



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

Protocol Approve Date: 15 November 2017

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

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

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



## PROTOCOL

### **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**

Efficacy and Immunogenicity of Norovirus GI.1/GII.4 Bivalent Virus-like Particle Vaccine in adults

**Sponsor:** Takeda Vaccines, Inc.  
40 Landsdowne Street  
Cambridge, MA 02139 USA

**Study Identifier:** NOR-211

**IND Number:** 014421                      **EudraCT Number:** Not Applicable

**Vaccine Name:** Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine

**Date:** 15 November 2017

**Version:** 3.0

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

## 1.0 ADMINISTRATIVE INFORMATION

### 1.1 Contacts

A separate contact information list will be provided to each site. Contact information is also provided in [Table 1.a](#).

The sponsor will provide investigators with site-specific emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the trial site. Information on trial related responsibilities is given in Section 3.1 and relevant guidelines provided to the site.

**Table 1.a Contact Information**

Issue	Contact
Serious adverse event and pregnancy reporting	PPD
Responsible Medical Officer (carries overall responsibility for the conduct of the trial)	

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

## 1.2 Approval

### REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki [1].
- International Council on Harmonization E6 (ICH) Good Clinical Practice: Consolidated Guideline (GCP) [2].
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

### SIGNATURES

PPD



Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

## INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki [1].
- ICH-GCP Consolidated Guideline [2].
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.4 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- [Appendix A](#)– Responsibilities of the investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in [Appendix B](#) of this protocol.

---

Signature of Investigator

Date

---

Investigator Name (print or type)

---

Investigator's Title

---

Location of Facility (City, State)

---

Location of Facility (Country)

### 1.3 Protocol Amendment

This document describes the changes in reference to the protocol incorporating Amendment N° 2.0. The purpose of this amendment is to:

- Prevent potential lost-to-follow up (LTFU) of subjects for safety collection at the end of study (EOS) visit on Day 45 by increasing the visit window.
- Increase flexibility for the timing of trial vaccine administration.
- Adapt the exclusion criteria for birth control measures to the study population.

#### 1.3.1 Amendment History

Date	Amendment Number	Protocol Version	Amendment Type	Region
27 July 2015	Not applicable	1.0	Not applicable	Global
9 February 2016	1.0	2.0	Non-substantial	Global
15 November 2017	2.0	3.0	Non-substantial	Global

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

### 1.3.2 Summary of Changes

---

#### Summary of Protocol Amendment 2.0 dated 15 November 2017 to Protocol Version 2.0 dated 9 February 2016

##### Rationale for the amendment:

- Prevent potential lost-to-follow up (LTFU) of subjects for safety collection at the end of study (EOS) visit on Day 45 by increasing the visit window.
- Increase flexibility for the timing of trial vaccine administration.
- Adapt the exclusion criteria for birth control measures to the study population.

---

##### Trial Summary Adapted to reflect the changes in the body of the protocol.

###### Section 2.1

###### Table 2-a footnote 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.

###### Table 2-a footnote 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. ***If the investigational trial dose is delayed beyond the day the routine immunizations required by the US military are given, the trial dose may be administered later during the training period. For subjects in Subset A, 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). For all subjects enrolled after Subset A, this information will be filed at the site as source documentation but not recorded in the eCRF.***

###### Table 2-a footnote 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 the end of the ~~AGE~~ ***active*** surveillance period (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 2-b footnote 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~~ ***at the next trial visit.*** Initial AGE symptom logs will be given at trial entry to record AGE symptoms. Subjects will be instructed to return any subsequent ***logs*** and the latest AGE symptom log ~~to the medical clinic~~ at the next trial visit.

###### Table 2-b footnote 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. ***If no samples are provided at AGE onset, samples should be obtained as soon as possible thereafter. If samples at AGE onset are inadequate ie too small for both RT-PCR to NoV and co-infection tests, the sample should be prioritized for RT-PCR to NoV and a subsequent sample should be obtained for co-infection testing as soon as possible thereafter. If samples become lost, destroyed, damaged or otherwise unavailable for use, AGE onset samples should be repeated as soon as possible.*** After the initial stool specimen is obtained at the onset of AGE; ***up*** to 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.

Trial Summary	Adapted to reflect the changes in the body of the protocol.
	<b>Table 2-c footnote a:</b> 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.
Section 6.1	This is a Phase 2b, double blind, randomized, multi-site, placebo-controlled, efficacy trial of a single dose of the IM NoV vaccine combined with Al(OH) <sub>3</sub> adjuvant compared to a single dose of placebo (saline) control. Based on prior incidence rates of AGE over multiple seasons in the US Military training installations, the estimated sample size for the trial is 2800-8700 healthy subjects aged 18 to 49 years who will be recruited from US 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, <i>Shigella</i> or Campylobacter). If there are < 30 cases (as defined above) at the end of the first season ( <del>September through May</del> ), the trial may be continued beyond the end of <del>May</del> <b>the first season</b> , may be stopped, or may be continued for a second season ( <del>September through May</del> ). If the accrual of cases (as defined above) is slower than expected, an interim analysis may be performed when approximately 30 cases of moderate or severe AGE due to any NoV strain have been accrued. For all enrolled subjects, accrual of additional AGE cases due to NoV will continue for all enrolled subjects until the end of each respective active AGE surveillance period (45 days). Thereafter, further enrollment of new subjects will be stopped.
Section 6.3	Trial participation is expected to be from enrollment through EOS (trial Day 45 for U.S. Navy subjects, trial Day 53 for U.S. Air Force subjects, and trial Day 72 for U.S. Marine subjects)
Section 7.2	<b>Criterion #15v:</b> <i>Abstinence, defined as refraining from heterosexual intercourse, ie sexual intercourse with risk of conception, during the entire study period.</i> <b>Criterion #17:</b> <i>If male and sexually active, the subject must be advised not to donate sperm from Day 1 through 6 months after the last dose of trial vaccine.</i>
Section 7.3	<b>Bullet 2:</b> <i>If the investigational trial dose is delayed beyond the day the routine immunizations required by the US military are given, the trial dose may be administered later during the training period.</i>
Section 7.4	<b>Number 3:</b> Lost to follow-up: The subject did not return to the clinic and attempts to contact the subject were unsuccessful <i>and/or the subject graduated and left the base</i> . Attempts to contact the subject must be documented.
Section 9.1.3	<b>Paragraph 1:</b> If the subject is interested to participate, trial staff will review the informed consent form and will highlight the key aspects of the trial. The consenting procedure may occur in small groups of up to three subjects at once. Notably, this procedure will be handled by non-uniformed trial staff not involved in the training of the subjects to avoid any feeling of coercion, <b>and also include an Ombudsman</b> [28].
Section 9.1.4	Individuals who received <b>Receipt of</b> any vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial with the exception of routine immunizations as per Military Procedures (see <a href="#">Appendix D</a> ). <b>If the investigational trial dose is delayed beyond the day the licensed vaccines are given, the trial dose may be subsequently administered later during the training period.</b>



<b>Trial Summary</b>	<b>Adapted to reflect the changes in the body of the protocol.</b>
Section 9.1.8	<p><b>Paragraph 1:</b>                  All subjects will have surveillance for AGE disease performed from Day 1 until the end of the active AGE disease surveillance period (Day 45 for U.S. Navy subjects, Day 53 for U.S. Air Force subjects, or Day 72 for U.S. Marine subjects).</p> <p><b>Paragraph 2:</b>                  Subjects will receive standard of care treatment for AGE disease, and a new AGE disease symptom log will be given to record AGE disease symptoms until they resolve. Subjects will be instructed to return <del>any subsequent and the latest AGE</del> <b>and any subsequent</b> disease symptom log to the <del>medical clinic</del> <b>trial site</b> at the next trial visit. A convalescent blood specimen for serology will be obtained once between 7 and 14 days after the onset of the AGE disease. After the initial stool specimen obtained at the onset of AGE disease: as available, three additional stool specimens will be obtained once between 7 and 14 days, once between 21 and 29 days and once at <del>end of the acute AGE surveillance period</del> <b>EOS</b>. These follow-on stool specimens will be analyzed for NoV by RT-PCR. <b><i>If an AGE event occurs within 7 days prior to the EOS visit (Day 45), a convalescent serum sample and a single optional stool sample should be collected at the EOS visit. There is no further follow-up for AGE after graduation from recruit training at Day 45.</i></b></p>
Section 9.1.13	For female subjects of child bearing potential, pregnancy testing using urine or serum will be performed within 72 hours prior to vaccination. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy as well as donation of ova <b>(or sperm in the case of male participants)</b> .
Section 9.3.6	<b>Heading:</b> Procedures at end of Active AGE Disease Surveillance Period (+/- 4 - 7 days)
Section 10.4.3	<b>Paragraph 1:</b> Collection of SAEs will be collected by close monitoring from the time that the subject is administered the trial vaccine (Day 1) up to the end of the active AGE disease surveillance period (at Day 45 for U.S. Navy subjects, at Day 53 for U.S. Air Force subjects, and at Day 72 for U.S. Marine subjects).
Section 16.0	Additional references.
Appendix D	Deletion of table with immunizations for U.S. Marine Corps recruits.
General	Minor grammatical and editorial changes. Replacement of IWRS with IRT. Removal of rectal swabs

Property of Takeda: For Non-Clinical Use Only. Subject to the Terms of Use

---

**Summary of Protocol Amendment 1.0 dated 9 February 2016 to Protocol Version 1.0 dated 27 July 2015**

---

**Rationale for the amendment:**

- Clarification of the timing of procedures prior to or on Day 1 and at EOS (Day 45 for US Navy subjects).

---

**Trial Summary      Adapted to reflect the changes in the body of the protocol.**

---

Section 2.1      The Schedule of Trial Procedures tables and text were modified to clarify the time window (1) prior to or on Day 1 and (2) at EOS (Day 45 for US Navy subjects). Table 2-b column headers were modified to add “after each AGE onset”.

Section 3.3      Inclusion of IVRS to IWRS in the list of abbreviations. Modifications made where applicable throughout the protocol.

***IWRS/IVRS: Interactive Web Response System /Interactive Voice Response System***

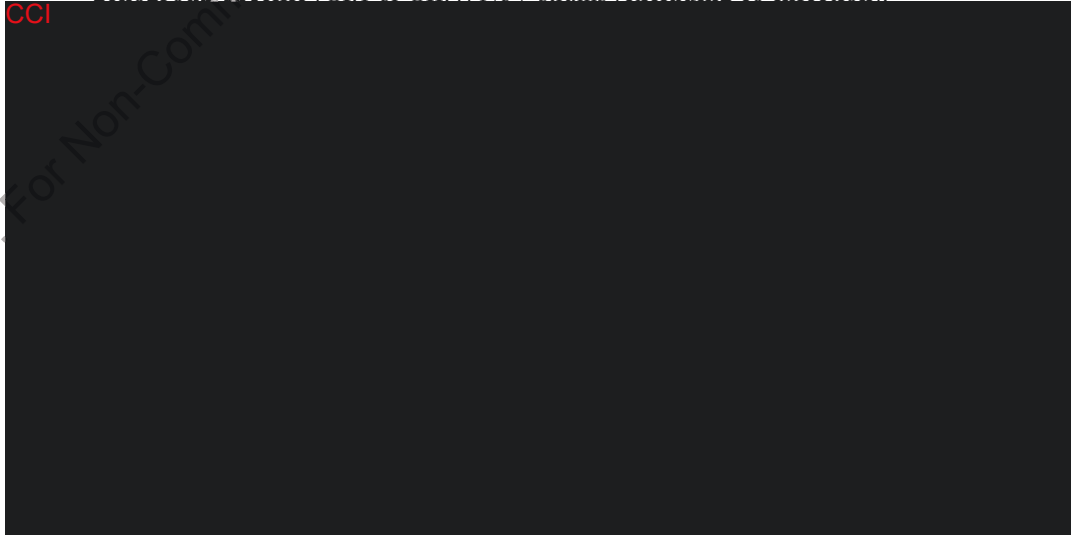
Section 4.1      3<sup>rd</sup> paragraph:

AGE surveillance data collected over multiple seasons (2011 through 2015~~4~~) from the Naval Health Research Center’s (NHRC) Enteric Disease Surveillance Program (EDSP) support that NoV was the predominant pathogen identified in cases of AGE among US military subjects at the Marine Corps Recruit Depot (MCRD-SD) in San Diego, California, at the MCRD in Parris Island (MCRD-PI), South Carolina, and at the Naval Recruit Training Center in Great Lakes (NRTC-GL), Illinois. AGE due to NoV was originally known as “winter vomiting disease”, and as expected, the highest detection rate of AGE due to NoV was during the months of September to May for both Marine and Navy subjects. The estimated population-based incidence of NoV illness at these training centers is 10 to 435 cases per 1000 subjects during training (an average of 7.6 weeks) in this high season (September-May) [communication from NHRC-EDSP].

Section 5.2.3      Correction of typographical errors (including parentheses were inadvertently switched, whereas the text was correct) – bullets 6 and 7:

- **Mild or greater** severity AGE occurring > 7 days after dosing due to the **genotype-specific (GI.1 or GII.4) NoV strains represented in the vaccine (excluding co-infection).**
- **Mild or greater** severity AGE occurring > 7 days after dosing due to the **genogroup-specific (GI.1 or GII.4) NoV strains (excluding co-infection).**

CCI



Trial Summary	Adapted to reflect the changes in the body of the protocol.
Section 6.1	<p data-bbox="428 363 574 394">1<sup>st</sup> paragraph:</p> <p data-bbox="428 394 1443 877">This is a Phase IIb, double blind, randomized, multi-site, placebo-controlled, efficacy trial of a single dose of the IM NoV vaccine combined with Al(OH)<sub>3</sub> adjuvant compared to a single dose of placebo (saline) control. Based on prior incidence rates of AGE over multiple seasons in the US Military training installations, the estimated sample size for the trial is 2800-8700 healthy subjects aged 18 to 49 years who will be recruited from US 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, <i>Salmonella</i>, <i>Shigella</i>, or <i>Campylobacter</i>). If there are &lt; 30 cases (as defined above) at the end of the first season (September <del>to</del> through May), the trial may be continued <b>beyond the end of May, may be stopped, or may be continued</b> for a second season (September <del>to</del> through May). If the accrual of cases (as defined above) is slower than expected, an interim analysis may be performed when approximately 30 cases of moderate or severe AGE due to any NoV strain have been accrued. For all enrolled subjects, accrual of additional AGE cases due to NoV will continue for all enrolled subjects until the end of each respective active AGE surveillance period (45, 53 or 72 days). Thereafter, further enrollment of new subjects will be stopped.</p> <p data-bbox="428 884 574 915">2<sup>nd</sup> paragraph:</p> <p data-bbox="428 915 1443 1245">Informed consent, blood draw, randomization and vaccination will occur in the first few days after subjects enter the recruit training facilities, <b>specifically within 7 days prior to vaccination or on Day 1</b>. Subjects who have signed the informed consent form, and meet eligibility criteria will <b>subsequently have blood drawn and</b> 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 <del>on Day 1</del>. On Day 1, subjects would receive <b>the study dose they were randomized to receive, after receipt of</b> the routine immunizations required by the US military. The licensed routinely required vaccines administered on Day 1, may include meningococcal, diphtheria-tetanus-acellular pertussis, influenza, adenovirus, hepatitis A/B, measles-mumps-rubella (MMR), varicella, polio, and pneumococcal vaccines per the site requirements.</p> <p data-bbox="428 1251 574 1283">3<sup>rd</sup> paragraph:</p> <p data-bbox="428 1283 1443 1434">For those ill subjects with AGE who meet case criteria, 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 <del>28</del> 29 days and once at end of the AGE surveillance period (EOS). <span style="color: red;">CCI</span></p> <p data-bbox="428 1497 574 1528">4<sup>th</sup> paragraph:</p> <p data-bbox="428 1528 1443 1587">All enrolled subjects will have sera collected four times during the trial, (<del>at</del> <b>once within 7 days prior to vaccination or on Day 1, and once on each of Days 8, 29, and EOS</b>).</p> <p data-bbox="428 1587 1443 1682">Footnotes c and d to the figure in the synopsis and in Figure 6a have been corrected (“Subset B” was inadvertently not included in the synopsis figure legend and in the identical Figure 6.a legend):</p> <p data-bbox="428 1682 1443 1740"><sup>c</sup>. All subjects will have a blood draw for serology. Subjects in subsets <b>A and B</b> will have diary card collection and review.</p> <p data-bbox="428 1740 1443 1795"><sup>d</sup>. All subjects will have a blood draw for serology. Subjects in subsets <b>A and B</b> will have safety assessment by interview.</p>

Trial Summary	Adapted to reflect the changes in the body of the protocol.
	<p><b>NoV AGE case definition in ill subjects:</b> (2<sup>nd</sup> bullet) A <i>NoV</i> AGE case is defined as meeting the work-up definition plus a NoV positive stool sample or <i>vomit</i> sample confirmed by RT-PCR. In circumstances where both stool and <i>vomit</i> samples are obtained, the subject will be considered NoV positive if either specimen is confirmed NoV positive by RT-PCR.</p>
Section 6.2	<p>4<sup>th</sup> paragraph: Enrollment will begin prior to or during the NoV high season (between September and May). If the number of AGE cases due to NoV has not been reached by the end of the first season (end of May), enrollment may be <b><i>continued if more AGE cases are actively accruing later in the current season, may be</i></b> stopped due to the lower incidence of NoV infection, and/or may be continued the following September (second season). This duration corresponds to the window of time during which ~ 30 AGE cases due to NoV (GI.1/GII.4 or any NoV genogroup GI or GII strain) <b><i>will occur in a single winter vomiting disease season (September to May); if &lt; 30 AGE cases occur, the trial may be stopped or continue for a second season.</i></b></p>
Section 6.3	<p>Trial participation is expected to be from <b><i>enrollment</i></b> vaccination on Day 1 through <b><i>EOS</i></b> (trial Day 45 for U.S. Navy subjects, trial Day 53 for U.S. Air Force subjects, and trial Day 72 for U.S. Marine subjects). <b><i>This duration corresponds to the window of time during which ~ 30 AGE cases due to NoV (GI.1/GII.4 or any NoV genogroup GI or GII strain) occur in a single winter vomiting disease season (September to May); if &lt; 30 AGE cases occur, the trial may be stopped or continue for a second season.</i></b></p>
Section 8.1	<p>1<sup>st</sup> paragraph: <b>CCI</b> manufactures the investigational NoV trial dose for IM administration <b><i>GI.1/GII.4 Bivalent VLP Vaccine</i></b>. The trial doses described in this protocol will be supplied by the sponsor. The trial doses will be supplied in tamper-evident, single dose cartons. Each dose and carton will contain a label that includes pertinent trial information and caution statements. The label text will be in English. The investigational trial dose to be used will be identifiable by a unique identification number and managed by the <b><i>IWRS/IVRS</i></b>.</p>
Section 8.2	<p>1<sup>st</sup> paragraph: The investigator or investigator's designee will access the <b><i>IWRS/IVRS</i></b> <b><i>within 7 days prior to or on Day 1</i></b> to obtain the subject number. Details of randomization and the <b><i>IWRS/IVRS</i></b> will be covered in the <b><i>IWRS/IVRS</i></b> user manual.</p>
Section 8.5	<p>4<sup>th</sup> paragraph: If a subject is unblinded, <b><i>no further doses of the trial vaccine are to be administered</i></b> the subject must be withdrawn from the trial. Subjects withdrawn from the trial due to unblinding should be followed for safety to the end of trial. Further details for dealing with safety follow-up for subjects withdrawn from the trial will be provided.</p>
Section 8.6	<p>Last paragraph: The pharmacist (or designated individual) at each site will be responsible for vaccine accountability and will document receipt, use, return, or destruction. Vaccine accountability documentation will be reviewed by the <b><i>unblinded</i></b> monitor during clinical monitoring visits.</p>
Section 9.1.3	<p>3<sup>rd</sup> paragraph Informed consent must be obtained prior to subject entering into the trial, and before any protocol-directed procedures are performed. <b><i>The informed consent may be obtained within 7 days prior to vaccination or on Day 1.</i></b></p>

Trial Summary	Adapted to reflect the changes in the body of the protocol.
Section 9.1.4	<p>3<sup>rd</sup> paragraph: All medications, vaccines and blood products including <del>specific history of antibiotic use and</del> <b>the</b> duration thereof, taken or received by the subjects within 3 months prior to the start of the trial are to be recorded on the source document and entered onto the Prior and Concomitant Medications eCRF. The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source documents or the eCRF.</p>
Section 9.1.7	<p>A saliva specimen will be collected once during the trial (<b>at any time pre- or post-vaccination</b>) <del>either on Day 1 or</del> from subjects in Subset A for assessment of HBGA secretor status <del>or at any time (pre- or post-vaccination) during the trial.</del></p>
Section 9.1.8	<p>1<sup>st</sup> paragraph: All subjects will have surveillance for AGE disease performed from Day 1 until the end of the active AGE disease surveillance period (Day 45 for U.S. Navy subjects, Day 53 for U.S. Air Force subjects, or Day 72 for U.S. Marine subjects). All participants will be given an AGE disease symptom log and a thermometer at trial entry <b>within 7 days prior to vaccination or on</b> (Day 1) and instructed to record their AGE disease symptoms and report to the medical clinic as soon as possible. The subjects will record in the AGE disease symptom log the onset time of vomiting and/or diarrhea, their temperature, the number of episodes of vomiting and/or diarrhea, and the stop time of vomiting and/or diarrhea to calculate duration of AGE. The subjects will also document whether the symptom(s) have had impact on their ability to train. The subjects will be <del>given</del> <b>instructed to use the provided</b> thermometers to measure and record their temperature on the AGE disease symptom log. <b>The subjects will be informed that the recommended route to take their temperature is oral and instructed to use this route.</b> At the medical clinic, the subject will be assessed to determine if they have an AGE disease that meets the work-up definition (see Section 6.1). Subjects who meet the work-up definition will be assessed for disease severity and provide a stool specimen (not rectal swabs) and <del>or vomitus</del> specimen for processing and later detection of NoV by RT-PCR. Subjects will only provide vomitus specimen if actively vomiting. All initial stool samples for each new onset episode of AGE will be analyzed for the following three enteric pathogens: <i>Salmonella</i>, <i>Shigella</i>, and <i>Campylobacter</i>.</p>
	<p>2<sup>nd</sup> paragraph: Subjects will receive standard of care treatment for AGE disease, and a new AGE disease symptom log will be given to record AGE disease symptoms until they resolve. Subjects will be instructed to return any subsequent and the latest AGE disease symptom log to the medical clinic at the next trial visit. A convalescent blood specimen for serology will be obtained once between 7 and 14 days after the onset of the AGE disease. After the initial stool specimen obtained at the onset of AGE disease: as available, three additional stool specimens will be obtained once between 7 and 14 days, once between 21 and <del>28</del> <b>29</b> days and once at end of the acute AGE surveillance period. These follow-on stool specimens will be analyzed for NoV by RT-PCR.</p>
Section 9.1.10	<p>2<sup>nd</sup> paragraph: All enrolled subjects will have blood drawn <b>once within 7 days prior to vaccination or on Day 1 and once on each of</b> Days <del>4, 8,</del> 29 and at the EOS (end of the active AGE surveillance period). For those subjects who develop AGE during the surveillance period, a single convalescent serum specimen will also be obtained once between 7 to 14 days after each new onset AGE episode.</p>

---

**Trial Summary**      **Adapted to reflect the changes in the body of the protocol.**

---

3<sup>rd</sup> paragraph:

CCI



---

Section 9.1.11

3<sup>rd</sup>  
CCI



---

Section 9.3.1

Section title:  
9.3.1 Screening Procedures (*within 7 days prior to vaccination or on Day 1*)

---

Section 9.3.2

Section title:  
9.3.2 Vaccination Procedures (*within 7 days prior to vaccination or on Day 1*)

---

2<sup>nd</sup> bullet (level 1):

Perform a urine or serum pregnancy test for female subjects of child-bearing potential. Refer to Section 9.1.14. ***The pregnancy test must be done within 72 hours prior to vaccination. If more than 72 hours have elapsed prior to vaccination, the pregnancy test must be repeated by either method.***

---

4<sup>th</sup> bullet (level 2):

Collect blood specimen ***once within 7 days prior to vaccination or on Day 1***. Refer to Sections 9.1.10 and 9.1.11. Blood should be taken from the subject using an aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in the Manual of Study Procedures.

---

5<sup>th</sup> bullet (level 2):

Collect saliva specimen ***once at any time during the trial*** from subjects in Subset A.

---

Trial Summary	Adapted to reflect the changes in the body of the protocol.
	<p>4<sup>th</sup> bullet (level 1):</p> <ul style="list-style-type: none"><li>Starting on the day of vaccination, the subject will check for specific types of events at the injection site (solicited local AEs), any specific generalized symptoms (solicited systemic AEs), body temperature (<i>by any method with oral route recommended</i>), any other symptoms or change in the subject's health status, and any medications taken. <b>The subjects will be informed that the recommended route to take their temperature is oral and will be instructed to use this route.</b> These solicited AEs and body temperature <i>will</i> be recorded in the diary <i>daily for 7 days</i>. Assessments should preferably take place in the evening at day's end.</li></ul>
Section 9.3.5	<p>3<sup>rd</sup> bullet:</p> <ul style="list-style-type: none"><li>Instruct subjects to come back to the medical clinic once between 7 and 14 days after the onset of the AGE disease for the collection of a convalescent blood specimen. Refer to Section 9.1.8. After the initial stool specimen obtained at the onset of AGE disease: as available, three additional stool specimens will be obtained once between 7 and 14 days, once between 21 and <del>28</del> <b>29</b> days and once at end of the acute AGE surveillance period. Refer to Section 9.1.8.</li></ul>
Section 9.3.6	<p>Section title: 9.3.6 Procedures at end of Active AGE Disease Surveillance Period (+/- <del>2</del> <b>4</b> days)</p>
Section 9.3.7	<p>Collect data on <i>AEs</i>.</p>
Section 10.1	<p>Table 10-a, Table 10-b footnotes: clarified body temperature is recommended to be taken by the oral route and to record the actual method taken on the CRF.</p>
Section 13.1.5	<p>2<sup>nd</sup> paragraph For subjects in Subsets A and B, safety will be assessed daily for 7 days after vaccination (including the day of vaccination) via collection of solicited AEs, including local AEs (injection site: pain, erythema, induration and swelling) and systemic AEs (headache, fatigue, myalgia, arthralgia, vomiting, and diarrhea). In addition, other indicators of safety will be collected (e.g., body temperature). <b>Body temperature will be summarized by actual route taken with no adjustment or conversion for route of measurement.</b></p>
Section 13.2	<p>1<sup>st</sup> paragraph: An interim analysis will be performed <del>on</del> <b>after</b> the first 200 subjects (Subset A) <del>have completed the EOS visit, and</del> <b>when</b> the assay results are completed. The anti-NoV GI.1 and GII.4 VLP antibody responses <b>at baseline (prior to or on Day 1) and</b> on Days <del>4, 8, 29</del> <b>4, 8, 29</b> and EOS, and the antibody responses <b>at baseline (prior to or on Day 1) and</b> on Days <del>4 and 29</del> <b>4 and 29</b> to adenovirus type 4, to meningococcal vaccine serogroup A, and to the seasonal influenza vaccine H3 strain, will be summarized by treatment group and provided to the sponsor and DMC for review. In addition, all available safety data for these subjects, including solicited AEs and unsolicited AEs, will be summarized and provided to the DMC for review. <b>Specifically, the interim safety and immunogenicity for this subset may be summarized separately as the results become available.</b></p>

Trial Summary	Adapted to reflect the changes in the body of the protocol.
Section 13.3	<p>2<sup>nd</sup> paragraph: 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 full trial period from September 2011 to September 2014. The expected background rate of NoV GI.1/GII.4 was calculated using <del>two</del> <b>three</b> assumptions. The incidence of NoV over the winter high season is the excess of AGE in the winter (first panel in Table 13-a) compared to the summer (second panel in Table 13-a) and can thus be calculated as the average weekly AGE incidence during the winter season minus the average weekly AGE incidence during the <del>preceding</del> <b>corresponding</b> summer season. This has been calculated in the last panel in Table 13-a. The second assumption is that 50% of the NoV cases are due to GI.1/GII.4 <del>which</del> <b>that</b> is compatible with the overall breakdown of the NHRC genotype analysis and the NoV genotypes identified by the 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 <b>reporting to the medical station are</b> all moderate or severe AGE cases <del>are reported to the medical station.</del></p>
	<p>3<sup>rd</sup> paragraph: 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 <i>Salmonella</i>, <i>Shigella</i>, or <i>Campylobacter</i>) is assumed to be 0.535–1.687% per subject-training period of observation based on NHRC AGE NoV surveillance data at the planned trial sites (Table 13-a). 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.1 or GII.4) NoV strains, excluding co-infection are confirmed. Thereafter, the trial will be closed to further enrollment.</p>
Appendix C	<p>Bullet 25: Female subjects of childbearing potential (e.g., non-sterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from <del>enrollment Day 1 and throughout</del> the duration of the trial. <del>Regular</del> <b>PP</b>regnancy tests will be performed <del>throughout the trial</del> for all female subjects of childbearing potential <b>as defined in the protocol and in the informed consent</b>. If a subject is found to be pregnant during trial, the investigator will offer the subject the choice to receive unblinded treatment information.</p>
General	Minor grammatical and editorial changes.



## TABLE OF CONTENTS

1.0	ADMINISTRATIVE INFORMATION .....	2
1.1	Contacts.....	2
1.2	Approval .....	3
1.3	Protocol Amendment .....	5
1.3.1	Amendment History .....	5
1.3.2	Summary of Changes.....	6
2.0	TRIAL SUMMARY .....	21
2.1	Schedule of Trial Procedures .....	33
3.0	TRIAL REFERENCE INFORMATION .....	37
3.1	Trial-Related Responsibilities.....	37
3.2	Principal Investigator/Coordinating Investigator.....	37
3.3	List of Abbreviations .....	38
3.4	Corporate Identification .....	40
4.0	INTRODUCTION .....	41
4.1	Background.....	41
4.2	Rationale for the Proposed Trial .....	42
5.0	TRIAL OBJECTIVES AND ENDPOINTS .....	43
5.1	Objectives .....	43
5.1.1	Primary Objective.....	43
5.1.2	Secondary Objectives.....	43
5.1.3	CCI .....	43
5.2	Endpoints .....	45
5.2.1	Primary Endpoint.....	45
5.2.2	Secondary Endpoints .....	45
5.2.3	CCI .....	45
6.0	TRIAL DESIGN AND DESCRIPTION .....	48
6.1	Trial Design .....	48
6.2	Justification for Trial Design, Dose, and Endpoints.....	50
6.3	Duration of Subject's Expected Participation in the Entire Trial .....	51
6.4	Premature Termination or Suspension of Trial or Investigational Site .....	51
6.4.1	Criteria for Premature Termination or Suspension of the Trial.....	51
6.4.2	Criteria for Premature Termination or Suspension of Investigational Sites .....	51
6.4.3	Procedures for Premature Termination or Suspension of the Trial or the Participation of Investigational Site(s).....	52

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS .....53

7.1 Inclusion Criteria .....53

7.2 Exclusion Criteria .....53

7.3 Criteria for Delay of Vaccination and/or Blood Sampling .....55

7.4 Criteria for Discontinuation or Withdrawal of a Subject.....55

7.5 Procedures for Discontinuation or Withdrawal of a Subject .....56

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT .....57

8.1 Trial Vaccine(s) and Materials.....57

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling .....57

8.1.2 Storage .....57

8.1.3 Dose and Regimen .....58

8.2 Trial Vaccine Assignment and Dispensing Procedures.....58

8.3 Randomization Code Creation and Storage.....59

8.4 Trial Vaccine Blind Maintenance .....59

8.5 Unblinding Procedure .....59

8.6 Accountability and Destruction of Sponsor-Supplied Vaccine(s) .....59

9.0 TRIAL PLAN .....61

9.1 Trial Procedures .....61

9.1.1 Screening Interview .....61

9.1.2 Review Inclusion/Exclusion Criteria .....61

9.1.3 Informed Consent.....61

9.1.4 Demographics, Medical History and Prior Medications.....61

9.1.5 Documentation of Trial Entrance/Randomization .....62

9.1.6 Physical Examination.....63

9.1.7 Assessment of HBGA secretor status .....63

9.1.8 AGE Disease Surveillance.....63

9.1.9 Identification of co-pathogens in stool of each subject with new onset AGE..63

9.1.10 **CCI** .....64

9.1.11 **CCI** .....64

9.1.12 Safety Assessments.....65

9.1.13 Pregnancy.....65

9.1.14 Documentation of Subjects who are not Randomized .....66

9.2 Monitoring Subject Treatment Compliance.....66

9.3 Schedule of Observations and Procedures .....66

9.3.1 Screening Procedures (within 7 days prior to vaccination or on Day 1) .....66

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

9.3.2	Vaccination Procedures (within 7 days prior to vaccination or on Day 1).....	67
9.3.3	Post-Vaccination procedures (Day 8 [+7 days] and Day 29 [+7 days]) .....	69
9.3.4	Clinic Visits after Vaccination (Day 8, Day 29, End of Active Surveillance) .....	69
9.3.5	Procedures at AGE Disease Visit .....	70
9.3.6	Procedures at End of Active AGE Disease Surveillance Period (- 7 days).....	71
9.3.7	Safety Follow-up.....	71
9.3.8	Post-Trial Care.....	71
9.4	Schedule of Additional Observations and Procedures for Subjects in Subsets A and B.....	71
9.5	Biological Sample Retention and Destruction.....	71
10.0	ADVERSE EVENTS.....	72
10.1	Definitions.....	72
10.1.1	Adverse Events (AEs).....	72
10.1.2	Solicited Adverse Events .....	72
10.1.3	Serious Adverse Events (SAEs).....	75
10.2	Causality of AEs .....	75
10.2.1	Relationship to Trial Procedures.....	75
10.2.2	Outcome of AEs.....	76
10.3	Additional Points to Consider for AEs .....	76
10.4	Procedures.....	77
10.4.1	Collection and Reporting of AEs.....	77
10.4.2	Collection and Reporting of Solicited AEs.....	78
10.4.3	Collection and Reporting of SAEs.....	78
10.5	Follow-up Procedures .....	79
10.5.1	AEs.....	79
10.5.2	SAEs .....	79
10.5.3	Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities .....	79
10.5.4	Post-Trial Events.....	79
11.0	TRIAL-SPECIFIC REQUIREMENTS .....	80
12.0	DATA HANDLING AND RECORDKEEPING .....	81
12.1	Electronic CRFs (eCRF).....	81
12.2	Record Retention .....	81
13.0	STATISTICAL METHODS.....	83

13.1	Statistical and Analytical Plans.....	83
13.1.1	Analysis Sets.....	83
13.1.2	Analysis of Demographics and Other Baseline Characteristics .....	83
13.1.3	Efficacy Analyses .....	83
13.1.4	CCI .....	84
13.1.5	Safety Analyses.....	84
13.1.6	CCI .....	85
13.2	Interim Analysis and Criteria for Early Termination.....	86
13.3	Determination of Sample Size .....	86
14.0	QUALITY CONTROL AND QUALITY ASSURANCE.....	88
14.1	Trial-Site Monitoring Visits.....	88
14.2	Protocol Deviations.....	88
14.3	Quality Assurance Audits and Regulatory Agency Inspections .....	88
15.0	ETHICAL ASPECTS OF THE TRIAL.....	89
15.1	IRB and/or IEC Approval .....	89
15.2	Subject Information, Informed Consent, and Subject Authorization .....	90
15.3	Subject Confidentiality .....	91
15.4	Publication, Disclosure, and Clinical Trial Registration Policy .....	91
15.4.1	Publication and Disclosure .....	91
15.4.2	Clinical Trial Registration.....	91
15.4.3	Clinical Trial Results Disclosure .....	92
15.5	Insurance and Compensation for Injury.....	92
16.0	REFERENCES .....	93

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

**LIST OF IN-TEXT TABLES**

Table 1.a	Contact Information .....	2
Table 2.a	Schedule of Trial Procedures for all Subjects (2800-8700 subjects) .....	33
Table 2.b	Schedule of Additional Trial Procedures and Analyses for the Subjects Meeting Work-up and AGE Case Definitions .....	35
Table 2.c	Schedule of Additional Trial Procedures and Analyses for Subsets A and B (200 subjects in each subset for a total of 400).....	36
Table 10.a	Local and Systemic AEs .....	73
Table 10.b	Intensity Assessment for Solicited safety parameters.....	74
Table 13.a	NHRC AGE NoV Surveillance Data at Planned Trial Sites.....	87
Table 16.a	Routine Immunizations for Newly Arriving U.S. Navy Subjects (NRTC-Great Lakes).....	102

**LIST OF IN-TEXT FIGURES**

Figure 6.a	Schematic of Trial Design .....	49
------------	---------------------------------	----

**LIST OF APPENDICES**

Appendix A	Responsibilities of the Investigator.....	96
Appendix B	Investigator Consent to Use of Personal Information.....	98
Appendix C	Elements of the Subject Informed Consent .....	99
Appendix D	Routine Immunizations.....	102
Appendix E	Five Point Scale Stool Chart.....	103

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

## 2.0 TRIAL SUMMARY

<b>Name of Sponsor(s):</b> 40 Landsdowne Street, Cambridge, MA 02139, USA		<b>Product Name:</b> Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine	
<b>Trial Title:</b> 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			
<b>IND No.:</b> 014421		<b>EudraCT No.:</b> Not applicable	
<b>Study Identifier:</b> NOR-211	<b>Phase:</b> 2b	<b>Trial Blinding Schema:</b> Double blind	
<p><b>Background and Rationale:</b></p> <p>Noroviruses (NoVs) cause an acute debilitating illness characterized by vomiting and diarrhea. According to the Centers for Disease Control and Prevention (CDC), 21 million cases of acute gastroenteritis (AGE) are due to NoV each year in the United States (US). NoVs have emerged as an important cause of outbreaks of viral gastroenteritis worldwide. These outbreaks can occur in all age groups, wherever people gather, and commonly result in significant morbidity and mortality, particularly in the very old and very young. In addition, NoV illnesses and outbreaks exact a significant socioeconomic toll on businesses, hospitals, schools and other closed settings, such as dormitories and military barracks.</p> <p>AGE is commonly reported within training and deployed US military populations. Viral-associated AGE is easily transmitted from human-to-human and can rapidly spread throughout an entire military unit causing widespread incapacitation often leading to disruption and reduction in operational readiness. NoV was found to be a major cause of AGE outbreaks and sporadic AGE cases among US military personnel deployed during the Persian Gulf War in 1991 as well as coalition forces in Gulf War II, Iraq and Afghanistan beginning in 2003. Similar outbreaks have been described in European military units deployed to these areas.</p> <p>AGE surveillance data collected over multiple seasons (2011 through 2014) from the Naval Health Research Center's (NHRC) Enteric Disease Surveillance Program (EDSP) support that NoV was the predominant pathogen identified in cases of AGE among US military subjects at the Marine Corps Recruit Depot (MCRD-SD) in San Diego, California, at the MCRD in Parris Island (MCRD-PI), South Carolina, and at the Naval Recruit Training Center in Great Lakes (NRTC-GL), Illinois. AGE due to NoV was originally known as "winter vomiting disease", and as expected, the highest detection rate of AGE due to NoV was during the months of September to May for both Marine and Navy subjects. The estimated population-based incidence of NoV illness at these training centers is 10 to 35 cases per 1000 subjects during training (an average of 7.6 weeks) in this high season (September-May).</p> <p>Currently, no vaccine exists for protection against AGE due to NoV. Given the disruptive effect of AGE due to NoV upon military training, readiness and performance, it is important to develop an effective vaccine. Takeda has conducted two proof of concept NoV vaccine and live oral challenge studies; a monovalent GI.1 VLP vaccine delivered as intranasal dry powder followed by live NoV genotype GI.1 oral challenge and a bivalent GI.1/GII.4 bivalent VLP vaccine delivered by intramuscular (IM) injection followed by live NoV genotype GII.4 oral challenge. Both trials showed that the VLP based vaccines reduced severity of AGE due to the challenge viruses. The more robust immunogenicity drove the decision to pursue the IM route of administration.</p> <p>The NoV GI.1/GII.4 bivalent VLP vaccine for IM injection to be evaluated in this trial contains both NoV GI.1 and NoV GII.4 VLPs as the antigens formulated with aluminum as aluminum hydroxide (Al(OH)<sub>3</sub>) adjuvant. Aluminum salt-based adjuvants have a demonstrated safety profile of over six decades. The GI.1 VLP represents a single GI.1 strain and the GII.4 VLP consists of a consensus sequence of three GII.4 strains (cVLP). NoV VLPs are non-infectious because they do not contain viral ribonucleic acid (RNA).</p> <p>Prior safety and immunogenicity data for the NoV vaccine given by the IM route are available from approximately 1000 adult subjects, evaluated in five Takeda clinical trials (LV03-104, LV03-105, NOR-107, NOR-201, and NOR-210). The NoV vaccine evaluated in these trials either contained both Al(OH)<sub>3</sub> plus monophosphoryl lipid A</p>			

(MPL) adjuvants combined or the Al(OH)<sub>3</sub> adjuvant alone. In clinical trials with the NoV vaccine, a single suspected unexpected serious adverse reaction (SUSAR) was reported, and to date, no other serious adverse events (SAEs) related to the vaccine were reported in these trials. Trial NOR-107 conducted in adults aged 18-64 years, a Phase II dosage, adjuvant justification, safety, and immunogenicity trial, evaluated 11 vaccine formulations, and showed that the NoV VLP vaccine adjuvanted with aluminum as Al(OH)<sub>3</sub> adjuvant was as immunogenic as the NoV VLP vaccine adjuvanted with Al(OH)<sub>3</sub> and MPL combined.

NoV outbreaks seriously impact military and civilian adult populations. Surveillance studies conducted over multiple years have demonstrated a consistently high incidence of NoV-related illness among US military subjects. Moreover, the success of a recent adenovirus vaccine efficacy (VE) trial in military subjects further supports the selection of the population for this trial. The primary goal of this Phase 2b clinical trial is to evaluate the efficacy of the NoV vaccine against moderate or severe acute gastroenteritis (AGE) due to genotype-specific (GI.1 and GII.4) NoV strains in 2800-8700 healthy US military adult subjects. Specifically, this trial will inform whether the NoV vaccine will provide protection against circulating NoV strains. Data from this trial will further inform the clinical development plan for Phase 3 of the NoV vaccine.

#### Trial Design:

This is a Phase 2b, double blind, randomized, multi-site, placebo-controlled, efficacy trial of a single dose of the IM NoV vaccine combined with Al(OH)<sub>3</sub> adjuvant compared to a single dose of placebo (saline) control. Based on prior incidence rates of AGE due to NoV over multiple seasons in the US Military training installations, the estimated sample size for the trial is 2800-8700 healthy subjects aged 18 to 49 years who will be recruited from US 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. If the accrual of cases (as defined above) is slower than expected, an interim analysis may be performed when approximately 30 cases of moderate or severe AGE due to any NoV strain have been accrued. For all enrolled subjects, accrual of additional AGE cases due to NoV will continue until the end of each respective active AGE surveillance period (45 days). 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 response technology (IRT), 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 US military. The licensed routinely required vaccines administered on Day 1, may include meningococcal, diphtheria-tetanus-acellular pertussis, influenza, adenovirus, hepatitis A/B, measles-mumps-rubella (MMR), varicella, polio, and pneumococcal vaccines per the site requirements.

For those ill subjects with AGE who meet case criteria, 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 end of the active surveillance period (EOS). 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 EOS).

These four sera will be evaluated in 400 subjects, 200 subjects in Subset A CCI [REDACTED]. The 200 subjects in Subset A will also be evaluated for immune response to selected antigens of the routinely administered vaccines.

All enrolled subjects will be evaluated for serious adverse events (SAEs) and any adverse events (AEs) that lead to

trial withdrawal throughout the active AGE surveillance period.

The 200 subjects in Subset A and 200 subjects in Subset B will be evaluated for solicited local and solicited systemic 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.

**Surveillance for AGE:**

Each enrolled subject will have surveillance for AGE performed from Day 1 until the end of the active AGE surveillance period (Day 45). 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 AGE in ill subjects:**

At the medical clinic, the subject will be assessed to determine if they have an AGE that meets the 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 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 and *vomit* 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 *vomit* sample confirmed by RT-PCR. In circumstances where both stool and *vomit* 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:**

- |                 |   |
|-----------------|---|
| <b>Mild</b>     | <ul style="list-style-type: none"><li>• 1 to 2 episodes of vomiting* within 24 hours AND/OR.</li><li>• 3 unformed stools** within 24 hours</li></ul>  |
| <b>Moderate</b> | <ul style="list-style-type: none"><li>• 3 to 5 episodes of vomiting* within 24 hours AND/OR</li><li>• 4 to 5 unformed stools** within 24 hours</li></ul>  |
| <b>Severe</b>   | <ul style="list-style-type: none"><li>• 6 or more episodes of vomiting* within 24 hours AND/OR</li><li>• 6 or more unformed stools** within 24 hours AND/OR</li><li>• Hospital admission and/or intravenous rehydration for mild or greater AGE</li></ul> |

\*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. Notably, co-pathogens were uncommon (found in less than 2% of AGE cases) in a multi-year surveillance trial in US military subjects.

CCI

CCI

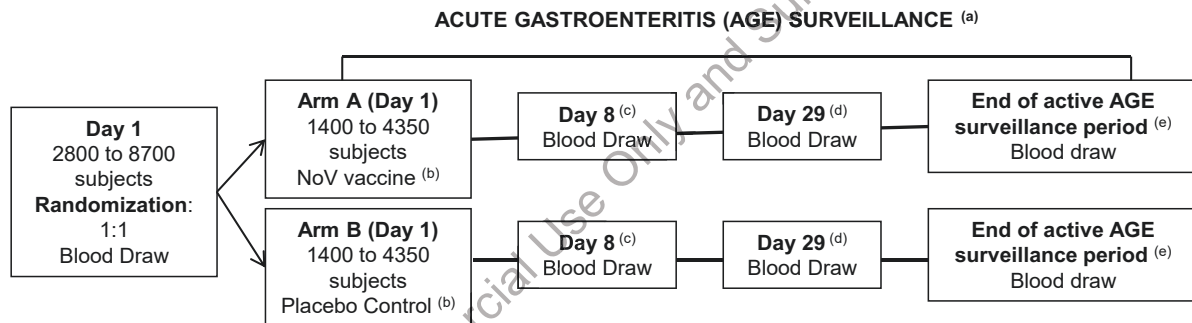
**Assessments for safety:**

- All subjects will be assessed for all SAEs and for all AEs leading to withdrawal from the trial for the entire AGE surveillance period. Specifically subject safety for these events will be assessed at the routine post-vaccination trial visits on Days 8 and 29, and EOS.
- Reactogenicity symptoms in Subsets A and B (total of 400 subjects): the initial 200 subjects enrolled in Subset A and the 200 subjects randomly selected across all sites (Subset B) will record solicited AEs, including body temperature, on diary cards for 7 days after vaccination (including the day of vaccination) to be collected on or after Day 8, and unsolicited AEs for 28 days after vaccination (including the day of vaccination) to be collected by interview on or after Day 29.

**Interim analysis:**

- An interim analysis will be performed on the first 200 subjects (Subset A) when the assay results are completed. The anti-NoV GI.1 and GII.4 VLP antibody responses at baseline (prior to or on Day 1) and on Days 8, 29 and EOS. CCI  
[REDACTED]  
[REDACTED]. Specifically, the interim safety and immunogenicity for this subset may be summarized separately as the results become available. The DMC is responsible for ongoing and cumulative safety data review for all NoV vaccine trials, regardless of age.

**Schematic of NOR-211:**



<sup>a</sup> Fresh stool and/or vomitus specimens for each new onset AGE disease episode and a convalescent serum once 7-14 days thereafter. As available, a 2<sup>nd</sup> and 3<sup>rd</sup> stool specimen will be obtained once 7-14 days, and once 21-28 days thereafter and at the end of active AGE surveillance period (Day 45).

<sup>b</sup> Routine immunizations administered as required by the US military.

<sup>c</sup> Blood draw for serology (all subjects). Diary card collection and review (subjects in subsets A and B).

<sup>d</sup> Blood draw for serology (all subjects). Safety assessment by interview (subjects in subsets A and B).

<sup>e</sup> Blood draw for serology (all subjects) at the end of active AGE surveillance period (Day 45).

**Primary Objective:**

- 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 (excluding co-infection with *Salmonella*, *Shigella* or *Campylobacter*).

**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 **any** NoV strain (**excluding co-infection** with *Salmonella*, *Shigella* or *Campylobacter*).

**Exploratory Objectives:**

CCI



Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

<b>CCI</b>	
<p><b>Subject Population:</b>  <b>Healthy subjects:</b> Yes.  <b>Planned Minimum Age:</b> 18 years.  <b>Planned Number of Subjects:</b> 2800-8700.  <b>Planned Number of Arms:</b> 2; 1:1 randomization.</p> <ul style="list-style-type: none"> <li>• <b>Arm A:</b> NoV GI.1/GII.4 bivalent VLP vaccine, referred to as NoV vaccine.</li> <li>• <b>Arm B:</b> Placebo (saline) control.</li> </ul>	
<p><b>Criteria for Inclusion:</b></p> <ul style="list-style-type: none"> <li>• The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any trial procedures after the nature of the trial has been explained according to local regulatory requirements.</li> <li>• Male or female subjects, 18 to 49 years of age.</li> <li>• Individuals who are in good health at the time of entry into the trial as determined by medical history and the clinical judgment of the investigator.</li> <li>• Individuals who can comply with trial procedures and are available for the duration of follow-up.</li> </ul>	
<p><b>Criteria for Exclusion:</b></p> <ul style="list-style-type: none"> <li>• Pregnancy.</li> <li>• Known hypersensitivity to any of the NoV GI.1/GII.4 bivalent VLP vaccine components (including excipients).</li> <li>• Subjects with known hypersensitivity or allergy to any of the licensed required concomitant vaccine components to be administered.</li> <li>• Any condition or circumstance that the investigator determines would interfere with trial evaluation or interpretation.</li> <li>• Subjects with known or suspected impairment or alteration of immune function.</li> <li>• Subjects with a history of AGE within 14 days of enrollment.</li> <li>• Subjects with a history of body temperature of 38.0°C (100.4°F) or higher within 3 days of intended trial vaccination.</li> <li>• Subjects who have received blood, blood products, and/or plasma derivatives or any parenteral immunoglobulin antibody preparation in the past 3 months.</li> <li>• Immunosuppressive therapy within 3 months or systemic (eg, oral or parenteral) corticosteroid treatment within 60 days prior to investigational trial dose administration.</li> <li>• Subjects participating in any clinical trial with another investigational product 30 days prior to the first trial visit or intending to participate in another clinical trial at any time during the conduct of this trial.</li> <li>• Subjects who are first-degree relatives of individuals involved in the conduct of the trial.</li> </ul>	
<p><b>Trial Vaccine(s):</b>  <u>NoV GI.1/GII.4 bivalent VLP vaccine</u> contains per 0.5 mL dose: 15 µg of GI.1 VLP and 50 µg of GII.4 VLP as antigens and 500 µg of aluminum as aluminum hydroxide (Al(OH)<sub>3</sub>) adjuvant.  <u>Control:</u> Placebo (saline) is 0.5 ml per dose of 0.9% sodium chloride for injection without preservative.</p>	
<p><b>Duration of the Trial:</b>                  Until ~ 30 AGE cases due to NoV; if &lt; 30 AGE cases occur in the first season, the trial may be continued for the same season, stopped or continued for a second season.</p>	<p><b>Period of Evaluation for Each Subject:</b>                  From enrollment through EOS (trial Day 45).</p>

**Main Criteria for Evaluation and Analyses:**

**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*).

**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*).

CCI

CCI

**Statistical Considerations:**

Analysis sets

**Safety Set:** The Safety Set will consist of all subjects who received the trial vaccines (NoV GI.1/GII.4 bivalent VLP vaccine or saline placebo). For all subjects in the Safety Set, SAEs and AEs leading to withdrawal from the trial will be assessed up to the EOS. For analyses of solicited AEs and unsolicited non-serious AEs, only subjects in Subsets A and B will be included.

**Full Analysis Set (FAS):** The FAS will include all subjects who are randomized and received the trial vaccination.

**Per-Protocol Set (PPS):** The PPS will include all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of subject's treatment assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving wrong trial treatment (3) receiving prohibited therapies, and (4) other major protocol violations that may be identified during blinded data reviews.

Analysis of demographics and other baseline characteristics

Age, gender, ethnicity, race, and other baseline characteristics will be summarized descriptively by treatment arm for all randomized subjects.

Efficacy analyses

For the primary endpoint, the primary analysis method will be based on the FAS and a Cox proportional hazard model with treatment as a factor, adjusted for gender and age, and stratified by site, with two-sided 95% confidence interval

(CI) provided for the estimate of VE. The primary efficacy objective is considered to be met if the lower bound of the 95% CI for the VE is above 0%, where VE is defined as  $1 - (\lambda_V/\lambda_C)$ , where  $\lambda_V$  and  $\lambda_C$  denote the hazard rates for the NoV vaccine and saline placebo arms, respectively.

Sensitivity analyses of the primary endpoint include: (1) analysis based on exact 95% CIs based on the FAS, and (2) analysis based on the PPS using the same model as in the primary analysis.

Evaluation of secondary **CCI** VE endpoints will be based on the FAS and analyzed using a similar approach to the primary endpoint, as described above.

Analyses of endpoints for recurrent events will be performed using proportional intensity (Andersen-Gill) models with treatment as a factor and stratified by site.

As measures of vaccine effectiveness, vaccine preventable disease incidence (VPDI), which is defined as the incidence in the saline placebo arm minus the incidence in the NoV vaccine arm, will be calculated for all-cause AGE occurring > 7 days after dosing, all-cause moderate or severe AGE occurring > 7 days after dosing, and all-cause severe AGE occurring > 7 days after dosing (all including co-infection).

The analysis of data for the duration of shedding by RT-PCR after AGE due to NoV will be descriptive.

The modified Vesikari score for subjects with confirmed NoV AGE occurring after >7 days after dosing will be summarized descriptively.

**CCI**

**CCI**

Safety analyses

In general, data imputation will not be performed for any missing safety data. The criteria for biologically implausible measurements will be defined in the statistical analysis plan. Any SAE or AE leading to trial withdrawal collected during the AGE surveillance period for all subjects in the Safety Set will be included.

*Solicited AEs*

For subjects in Subsets A and B, safety will be assessed daily for 7 days after vaccination (including the day of vaccination) via collection of solicited AEs, including local AEs (injection site: pain, erythema, induration and swelling) and systemic AEs (headache, fatigue, myalgia, arthralgia, vomiting, and diarrhea). In addition, other indicators of safety will be collected (eg, body temperature). Body temperature by the actual route taken will be summarized with no adjustment or conversion for route of measurement.

For each solicited AE, the percentage of subjects will be summarized by event severity for each day from Day 1 to Day 7 (including the day of vaccination) and overall. Summaries of the day of first onset of each event and the number of days subjects reported experiencing each event will also be provided. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

*Unsolicited AEs*

Any SAEs, and AEs leading to trial withdrawal (all subjects), and any other unsolicited AEs for 28 days (Subsets A and B), will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), and summarized by system organ class (SOC) and preferred term (PT) for each treatment arm.

Any unsolicited AE collected up to Day 29 by interview with subjects in Subsets A and B will be included in the Safety Set.

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. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. Unsolicited AEs will be summarized as follows: by SOC and PT; by SOC, PT, and severity; by SOC, PT, and relationship (causality) to the investigational trial dose; and by SOC and PT including events with frequency greater than 2%.

Unless otherwise specified, unsolicited AEs for Subsets A and B will be summarized in the following 3 ways: 1) overall up to 28 days after the vaccination (including the day of vaccination), 2) with onset between 1 and 7 days after the vaccination (including the day of vaccination), and 3) with onset between 8 and 28 days after the vaccination (including the day of vaccination).

**Interim Analysis:**

An interim analysis will be performed on the first 200 subjects (Subset A) when the assay results are completed. The anti-NoV GI.1 and GII.4 VLP antibody responses at baseline (prior to or on Day 1) and on Days 8, 29 and EOS, C

CI

In addition, all available safety data for these subjects, including solicited AEs and unsolicited AEs, will be summarized and provided to the DMC for review. Specifically, the interim safety and immunogenicity for this subset may be summarized separately as the results become available.

If the accrual of cases for the primary endpoint is slower than expected, a second interim analysis may be performed when approximately 30 cases of moderate or severe AGE due to any NoV strain have been accrued.

The trial team responsible for trial conduct (both from Takeda and Clinical Research Organization [CRO]) will remain blinded to individual treatment assignment information for the subjects throughout the trial.

**Sample Size Justification:**

Assuming true 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 compared to the summer 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. 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 NHRC genotype analysis and the NoV genotypes identified by the 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.1 or GII.4) NoV strains, excluding co-infection are confirmed. Thereafter, the trial will be closed to further enrollment.

**Data Monitoring Committee:**

An overall DMC is established to evaluate overall safety of the NoV program on an ongoing basis. The DMC will review the safety and immunogenicity results to the NoV vaccine (Subset A) and the results to the selected co-administered vaccines (Subset A). The overall program DMC charter is a separate document.

NOR-211 Version 3.0 (15 November 2017)

## 2.1 Schedule of Trial Procedures

**Table 2.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 <sup>(a)</sup> (Day 45/ET)
Visit window	-7 days		+ 7 days	+ 7 days	- 7 days
Visits	X	X	X	X	X
Screening interview	X				
Signed informed consent	X				
Assessment of eligibility criteria <sup>(b)</sup>	X	X			
Demographics	X				
Medical history	X				
Prior medications	X				
Concomitant medications & vaccinations		X			
Pregnancy screening <sup>(c)</sup>		X			
Randomization <sup>(d)</sup>		X			
Trial treatment <sup>(d)</sup>		X			
SAEs <sup>(e)</sup>		X	X	X	X
Blood draw (10-15 mL) <sup>(f)</sup>		X	X	X	X

(a) Trial personnel will follow subjects through Day 45. If a subject early terminates (ET), Day 45 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 prior to 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. If the investigational trial dose is delayed beyond the day the routine immunizations required by the US military are given, the trial dose may be administered later during the training period. For subjects in Subset A, 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

**CONFIDENTIAL**

recorded on the subject's source documents (by manufacturer, lot number, expiry date) and subsequently recorded in the electronic case report form (eCRF). For all subjects enrolled after Subset A, this information will be filed at the site as source documentation but not recorded in the 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 the end of the active surveillance period (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.

Note: ET: early termination visit

**CONFIDENTIAL**

**Table 2.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 after each AGE onset	Once Day 21 – 29 after each AGE onset	End of active AGE Surveillance period <sup>a</sup> (Day 45/ET - 7 days)
Visit window		+ 7 days	+ 7 days	
AGE symptom log <sup>(a)</sup>	X			
Stool sample collection <sup>(b)</sup>	X	X	X	X
Vomitus sample collection <sup>(b)</sup>	X			
Convalescent blood draw (5 -10 mL) <sup>(c)</sup>		X		

In case of AGE:

- (a) During the AGE surveillance period (Day 1 through Day 45), those subjects, who present with AGE, will be instructed to record their AGE symptoms on the logs and report for assessment at the next trial visit. Initial AGE symptom logs will be given at trial entry to record AGE symptoms. Subjects will be instructed to return any subsequent logs and the latest AGE symptom log 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. If no samples are provided at AGE onset, samples should be obtained as soon as possible thereafter. If samples at AGE onset are inadequate ie too small for both RT-PCR to NoV and co-infection tests, the sample should be prioritized for RT-PCR to NoV and a subsequent sample should be obtained for co-infection testing as soon as possible thereafter. If samples become lost, destroyed, damaged or otherwise unavailable for use, AGE onset samples should be repeated as soon as possible. After the initial stool specimen is obtained at the onset of AGE; up to three additional stool specimens (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.

CONFIDENTIAL

**Table 2.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 <sup>a</sup>	Day 29	End of active AGE Surveillance period <sup>(a)</sup> (Day 45/ET)
Visit window	- 7 days		+ 7 days	+ 7 days	- 7 days
Subsets A and B subjects only - Concomitant medications			X	X	
Subset A and B subjects only - Diary card <sup>b</sup>					
Distribution		X			
Review/collection			X		
Subset A and B subjects only – solicited and unsolicited AEs <sup>(b)</sup>		X	X	X	
Subset A subjects only - Saliva specimen <sup>(c)</sup>		X			
Subset A subjects only – Additional Blood volume (5 – 10 mL) <sup>(d)</sup>		X		X	

- (a) Trial personnel will follow subjects through Day 45. If a subject early terminates (ET), Day 45 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 serum anti-NoV antibody immune responses by secretor status. A single saliva specimen will be collected from these subset A 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 Day 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.

Note: ET: early termination

CONFIDENTIAL

### **3.0 TRIAL REFERENCE INFORMATION**

#### **3.1 Trial-Related Responsibilities**

The sponsor will perform all trial-related activities with the exception of those identified in the Trial-Related Responsibilities template. The identified vendors in the template for specific trial-related activities will perform these activities in full or in partnership with the sponsor.

#### **3.2 Principal Investigator/Coordinating Investigator**

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

### 3.3 List of Abbreviations

AE	Adverse Event
AGE	Acute Gastroenteritis
CFR	Code of Federal Regulations
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
<b>CCI</b>	
EOS	End of Active Surveillance Period
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Genogroup I
GII	Genogroup II
GI.1	Genogroup I, Genotype 1
GII.4	Genogroup II, Genotype 4
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
HAI	Hemagglutination-inhibition
HBGA(s)	Histoblood Group Antigen(s)
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
MMR	Measles-mumps-rubella
MedDRA	Medical Dictionary for Regulatory Activities
MPL	Monophosphoryl Lipid A
NHRC	Naval Health Research Center
NHRC-EDSP	Enteric Disease Surveillance Program
NoV	Norovirus
NRTC	Navy Recruit Training Center
Pan-Ig	Total Immunoglobulin
PCR	Polymerase Chain Reaction
PPS	Per-Protocol Analysis Set
PT	Preferred Term
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SBA	Serum Bactericidal Assay
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
VE	Vaccine Efficacy
VLP	Virus-like Particles
VPDI	Vaccine Preventable Disease Incidence

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use



### 3.4 Corporate Identification

TV	Takeda Vaccines, Inc.
VBV	Vaccines Business Unit

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

## 4.0 INTRODUCTION

### 4.1 Background

Noroviruses (NoVs) cause an acute debilitating illness characterized by vomiting and diarrhea [3]. According to the Centers for Disease Control and Prevention (CDC), 21 million cases of acute gastroenteritis (AGE) are due to NoV each year in the United States (US) [4, 5]. NoVs have emerged as an important cause of outbreaks of viral gastroenteritis worldwide. These outbreaks can occur in all age groups, wherever people gather, and commonly result in significant morbidity and mortality, particularly in the very old and very young [6, 7]. In addition, NoV illnesses and outbreaks exact a significant socioeconomic toll on businesses, hospitals, schools and other closed settings, such as dormitories and military barracks.

AGE is commonly reported within training and deployed US military populations [8-13]. Viral-associated AGE is easily transmitted from human-to-human and can rapidly spread throughout an entire military unit causing widespread incapacitation often leading to disruption and reduction in operational readiness. NoV was found to be a major cause of AGE outbreaks and sporadic AGE cases among US military personnel deployed during the Persian Gulf War in 1991 [13] as well as coalition forces in Gulf War II, Iraq and Afghanistan beginning in 2003. Similar outbreaks have been described in European military units deployed to these areas.

AGE surveillance data collected over multiple seasons (2011 through 2014) from the Naval Health Research Center's (NHRC) Enteric Disease Surveillance Program (EDSP) support that NoV was the predominant pathogen identified in cases of AGE among US military subjects at the Marine Corps Recruit Depot (MCRD-SD) in San Diego, California, at the MCRD in Parris Island (MCRD-PI), South Carolina, and at the Naval Recruit Training Center in Great Lakes (NRTC-GL), Illinois. AGE due to NoV was originally known as "winter vomiting disease", and as expected, the highest detection rate of AGE due to NoV was during the months of September to May for both Marine and Navy subjects. The estimated population-based incidence of NoV illness at these training centers is 10 to 35 cases per 1000 subjects during training (an average of 7.6 weeks) in this high season (September-May) [communication from NHRC-EDSP].

Currently, no vaccine exists for protection against AGE due to NoV. Given the disruptive effect of AGE due to NoV upon military training, readiness and performance, it is important to develop an effective vaccine. Takeda has conducted two proof of concept NoV vaccine and live oral challenge studies; a monovalent GI.1 VLP vaccine delivered as intranasal dry powder followed by live NoV genotype GI.1 oral challenge [14-18] and a bivalent GI.1/GII.4 bivalent VLP vaccine delivered by intramuscular (IM) injection followed by live NoV genotype GII.4 oral challenge [19, 20]. Both trials showed that the VLP based vaccines reduced severity of AGE due to the challenge viruses. The more robust immunogenicity drove the decision to pursue the IM route of administration.

The NoV GI.1/GII.4 bivalent VLP vaccine for IM injection to be evaluated in this trial contains both NoV GI.1 and NoV GII.4 VLPs as the antigens formulated with aluminum as aluminum hydroxide (Al(OH)<sub>3</sub>) adjuvant. Aluminum salt-based adjuvants have a demonstrated safety profile of over six decades [21]. The GI.1 VLP represents a single GI.1 strain and the GII.4 VLP consists

of a consensus sequence of three GII.4 strains (cVLP). NoV VLPs are non-infectious because they do not contain viral ribonucleic acid (RNA).

Prior safety and immunogenicity data for the NoV vaccine given by the IM route are available from approximately 1000 adult subjects, evaluated in five Takeda clinical trials (LV03-104 [20], LV03-105 [19], NOR-107, NOR-201, and NOR-210). The NoV vaccine evaluated in these trials either contained both Al(OH)<sub>3</sub> plus monophosphoryl lipid A (MPL) adjuvants combined or the Al(OH)<sub>3</sub> adjuvant alone. In clinical trials with the NoV vaccine, a single suspected unexpected serious adverse reaction (SUSAR) was reported, and to date, no other serious adverse events (SAEs) related to the vaccine were reported in these trials. Trial NOR-107 conducted in adults aged 18-64 years, a Phase II dosage, adjuvant justification, safety, and immunogenicity trial, evaluated 11 vaccine formulations, and showed that the NoV VLP vaccine adjuvanted with aluminum as Al(OH)<sub>3</sub> adjuvant was as immunogenic as the NoV VLP vaccine adjuvanted with Al(OH)<sub>3</sub> and MPL combined.

Refer to the current Investigator Brochure of Takeda's NoV GI.1/GII.4 bivalent VLP vaccine for additional product information and a more detailed review of pre-clinical and clinical studies [22].

#### 4.2 Rationale for the Proposed Trial

NoV outbreaks seriously impact military and civilian adult populations. Surveillance studies conducted over multiple years have demonstrated a consistently high incidence of NoV-related illness among US military subjects. Moreover, the success of a recent adenovirus vaccine efficacy (VE) trial in military subjects further supports the selection of the population for this trial [23]. The primary goal of this Phase 2b clinical trial is to evaluate the efficacy of the NoV vaccine against moderate or severe acute gastroenteritis (AGE) due to genotype-specific (GI.1 and GII.4) NoV strains in 2800-8700 healthy US military adult subjects. Specifically, this trial will inform whether the NoV vaccine will provide protection against circulating NoV strains. Data from this trial will further inform the clinical development plan for Phase 3 of the NoV vaccine.

The trial will be conducted in accordance with the protocol, the International Conference on Harmonization and Good Clinical Practice (ICH-GCP) Guidelines, 21 Code of Federal Regulations (CFR) Part 56 & 50, and applicable regulatory requirements.

## 5.0 TRIAL OBJECTIVES AND ENDPOINTS

### 5.1 Objectives

#### 5.1.1 Primary Objective

- 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 (**excluding co-infection** with *Salmonella*, *Shigella* or *Campylobacter*).

#### 5.1.2 Secondary Objectives

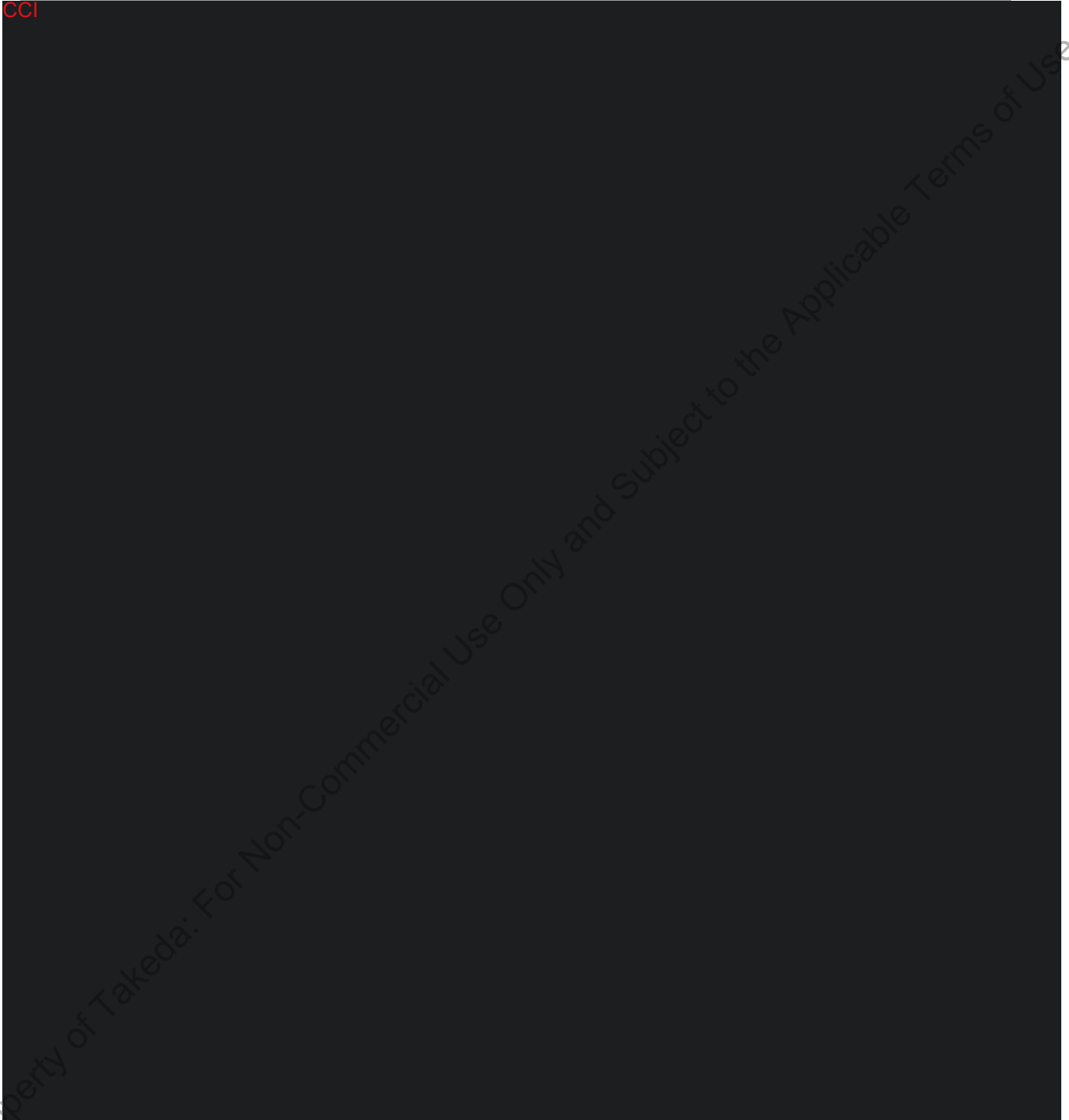
##### Secondary Efficacy Objectives:

- 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 **any** NoV strain (**excluding co-infection** with *Salmonella*, *Shigella* or *Campylobacter*).

CCI



CCI



Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use



Safety Exploratory Objectives:

- To evaluate the safety and tolerability of a single dose of the NoV bivalent VLP vaccine compared to placebo (saline) control, as measured by SAEs and AEs leading to withdrawal for all subjects.
- To evaluate the safety of a single dose of the NoV bivalent VLP vaccine compared to placebo (saline) control, as measured by solicited local and systemic AEs and unsolicited AEs after trial injection (Subset A and B).

**5.2 Endpoints**

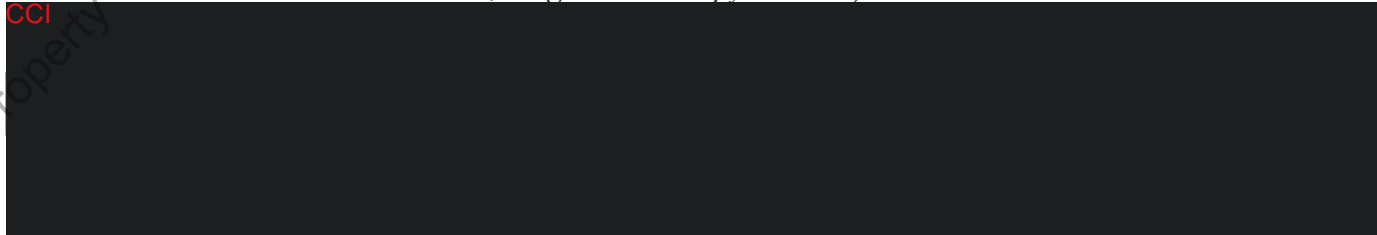
**5.2.1 Primary Endpoint**

- **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*).

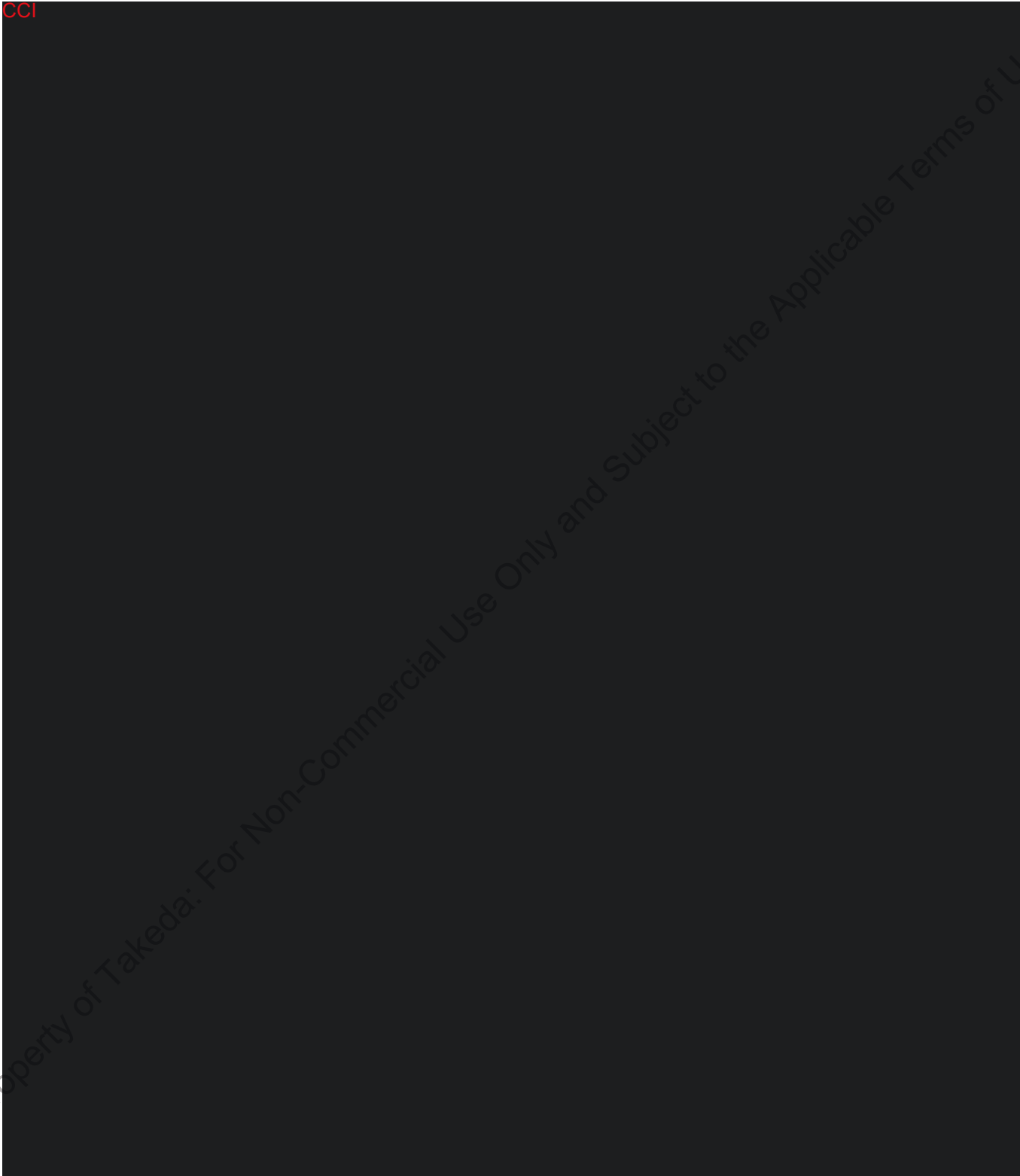
**5.2.2 Secondary Endpoints**

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*).

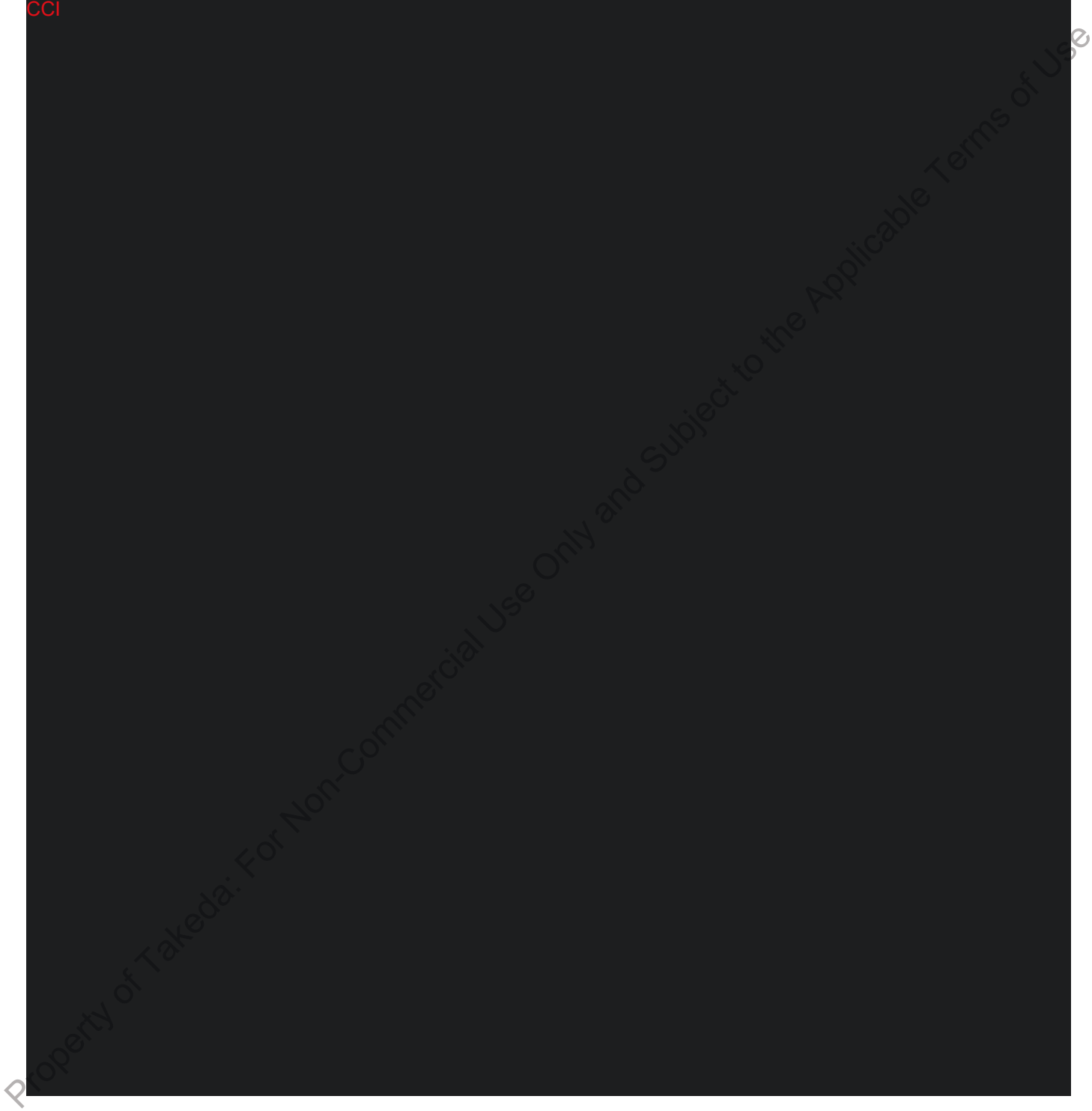


CCI



Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI



Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use



## 6.0 TRIAL DESIGN AND DESCRIPTION

### 6.1 Trial Design

This is a Phase 2b, double blind, randomized, multi-site, placebo-controlled, efficacy trial of a single dose of the IM NoV vaccine combined with Al(OH)<sub>3</sub> adjuvant compared to a single dose of placebo (saline) control. Based on prior incidence rates of AGE over multiple seasons in the US Military training installations, the estimated sample size for the trial is **2800-8700** healthy subjects aged 18 to 49 years who will be recruited from US 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. If the accrual of cases (as defined above) is slower than expected, an interim analysis may be performed when approximately 30 cases of moderate or severe AGE due to any NoV strain have been accrued. For all enrolled subjects, accrual of additional AGE cases due to NoV will continue for all enrolled subjects until the end of each respective active AGE surveillance period (45 days). 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 response technology (IRT), 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 US military. The licensed routinely required vaccines administered on Day 1, may include meningococcal, diphtheria-tetanus-acellular pertussis, influenza, adenovirus, hepatitis A/B, measles-mumps-rubella (MMR), varicella, polio, and pneumococcal vaccines per the site requirements.

For those ill subjects with AGE who meet case criteria, a fresh stool sample and *vomit* 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 end of the active surveillance period (EOS). 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 EOS).

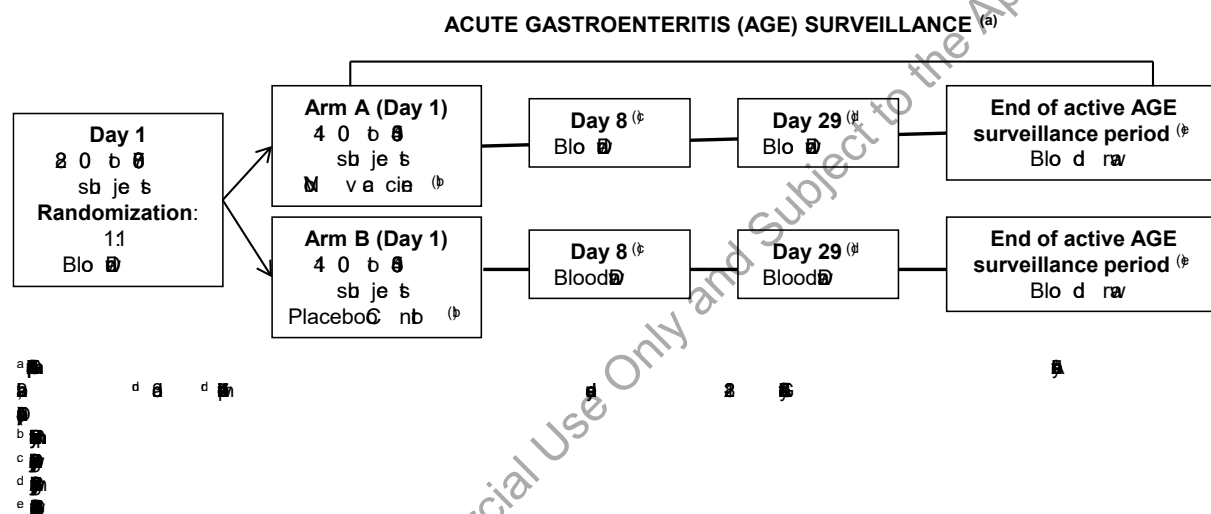
CCI [REDACTED]. The 200 subjects in Subset A will also be evaluated for immune response to selected antigens of the routinely administered vaccines.

All enrolled subjects will be evaluated for serious adverse events (SAEs) and any adverse events (AEs) that lead to trial withdrawal throughout the active AGE surveillance period.

The 200 subjects in Subset A and 200 subjects in Subset B will be evaluated for solicited local and solicited systemic 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.

A schematic of the trial design is included as [Figure 6.a](#). A schedule of trial procedures is provided in Section 2.1.

**Figure 6.a Schematic of Trial Design**



**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 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) ([Appendix E](#)).

Subjects who meet the work-up definition will provide a fresh stool specimen, 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 *vomit* sample confirmed by RT-PCR. In circumstances where both stool and *vomit* 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:

- |                 |   |
|-----------------|---|
| <b>Mild</b>     | • 1 to 2 episodes of vomiting <sup>a</sup> within 24 hours AND/OR.          |
|                 | • 3 unformed stools <sup>b</sup> within 24 hours                            |
| <b>Moderate</b> | • 3 to 5 episodes of vomiting <sup>a</sup> within 24 hours AND/OR           |
|                 | • 4 to 5 unformed stools <sup>b</sup> within 24 hours                       |
| <b>Severe</b>   | • 6 or more episodes of vomiting <sup>a</sup> within 24 hours AND/OR        |
|                 | • 6 or more unformed stools <sup>b</sup> within 24 hours AND/OR             |
|                 | • Hospital admission and/or intravenous rehydration for mild or greater AGE |

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

(b) 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'.

## 6.2 Justification for Trial Design, Dose, and Endpoints

NoV outbreaks seriously impact military adult populations; this justifies the selection of this population for the trial.

Data generated to date with Takeda's NoV GI.1/GII.4 bivalent VLP vaccine administered by IM injection from several Phase I or II studies (LV03-104, NOR-107 and NOR-201) with various dosages of antigen (see IB), show that peak immune responses were observed 8 days after the first dose, with a second dose given 28 days later having only a limited effect. Thus, a single dose regimen will be evaluated in the present trial. The aluminum concentration per dose was selected empirically from data that demonstrated that this amount of aluminum enhanced the immunogenicity of the vaccine [21]. Aluminum salt-based adjuvants have a demonstrated safety profile of over six decades [21]. 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)<sub>3</sub>. Approximately 1000 subjects have received the NoV bivalent vaccine by IM injection and all doses contained the Al(OH)<sub>3</sub> adjuvant.

The U.S. Military administers multiple licensed vaccines to protect enlisted recruits in basic training (Appendix D). The immunogenicity of the co-administration of those vaccines on the same day with the NoV vaccine has not previously been assessed. The collection of solicited and unsolicited symptoms following these vaccinations is consistent with other vaccine evaluation studies. These data will be provided to the DMC for their review. (Refer to Section 13.2. Interim Analysis)

Enrollment will begin prior to or during the NoV high season (between September and May). If the number of AGE cases due to NoV has not been reached by the end of the first season (end of May), enrollment may be continued if more AGE cases are actively accruing later in the current season, may be stopped due to the lower incidence of NoV infection, and/or may be continued the following September (second season). This duration corresponds to the window of time during which ~ 30 AGE cases due to NoV (GI.1/GII.4 or any NoV genogroup GI or GII strain) will occur.

The AGE disease severity definitions are based on the proceedings of the External Clinical Expert meeting: NoV vaccine Phase 3 efficacy trial designs working session (internal document) and CTCAE Version 4.0 [26]. Unformed stools are those meeting a 3 or greater severity of diarrhea on a 5-point scale [25] (Appendix E). Detection of NoV by RT-PCR in *vomit* in addition to stool, has been described [27] and *vomit* specimens will also be evaluated when collected in addition to the stool specimens.

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

Trial participation is expected to be from enrollment through EOS (trial Day 45).

### 6.4 Premature Termination or Suspension of Trial or Investigational Site

#### 6.4.1 Criteria for Premature Termination or Suspension of the Trial

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

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

#### 6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

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

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

## 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

### 7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria: [Criteria 1-4 are required for all trials]

1. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any trial procedures after the nature of the trial has been explained according to local regulatory requirements.
2. Male or female subjects, 18 to 49 years of age.
3. Individuals who are in good health at the time of entry into the trial as determined by medical history and the clinical judgment of the investigator.
4. Individuals who can comply with trial procedures and are available for the duration of follow-up.

### 7.2 Exclusion Criteria

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

1. Pregnancy.
2. Known hypersensitivity to any of the NoV GI.1/GII.4 bivalent VLP vaccine components (including excipients).
3. Subjects with known hypersensitivity or allergy to any of the licensed required concomitant vaccine components to be administered (including excipients of these vaccines).
4. Any condition or circumstance that the investigator determines would interfere with trial evaluation or interpretation.
5. Subjects with known or suspected impairment or alteration of immune function.
6. Subjects with a history of AGE within 14 days of enrollment.
7. Subjects with a history of body temperature of 38.0°C (100.4°F) or higher within 3 days of intended trial vaccination.
8. Subjects who have received blood, blood products, and/or plasma derivatives or any parenteral immunoglobulin antibody preparation in the past 3 months.
9. Immunosuppressive therapy within 3 months or systemic (eg, oral or parenteral) corticosteroid treatment within 60 days prior to investigational trial dose administration.
10. Subjects participating in any clinical trial with another investigational product 30 days prior to the first trial visit or intending to participate in another clinical trial at any time during the conduct of this trial.

11. Subjects who are first-degree relatives of individuals involved in the conduct of the trial.
12. Individuals with any history of progressive or severe neurologic disorder, seizure disorder or neuro-inflammatory disease (eg Guillain-Barré syndrome).
13. Individuals with history or any illness that, in the opinion of the investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial.
14. Individuals who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial with the exception of routine immunizations as per Military Procedures (see [Appendix D](#)).
15. If female of childbearing potential, sexually active, and has not used any of the “acceptable contraceptive methods” for at least 2 months prior to trial entry:
  - a. Of childbearing potential is defined as status post onset of menarche and not meeting any of the following conditions: menopausal for at least 2 years, status after bilateral tubal ligation for at least 1 year, status after bilateral oophorectomy, or status after hysterectomy.
  - b. Acceptable birth control methods are defined as one or more of the following:
    - i. Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring).
    - ii. Barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse.
    - iii. Intrauterine device (IUD).
    - iv. Monogamous relationship with vasectomized partner. Partner must have been vasectomized for at least six months prior to the subjects’ trial entry.
    - v. Abstinence, defined as refraining from heterosexual intercourse, ie sexual intercourse with risk of conception, during the entire study period.
16. If female of childbearing potential and sexually active, refusal to use an “acceptable contraceptive method” from Day 1 through 6 months after the last dose of trial vaccine. In addition, they must be advised not to donate ova during this period (Section [9.1.13](#)).
17. If male and sexually active, the subject must be advised not to donate sperm from Day 1 through 6 months after the last dose of trial vaccine.
18. Any positive or indeterminate pregnancy test.

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

### 7.3 Criteria for Delay of Vaccination and/or Blood Sampling

After enrollment, subjects may encounter clinical circumstances that warrant a delay in the administration of trial vaccination. These situations are listed below. In the event that a subject meets a criterion for delay of vaccination, the subject may receive trial vaccination once the window for delay has passed as long as the subject is otherwise eligible for trial participation.

- Subjects who have received antipyretics/analgesic medications within 24 hours prior to the intended vaccine administration.
- If the investigational trial dose is delayed beyond the day the routine immunizations required by the US military are given, the trial dose may be administered later during the training period.

### 7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the trial should be recorded in the [electronic] case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.14.

1. Protocol deviation: The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety or rights.
2. Adverse Event: The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
3. Lost to follow-up: The subject did not return to the clinic and attempts to contact the subject were unsuccessful and/or the subject graduated and left the base. Attempts to contact the subject must be documented.
4. Withdrawal by subject: The subject wishes to withdraw from the trial. The reason for withdrawal, if provided, should be recorded in the eCRF.

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

5. Trial terminated by sponsor.
6. Pregnancy: Any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further trial vaccines. The site should maintain contact with the pregnant subject and complete a "Clinical Trial Pregnancy Form" as soon as possible. In addition, the subject should be followed-up until the birth of the child, or spontaneous or voluntary termination; when pregnancy outcome information becomes available, the information should be captured using the same form. The subject should be reported as a withdrawal from trial and the reason for withdrawal (eg pregnancy) recorded in detail on the "Trial Termination" eCRF and subject's medical records.



7. Other.

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

**7.5 Procedures for Discontinuation or Withdrawal of a Subject**

The investigator may discontinue or withdraw a subject’s trial participation at any time during the trial when the subject meets the trial termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the trial. Should a subject’s participation be discontinued, the primary criterion for termination must be recorded, if possible. Subjects who withdraw from the trial or whose participation is discontinued should be followed-up for safety. Discontinued or withdrawn subjects will not be replaced.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

## 8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

### 8.1 Trial Vaccine(s) and Materials

#### 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

CCI manufactures the investigational NoV GI.1/GII.4 Bivalent VLP Vaccine.

The trial doses described in this protocol will be supplied by the sponsor. The trial doses will be supplied in tamper-evident, single dose cartons. Each dose and carton will contain a label that includes pertinent trial information and caution statements. The label text will be in English. The investigational trial dose to be used will be identifiable by a unique identification number and managed by the IRT.

##### 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)<sub>3</sub>.

After the syringe has been shaken, a uniformly turbid suspension should be observed.

##### Placebo (saline) control

The placebo (saline) control is 0.5 mL per dose of 0.9% sodium chloride for injection without preservatives for single injection. 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. Alternatively, saline without preservatives may be sourced in vials and will be prepared for single injection in syringes to closely match the NoV vaccine.

Details and handling of the NoV and placebo trial doses will be specified in the Pharmacy Manual.

#### 8.1.2 Storage

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

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

day. Temperature excursions must be reported to the sponsor as soon as possible and use of these vaccines requires sponsor approval.

### 8.1.3 Dose and Regimen

Subjects will receive on Day 1 either one dose of the NoV GI.1/GII.4 bivalent VLP vaccine or saline placebo according to their random assignment.

Routine vaccinations will be sourced and administered by and per US military procedures. (Refer to [Appendix D](#).)

## 8.2 Trial Vaccine Assignment and Dispensing Procedures

The investigator or investigator's designee will access the IRT within 7 days prior to or on Day 1 to obtain the subject number. Details of randomization and the IRT will be covered in the IRT user manual.

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

The trial dose identification number to be administered will be assigned by the IRT.

The vaccination will be administered by the unblinded designee according to the instructions in the Pharmacy Manual.

Each subject will receive either 1 trial dose of NoV GI.1/GII.4 bivalent VLP vaccine or saline placebo on Day 1. The NoV GI.1/GII.4 bivalent VLP vaccine or saline placebo will be administered by IM injection into the middle third of the deltoid muscle.

If sponsor-supplied vaccine is lost or damaged, the site can request a replacement from the IRT. Expired vaccines must not be administered.

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

### PRECAUTIONS TO BE OBSERVED IN ADMINISTERING THE TRIAL VACCINE:

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

Eligibility for subsequent trial procedures is determined by following the criteria outlined in Section [7.0](#).

Trial vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

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

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

### **8.3 Randomization Code Creation and Storage**

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

### **8.4 Trial Vaccine Blind Maintenance**

The trial vaccine blind will be maintained by the unblinded designee.

### **8.5 Unblinding Procedure**

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

For unblinding a subject, the trial vaccine blind can be obtained by the investigator, by accessing the IRT.

The sponsor's Pharmacovigilance Department must be notified as soon as possible if the trial vaccine blind is broken by the investigator. Notably, the completed unblinding form must be sent within 24 hours. The date, time, and reason the blind is broken must be recorded in the source document and the same information (except the time) must be recorded on the eCRF.

If a subject is unblinded, the subject must be withdrawn from the trial. Subjects withdrawn from the trial due to unblinding should be followed for safety to the end of trial. Further details for dealing with safety follow-up for subjects withdrawn from the trial will be provided.

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

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

The investigator or designee must ensure that the sponsor-supplied vaccine is used in accordance with the approved protocol and is administered only to subjects enrolled in the trial. To document appropriate use of sponsor-supplied vaccine(s) (NoV GI.1/GII.4 bivalent VLP vaccine and saline

placebo), the investigator must maintain records of all sponsor-supplied vaccine delivery to the site, site inventory, administration and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied vaccine(s), the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the trial vaccine is received within the labeled storage conditions (ie no cold chain break has occurred during transit), and is in good condition. If quantity and conditions are acceptable, investigator or designee will acknowledge receipt of the shipment by recording in IRT.

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

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

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

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

The investigator must record the current inventory of all sponsor-supplied vaccines [(NoV GI.1/GII.4 bivalent VLP vaccine and saline placebo) in a sponsor-approved vaccine accountability log. The following information will be recorded as a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied vaccine(s), expiry date and amount. The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied vaccine is administered.

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

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

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

## 9.0 TRIAL PLAN

### 9.1 Trial Procedures

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

#### 9.1.1 Screening Interview

Within the first few days after entry into the recruit training facilities, subject groups will be given a brief description of the trial. The trial will be introduced and explained by a trial staff member. A visual aid/video may be used. Subjects will be asked if they are interested to participate in the trial. If so, the subjects will undergo a screening interview. Notably, the screening interview will be performed by non-uniformed trial staff not involved in the training of the subjects to avoid any feeling of coercion [28]. Subjects may receive the routine immunizations required by the US military, before or after the screening interview. No flyers, emails or posters are planned to recruit potential trial subjects.

#### 9.1.2 Review Inclusion/Exclusion Criteria

Eligibility by review of inclusion/exclusion criteria will be documented after informed consent (see Section 9.1.3) and before randomization (Refer to Sections 7.1 and 7.2).

#### 9.1.3 Informed Consent

If the subject is interested to participate, trial staff will review the informed consent form and will highlight the key aspects of the trial. The consenting procedure may occur in small groups of up to three subjects at once. Notably, this procedure will be handled by non-uniformed trial staff not involved in the training of the subjects to avoid any feeling of coercion, and also include an Ombudsman [28].

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

Informed consent must be obtained prior to the subject entering into the trial, and before any protocol-directed procedures are performed. The informed consent may be obtained within 7 days prior to vaccination or on Day 1.

A unique subject number (screening number) will be assigned to each subject after informed consent is obtained from the IRT. If all eligibility criteria are fulfilled, this subject number will become the definitive subject number and will be used throughout the trial. Subject numbers assigned to subjects who fail screening should not be reused (Section 9.1.14).

#### 9.1.4 Demographics, Medical History and Prior Medications

Demographic information to be obtained will include date of birth, gender, ethnicity, race as described by the subject.

Medical History will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for trial participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during trial participation, if it represents an exacerbation of an underlying disease/preexisting problem. Adverse medical occurrences that occur after the subject signs the informed consent form but before administration of the trial dose, are to be documented in the Medical History.

All medications, vaccines and blood products including the duration thereof, taken or received by the subjects within 3 months prior to the start of the trial are to be recorded on the source document and entered onto the Prior and Concomitant Medications eCRF. The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source documents or the eCRF.

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

These data must be written in the source documents.

Prohibited Therapies (and see also Sections 7.2 and 7.3):

- Parenteral Ig preparation, blood products, and/or plasma derivatives within 3 months of trial vaccination;
- Immunosuppressive therapy within 3 months or systemic (eg, oral or parenteral) corticosteroid treatment within 60 days prior to trial dose administration;

Receipt of any vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial with the exception of routine immunizations as per Military Procedures (see Appendix D). If the investigational trial dose is delayed beyond the day the licensed vaccines are given, the trial dose may be subsequently administered later during the training period.

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

### 9.1.5 Documentation of Trial Entrance/Randomization

Only subjects who have signed the informed consent form, meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance/randomization into the vaccination phase. The list of randomization assignments is produced by the unblinded statistician and processed by IRT.

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

### 9.1.6 Physical Examination

Subjects have already undergone physical examination per Military Entrance Processing. Entry criteria will be based on investigator judgment and by review of the subject's medical history.

### 9.1.7 Assessment of HBGA Secretor Status

A saliva specimen will be collected once during the trial (at any time pre- or post-vaccination) from subjects in Subset A for assessment of HBGA secretor status.

### 9.1.8 AGE Disease Surveillance

All subjects will have surveillance for AGE disease performed from Day 1 until the end of the active AGE disease surveillance period (Day 45). All participants will be given an AGE disease symptom log and a thermometer at trial entry within 7 days prior to vaccination or on Day 1 and instructed to record their AGE disease symptoms and report to the medical clinic as soon as possible. The subjects will record in the AGE disease symptom log the onset time of vomiting and/or diarrhea, their temperature, the number of episodes of vomiting and/or diarrhea, and the stop time of vomiting and/or diarrhea to calculate duration of AGE. The subjects will also document whether the symptom(s) have had impact on their ability to train. The subjects will be instructed to use the provided thermometers to measure and record their temperature on the AGE disease symptom log. The subjects will be informed that the recommended route to take their temperature is oral and instructed to use this route. At the medical clinic, the subject will be assessed to determine if they have an AGE disease that meets the work-up definition (see Section 6.1). Subjects who meet the work-up definition will be assessed for disease severity and provide a stool specimen and *vomit* specimen for processing and later detection of NoV by RT-PCR. Subjects will only provide *vomit* specimen if actively vomiting. All initial stool samples for each new onset episode of AGE will be analyzed for the following three enteric pathogens: *Salmonella*, *Shigella*, and *Campylobacter*.

Subjects will receive standard of care treatment for AGE disease, and a new AGE disease symptom log will be given to record AGE disease symptoms until they resolve. Subjects will be instructed to return the latest AGE and any subsequent disease symptom log to the trial site at the next trial visit. A convalescent blood specimen for serology will be obtained once between 7 and 14 days after the onset of the AGE disease. After the initial stool specimen obtained at the onset of AGE disease: as available, three additional stool specimens will be obtained once between 7 and 14 days, once between 21 and 29 days and once at EOS. These follow-on stool specimens will be analyzed for NoV by RT-PCR. If an AGE event occurs within 7 days prior to the EOS visit (Day 45), a convalescent serum sample and a single optional stool sample should be collected at the EOS visit. There is no further follow-up for AGE after graduation from recruit training at Day 45.

### 9.1.9 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. Notably, co-pathogens were uncommon (found in less than 2% of AGE cases) in a multi-year surveillance trial in US military subjects.

CCI



Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI

### 9.1.12 Safety Assessments

Safety assessments will include collection and recording of solicited local (injection site) and systemic AEs, and unsolicited adverse events (serious and non-serious). Refer to Section 10.1 for safety definitions. Details on collection and reporting of AEs are in Section 10.5.

All subjects will be assessed for all SAEs and for all AEs leading to withdrawal from the trial for the entire AGE surveillance period. Specifically, subject safety for these events will be assessed at the routine post-vaccination trial visits on Days 8 and 29, and EOS.

Reactogenicity symptoms in Subsets A and B (total of 400 subjects): The initial 200 subjects enrolled in Subset A, and the 200 subjects randomly selected across all sites (Subset B) will record solicited AEs, including body temperature, on diary cards for 7 days after vaccination (including the day of vaccination) to be collected on or after Day 8, and unsolicited AEs for 28 days after vaccination (including the day of vaccination) to be collected by interview on or after Day 29.

#### Contraception and Pregnancy Avoidance Procedure

For female subjects of child bearing potential, pregnancy testing using urine or serum will be performed within 72 hours prior to vaccination. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy as well as donation of ova (or sperm in the case of male participants).

Refer to Section 7.2.

### 9.1.13 Pregnancy

To ensure subject safety and the safety of the unborn child, each pregnancy in a subject having received a trial vaccine must be reported to the sponsor within 24 hours of the site learning of its occurrence. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital

abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended.

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

Should the pregnancy occur after administration of a blinded trial vaccine, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator and procedures must be followed as described in Section 8.5.

#### **9.1.14 Documentation of Subjects who are not Randomized**

Investigators must account for all subjects who sign an informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF. The IRT should be contacted as a notification of non-randomization.

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

- Screen failure (did not meet one or more inclusion criteria or did meet one or more exclusion criteria),
- Withdrawal by subject,
- Trial terminated by sponsor.

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

### **9.2 Monitoring Subject Treatment Compliance**

The investigator will record all injections of trial vaccine given to the subject in the eCRF.

### **9.3 Schedule of Observations and Procedures**

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

#### **9.3.1 Screening Procedures (Within 7 Days Prior to Vaccination or On Day 1)**

1. Informed consent (Section 9.1.3; Appendix C).
2. Demographics.
  - a. Concomitant medications and vaccinations.
  - b. Medical history.
3. Review of systems: Review of systems is a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
4. Assessment of eligibility criteria.

5. The site should schedule the next trial activity;
6. The subject will receive a written reminder of the next planned trial activity.

### 9.3.2 Vaccination Procedures (Within 7 Days Prior to Vaccination or On Day 1)

- Prior to vaccination:
  - Confirm eligibility. Refer to Sections 7.1 and 7.2;
- Perform a urine or serum pregnancy test for female subjects of child-bearing potential. Refer to Section 9.1.13. The pregnancy test must be done within 72 hours prior to vaccination. If more than 72 hours have elapsed prior to vaccination, the pregnancy test must be repeated by either method.
- If the subject meets all eligibility criteria:
  - Randomize subject. Refer to Section 9.1.5;
  - Collect data on concomitant medications and vaccinations. Refer to Section 9.1.4;
  - Collect blood specimen once within 7 days prior to vaccination or on Day 1. Refer to Sections 9.1.10 and 9.1.11. Blood should be taken from the subject using an aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in the Manual of Study Procedures.
  - Collect saliva specimen once at any time during the trial from subjects in Subset A.
  - Provide diary cards for subjects in Subsets A and B.
  - Careful training of the subject on how to measure local AEs and body temperature, how to complete the diary card and how often to complete the diary card. Training of the subject on how to measure an injection site AE should be performed while the subject is under observation after vaccination.

Diary card instructions must include the following:

- The subject must understand that timely completion of the diary card on a daily basis is a critical component of trial participation. The subject should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card should include a single strikethrough line with a brief explanation for any change and be initialed and dated.

Please note:

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

- The Diary Card should be reviewed with the subject.

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

After vaccination, the subject will be observed for at least 15 minutes. Information should be recorded in the electronic data capture (EDC) system. The investigator or delegate will take the opportunity to remind the subject how to measure solicited AEs and body temperature as part of this observation period. All safety data will be collected in the subject's source documents.

- The subject will receive a written reminder of the next planned trial activity. The subject will be reminded to complete the Diary card daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable)

if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All contact details will be provided to the subject.

- Vaccinate subject according to the assigned investigational trial dose. Refer to Section 8.1.3;
- Following vaccination:
  - Observe subjects for at least 15 minutes after vaccination;
- Provide AGE disease symptom log. Refer to Section 9.1.8.
  - The site should schedule the next trial activity;
  - The subject will receive a written reminder of the next planned trial activity.
- Subjects will be instructed to complete the AGE disease symptom log and to come to the medical clinic if they experience vomiting, diarrhea or other symptoms of AGE disease. Refer to Section 9.1.8.

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

### 9.3.3 Post-Vaccination Procedures (Day 8 [+7 Days] and Day 29 [+7 Days])

The following post-vaccination procedures will be performed on Day 8 and Day 29:

- Collect blood specimen. Refer to Sections 9.1.10 and 9.1.11:

Blood should be taken from the subject using an aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in the Manual of Study Procedures.

- The site should schedule the next trial activity;
- The subject will receive a written reminder of the next planned trial activity.

Subjects will be instructed to complete the AGE disease symptom log and to come to the medical clinic if they experience vomiting, diarrhea or other symptoms of AGE disease. Refer to Section 9.1.8.

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

### 9.3.4 Clinic Visits after Vaccination (Day 8, Day 29, End of Active Surveillance)

For all enrolled subjects, clinic visits that do NOT include a study investigational vaccination will be performed on Day 8, Day 29, and the EOS.

Blood should be taken from all subjects at these time points using an aseptic venipuncture technique for later serological testing.

For all enrolled subjects, at the Day 8, 29 and EOS clinic visits, any SAEs or AEs leading to trial withdrawal will be collected by interview and recorded by the trial staff. The healthcare professional reviewing these data will discuss the AEs (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are present and/or concomitant medications have been used.

For the 400 subjects in Subsets A and B, the Diary Card will be reviewed on or after the Day 8 clinic visit. At the Day 29 clinic visit, the unsolicited AEs that occurred within the prior 28 days will be collected by interview for these 400 subjects.

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

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

### 9.3.5 Procedures at AGE Disease Visit

- AGE disease surveillance: Refer to Section 9.1.8 and Table 2.b.
- Provide new AGE disease symptom log and instruct subjects to return any subsequent and the latest AGE disease symptom log to the medical clinic at the next trial visit;
- Instruct subjects to come back to the medical clinic once between 7 and 14 days after the onset of the AGE disease for the collection of a convalescent blood specimen. Refer to Section 9.1.8. After the initial stool specimen obtained at the onset of AGE disease: as available, three additional stool specimens will be obtained once between 7 and 14 days, once between 21 and 29 days and once at end of the acute AGE surveillance period. Refer to Section 9.1.8.

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

### 9.3.6 Procedures at End of Active AGE Disease Surveillance Period (- 7 days)

- Collect blood specimen. Refer to Sections [9.1.10](#) and [9.1.11](#):
- Blood should be taken from the subject using an aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in the Manual of Study Procedures.
- Confirm that a saliva specimen was previously collected from subjects in Subset A. If not done, please collect at this visit.

### 9.3.7 Safety Follow-up

- Collect data on AEs. Refer to Section [10.4](#).

### 9.3.8 Post-Trial Care

No post-trial care will be provided.

## 9.4 Schedule of Additional Observations and Procedures for Subjects in Subsets A and B

Observations and procedures in addition to those described in Section [9.3](#) will be performed for subjects in Subsets A and B as detailed in [Table 2.c](#).

## 9.5 Biological Sample Retention and Destruction

As per the Manual of Study Procedures, collected specimens (blood, stool, *vomit*, and saliva) will be processed, stored and frozen at each of the clinical sites until shipment to the central laboratory for analysis. The sponsor has put into place a system to protect subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction. The NHRC shall receive an aliquot of biologic specimens (ie stool, serum, and saliva, or nucleic acid extracted from saliva) where adequate specimens remain after all testing in support of regulatory approval for commercial sale of trial drug has been completed. Any further testing of excess biological specimens will only be done after all testing in support of regulatory approval for commercial sale is completed, an appropriate IRB has reviewed and approved further testing proposed and both parties, Takeda and NHRC agree in writing to such testing.



## 10.0 ADVERSE EVENTS

### 10.1 Definitions

#### 10.1.1 Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a trial vaccine; it does not necessarily have to have a causal relationship with trial vaccine administration.

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

AEs will be graded by the investigator in the following manner:

Mild	Grade 1	• Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities. Relieved with or without symptomatic treatment.
Moderate	Grade 2	• Sufficient discomfort is present to cause interference with normal activity. Only partially relieved with symptomatic treatment.
Severe	Grade 3	• Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities. Not relieved with symptomatic treatment

#### 10.1.2 Solicited Adverse Events

The occurrence of selected indicators of safety (Table 10.a) will be measured/collected for subjects included in Subset A. These will be summarized in the final report under the category “solicited adverse events” to differentiate them from other AEs which were not solicited. Any solicited local or systemic AE observed as continuing on Trial Day 8 will be recorded as an AE on the Adverse Event eCRF.

**Table 10.a Local and Systemic AEs**

Local AEs (injection site):	Pain
	Erythema
	Induration
	Swelling
Systemic AEs (adult/child $\geq$ 6 years):	Headache
	Fatigue
	Myalgia
	Arthralgia
	Vomiting
	Diarrhea
	Fever

Note: Body temperature will be collected and recorded. The site staff will record the actual route taken on the CRF. Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method used [29]. The subjects will be informed that the recommended route to take their temperature is oral and will be instructed to use this route.

The intensity of solicited safety parameters will be assessed as described in [Table 10.b](#).

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

**Table 10.b Intensity Assessment for Solicited Safety Parameters**

Adverse Event	Intensity grade	Severity/Intensity
Pain at injection site	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
Erythema at injection site <sup>(a)</sup>	0	<25 mm
	1	Mild: $\geq 25 - \leq 50$ mm
	2	Moderate: $> 50 - \leq 100$ mm
	3	Severe: $> 100$ mm
Induration at injection site <sup>(a)</sup>	0	<25 mm
	1	Mild: $\geq 25 - \leq 50$ mm
	2	Moderate: $> 50 - \leq 100$ mm
	3	Severe: $> 100$ mm
Swelling at injection site <sup>(a)</sup>	0	<25 mm
	1	Mild: $\geq 25 - \leq 50$ mm
	2	Moderate: $> 50 - \leq 100$ mm
	3	Severe: $> 100$ mm
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 <sup>(b)</sup>	Record body temperature in °C/°F	

- (a) Subjects are to record greatest surface diameter in mm in the Diary;
- (b) Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method used. Body temperature will be collected and recorded. The site staff will record the actual route taken on the CRF. The subjects will be informed that the recommended route to take their temperature is oral and will be instructed to use this route.

### 10.1.3 Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that:

1. Results in DEATH.
2. Is LIFE THREATENING.
  - The term “life threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT in the offspring of a subject.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
  - May require intervention to prevent items 1 through 5 above.
  - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

## 10.2 Causality of AEs

Relatedness (causality) to vaccine will also be assessed by the investigator. The relationship of each AE, including solicited systemic AEs (solicited local AEs are considered as related) to trial vaccine(s) will be assessed using the following categories:

Related: There is suspicion that there is a relationship between the trial vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that the trial vaccine contributed to the AE.

Not Related: There is no suspicion that there is a relationship between the trial vaccine and the AE; there are other more likely causes and administration of the trial vaccine is not suspected to have contributed to the AE.

### 10.2.1 Relationship to Trial Procedures

Relationship (causality) to trial procedures should be determined for all AEs/SAEs.

The relationship should be assessed as “Yes” if the investigator considers that there is reasonable possibility that an event is due to a trial procedure. Otherwise, the relationship should be assessed as “No”.

### 10.2.2 Outcome of AEs

Resolved:	The subject has fully recovered from the event or the condition has returned to the level observed at baseline
Resolving:	The event is improving but the subject is still not fully recovered
Not resolved:	The event is ongoing at the time of reporting and the subject has still not recovered
Resolved with <i>sequelae</i> :	As a result of the AE, the subject suffered persistent and significant disability/incapacity (eg became blind, deaf or paralysed)
Fatal:	The subject died due to the event. If the subject died due to other circumstances than the event, the outcome of the event per se should be stated otherwise (eg Not Resolved or Resolving)
Unknown:	If outcome is not known or not reported.

### 10.3 Additional Points to Consider for AEs

An untoward occurrence generally may:

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

Diagnoses vs. signs and symptoms:

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

Worsening of AEs:

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

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

## 10.4 Procedures

### 10.4.1 Collection and Reporting of AEs

Any unsolicited AEs (see Sections 9.1.12 and 10.1.1) for 28 days after the vaccination (including the day of vaccination) will be collected on or after Day 29 by interview of subjects in Subsets A and B. All findings for subjects in Subsets A and B experiencing AEs must also be reported in the subject's medical records.

All AEs, whether considered related with the use of the trial vaccine or not, must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an AE eCRF or SAE form, as necessary. Reporting of SAEs and AEs that led to trial withdrawal from Day 29 onwards will be spontaneous or retrospectively collected at the end of the active AGE disease surveillance period.

The following information will be documented for each event:

- Reported term for the AE.
- Start and end date.
- Serious (Y/N).
- Severity.
- Investigator's opinion of the causality (relationship) between the event and administration of trial vaccine(s) ("related" or "not related").
- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure.

- [If multiple doses] Action taken with the trial treatment (trial vaccine).
- Outcome of event.

#### 10.4.2 Collection and Reporting of Solicited AEs

The occurrence of selected indicators of safety will be recorded on diary cards by the subjects included in Subsets A and B for 7 days after the vaccination (including the day of vaccination) and will be recorded on the “Local and Systemic Reactions” eCRF, as appropriate. Any solicited local or systemic AE observed as continuing on trial Day 8 will be recorded as an unsolicited AE on the AE eCRF. Any solicited local or systemic AE that resolved before Day 8 but recurred at a later time (ie, is discontinuous), will be recorded as an unsolicited AE on the AE eCRF.

Any solicited AE that meets any of the following criteria must be entered as an AE on the AE eCRF:

- Solicited local or systemic AEs that lead the subject to withdraw from the trial.
- Solicited local or systemic AEs that lead to the subject being withdrawn from the trial by the investigator.
- Solicited local and systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.3)

#### 10.4.3 Collection and Reporting of SAEs

Collection of SAEs will be collected by close monitoring from the time that the subject is administered the trial vaccine (Day 1) up to the end of the active AGE disease surveillance period (at Day 45).

For all subjects, SAE reporting will be collected at the clinic visits on Days 8, 29, and EOS. Any ongoing SAEs at the end of the active AGE disease surveillance period will be followed in the electronic health databases and personnel medical records of those subjects who remain active in the military.

SAEs should be reported according to the following procedure:

A sponsor SAE form that is part of the Investigator Site File must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator’s name.
- Name of the trial vaccine(s) – if no unblinding is necessary, in a blinded way.
- Causality assessment.

During the active AGE disease surveillance period, the SAE form should be transmitted within 24 hours to the attention of the contact(s) in the list provided to each site. All findings in subjects experiencing SAEs must also be reported in the subject's medical records. In case of death, a full pathologist's report should be supplied, if possible

## **10.5 Follow-up Procedures**

### **10.5.1 AEs**

All AEs will be monitored until resolution or a stable status is reached or until a formal diagnosis can be made. AEs will not be monitored after the training has ended, unless deemed necessary by the sponsor.

### **10.5.2 SAEs**

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, laboratory tests, discharge summary, postmortem results) should be sent to the sponsor.

All SAEs should be followed up until resolution or permanent outcome of the event or until otherwise explained. The timelines and procedure for follow-up reports are the same as those for the initial report. Ongoing SAEs at the end of trial visit will be followed by the Principal Investigator by review of the subject's electronic health databases and personnel medical records.

### **10.5.3 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities**

The sponsor or designee will be responsible for reporting to regulatory authorities, including investigators and IRBs or IECs, as applicable, all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs reported up to the end of the active AGE disease surveillance period, in accordance with national regulations in the countries where the trial is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the trial vaccine administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to their IRB or IEC in accordance with national regulations.

### **10.5.4 Post-Trial Events**

Any SAE that occurs outside of the protocol-specified observation period or after the end of the trial but considered to be caused by the trial vaccine must be reported to the sponsor. These SAEs will be processed by the sponsor's Pharmacovigilance Department. Instructions for how to submit these SAEs will be provided in a handout in the Investigator Site File.



## 11.0 TRIAL-SPECIFIC REQUIREMENTS

An overall DMC is established to evaluate safety of the NoV program on an ongoing basis. The DMC will review the safety and immunogenicity results to the NoV vaccine (Subset A) and the results to the selected co-administered vaccines (Subset A). The program DMC charter is a separate document.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

## 12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, SAEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (system organ class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Low Level Term (LLT), Preferred Term (PT), and their corresponding descriptive terms). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

### 12.1 Electronic CRFs (eCRF)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These eCRFs are used to transmit the information collected in the performance of this trial to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by sponsor personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator or designee must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the trial site during periodic visits by trial monitors. The sponsor or its designee will be permitted to review a subject's medical and hospital records pertinent to the trial to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

### 12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.0 and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records. Temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), copies of eCRFs, including the audit trail, and detailed records of vaccine disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Furthermore, the International Conference on Harmonization (ICH) E6 Section 4.9.5

requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified indication being investigated or, if an application is not approved until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the trial records should be retained for an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

## 13.0 STATISTICAL METHODS

### 13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A blinded data review will be conducted prior to unblinding of subject's vaccination assignments. This review will assess the accuracy and completeness of the trial database, subject evaluability, and appropriateness of the planned statistical methods.

#### 13.1.1 Analysis Sets

**Safety Set:** The Safety Set will consist of all subjects who received the trial vaccines (NoV GI.1/GII.4 bivalent VLP vaccine or saline placebo). For all subjects in the Safety Set, SAEs and AEs leading to withdrawal from the trial will be assessed up to the EOS. For analyses of solicited AEs and unsolicited non-serious AEs, only subjects in Subsets A and B will be included.

**Full Analysis Set (FAS):** The FAS will include all subjects who are randomized and received the trial vaccination.

**Per-Protocol Set (PPS):** The PPS will include all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of subject's treatment assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving wrong trial treatment (3) receiving prohibited therapies, and (4) other major protocol violations that may be identified during blinded data reviews.

#### 13.1.2 Analysis of Demographics and Other Baseline Characteristics

Age, gender, ethnicity, race, and other baseline characteristics will be summarized descriptively by treatment arm for all randomized subjects.

#### 13.1.3 Efficacy Analyses

For the primary endpoint, the primary analysis method will be based on the FAS and a Cox proportional hazard model with treatment as a factor, adjusted for gender and age, and stratified by site, with two-sided 95% confidence interval (CI) provided for the estimate of VE. The primary efficacy objective is considered to be met if the lower bound of the 95% CI for the VE is above 0%, where VE is defined as  $1 - (\lambda_V/\lambda_C)$ , where  $\lambda_V$  and  $\lambda_C$  denote the hazard rates for the NoV vaccine and saline placebo arms, respectively.

Sensitivity analyses of the primary endpoint include: (1) analysis based on exact 95% CIs based on the FAS [30], and (2) analysis based on the PPS using the same model as in the primary analysis.

Evaluation of secondary CCI VE endpoints will be based on the FAS and analyzed using a similar approach to the primary endpoint, as described above.

Analyses of endpoints for recurrent events will be performed using proportional intensity (Andersen-Gill) models with treatment as a factor and stratified by site.

As measures of vaccine effectiveness, vaccine preventable disease incidence (VPDI), which is defined as the incidence in the saline placebo arm minus the incidence in the NoV vaccine arm, will be calculated for all-cause AGE occurring > 7 days after dosing, all-cause moderate or severe AGE occurring > 7 days after dosing, and all-cause severe AGE occurring > 7 days after dosing (all including co-infection).

The analysis of data for the duration of shedding by RT-PCR after AGE due to NoV will be descriptive.

The modified Vesikari score for subjects with confirmed NoV AGE occurring after >7 days after dosing will be summarized descriptively.

CCI



### 13.1.5 Safety Analyses

In general, data imputation will not be performed for any missing safety data. The criteria for biologically implausible measurements will be defined in the statistical analysis plan. Any SAE or AE leading to trial withdrawal collected during the AGE surveillance period for all subjects in the Safety Set will be included.

#### *Solicited AEs*

For subjects in Subsets A and B, safety will be assessed daily for 7 days after vaccination (including the day of vaccination) via collection of solicited AEs, including local AEs (injection site: pain, erythema, induration and swelling) and systemic AEs (headache, fatigue, myalgia, arthralgia, vomiting, and diarrhea). In addition, other indicators of safety will be collected (eg, body temperature). Body temperature will be summarized by actual route taken with no adjustment or conversion for route of measurement.

For each solicited AE, the percentage of subjects will be summarized by event severity for each day from Day 1 to Day 7 (including the day of vaccination) and overall. Summaries of the day of first onset of each event and the number of days subjects reported experiencing each event will also be provided. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

*Unsolicited AEs*

Any SAEs, and AEs leading to trial withdrawal (all subjects), and any other unsolicited AEs for 28 days (Subsets A and B), will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), and summarized by system organ class (SOC) and preferred term (PT) for each treatment arm.

Any unsolicited AE collected up to Day 29 by interview with subjects in Subsets A and B will be included in the Safety Set.

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. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. Unsolicited AEs will be summarized as follows: by SOC and PT; by SOC, PT, and severity; by SOC, PT, and relationship (causality) to the investigational trial dose; and by SOC and PT including events with frequency greater than 2%.

Unless otherwise specified, unsolicited AEs for Subsets A and B will be summarized in the following 3 ways: 1) overall up to 28 days after the vaccination (including the day of vaccination), 2) with onset between 1 and 7 days after the vaccination (including the day of vaccination), and 3) with onset between 8 and 28 days after the vaccination (including the day of vaccination).

CCI



CCI

### 13.2 Interim Analysis and Criteria for Early Termination

An interim analysis will be performed on the first 200 subjects (Subset A) when the assay results are completed. The anti-NoV GI.1 and GII.4 VLP antibody responses at baseline (prior to or on Day 1) and on Days 8, 29 and EOS. CCI

In addition, all available safety data for these subjects, including solicited AEs and unsolicited AEs, will be summarized and provided to the DMC for review. Specifically, the interim safety and immunogenicity for this subset may be summarized separately as the results become available.

If the accrual of cases for the primary endpoint is slower than expected, a second interim analysis 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.

The trial team responsible for trial conduct (both from Takeda and Clinical Research Organization [CRO]) will remain blinded to individual treatment assignment information for the subjects throughout the trial.

### 13.3 Determination of Sample Size

Assuming true 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.a) compared to the summer (second panel in Table 13.a) 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.a. 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 NHRC genotype analysis and the NoV genotypes identified by the 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.1 or GII.4) NoV strains, excluding co-infection are confirmed. Thereafter, the trial will be closed to further enrollment.

**Table 13.a NHRC AGE NoV Surveillance Data at Planned Trial Sites**

<b>AGE Incidence Rate (Oct-May)</b>				
	<b>2011-2012</b>	<b>2012-2013</b>	<b>2013-2014</b>	<b>All Years</b>
<b>MCRD PI</b>	0.24%	0.41%	0.16%	<b>0.24%</b>
<b>MCRD SD</b>	0.52%	0.64%	0.36%	<b>0.37%</b>
<b>Great Lakes</b>	0.37%	1.41%	0.83%	<b>0.80%</b>
<b>Total</b>	<b>0.32%</b>	<b>0.74%</b>	<b>0.39%</b>	<b>0.44%</b>
<b>AGE Incidence Rate (Jun-Sep)</b>				
	<b>2011-2012</b>	<b>2012-2013</b>	<b>2013-2014</b>	<b>All Years</b>
<b>MCRD PI</b>	0.20%	0.06%	0.09%	<b>0.11%</b>
<b>MCRD SD</b>	0.20%	0.17%	0.12%	<b>0.17%</b>
<b>Great Lakes</b>	0.29%	0.71%	0.39%	<b>0.46%</b>
<b>Total</b>	<b>0.19%</b>	<b>0.28%</b>	<b>0.19%</b>	<b>0.23%</b>
<b>AGE Winter Rates - AGE Summer Rates</b>				
	<b>2011-2012</b>	<b>2012-2013</b>	<b>2013-2014</b>	
<b>Total</b>	0.13%	0.46%	0.20%	
<b>50% GI.1/GII.4</b>	0.07%	0.23%	0.10%	



## 14.0 QUALITY CONTROL AND QUALITY ASSURANCE

### 14.1 Trial-Site Monitoring Visits

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

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

### 14.2 Protocol Deviations

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

### 14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

## 15.0 ETHICAL ASPECTS OF THE TRIAL

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

### 15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable local or regional requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained. Those US sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol’s review and approval. This protocol, the Investigator’s Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB’s or IEC’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the trial (ie, before shipment of the sponsor-supplied Vaccine or trial specific screening activity). The IRB or IEC approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB or IEC, and submission of the investigator’s final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

## 15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the trial. The informed consent form and the subject information sheet (if applicable) further explain the nature of the trial, its objectives, and potential risks and benefits, as well as the date informed consent are given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

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

The subject must be given ample opportunity to: (1) inquire about details of the trial and (2) decide whether or not to participate in the trial. If the subject determines he or she will participate in the trial, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject at the time of consent and prior to the subject entering into the trial. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to the subject entering into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

All revised informed consent forms must be reviewed and signed by relevant subject in the same manner as the original informed consent. The date the revised consent was obtained should be

recorded in the subject's medical record and eCRF, and the subject should receive a copy of the revised informed consent form.

### 15.3 Subject Confidentiality

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

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

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

### 15.4 Publication, Disclosure, and Clinical Trial Registration Policy

#### 15.4.1 Publication and Disclosure

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

#### 15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, the sponsor will, as a minimum register all clinical trials conducted in subjects that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation. The sponsor contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

### **15.4.3 Clinical Trial Results Disclosure**

The sponsor will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

Trial completion corresponds to the date on which the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

### **15.5 Insurance and Compensation for Injury**

Each subject in the trial must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical trial insurance against the risk of injury to clinical trial subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

## 16.0 REFERENCES

1. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.  
<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> - Accessed 13 November 2017.
2. Guideline for good clinical practice.  
[http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf) - Accessed 31 May 2017.
3. Atmar RL, Estes MK. The epidemiologic and clinical importance of norovirus infection. *Gastroenterol Clin North Am.* 2006;35:275-90.
4. Hall AJ, Lopman BA, Payne DC, Patel MM, Gastañaduy PA, Vinjé J, Parashar UD. Norovirus disease in the United States. *Emerg Infect Dis.* 2013;19:1198-205.
5. Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, Griffin PM, Tauxe RV. Food-related illness and death in the United States. *Emerg Infect Dis.* 1999;5:607-25.
6. Trivedi TK, DeSalvo T, Lee L, Palumbo A, Moll M, Curns A, Hall AJ, Patel M, Parashar UD, Lopman BA. Hospitalizations and mortality associated with norovirus outbreaks in nursing homes, 2009-2010. *JAMA.* 2012;308:1668-75.
7. Payne DC, Vinjé J, Szilagyi PG, Edwards KM, Staat MA, Weinberg GA, Hall CB, Chappell J, Bernstein DI, Curns AT, Wikswo M, Shirley SH, Hall AJ, Lopman B, Parashar UD. Norovirus and medically attended gastroenteritis in U.S. children. *N Engl J Med.* 2013;368:1121-30.
8. Porter CK, Faix DJ, Shiao D, Espiritu J, Espinosa BJ, Riddle MS. Postinfectious gastrointestinal disorders following norovirus outbreaks. *Clin Infect Dis.* 2012;55:915-22.
9. St Clair KJ, Patel S. Initial descriptive and analytical data on an outbreak of norovirus infection at marine corps recruit depot Parris Island, South Carolina. *J Infect Dis.* 2008;198:941-2.
10. Enteric Disease Surveillance Program. AGE surveillance summary report for study weeks 22-25 (June 2013). Department of Operational Infectious Diseases, Naval Health Research Center, San Diego, CA.
11. McCarthy M, Estes MK, Hyams KC. Norwalk-like virus infection in military forces: epidemic potential, sporadic disease, and the future direction of prevention and control efforts. *J Infect Dis.* 2000;181 Suppl 2:S387-91.
12. Sharp TW, Hyams KC, Watts D, Trofa AF, Martin GJ, Kapikian AZ, Green KY, Jiang X, Estes MK, Waack M, et al. Epidemiology of Norwalk virus during an outbreak of acute gastroenteritis aboard a US aircraft carrier. *J Med Virol.* 1995;45:61-7.
13. Hyams KC, Malone JD, Kapikian AZ, Estes MK, Xi J, Bourgeois AL, Paparello S, Hawkins RE, Green KY. Norwalk virus infection among Desert Storm troops. *J Infect Dis.* 1993;167:986-7.

14. Ball JM, Graham DY, Opekun AR, Gilger MA, Guerrero RA, Estes MK. Recombinant Norwalk virus-like particles given orally to volunteers: phase I study. *Gastroenterology*. 1999;117:40-8.
15. Tacket CO, Mason HS, Losonsky G, Estes MK, Levine MM, Arntzen CJ. Human immune responses to a novel norwalk virus vaccine delivered in transgenic potatoes. *J Infect Dis*. 2000;18:302-5.
16. Tacket CO, Sztein MB, Losonsky GA, Wasserman SS, Estes MK. Humoral, mucosal, and cellular immune responses to oral Norwalk virus-like particles in volunteers. *Clin Immunol*. 2003;108:241-7.
17. El-Kamary SS, Paetti MF, Mendelman PM, Frey SE, Bernstein DI, Treanor JJ, Ferreira J, Chen W, Sublett R, Richardson C, Bargatze RF, Sztein MB, and Tacket CO. 2010. Adjuvanted intranasal Norwalk virus-like particle vaccine elicits antibodies and antibody secreting cells that express homing receptors in mucosal and peripheral lymphoid tissues. *J. Infect. Dis*. 202: 1649-58 (see Erratum *J. Infect. Dis*. 2011;203:1036).
18. Atmar RL, Bernstein DI, Harro CD, Al-Ibrahim MS, Chen WH, Ferreira J, Estes MK, Graham DY, Opekun AR, Richardson C, Mendelman PM. Norovirus vaccine against experimental human Norwalk Virus illness. *N Engl J Med*. 2011;365:2178-87.
19. Bernstein DI, Atmar RL, Lyon GM, Treanor JJ, Chen WH, Jiang Xi, Vinjé J, Gregoricus N, Frenck RW, Moe CL, AL-Ibrahim MS, Barrett J, Ferreira J, Estes MK, Graham DY, Goodwin R, Borkowski A, Clemens R, Mendelman PM. Norovirus vaccine against experimental human GII.4 virus illness: a challenge study in healthy adults. *J Infect Dis*. In press.
20. Treanor JJ, Atmar RL, Frey SE, Gormley R, Chen WH, Ferreira J, Goodwin R, Borkowski A, Clemens R, Mendelman PM. A Novel Intramuscular Bivalent Norovirus Virus-Like Particle Vaccine Candidate-Reactogenicity, Safety, and Immunogenicity in a Phase 1 Trial in Healthy Adults. *J Infect Dis*. 2014 Jun 20. pii: jiu337.
21. Baylor NW, Egan W, Richman P. Aluminum salts in vaccines-US perspective. *Vaccine*. 2002 May 31;20 Suppl 3:S18-23. Review. Erratum in: *Vaccine*. 2002;20:3428.
22. Investigator Brochure (Edition 5.0; 29 November 2016). "Intramuscular norovirus GI.1/GII.4 bivalent virus-like particle (VLP) vaccine adjuvanted with monophosphoryl lipid A (MPL) and aluminum hydroxide [Al(OH)<sub>3</sub>].
23. Kuschner RA, Russell KL, Abuja M, Bauer KM, Faix DJ, Hait H, Henrick J, Jacobs M, Liss A, Lynch JA, Liu Q, Lyons AG, Malik M, Moon JE, Stubbs J, Sun W, Tang D, Towle AC, Walsh DS, Wilkerson D. A phase 3, randomized, double-blind, placebo-controlled study of the safety and efficacy of the live, oral adenovirus type 4 and type 7 vaccine, in U.S. military recruits. *Vaccine*. 2013;31:2963-71.
24. Reeck A, Kavanagh O, Estes MK, Opekun AR, Gilger MA, Graham DY, Atmar RL. Serological correlate of protection against norovirus-induced gastroenteritis. *J Infect Dis*. 2010;202:1212-8.

25. Levine MM, Bergquist EJ, Nalin DR, Waterman DH, Hornick RB, Young CR, Sotman S. Escherichia Coli strains that cause diarrhea but do not produce heat-labile or heat-stable enterotoxins and are non-invasive. *Lancet*. 1978;1(8074):1119-22.
26. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute (2009). Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. [http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE\\_4.0\\_2009-05](http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.0_2009-05).
27. Atmar RL, Opekun AR, Gilger MA, Estes MK, Crawford SE, Neill FH, Ramani S, Hill H, Ferreira J, Graham DY. Determination of the 50% human infectious dose for norwalk virus. *J Infect Dis*. 2014;209:1016-22.
28. DoD\_Directive\_3216.02 (2011). "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research."
29. Marcy SM, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, Hansen J, Labadie J, Lee L, Martin BL, O'Brien K, Rothstein E, Vermeer P. Brighton Collaboration Fever Working Group. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. *Vaccine*. 2004;22:551-6.
30. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--the design and analysis of cohort studies. Lyon, France: International Agency for Research on Cancer, 1987.
31. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med*. 1989;8:431-40.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use



## Appendix A Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist with the protocol.
3. Ensure that trial related procedures, including trial specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
5. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56 ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the trial to the IRB/IEC, and issue a final report within 3 months of trial completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 56 ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the trial, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject
9. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied vaccines, and return all unused sponsor-supplied vaccines to the sponsor.

12. Report AEs to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.
13. Review and provide a signature as approval of the content of the clinical study report.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

## Appendix B Investigator Consent to Use of Personal Information

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

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the trial and/or other clinical studies.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other vaccines used in other clinical studies that may contain the same chemical compound present in the investigational vaccine.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting investigator site contact information, trial details and results on publicly accessible clinical trial registries, databases, and websites.

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

## Appendix C Elements of the Subject Informed Consent

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

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

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the trial. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
  - a) That personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
  - b) It is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
  - c) That personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the investigational vaccine(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
  - d) That subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the trial to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
  - e) That the subject's identity will remain confidential in the event that trial results are published.

25. Female subjects of childbearing potential (eg, non-sterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from enrollment through the duration of the trial. Pregnancy tests will be performed for all female subjects of childbearing potential as defined in the protocol and in the informed consent. If a subject is found to be pregnant during trial, the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

**Appendix D Routine Immunizations**

**Table 16.a Routine Immunizations for Newly Arriving U.S. Navy Subjects (NRTC-Great Lakes)**

Vaccine	Number of Doses	Trial Day 1 <sup>(a)</sup>	Trial Day 32
TWINRIX (Hepatitis A + Hepatitis B) <sup>(b)</sup>	2	X	X
VARICELLA <sup>(c)</sup>	2	X	X
MMR <sup>(c)</sup>	2	X	X
POLIO (inactivated)	1		X
TYPHOID FEVER	1	-	X
YELLOW FEVER	1	-	X
GARDASIL (human papillomavirus)	1	-	X
MENACTRA <sup>(d)</sup>	1	X	-
INFLUENZA (seasonal; live nasal or inactivated injectable)	1	X	-
ADENOVIRUS (live, Types 4&7) <sup>(e)</sup>	1	X	-
Tdap <sup>(f)</sup>	1	X	-

(a) Licensed concomitant vaccines that may be administered the same day as the NoV GI.1/GII.4 bivalent VLP vaccine or placebo.

(b) Hepatitis A Inactivated and hepatitis B (Recombinant) vaccine. Subjects will receive these vaccines based on their low titers.

(c) Varicella and Measles, Mumps and Rubella (MMR) vaccines. Varivax and/or MMR are given as noted (15 to 25% of subjects have received these vaccines based on their low titers).

(d) Menactra- meningococcal Groups A, C, Y, and W-135 meningitis vaccine.

(e) Adenovirus live vaccine consists of a single administration of an oral enteric-coated dose of type 4 plus a separate enteric-coated dose of type 7 at the same time.

(f) Combined tetanus-diphtheria-acellular pertussis vaccine.

Note: due to availability, recalls, shortages, and updates, moving between brands may be required

## Appendix E Five Point Scale Stool Chart

Five Point Scale Stool Chart [25]:

Grade 1:	Fully formed (normal)
Grade 2:	Soft (normal)
Grade 3:	Thick liquid (diarrheal)
Grade 4:	Opaque watery (diarrheal)
Grade 5:	Rice-water (diarrheal)

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use



Signature Page for NOR-211 Protocol Amendment 2, Version 3.0, 15 November 2017

Title: Phase IIb, Double-Blind, Randomized, Placebo Controlled Trial to Evaluate

Approval	PPD	
Approval		
Approval		
Approval		

Document Number: TAK-214-00491 v3.0

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use