Title: A Randomized, Observer Blind, Phase 3 Trial to Investigate the Immunogenicity and Safety of the Co-administration of a Subcutaneous Tetravalent Dengue Vaccine Candidate (TDV) and an Intramuscular Hepatitis A Virus (Inactivated) Vaccine in Healthy Subjects Aged 18 to 60 Years in Non-endemic Country for Dengue

NCT Number: NCT03525119

SAP Approve Date: 13 September 2019

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

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

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

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: DEN-314

A Randomized, Observer Blind, Phase 3 Trial to Investigate the Immunogenicity and Safety of the Co-administration of a Subcutaneous Tetravalent Dengue Vaccine Candidate (TDV) and an Intramuscular Hepatitis A Virus (Inactivated) Vaccine in Healthy Subjects Aged 18 to 60 Years in Non-endemic Country for Dengue

Immunogenicity and Safety of TDV Co-administered with an Hepatitis A Virus Vaccine

PHASE 3

Version: Final, 1.0

Date: 13 September 2019

Prepared by:

PPD

Based on:

Protocol Version: 5.0

Protocol Date: 11 March 2019

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of covariance
CRO	Contract research organization
DENV	Wild type dengue virus
eCRF	electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
FAS	Full Analysis Set
GMT	Geometric mean titers
GMC	Geometric mean concentrations
GMFR	Geometric mean fold rise
GSD	Geometric standard deviation
HAV	Hepatitis A virus
IM	Intramuscular
IP	Investigational Product
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
M0, 1, 3, 4, 9	Month 0, 1, 3, 4, 9
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Drug Regulatory Activities
MNT_{50}	Microneutralization test 50%
NI	Non-inferiority
PPS	Per-Protocol Set
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SOC	System Organ Class
TDV	Tetravalent dengue vaccine candidate
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objective

- To demonstrate non-inferiority (NI) of the immune response to 1 dose of hepatitis A virus (HAV) vaccine in HAV/wild type dengue virus (DENV)-naive subjects 1 month following co-administration with 1 dose of TDV when compared to 1 dose of HAV vaccine co-administered with placebo.

4.2 Secondary Objectives

Immunogenicity:

- To describe the immune response to TDV in HAV/DENV-naive subjects 1 month following a second dose of TDV, given at 3 months after the first dose of TDV that was co-administered with the HAV vaccine or placebo.
- To describe the immune response to TDV in HAV/DENV-naive subjects 1 month following a first dose of TDV co-administered with HAV vaccine or placebo.
- To describe the immune response to the HAV vaccine in HAV/DENV-naive subjects 1 month following 1 dose of HAV vaccine co-administered with TDV or placebo.

Safety:

- To assess the safety profile after each vaccine injection in all trial groups.

4.3 Study Design

This is a randomized, observer blind, phase 3 trial in 900 healthy adult subjects aged 18 to 60 years (distributed across the entire age range) based in a non-endemic country for dengue and HAV to investigate the immunogenicity and safety of 2 doses of TDV (subcutaneous [SC] injection), with and without co-administration of a single dose of HAV vaccine (intramuscular [IM] injection). Subjects will be randomized equally (1:1:1 ratio) to 1 of the following 3 trial groups (300 subjects per group):

- Group 1: HAV vaccine (IM) and placebo (SC) co-administered on Day 1 (Month 0 [M0]); placebo (SC) administered on Day 90 (Month 3 [M3]).
- Group 2: TDV (SC) and placebo (IM), co-administered on Day 1 (M0); TDV (SC) administered on Day 90 (M3).
- Group 3: TDV (SC) and HAV vaccine (IM), co-administered on Day 1 (M0); TDV (SC) administered on Day 90 (M3).

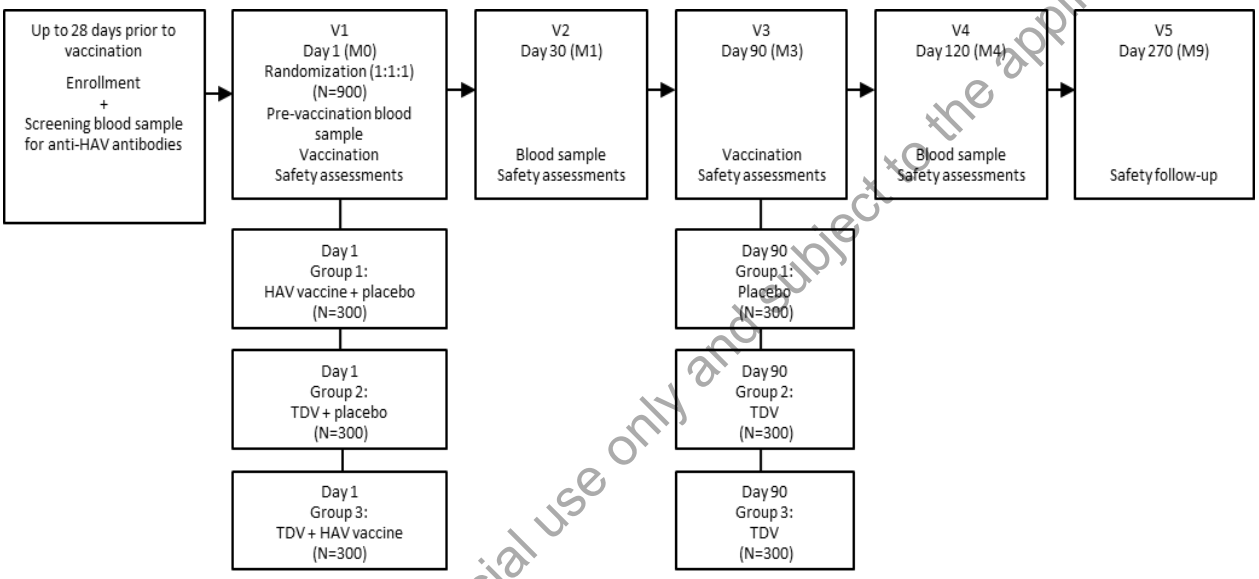
360 subjects (120 per group) will be randomly selected for inclusion in the immunogenicity subset using an interactive response technology.

Co-administered trial vaccines will be injected in opposite arms. A blood sample for an anti-HAV antibody test will be collected at Screening from all subjects to exclude any subjects

who are positive for anti-HAV antibodies. All subjects will be followed-up for 6 months following the second vaccination on Day 90 (M3); the trial duration will therefore be 270 days or 9 months for each subject (not including the screening period).

A schematic of the trial design is included as Figure 4.a. A schedule of trial procedures is provided in Appendix A.

Figure 4.a Schematic of Trial Design



M=Month, V=Visit
Notes:
(i) A blood sample for an anti-HAV antibody test will be collected at Screening from all subjects.
(ii) Blood samples for immunogenicity assessments will only be collected from subjects included in the immunogenicity subset (120 subjects in each group) at pre-first trial vaccination (Day 1 [M0]), 1 month post first trial vaccination (Day 30 [M1]), and 1 month post second trial vaccination (Day 120 [M4]).
(iii) Safety will be assessed in all subjects.

Immunogenicity evaluation (immunogenicity subset):

Dengue neutralizing antibodies will be measured (by microneutralization test 50% [MNT_{50}]) using blood samples collected pre-first trial vaccination (Day 1 [M0]), 1 month post first trial vaccination (Day 30 [Month 1 (M1)]), and 1 month post second trial vaccination (Day 120 [Month 4 (M4)]).

Blood samples for the measurement of anti-HAV antibodies (as measured by enzyme-linked immunosorbent assay [ELISA]) will be collected at pre-first trial vaccination Day 1 [M0] and 1 month post first trial vaccination (Day 30 [M1]).

Safety evaluation (all subjects):

- Diary cards (paper or electronic) will be distributed to all subjects for the recording of:
  - Solicited local adverse events (AEs) for 7 days following each trial vaccination (day of vaccination + 6 subsequent days). These will include: injection site pain, injection site erythema, and injection site swelling at each injection site.
  - Solicited systemic AEs for 14 days following each trial vaccination (day of vaccination + 13 subsequent days). These will include: fever, headache, asthenia, malaise, and myalgia.
- Unsolicited AEs will be collected by interview and recorded for all subjects for 28 days following each trial vaccination (day of vaccination + 27 subsequent days).
- Serious adverse events (SAEs), AEs leading to subject discontinuation or withdrawal, and medically attended advsere events (MAAEs) will be collected for the trial duration. MAAEs are defined as AEs leading to a medical visit to or by a healthcare professional (including visits to an emergency department), but not fulfilling seriousness criteria.

Data collection will be by electronic Case Report Form (eCRF).

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

Immunogenicity (immunogenicity subset):

Proportion of subjects HAV/DENV-naive at Baseline who are seroprotected against HAV at Day 30 (M1) as measured by ELISA (seroprotection rate) in a subset of 120 subjects per group (immunogenicity subset).

- Seroprotection is defined as serum anti-HAV antibody levels ≥10 mIU/mL.
- Due to assay limitations only subjects with anti-HAV antibody levels ≥12.5 mIU/mL, will be classified as seroprotected for the analysis.
- Subjects with anti-HAV antibody levels below the lower limit of quantification (i.e. <12.5 mIU/mL) will be classified as seronegative.
- Immunological HAV/DENV-naive is defined as having anti-HAV antibody levels below the lower limit of quantification <12.5 mIU/mL (ELISA) and reciprocal neutralizing titers for all 4 dengue serotypes of <10 (MNT_{50}).

5.2 Secondary Endpoints

Immunogenicity (immunogenicity subset):

- Geometric mean titers (GMT) of neutralizing antibodies (as measured by MNT_{50}) for each of the 4 dengue serotypes at Day 30 (M1) and Day 120 (M4) in subjects HAV/DENV-naive at Baseline.
- Proportion of subjects HAV/DENV-naive at Baseline who are seropositive for each of the 4 dengue serotypes at Day 30 (M1) and Day 120 (M4) (seropositivity rate). Seropositivity is defined as a reciprocal neutralizing titer ≥10.
- Proportion of subjects HAV/DENV-naive at Baseline who are seropositive for multiple (2, 3 or 4) dengue serotypes at Day 30 (M1) and Day 120 (M4) (seropositivity rate for multiple serotypes).
- Geometric mean concentrations (GMC) of anti-HAV antibodies (as measured by ELISA) at Day 30 (M1) in subjects HAV/DENV-naive at Baseline.

Safety (all subjects):

- Frequency and severity of solicited local (injection site[s]) AEs for 7 days (day of vaccination + 6 subsequent days) and solicited systemic AEs for 14 days (day of vaccination + 13 subsequent days) after each trial vaccination.
- Percentage of subjects with any unsolicited AEs for 28 days (day of vaccination + 27 subsequent days) after each trial vaccination.
- Percentage of subjects with SAEs throughout the trial.
- Percentage of subjects with MAAEs throughout the trial.

5.3 Exploratory Endpoint

- Geometric mean fold rise (GMFR) of anti-HAV antibodies from Baseline (as measured by ELISA) at Day 30 (M1).

6.0 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary objective of showing NI of the immune response to the HAV vaccine when co-administered with TDV compared with HAV vaccine co-administered with placebo assuming a significance level of 0.025 (1-sided) and a seroprotection rate of 95% in HAV/DENV-naive adults 1 month after HAV vaccination in Group 1 and Group 3 (co-administration with placebo [saline] and TDV, respectively).

A sample size of 120 subjects per group, adjusted for approximately 15% subjects not evaluable for the immunogenicity assessments is sufficient to achieve approximately 90% power for showing NI for the primary endpoint assuming a NI margin of 10% and 95% seroprotection rate at Day 30 (M1).

The total sample size of 900 subjects is to ensure that a sufficient number of healthy DENV-naive adults will be vaccinated at the program level to support the safe use of TDV in travelers.

The power calculations were based on nQuery Advisor® 6.01.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

This statistical analysis plan (SAP) was developed based on the information provided in Protocol DEN-314, Version 5.0 dated 11 March 2019 [1] and on the International Conference on Harmonization (ICH) E3 [2] and E9 [3] Guidelines. This document will provide further details regarding the definition of the analysis variables and analysis methodology used to address all trial objectives.

All statistical outputs will be generated using statistical analysis system SAS Version 9.2 or higher.

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

7.1.1 Data Presentation

Summary tables for categorical variables will display both frequencies and percentages. For those categorical variables with defined categories in the eCRF, all possible categories will be displayed, even if the subject count is zero. For any other categorical variables recorded (eg, category of AE or medication/vaccination), only categories with at least 1 subject count will be displayed. Percentages will be presented with 1 decimal place (eg, 80.3%).

Summary tables for continuous variables will display the number of subjects with non-missing values, means or geometric means, medians, SD or geometric standard deviations (GSD), and minimum and maximum values. Minimum and maximum values will be presented with the same number of decimal places as the recorded data. Means, geometric means, and medians will be presented with 1 more decimal place than the recorded data. SD will be presented with 2 more decimal places than the recorded data.

Summaries for selected immunogenicity and safety variables may also include CI around parameter estimates (means or percentages), and SEMs. The CI will be presented with the same number of decimal places as the parameter estimate itself. SEM will be presented with 2 more decimal places than the recorded data.

All collected data will be displayed in the listings sorted by trial group, by site number, by subject number, and by date/time of the recorded event if applicable (eg, date/time of vaccination, date/time of blood draw, date/time of AE). Screen failures data will be grouped and listed separately.

In all outputs, trial groups will be labeled as:

- Group 1: HAV+P/P;
- Group 2: P+TDV/ TDV;
- Group 3: HAV+TDV/TDV.

7.1.2 Study Day, Baseline and Analysis Window Definitions

Study Day 1 (M0) is defined as the date of the first vaccination, as recorded on the eCRF vaccination form. Other Study Days are defined relative to Study Day 1 (M0), with Day -1 being the day prior to Day 1 (M0).

Baseline is defined as the last non-missing measurement taken before the first trial vaccination. Where time is available, the time of the measurement must be prior to the trial vaccination time. Day 1 (M0) measurements taken after the first trial vaccination time are considered as post-Baseline values.

A windowing convention for immunogenicity and safety (vital signs) data will be used to determine the analysis value of a variable at a given trial visit. Following the schedule of trial procedures (Appendix A), the analysis visit windows for each visit will be calculated relative to the day on which each trial dose was administered (Day 1 [M0] and Day 90 [M3]). If several measurements of a variable are obtained for a given subject within the same visit window, the measurement taken at the date that is closest to the scheduled visit date will be used. If the 2 measurements are equidistant from the scheduled visit, the later date will be used. Both scheduled and unscheduled visits will be considered equally.

Table 7.a Analysis Visit Windows

Visit	Study Day (Month)	Scheduled Vaccination	Analysis Visit Windows		
			Safety Set (Vital Signs)	Full Analysis Set	Per-Protocol Set
V1	Day 1 (M0)	Dose 1	Prior [≤1 day] (a) to Dose 1	Prior [≤1 day] (a) to Dose 1	Prior [≤1 day] (a) to Dose 1
V2	Day 30 (M1)		2 – 75 days (b) after Dose 1	2 – 75 days (b) after Dose 1	29 – 37 days (b) after Dose 1
V3	Day 90 (M3)	Dose 2	Not applicable (no vital signs collected)	Not applicable (no blood draw)	Not applicable (no blood draw)
V4	Day 120 (M4)		2 – 105 days (b) after Dose 2 or 76 days – 195 days (b) after Dose 1 (c)	≥2 days (b) after Dose 2 or ≥76 days (b) after Dose 1 (c)	29 – 37 days (b) after Dose 2
V5	Day 270 (M9)		≥106 days (b) after Dose 2 or ≥196 days (b) after Dose 1 (c)	Not applicable (no blood draw)	Not applicable (no blood draw)

(a) Blood draw for immunogenicity assessments and assessment of vital signs must be prior to the vaccination scheduled for the same visit, and where time is available, the time of the blood/vital signs collection must be prior to the vaccination time. Day 1 (M0) measurements taken after the first trial vaccination time are considered post-Baseline values.
(b) Number of days after the visit is calculated with 1 day increment. For example, for V2 number of days after V1 is calculated as [Date of V2] – [Date of V1] + 1 (day).
(c) Applies to subjects who missed the second dose at V3.

7.1.3 Handling of Missing Data

Data will be presented in the listings as reported. For the summaries and analyses, following conventions apply.

Missing Immunogenicity Data (Immunogenicity Subset)

Dengue neutralizing antibody titers (MNT_{50}) that are below the lower limit of detection (LLOD, 10) will be imputed with a value of 5 (half of the LLOD). Reported value between the LLOD and the lower limit of quantification (LLOQ, which differs between serotypes) will be imputed as the mid-point between the LLOD and LLOQ. For example, given a LLOQ of 68 for a serotype, values between 10 and 68 will be imputed as 39 for this serotype.

HAV antibody titers (ELISA) that are below the lower limit of detection/quantification (LLOD = LLOQ = 12.5 mIU/mL) will be imputed with a value of 6.25.

No imputation method will be used for missing immunogenicity data and all analyses will be based on complete records only.

Missing or Partial Dates of Unsolicited AE

Missing and partial unsolicited AE start dates will be imputed only to determine the temporal relationship between the start date of the event and the dose date of the most appropriate vaccination that the AE should be temporally allocated with (ie, Vaccination 1 or 2).

The following rules apply when determining the temporally allocated vaccination:

- If the AE start and end dates are both completely missing, the AE will be allocated with the first trial vaccination;
- If only the month and/or year of AE start is/are available, the AE will be allocated with the latest vaccination that occurred prior to AE start date;
- If the AE start date is completely missing, or if the available start date information is insufficient to distinguish between the two trial vaccinations, but a partial AE end date (ie, month and/or year) is available, the AE end date will be assessed and the AE will be allocated with the vaccination after which the event ends. This is based on the assumption that any AE starting after Vaccination 1 and ongoing on the day of Vaccination 2 would be identified during the clinical assessments that are performed before administration of the second dose of IP. If partial end date information indicates possible allocation with both trial vaccinations, the AE will be allocated with the first trial vaccination.

Missing AE Severity or Relationship to Investigational Products (IPs)

Missing AE severity (mild/moderate/severe) and missing AE relationship to IP (related/not related) will be handled using the conservative approach:

- unsolicited AE with missing severity will be considered as 'severe',
- solicited systemic or unsolicited AE with missing relationship will be considered as 'related'.

No other imputation for missing AE data will be implemented.

Missing or Partial Dates for Medications or Vaccines

Missing and partial dates for a medication/vaccine will be assessed, only to distinguish between a prior or concomitant medication/vaccine. A medication will be considered prior only if the partial end date indicates that it was stopped before the first trial vaccination. A vaccine will be considered prior only if the partial vaccination date indicates that it was given before the first trial vaccination. In all other cases medications or vaccines will be considered concomitant.

Missing End Dates of Medical History/Concurrent Medical Conditions

In case the "End Date" or "End Date Unknown" fields are missing on the medical history/ concurrent medical conditions form of the eCRF and from the partial date it can't be concluded that the event is clearly a medical history, the event will be considered a concurrent medical condition.

7.1.4 Handling of Implausible Values

Data outside the plausible ranges as defined in Table 7.b will be excluded from analyses, but the data will be presented as recorded and flagged in data listings.

Table 7.b Plausible Data Ranges

	Parameter	Plausible range
Demographics	Height	110 – 210 cm
	Weight	20 – 200 kg
Solicited AE	Swelling	≤ 500 mm
	Erythema	≤ 500 mm
	Body Temperature [(a)]	32 – 43°C
Vital Signs	Heart Rate	40 – 200 beats/min
	Systolic Blood Pressure	70 – 180 mmHg
	Diastolic Blood Pressure	30 – 120 mmHg
	Respiratory Rate	5 – 80 breaths/min

(a) Also applicable to body temperature measurements collected as vital sign.

7.2 Analysis Sets

All Screened: All subjects who signed the informed consent, regardless of whether subjects were screen failures.

Randomized Set: All randomized subjects, regardless of whether any dose of the IPs was received.

Summary tables generated for the Randomized Set will present trial groups "as randomized", ie, according to the combination of IPs a subject was designated to receive, which may be different from the IPs the subject actually received. For example, a subject randomized to TDV group (Group 2) but vaccinated with HAV and TDV (Group 3) will be analyzed in the TDV group (Group 2).

Safety Set: All randomized subjects who received at least 1 dose of IPs.

All summaries generated for the Safety Set will present trial groups "as vaccinated", ie, according to the combination of IPs the subject actually received rather than to which he/she was randomized. For example, a subject randomized to TDV group (Group 2) but vaccinated with HAV and TDV (Group 3) will be analyzed in the HAV and TDV group (Group 3). Subjects who received a combination of IPs that was not planned for any trial group (if any) will be considered in a separate group (eg, Placebo and HAV administered on Day 1 [M0] and TDV administered on Day 90 [M3]). Data for this group, labelled as "Unplanned IPs sequence", will be displayed in selected summaries and in all listings and subject mappings generated for the Safety Set.

HAV Full Analysis Set (FAS): All randomized subjects in the immunogenicity subset who received at least 1 dose of trial vaccine and for whom both valid pre-dose (Baseline) and post-dose (Day 30 [M1]) measurements are available for HAV immunogenicity assessments.

TDV FAS: All randomized subjects in the immunogenicity subset who received at least 1 dose of trial vaccine and for whom a valid pre-dose (Baseline) and at least 1 post-dose measurement are available for TDV immunogenicity assessments.

Trial groups for both HAV FAS and TDV FAS will be defined "as randomized".

HAV Per–Protocol set (PPS): All subjects from the HAV FAS who have no major protocol violations, excluding subjects who are seropositive for dengue virus or seroprotected against HAV at Baseline.

TDV PPS: All subjects from the TDV FAS who have no major protocol violations, excluding subject who are seropositive for dengue virus or seroprotected against HAV at Baseline. Major protocol violations are defined as deviations from the protocol that could potentially have a significant impact on the immunogenicity results of a subject. These violations will be identified via programming and a blinded data review prior to database lock and unblinding of the IPs assignment for final analysis, using criteria described in Table 7.c. Subjects who received IPs that were different from the IPs assigned at randomization (randomization errors) will be identified after unblinding.

Other major protocol deviations may be identified during blinded data reviews of the data listings and deviation logs throughout the trial. Any changes to PPS exclusion criteria after approval of the SAP will be documented separately and approved prior to unblinding of subjects' trial group assignment for the final analysis.

The reasons for exclusion of subjects from analysis sets will be summarized by trial group for the Randomized Set (Immunogenicity subset), separately for HAV and TDV immunogenicity analysis sets.

Table 7.c Criteria for Exclusion of Subjects from PPS

Criteria for Exclusion		Method of Identification
HAV PPS	**TDV PPS**	
Not receiving at least 1 dose of trial vaccine[a]		Programmatically using dosing data
Not providing a valid pre-dose (Baseline) and at least 1 post-dose measurement for HAV immunogenicity assessment[b]	Not providing a valid pre-dose (Baseline) and at least 1 post-dose measurement for TDV immunogenicity assessment[b]	Programmatically using immunogenicity data
Subjects seropositive[c] to any serotype of dengue neutralizing titers at Baseline (Day1 [M0])		Programmatically using immunogenicity data
Subjects with serum anti-HAV antibody levels ≥12.5 mIU/mL at Baseline (Day1 [M0]).		Programmatically using immunogenicity data
Subject meets any of the exclusion criteria		Through protocol deviation review, programmatically using eCRF-recorded data
	Not receiving both Vaccination(s) 1 and Vaccination 2	Programmatically using dosing data
	Receiving Vaccination 2 (ie, outside Day 90 [-15/+25 days])	Programmatically using dosing data
Randomization Errors: Receiving at Vaccination 1 or at Vaccination 2 IP(s) different from which subject was randomized to		Identified after unblinding (eg, a subject who was randomized to receive TDV but received HAV).
Product preparation error		Through protocol deviation review
Use of prohibited medications/vaccines[d]		Identified by clinical science review of eCRF-recorded medication/vaccines data

(a) Subjects with this deviation will be excluded from the Safety Set, and thus also from the FAS and PPS.
(b) Subjects with this deviation will be excluded from the FAS, and thus also from the PPS.
(c) Reciprocal neutralizing titer ≥ 10.
(d) Subject can be excluded from only one of the PPS depending on the time of medication/vaccine use.

7.3 Disposition of Subjects

Trial information will be presented for all screened subjects including: the date the first subject signed the informed consent form, the date of the first subject's first visit, the date of last subject's last visit, the date of first subject's first vaccination, the date of last subject's first vaccination, the date of first subject's second vaccination, the date of last subject's second vaccination. In addition, details will be provided for versions of: the Medical Dictionary for Regulatory Activities (MedDRA), the World Health Organization Drug Dictionary (WHODrug), and the SAS used for analyses.

The randomization eligibility summary for all screened subjects will include: the number of screened subjects, the number of subjects eligible for randomization, the number of subjects not

eligible for randomization and the primary reason(s) for ineligibility for randomization. The number of screen failures and their characteristics will also be summarized.

Disposition summary for all randomized subjects and all randomized subjects in the immunogenicity subset will include:

- Number of randomized subjects by site;
- Number of randomized subjects and number of subjects randomized but not dosed (including the reason);
- Number of subjects completing the vaccination regimen/trial visits;
- Number of subjects who prematurely discontinued the vaccination regimen/trial (IPs or trial withdrawals);
- Primary reason(s) for premature discontinuation of the vaccination regimen/trial.

Significant protocol deviations captured in the eCRF will be summarized by trial group for all randomized subjects and for all randomized subjects included in the immunogenicity subset.

Number of subjects in analysis sets will also be provided as a separate summary.

7.4 Demographic and Other Baseline Characteristics

Age, gender, race, and other Baseline characteristics will be summarized descriptively for the Randomized Set, Randomized Set (Immunogenicity Subset), Safety Set, HAV FAS, TDV FAS and both corresponding PPS. These summaries will include baseline seropositivity status for dengue (seropositive [reciprocal neutralizing titer ≥10 for at least 1 dengue serotype] or seronegative [reciprocal neutralizing titer <10 for all dengue serotypes]), baseline seropositivity status for each and multiple dengue serotypes, and baseline seroprotection status against HAV (yes/no).

7.5 Medical History and Concurrent Medical Conditions

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

Medical history and concurrent medical conditions will be coded using the MedDRA coding system. Summary tables for each trial group will be provided by System Organ Class (SOC) and Preferred Term (PT) for the Safety Set.

7.6 Medication History and Concomitant Medications

A prior medication/vaccine (history) is any medication/vaccine for which intake was stopped before administration of the first dose of IPs. A concomitant medication/vaccine is any medication/vaccination ongoing at the time of the first trial vaccination, or taken on or after the administration of the first dose of IPs.

Medication history, vaccination history, concomitant medications, and concomitant vaccines will be coded using the WHODrug.

Summary tables for medication history and concomitant medications will be provided for each trial group by Anatomical Therapeutic Chemical class level 2 name and preferred medication name. Vaccination history and concomitant vaccines will be summarized for each trial group using the vaccine type and name as recorded in the eCRF. Summary tables will be provided for the Safety Set.

7.7 Investigational Products Exposure and Compliance

The Investigator will record in the eCRF all injections of the IPs given to the subject. A summary of IP compliance will be presented for the Safety Set. This summary will include: the number and percentage of subjects who received both doses of IP; the number and percentage of subjects who only received the first dose of IPs; the number of subjects who prematurely discontinued the trial before receiving the second dose of IPs; and the reason(s) for discontinuation. This summary will be prepared by trial group, including a separate group of subjects who received unplanned IP sequence (if any).

Trial follow-up is defined as the time period between the first trial vaccination and the end of the trial, inclusive. Follow-up duration will be summarized by trial group for the Safety Set as a continuous variable (n, mean, median, SD, minimum and maximum), and also as a categorical variable (frequency and percentage) for the following intervals: 1 – 30 days, 31 – 90 days, 91 – 120 days, 121 – 270 days, and >270 days. Additionally, the duration of follow-up after the second dose of IPs (defined as the number of days from second vaccination to the end of the trial, inclusive) will be summarized in a similar way as a continuous variable and also as a categorical variable for the following intervals: 1 – 30 days, 31 – 90 days, 91 – 180 days, >180 days.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Descriptive Summaries

Descriptive statistics will be provided for the primary and secondary immunogenicity endpoints by trial group and for each dengue serotype (when relevant).

For dengue antibody titers (MNT_{50})/ HAV antibody concentrations (ELISA) these will include:

- Number of subjects with non-missing assessment, GMT/GMC with 95% CI, GSD, median, minimum, and maximum. The GMT/GMC, 95% CI and GSD will be calculated

as the anti-logarithm transformation of the means, 95% CI and SDs of the log-transformed titers/concentrations.

For seropositivity (dengue virus)/seroprotection (HAV) these will include:

- Number and percentage of seropositive/seroprotected subjects and corresponding 95% CIs calculated by the exact (Clopper-Pearson) method [4].

Graphical Presentations (for PPS and FAS)

Graphical presentations for immunogenicity endpoints will be provided by trial group and will include:

- Bar graphs presenting the percentage of seropositive (for each of 4 dengue serotypes and for multiple serotypes)/seroprotected (HAV) subjects and the 95% CIs, for all visits;
- Line plots of GMTs (for each of 4 dengue serotypes)/GMCs (HAV) at each visit, including the 95% CIs;
- Reverse cumulative distribution curves of antibody titers (for each of the 4 dengue serotypes) at Day 120 (M4) for Groups 2 and 3, and reverse cumulative distribution curves of antibody concentrations (HAV) at Day 30 (M1) for Groups 1 and 3.

7.10.1 Primary Immunogenicity Analysis

The primary immunogenicity endpoint for this trial is HAV seroprotection rates at Day 30 (M1) in subjects HAV/DENV-naive at Baseline. This endpoint will be measured in those subjects included in the immunogenicity subset and will be used to evaluate the NI of co-administration of HAV and TDV vs administration of HAV alone.

A descriptive summary of the primary immunogenicity endpoint will be provided for each trial group. Rates difference for primary comparison (Group 1 – Group 3) will be presented in the separate summary, together with 95% CI calculated using Newcombe score method [5]. NI of co-administration of HAV and TDV to HAV alone will be concluded if the upper bound of the 95% CI is less than NI margin of 10%.

The primary immunogenicity analysis will be provided for the HAV PPS. A supportive analysis will be provided using the HAV FAS. Descriptive summaries will be provided for both the HAV FAS and HAV PPS.

The following sensitivity analyses to further evaluate the primary endpoint will be provided:

- Both the descriptive summary and non-inferiority comparison will be repeated for:
  - HAV-PPS including subjects with a baseline anti-HAV antibody level of ≥12.5 – ≤70 mIU/mL;
  - HAV-PPS including subjects with any baseline anti-HAV antibody level (ie, inclusive of subjects HAV naïve at baseline and subjects seroprotected against HAV at baseline);

- HAV-PPS including subjects seropositive for dengue at baseline;
- HAV-PPS including subjects seropositive for dengue at baseline or with a baseline anti-HAV antibody level of ≥12.5 – ≤70 mIU/mL;
- HAV-PPS including subjects seropositive for dengue at baseline or with any baseline anti-HAV antibody level (ie, inclusive of subjects HAV naïve at baseline and subjects seroprotected against HAV at baseline).

7.10.2 Secondary Immunogenicity Analysis

Secondary immunogenicity endpoints in this trial are

- GMC of anti-HAV antibodies on Day 30 (M1) in subjects HAV/DENV-naive at Baseline;
- GMT of neutralizing antibodies for each of the 4 dengue serotypes at Day 30 (M1) and Day 120 (M4) in subjects HAV/DENV-naive at Baseline;
- Proportion of subjects HAV/DENV-naive at Baseline who are seropositive for each of the 4 dengue serotypes at Day 30 (M1) and Day 120 (M4) (seropositivity rate).
- Proportion of subjects HAV/DENV-naive at Baseline who are seropositive for multiple (2, 3 or 4) dengue serotypes at Day 30 (M1) and Day 120 (M4) (seropositivity rate for multiple serotypes).

Similar to the primary endpoint, secondary immunogenicity endpoints will be measured in subjects included in the immunogenicity subset.

Seropositivity for multiple dengue serotypes will be assessed in following categories:

- for only 1 of the 4 dengue serotypes (monovalent),
- for any 2 of the 4 dengue serotypes (bivalent),
- for any 3 of the 4 dengue serotypes (trivalent),
- for all 4 dengue serotypes (tetravalent),
- for at least 2 dengue serotypes (at least bivalent),
- for at least 3 dengue serotypes (at least trivalent).

GMC of anti-HAV antibodies will be summarized descriptively and graphically for the HAV PPS and HAV FAS. Other secondary immunogenicity endpoints will be summarized descriptively and graphically for the TDV PPS and TDV FAS.

7.10.3 Exploratory Analysis

GMFR of anti-HAV antibodies at Day 30 by trial group and stratified for baseline anti-HAV antibodies level (3 strata: <12.5mIU/mL / ≥12.5 – ≤70 mIU/mL / >70mIU/mL and overall) will

be summarized descriptively using HAV-PPS including subjects seroprotected against HAV at baseline for subjects included in the immunogenicity subset.

7.11 Safety Analysis

All summaries of safety data will be provided for the Safety Set.

7.11.1 Adverse Events

AE data will be summarized by trial group after each vaccination and after any vaccination.

Solicited local (injection site) and systemic AEs are collected for at least 30 min after each vaccination at the site (in-clinic assessment) and then using diary cards that are provided to the subject. Unsolicited AEs are collected by interview. Subjects will be evaluated for solicited local (injection site) AEs for 7 days (day of vaccination + 6 days), solicited systemic AEs for 14 days (day of vaccination + 13 days), and unsolicited AEs for 28 days (day of vaccination + 27 days), following each vaccination. MAAEs, AEs leading to IP withdrawal or trial discontinuation, and SAEs will be collected throughout the trial from first vaccination (Day 1 [M0]) until the end of the trial (Day 270 [M9]).

Reactogenicity (Solicited AEs)

Solicited local (injection site) AEs include injection site pain, injection site erythema, and injection site swelling; for erythema and swelling, the subject will record the greatest surface diameter in mm but for the summaries and listings these data will be converted to cm. The intensity of erythema and swelling will be derived from the recorded diameters.

Solicited systemic AEs include headache, asthenia, malaise, myalgia, and fever (defined as a body temperature ≥38°C). Fever data will be presented using the proposed temperature increments published by the Brighton Collaboration Fever Working Group [6]. Intensity grades for solicited safety parameters are defined in Appendix B.

For each solicited AE, the number and percentage of subjects reporting an event will be summarized by event intensity at the following time intervals, following each vaccination:

- 30 minutes after each vaccination (in-clinic, assessed by investigator);
- Days 1 – 7 (overall, for local [injection site] AEs) or Days 1 – 14 (overall, for systemic AEs) following each vaccination;
- Days 1 – 7 (daily, for local [injection site] AEs) or Days 1 – 14 (daily, for systemic AEs) following each vaccination;
- Days 1 – 3, Days 4 – 7 (overall, for local [injection site] AEs) or Days 1 – 7, Days 8 – 14 (overall, for systemic AEs) following each vaccination.

Percentages will be calculated based on the number of subjects who received the respective dose of IPs and provided at least 1 record (none, mild, moderate or severe) for this AE in the relevant time interval. For example, subjects reporting solicited AEs (at least 1 non-missing record) for Days 1 – 3 will only be included in denominator for the Days 1 – 3 and Days 1 – 7 summaries,

but will be excluded from denominator for Days 4 – 7 summaries. For subjects with more than 1 episode of the same event, the maximum intensity will be used in summaries.

Concomitantly administered vaccines (eg, HAV and Placebo) will be injected into opposite arms at the first vaccination. Solicited local (injection site) AEs reported after the first vaccination will be summarized by co-administered IPs, as displayed in the Table 7.d, and by route of administration (IM/SC). Arm (left/right) and Vaccine ID collected on the vaccination page of eCRF for Vaccination 1 will be used to identify which IP corresponds to solicited local (injection site) AEs reported for left and right arm at 30 min (in-clinic) and Day 1 – Day 7 (diary card) assessments.

Table 7.d Summaries of solicited local (injection site) AEs following first vaccination

	Group 1 HAV+P	Group 2 P+TDV	Group 3 HAV+TDV
Summary: HAV, Placebo, HAV	HAV	Placebo	HAV
Summary: Placebo, TDV, TDV	Placebo	TDV	TDV

All solicited local (injection site) AEs are considered as related to the IP. For solicited systemic AEs, the relationship to the IP is assessed by the investigator.

The number and percentage of subjects with solicited systemic AEs will be summarized by relationship to the IP for the following time intervals:

- 30 minutes after each vaccination;
- Days 1 – 14 (overall) following each vaccination.

If a subject reports more than 1 episode of the same event, then the strongest relationship will be included in the summaries: a subject who reported both related and unrelated episodes for the same AE will be counted in the related category.

A summary of the day of first onset of each event and the number of days that subjects reported experiencing each event will be presented following each vaccination. The number of days a subject reported each event is calculated as the total of all days the subject reported the event, regardless of whether the event was reported on consecutive days.

An overview table for solicited AEs will be provided. This will include:

- 30 minutes post-vaccination events (solicited local [injection site] and systemic AEs combined);
- Solicited AEs (solicited local [injection site] and systemic AEs combined);
- Solicited local (injection site) AEs;
- Solicited systemic AEs (overall and by relationship to IP);

- Prolonged solicited AEs (overall and for solicited local [injection site] and systemic AEs separately).

A summary of the first day of onset for each solicited AE and, the number of days the subject reports experiencing the AE will be presented for each vaccination. The number of days a subject reports each event is calculated as the total number of days the subject reports this event, regardless of whether the event was reported on consecutive days.

Persistent/prolonged solicited local (injection site) or systemic AEs continuing on Day 8 and Day 15, respectively, following each trial vaccination will be captured as an AE recorded in the Adverse Event eCRF. These AEs will not be included in the summaries of unsolicited AEs, and will be presented in separate listings. Any solicited local (injection site) or systemic AEs that resolved before 8 days and 15 days, respectively, following each trial vaccination, but recurring at a later time (ie, discontinued), will be recorded as an unsolicited AE on the Adverse Event eCRF.

Unsolicited AEs

Unsolicited AEs will be assessed for 28 days following each vaccination (day of vaccination + 27 days). MAAEs, AEs leading to IP withdrawal or trial discontinuation, and all SAEs will be collected for the duration of the trial: from Day 1 (M0) through Day 270 (M9).

All unsolicited AEs, including MAAEs, SAEs and AEs leading to IP withdrawal or trial discontinuation will be coded using the current version of MedDRA. Summary tables of unsolicited AEs will include the number of events and the number and percentage of subjects who experienced events. Percentages will be calculated based on the number of subjects in the Safety Set who received the respective dose of the IP. Subjects who report more than 1 occurrence for a particular MedDRA term (level) will only be counted once in the summaries. Where relationship or severity is concerned, the AE with the most closely related occurrence or the highest known severity will be counted, following a conservative approach.

Unsolicited AEs collected up to 28 days post-vaccination will be summarized as follows:

- by SOC and PT;
- by SOC and PT including PT events with frequency greater than 2% in any trial group;
- by SOC and PT for IP-related AEs;
- by SOC and PT including PT events with a frequency greater that 2% in any trial group for IP related AEs;
- by SOC, PT, and severity (mild, moderate, severe);
- by SOC, PT, and severity (mild/moderate/severe) for IP related AEs.

MAAEs, SAEs, and AEs leading to IP withdrawal or trial discontinuation will be summarized for the duration of the trial as follows:

- By SOC and PT;

- By SOC and PT for IP related AEs;
- By SOC, PT, and severity (mild/moderate/severe) – for MAAEs only.

The summary of SAEs by SOC and PT after any vaccination, and the summary of AEs leading to IP withdrawal or trial discontinuation by SOC and PT will include a separate group for subjects who received an unplanned IP sequence (if any).

In addition, overview tables by trial group will be generated for unsolicited AEs collected up to 28 days post-vaccination, MAAEs, SAEs and AEs leading to IP withdrawal and/or trial discontinuation including the variables as outlined in Table 7.e.

Table 7.e Overview of Unsolicited Adverse Events

	All AEs (within 28 days post-vaccination)	SAEs	MAAEs	AEs leading to IPs withdrawal or trial discontinuation
Relationship to IP(s)	✓	✓	✓	✓
Relationship to trial procedure	✓	✓	✓	✓
Severity	✓	✓	✓	✓
AEs leading to IPs withdrawal and/or trial discontinuation	✓	✓	✓	
AEs leading to IPs withdrawal	✓	✓	✓	✓
AEs leading to trial discontinuation	✓	✓	✓	✓
MAAEs	✓			✓
SAEs and non-serious AEs	✓			✓
Deaths	✓	✓		✓

For disclosure of trial results an additional AE table by SOC and PT including PT events with a frequency greater than 2% in any trial group will be provided for all non-serious unsolicited AE up to 28 days post-vaccination, for all MAAEs during the entire trial duration, and for all non-serious AEs leading to IP withdrawal and/or trial discontinuation during the entire trial duration. This summary table is need for after any vaccination only and will also include a separate group for subjects who received an unplanned IP sequence (if any).

Subject mappings (a list of subject identification numbers in each category of SOC and PT and each trial group) will be provided for all unsolicited AEs, SAEs, MAAEs and AEs leading to IP withdrawal or trial discontinuation.

7.11.2 Clinical Laboratory Evaluations

Not applicable.

7.11.3 Vital Signs

Vital signs will be measured on Day 30 (M1), Day 120 (M4), and Day 270 (M9). Summary statistics (number of subjects, mean, SD, median, minimum, and maximum) will be calculated for all observed vital signs and for each vital sign change from Baseline. Summaries will be prepared for each trial group and each trial visit.

7.11.4 12-Lead ECGs

Not applicable.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

No interim analysis is planned for this trial.

7.13 Changes in the Statistical Analysis Plan

Seropositivity for multiple (2, 3 or 4) dengue serotypes was added as secondary endpoint, for consistency with other phase 3 TDV trials. Full analysis set and per protocol analysis set are defined separately for endpoints related to HAV and DENV antibody levels.

Sensitivity analyses on primary endpoint were added to support primary analyses. Descriptive summary and non-inferiority comparison on HAV antibody level were repeated by including subjects with HAV antibody at various level at baseline and subjects with or without TDV seropositive subjects at baseline into HAV-PPS. GMFR of HAV antibody level stratified by HAV antibody levels at baseline was added as exploratory endpoint.

8.0 REFERENCES

1. A Randomized, Observer Blind, Phase 3 Trial to Investigate the Immunogenicity and Safety of the Co-administration of a Subcutaneous Tetravalent Dengue Vaccine Candidate (TDV) and an Intramuscular Hepatitis A Virus (Inactivated) Vaccine in Healthy Subjects Aged 18 to 60 Years in Non-endemic Country(ies) for Dengue, Takeda Vaccines, Inc., Protocol No. DEN-314, Version 5.0, dated 11 March 2019.
2. ICH Harmonized Tripartite Guideline – Clinical Trial Reports: Structure and Content, E3 (http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/structure-and-content-of-clinical-study-reports.html).
3. ICH Harmonized Tripartite Guideline – Statistical Principles for Clinical Trials, E9 (http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/statistical-principles-for-clinical-trials.html).
4. Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26: 404-13.
5. Newcombe, RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998; 17(8): 873-890.
6. Marcy SM, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis and presentation. Vaccine. 2004;22(5-6): 551-6.

Appendix A Schedule of Trial Procedures

Table 8.a Schedule of Trial Procedures

Visits			**1**	**2** [a]	**3**	**4** [a]	**5**
Day		**Screening**	**Day 1 (M0)**	**Day 30 (M1)**	**Day 90 (M3)**	**Day 120 (M4)**	**Day 270 (M9) (ET)** [b]
Visit window (days)		**Up to 28 days prior to vaccination**	**0**	**-1/+7**	**-4/+7**	**-1/+7**	**-7/+14**
Informed consent		X					
Assessment of eligibility criteria [c]		X	X				
Demographics		X					
Medical history		X					
Prior medications		X					
Concomitant medications/vaccinations [d]		X	X	X	X	X	X
Check criteria for delay of trial vaccination			X		X		
Check contraindications to trial vaccination					X		
Review of systems			X		X		
Complete physical examination [e]		X	X		X		
Targeted physical examination [f]				X		X	X
Vital signs				X		X	X
Pregnancy test [g]		X	X		X		
Pregnancy avoidance counseling [h]		X	X	X	X	X	
Blood collection for screening (up to 2 mL)[i]		X					
Randomization			X				
Blood Collection	Anti-HAV antibodies (5 mL) [j]		X	X			
	Dengue neutralizing antibodies (5 mL) [j]		X	X		X	
Vaccination			X		X		
Injection site evaluation [k]			X		X		
Diary card [l]	Distribution		X		X		
	Review/collection			X		X	
Unsolicited adverse events [m]			X	X	X	X	
Serious adverse events and AEs leading to subject discontinuation or withdrawal [n]			X	X	X	X	X
Medically attended adverse events [n]			X	X	X	X	X

ET=early termination, HAV= hepatitis A virus, M=month
Footnotes:

(a) Visit 2 and Visit 4 should occur 30 days (at least 29 days) after the first and second trial vaccination, respectively.
(b) If the subject terminates early, Day 270 (M9) procedures should be performed.
(c) Review of inclusion/exclusion criteria will be performed at Screening and prior to the first trial vaccination on Day 1 (M0). After eligibility is assessed at Day 1 (M0), subjects will be randomized 1) to one of the 3 trial groups and 2) to be included in the immunogenicity subset (120 subjects in each group).
(d) All concomitant medications and vaccine history from 1 month (minimum 28 days) prior to administration of each study vaccine dose(s) up to 1 month (minimum 28 days) thereafter, steroids and immunostimulants within 60 days prior to Day 1 (M0), immunoglobulins and blood products within 3 months prior to Day 1 (M0), and immunosuppressive therapy within 6 months prior to Day 1 (M0).
(e) Physical examination including measurement of weight and height; body mass index will be calculated automatically.
(f) Subjects may undergo a targeted symptom-directed physical examination. Clinically significant changes from the Baseline examination should be recorded in the subject's source documents and electronic Case Report Form (eCRF).
(g) For female subjects of childbearing potential, serum pregnancy testing will be performed at the screening visit and thereafter serum or urine pregnancy testing is acceptable; where the results of a urine pregnancy test are in doubt, a serum pregnancy test will be performed to verify the result. Results must be confirmed and documented as negative prior to each trial vaccine administration. Additional pregnancy tests may be performed during the trial if deemed necessary by the Investigator.
(h) Females of childbearing potential who are sexually active will be reminded during trial visits to adhere to acceptable contraceptive methods up to 6 weeks post second trial vaccination at Day 90 (M3).
(i) A blood sample for anti-HAV antibodies will be collected from all subjects.
(j) Blood samples for immunogenicity assessments for subjects included in the immunogenicity subset. Blood sampling at Day 1(M0) should be performed pre-first trial vaccination.
(k) Injection site assessed by trial staff for pain, erythema, and swelling for at least 30 minutes after vaccine administration.
(l) Diary cards (paper or electronic) will be distributed for the collection of 1) solicited local (injection site[s]) adverse events (AE) for 7 days (day of vaccination + 6 subsequent days) following each trial vaccination, and 2) solicited systemic AEs for 14 days (day of vaccination + 13 subsequent days) following each trial vaccination. The Investigator will categorize events by severity (mild, moderate or severe) and will assess causality to vaccine administration (related or not related).
(m) Unsolicited AEs for 28 days (day of vaccination + 27 subsequent days) following each trial vaccination will be collected by interview and recorded for all subjects at Day 30 (M1) and Day 120 (M4). The Investigator will categorize events by severity (mild, moderate or severe) and will assess causality to trial vaccine administration (related or not related). If solicited local and systemic AEs continue on Day 8 and Day 15, respectively, following each trial vaccination, record the extended information on the Adverse Event eCRF.
(n) Medically attended AEs, serious AEs, and AEs leading to subject discontinuation or withdrawal will be collected from the first vaccination onwards, for the trial duration.

Appendix B Solicited Local (Injection Site) and Systemic Adverse Events and Severity

Table 8.b Solicited Local (Injection Site) and Systemic AEs

Solicited local (injection site) AEs:	Pain Erythema Swelling
Solicited systemic AEs:	Fever [(a)] Headache Asthenia Malaise Myalgia

(a) Fever is defined as a body temperature ≥38°C (100.4°F) regardless of the method used [6].

Table 8.c Severity of Solicited Safety Parameters

Adverse Event	Severity grade	Severity
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[(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50–≤100 mm
	3	Severe: >100 mm
Swelling at injection site[(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Headache	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without treatment
	3	Severe: Prevents normal activity with or without treatment
Asthenia	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Malaise	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
Fever[(b)]	NA	None
	NA	38.0-<38.5°C
	NA	38.5-<39.0°C
	NA	39.0-<39.5°C
	NA	39.5-<40.0°C
	NA	40.0-<40.5°C
	NA	40.5-<41.0°C
	NA	≥41.0°C

(a) Subjects are to record greatest surface diameter in mm on the diary card.

(b) Fever is defined as a body temperature of ≥38°C regardless of the measurement method [6].

Signature Page for DEN-314 Statistical Analysis Plan, Version 1.0, September 13,
Title:

Approval	PPD

Document Number: TAK-003-05100 v1.0