53 for U.S. Air Force, and Day 72 for U.S. Marines), those subjects who present with AGE, will be instructed to record their AGE symptoms on the logs and report to the medical clinic for assessment. Initial AGE symptom logs will be given at trial entry to record AGE symptoms. Subjects will be instructed to return any subsequent and the latest AGE symptom log to the medical clinic at the next trial visit.

(b) For those subjects who present with AGE, a stool specimen and a vomitus specimen (vomitus if available) will be collected as soon as possible after the onset of each new episode of AGE for processing and subsequent RT-PCR testing. After the initial stool specimen is obtained at the onset of AGE; three additional stool specimens as available (optional), will be obtained once between 7 and 14 days, once between 21 and 29 days and once at EOS. The onset of AGE is defined as the date the subject initially presents with vomiting and diarrhea.

(c) For those subjects who present with AGE, a convalescent blood sample of 5 – 10 mL of blood will be collected once between 7 and 14 days after the onset of each new episode of AGE, defined as the date the subject initially presents with vomiting or diarrhea.

Table 8.c Schedule of Additional Trial Procedures and Analyses for Subsets A and B (200 subjects in each subset for a total of 400)

Procedure	Screening	Day 1	Day 8 [(a)]	Day 29	End of active AGE surveillance period[(a)] (Day 45 / Day 53 /Day 72) /ET
Visit window	- 7 days		+ 7 days	+ 7 days	+/- 4 days
Subsets A and B subjects only – Concomitant medications			X	X	
Subset A and B subjects only – Diary card [(b)]					
Distribution		X			
Review/collection			X		
Subset A and B subjects only – Solicited and unsolicited AEs[(b)]		X	X	X	
Subset A subjects only – Saliva specimen [(c)]		X			
Subset A subjects only – Additional Blood volume (5-10 mL) [(d)]		X		X	

Source: Protocol Version 2.0, Table 2-3.
ET=early termination

(a) Trial personnel will follow U.S. Navy subjects through Day 45, U.S. Air Force subjects through Day 53, and U.S. Marine subjects through Day 72. If a subject early terminates (ET), Day 45, Day 53 or Day 72 procedures, as applicable, should be performed.

(b) For Subset A and B subjects only, a diary card for daily collection of solicited AEs for 7 days following vaccination (including the day of vaccination) will be recorded by the subject, reviewed with the subject, and entered into the eCRF. For Subset A and B subjects only, Unsolicited AEs for 28 days following vaccination (including the day of vaccination) will be collected by interview with the subjects on Day 29 and categorized by the investigator by severity (mild, moderate or severe) and causality (related or not related to trial vaccine).

(c) For Subset A only, saliva will be collected and assayed for secretor status (positive or negative for FUT-2 gene expression, respectively), to analyze the anti-NoV antibody immune responses by secretor status. A single saliva specimen will be collected from these subjects once anytime during the trial (within 7 days prior to or after vaccination).

(d) An additional volume of 5 – 10 mL of blood will be collected at the same two time points, once within 7 days prior to vaccination or on Days 1 and once on Day 29 from the first 200 subjects enrolled (Subset A only) to assess immunogenicity to selected co-administered vaccines. These sera will be tested for antibody responses to adenovirus vaccine type 4, to meningococcal vaccine serogroup A, and to the seasonal influenza vaccine strain type A/H3.

Appendix B Modified Vesikari Scale

Modified Vesikari Scale (17 Point Scale)	
Duration of Diarrhea (days)	**Points**
1	1
2-3	2
=>4	3
Maximum Number of Diarrheal Stools/ 24 hours	
1-3	1
4-5	2
=>6	3
Duration of Vomiting (days)	
1	1
2	2
=>3	3
Maximum Number of Vomiting Episodes/ 24 hours	
0	0
1	1
2-4	2
=>5	3
Fever	
<=37	0
37.1-38.4	1
38.5-38.9	2
=>39	3
Dehydration	
None	0
IV Treatment	2

Source: Freedman SB, Eltorky M, Gorelick M. Evaluation of a gastroenteritis severity score for use in outpatient settings. Pediatrics 2010;125:e1278–85 [6].

Appendix C Severity Grading Scale for Solicited Local AEs

Adverse Event	Intensity Grade	Severity/Intensity
Pain at injection site	0	None
	1	Mild: Not interference with daily activity
	2	Moderate: Interference with daily activity with or without treatment
	3	Severe: Prevents daily activity with or without treatment
Erythema at injection site [(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Swelling at injection site[(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Induration at injection site[(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm

Source: Protocol Version 2.0, Table 10-2.
(a) Subjects are to record greatest surface diameter in mm in the diary.

Missing Measurements

Subjects are instructed on the solicited AE diary card to enter a value of zero for erythema/redness, swelling, and induration if the AE isn't present. As much as possible, there should not be a missing value for the measurement of any of these three solicited AEs. It is understood that this study population operation is on a demanding schedule and it is understandable if subjects are unable to find the time to perform the necessary measurements to complete the recording of these data. In the eCRF completion guidelines the site was instructed to record a value of 999 if the event was present but a measurement wasn't taken. A value of 888 should be entered onto the eCRF if the measurement/severity is truly missing.

Appendix D Severity Grading Scale for Solicited Systemic AEs and Fever

Adverse Event	Intensity Grade	Severity/Intensity
Headache	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without treatment
	3	Severe: Prevents daily activity with or without treatment
Fatigue	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Myalgia	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Arthralgia	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Vomiting	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Diarrhea	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Fever	Defined as ≥ 38°C (100.4°F) regardless of method used	

Source: Protocol Version 2.0, Table 10-2.

Fever Present?	Temperatures ºC
No	< 38.0ºC
Yes	38°C – 38.4°C
	38.5°C – 38.9°C
	39°C – 39.4°C
	39.5°C – 39.9°C
	40°C or higher

Source: Takeda Vaccines Pharmacovigilance.
Note: Temperature intervals given above are inclusive.

Signature Page for NOR-211 Statistical Analysis Plan, Version 2.0, 14 June 2018

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