Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Demonstrate Lot-to-Lot Consistency of 3 Lots of a Tetravalent Dengue Vaccine Candidate in Healthy Adults in Non-Endemic Country(ies) for Dengue

NCT Number: NCT03423173

SAP Approve Date: 31 January 2019

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: DEN-304

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Demonstrate Lot-to-Lot Consistency of 3 Lots of a Tetravalent Dengue Vaccine Candidate in Healthy Adults in Non-Endemic Country(ies) for Dengue

Lot-to-lot Consistency of 3 Lots of TDV in Non-Endemic Country(ies) for Dengue

PHASE 3

Version: Final, 2.0

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Prepared by:

PPD

Based on:

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1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

1.0 TITLE PAGE 1
1.1 Approval Signatures 2
2.0 TABLE OF CONTENTS 3
3.0 LIST OF ABBREVIATIONS 5
4.0 OBJECTIVES 6
4.1 Primary Objectives 6
4.2 Secondary Objectives 6
4.3 Study Design 6
5.0 ANALYSIS ENDPOINTS 9
5.1 Primary Endpoint 9
5.2 Secondary Endpoints 9
6.0 DETERMINATION OF SAMPLE SIZE 10
7.0 METHODS OF ANALYSIS AND PRESENTATION 11
7.1 General Principles 11
7.1.1 Data Presentation 11
7.1.2 Study Day, Baseline and Analysis Visit Window Definitions 12
7.1.3 Handling of Missing Data 13
7.1.4 Implausible Values 14
7.2 Analysis Sets 15
7.3 Disposition of Subjects 16
7.4 Demographic and Other Baseline Characteristics 17
7.5 Medical History and Concurrent Medical Conditions 17
7.6 Medication History and Concomitant Medications 18
7.7 Investigational Product Exposure and Compliance 18
7.8 Efficacy Analysis 18
7.9 Pharmacokinetic/Pharmacodynamic Analysis 18
7.10 Other Outcomes 19
7.10.1 Primary Immunogenicity Analysis 19
7.10.2 Secondary Immunogenicity Analysis 20
7.11 Safety Analysis 21
7.11.1 Adverse Events 21
7.11.2 Clinical Laboratory Evaluations 24
7.11.3 Vital Signs 25
7.11.4 12-Lead ECGs 25

7.11.5 Other Observations Related to Safety 25
7.12 Interim Analysis 25
7.13 Changes in the Statistical Analysis Plan 25
7.13.1 Amendment History 25
7.13.2 Summary of Changes 26
8.0 REFERENCES 28

LIST OF IN-TEXT TABLES

Table 7.a Analysis Visit Windows 13
Table 7.b Plausible Data Ranges 15
Table 7.c Criteria for Exclusion of Subjects from PPS 16
Table 7.d Variables to be Included in the Overview of Unsolicited Adverse Events 24

LIST OF IN-TEXT FIGURES

Figure 4.a Schematic of Trial Design 7

LIST OF APPENDICES

Appendix A Schedule of Trial Procedures 29
Appendix B Intensity Grades for Solicited Safety Parameters 31

3.0 LIST OF ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of variance
CRO	Contract research organization
CSR	Clinical Study Report
eCRF	electronic Case Report Form
FAS	Full Analysis Set
GMT	Geometric mean titer
GSD	Geometric standard deviation
IP	Investigational product
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
M0, 3, 4, 9	Month 0, 3, 4, 9
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MNT_{50}	Microneutralization test 50%
PPS	Per-Protocol Set
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SOC	System Organ Class
TDV	Tetravalent dengue vaccine candidate
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

- To demonstrate lot-to-lot consistency of 3 consecutive tetravalent dengue vaccine candidate (TDV) lots in terms of equivalence of immune responses at 1 month post second dose.

4.2 Secondary Objectives

Immunogenicity:

- To describe the seropositivity rates for all dengue serotypes at 1 month and at 6 months post second TDV dose or placebo, where seropositivity is defined as a reciprocal neutralizing titer ≥10.
- To describe the persistence of the immune response at 6 months post second dose of TDV or placebo in dengue-naive subjects.

Safety:

- To assess the safety profile following each vaccination or placebo in all groups.

4.3 Study Design

This is a randomized, double-blind, placebo-controlled phase 3 trial with 924 healthy subjects aged 18 to 60 years.

The trial will be conducted in country(ies) non-endemic for dengue to investigate lot-to-lot consistency in terms of equivalence of the immunogenicity of 3 consecutive TDV lots administered as a 2-dose regimen 3 months apart via subcutaneous injection. Subjects will be randomized (2:2:2:1 ratio) to one of 4 trial groups to receive TDV (Lots 1, 2 or 3; 264 subjects per group) or placebo (132 subjects):

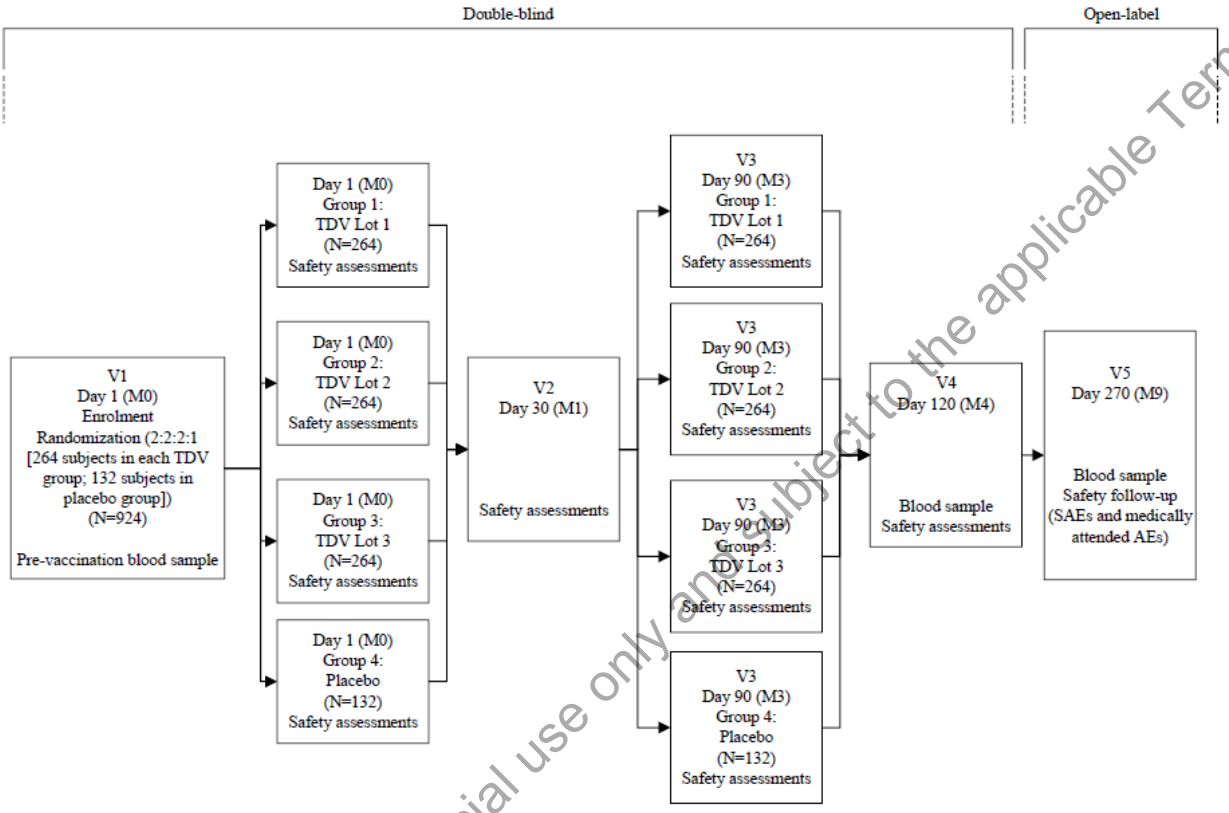
- Group 1: TDV Lot 1 administered on Day 1 (Month 0 [M0]) and Day 90 (Month 3 [M3]);
- Group 2: TDV Lot 2 administered on Day 1 (M0) and Day 90 (M3);
- Group 3: TDV Lot 3 administered on Day 1 (M0) and Day 90 (M3);
- Group 4: Placebo administered on Day 1 (M0) and Day 90 (M3).

For immunogenicity assessments, an immunogenicity subset of 616 subjects will be utilized (Groups 1-3: 176 subjects per group and Group 4: 88 subjects). Subjects will be randomly selected for inclusion in the immunogenicity subset using an interactive response technology.

All subjects will be followed-up for 6 months post second vaccination on Day 90 (M3) through Day 270 (Month 9 [M9]); the trial duration will be approximately 270 days (9 months) for each subject.

A schematic of the trial design is included in Figure 4.a.

Figure 4.a Schematic of Trial Design



M=Month, V=Visit

Note: Blood samples for immunogenicity will only be collected from the immunogenicity subset (Groups 1-3: 176 subjects each and Group 4: 88 subjects).

Immunogenicity evaluation (immunogenicity subset):

- Neutralizing antibodies will be measured by microneutralization test 50% (MNT_{50}) using blood samples collected pre first vaccination (Day 1 [M0]) and post second vaccination (Day 120 [Month 4] (M4) and Day 270 [M9]).

Safety evaluation (all subjects):

- Diary cards will be distributed for the recording of:
  - Solicited local (injection site) adverse events (AEs) for 7 days following each TDV/placebo dose on Day 1 (M0) and Day 90 (M3) (day of vaccination + 6 days). These will include: injection site pain, injection site erythema, and injection site swelling.
  - Solicited systemic AE for 14 days following each TDV/placebo dose on Day 1 (M0) and Day 90 (M3) (day of vaccination + 13 days). These will include: fever, headache, asthenia, malaise, and myalgia.

- Unsolicited AEs for 28 days following each TDV/placebo dose on Day 1 (M0) and Day 90 (M3) (day of vaccination + 27 days) will be collected by interview and recorded for all subjects.
- Serious adverse events (SAEs), medically attended AEs (MAAEs) and AEs leading to discontinuation or withdrawal will be collected for the trial duration. MAAEs are defined as AEs leading to an unscheduled visit to or by a healthcare professional (including visits to an emergency department) that do not fulfill the seriousness criteria.

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

5.0 ANALYSIS ENDPOINTS

Trial objectives will be assessed using following endpoints.

5.1 Primary Endpoint

- Geometric mean titers (GMT) of neutralizing antibodies (by MNT_{50}) for each of the 4 dengue serotypes at Day 120 (M4), measured for subjects included in the immunogenicity subset.

5.2 Secondary Endpoints

Immunogenicity (immunogenicity subset):

- Seropositivity rates (% of seropositive subjects) for each of the 4 dengue serotypes at Day 120 (M4) and Day 270 (M9).
- Seropositivity rates (% of seropositive subjects) for multiple dengue serotypes at Day 120 (M4) and Day 270 (M9).
- GMT of neutralizing antibodies (by MNT_{50}) for each of the 4 dengue serotypes at Day 270 (M9).

Safety (all subjects):

- Frequency and severity of solicited local (injection site) AEs for 7 days (day of vaccination + 6 days) and solicited systemic AE for 14 days (day of vaccination + 13 days) after each TDV/placebo dose on Day 1 (M0) and Day 90 (M3).
- Percentage of subjects with any unsolicited AEs for 28 days (day of vaccination + 27 days) after TDV/placebo dose on Day 1 (M0) and Day 90 (M3).
- Percentage of subjects with SAEs throughout the trial.
- Percentage of subjects with MAAEs throughout the trial.

6.0 DETERMINATION OF SAMPLE SIZE

It is assumed that the natural logarithms of titers of neutralizing antibodies for each of the 4 dengue serotypes are independent and have normal distribution, with SDs of 1.35, 0.86, 1.21, and 1.27, respectively. A sample size of 137 evaluable subjects in each of the 3 TDV groups (Groups 1-3) is sufficient to achieve approximately 90% overall power for establishing lot-to-lot consistency in terms of equivalence of immune responses to 3 consecutive TDV lots, based on the 95% CI of the titer ratios, with equivalence margins of 0.5 and 2.0. This sample size assumes no variation among the 3 TDV lots; that is, for each serotype, the true ratio of GMT is 1.0 between the first and second lots and between the second and third lots.

Further adjusted for approximately 20% dropouts and non-evaluable subjects, taking into account the ratio between the immunogenicity subset and its complement, and using a 2:2:2:1 randomization ratio, the sample size required to evaluate lot-to-lot consistency is approximately 616 subjects; 176 subjects in each of the 3 TDV groups and 88 subjects in the placebo group.

To ensure sufficient size of the safety database in dengue non-endemic regions, the overall sample size for the trial is 924 subjects: 264 subjects in each TDV group (Group 1-3) and 132 subjects in the placebo group (Group 4).

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-304 Version 4.0 dated 29 October 2018 [1] and on International Conference on Harmonization E3 [2] and E9 [3] Guidelines. The SAP details definitions of the analysis variables and analyses methodology used to address trial objectives.

All statistical outputs will be generated using the statistical analysis system SAS® version 9.2 or higher.

A blinded data review will be conducted prior to unblinding of subjects' 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 the 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 identification 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.

Trial groups will be labeled as TDV Lot 1, TDV Lot 2, TDV Lot 3 and Placebo in all of the outputs.

7.1.2 Study Day, Baseline and Analysis Visit Window Definitions

Study Day 1 (M0) is defined as the date of the first trial vaccination, as recorded on the eCRF vaccination form. Other Study Days are calculated 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 the time is available, the time of the measurement must be prior to the first 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 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.

The analysis windows are displayed in the Table 7.a.

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 – 60 days [(b)] after Dose 1	Not applicable (no blood draw)	Not applicable (no blood draw)
V3	Day 90 (M3)	Dose 2	61 – 105 days [(b)] after Dose 1 and prior [≤ 1 day] [(a)] to Dose 2	Not applicable (no blood draw)	Not applicable (no blood draw)
V4	Day 120 (M4)		2 – 105 days [(b)] after Dose 2 or 106 – 195 days [(b)] after Dose 1 [(c)]	2 – 105 days [(b)] after Dose 2 or 2 – 195 days [(b)] after Dose 1 [(c)]	29 – 37 days [(b)(d)] after Dose 2
V5	Day 270 (M9)		≥106 days [(b)] after Dose 2 or ≥196 days [(b)] after Dose 1 [(c)]	≥106 days [(b)] after Dose 2 or ≥196 days [(b)] after Dose 1 [(c)]	173 – 194 days [(b)] after Dose 2

M=month, V=visit

(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.

(d) Analysis evaluating primary endpoint with visit window of -15/+25 days will also be performed.

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}) which are below the lower limit of detection (LLOD, 10) will be imputed with a value of 5 (half of the LLOD). Reported values between the LLOD and the lower limit of quantification (LLOQ) which differs between serotypes, will be imputed with the mid-point between the LLOD and LLOQ. For example, given a LLOQ of 18 for a serotype, all values between 10 and 18 will be imputed with 14 for this serotype.

No imputation methods 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 may 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 associated with (Vaccination 1 or 2). The following rules apply when determining the associated 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 the year of the AE start is/are available, the AE will be allocated with the latest vaccination prior to the AE start date;
- If the AE start date is completely missing, or the available start date information is insufficient to distinguish between the 2 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 vaccinations, the AE will be allocated with the first trial vaccination.

Missing AE Severity or Relationship to Investigational Product (IP)

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 of Medications or Vaccinations

Missing and partial dates for medications or vaccinations will be assessed, only to determine the relationship between the end date of the medication or vaccination and the first dose of IP (ie, to distinguish if a medication or vaccine is prior or concomitant). 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 vaccinations 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 concurrent medical condition.

7.1.4 Implausible Values

Data outside the plausible ranges (according to the Table 7.b) will be excluded from analyses, but 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

Randomized Set: The Randomized Set will include all randomized subjects, regardless of whether a dose of the IP was received.

Summary tables generated for the Randomized Set will present trial groups "as randomized", ie, according to the IP a subject was assigned to receive, which may be different from the IP the subject actually received. For example, a subject randomized to Group 1 (TDV Lot 1) but vaccinated with TDV Lot 2 will be analysed in the Group 1 (TDV Lot 1).

Safety Set: The Safety Set will include all randomized subjects who received at least 1 dose of IP.

All summaries generated for the Safety Set will present trial groups "as vaccinated", ie, according to the IP subject actually received rather than the IP to which subject was randomized. For example, a subject randomized to Group 1 (TDV Lot 1) but vaccinated with TDV Lot 2 will be analyzed in the Group 2 (TDV Lot 2). Subjects who received different IPs at first and second vaccinations (if any, eg, subject vaccinated with TDV Lot 1 at first vaccination and with TDV Lot 2 at second vaccination) will be considered in a separate group. Data for this group, labelled as "Unplanned IP sequence", will be displayed in selected summaries and all listings and subject mappings generated for the Safety Set.

Full Analysis Set (FAS): The FAS will include all randomized subjects in the immunogenicity subset who received at least 1 dose of IP, and who have a valid pre-dose (Baseline) measurement and at least 1 valid post-dose measurement available for the immunogenicity assessments.

Trial groups for the FAS will be defined "as randomized".

Per-Protocol Set (PPS): The PPS will include all subjects in the FAS who have no major protocol violations. Any subjects seropositive for any dengue serotypes at Baseline will be excluded from the PPS.

Major protocol violations are defined as deviations from the protocol, which have potentially significant impact on the immunogenicity results of a given subject. These violations will be

identified via programming and a blinded data review prior to database lock and unblinding of the IP assignment, using criteria described in Table 7.c. Subjects who received IP different from the assigned IP (randomization errors) will be identified after unblinding.

Table 7.c Criteria for Exclusion of Subjects from PPS

Criteria for Subject Exclusion	Method of Identification
Not receiving at least 1 dose of trial vaccine [(a)]	Identified programmatically using dosing data.
Not having a valid pre-dose (Baseline) measurement and an least 1 valid post-dose measurement for immunogenicity assessment [(b)]	Identified programmatically using immunogenicity data
Seropositivity [(c)] to any serotype of dengue at Baseline	Identified programmatically using immunogenicity data.
Receiving only 1 dose of the IP	Identified programmatically using dosing data.
Receiving the second dose (Day 90 [M3]) outside of the scheduled visit window [(d)]	Identified programmatically using dosing data.
Randomization Errors: receiving a different IP than the assigned IP (refers to the incorrect administration of any of the 3 lots of TDV or placebo on Day 1 [M0] or Day 90 [M3])	Identified after unblinding [(e)]
Product preparation error	Identified through blinded protocol deviation log.
Subject meets any of the trial exclusion criteria	Identified through protocol deviation review, Identified programmatically using eCRF-recorded data.
Use of prohibited medications/vaccines	Identified by clinical science review of eCRF-recorded medication/vaccines data.

(a) Subjects with this protocol violation will be excluded from Safety Set, and thus also from FAS and PPS.
(b) Subjects with this protocol violation will be excluded from FAS, and thus also from PPS.
(c) Reciprocal neutralizing titer ≥ 10.
(d) For primary analysis visit window of -4/+7 days will be applied; analysis evaluating primary endpoint with visit window of -15/+25 days will also be performed.
(e) Eg, a subject who was randomized to a particular TDV lot but received another TDV lot or placebo, or a subject who was randomized to placebo but received TDV.

Other major protocol violations may be identified for the data listings and deviation logs throughout the trial, subject to medical review. 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 final analysis.

Reasons for exclusions of subjects from analysis sets will be summarized by trial group for the Randomized Set (Immunogenicity subset).

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 the first subject first vaccination, the date of the first subject second vaccination, the date of the last

subject first vaccination, the date of the last subject second vaccination, and the date of the last subject's last visit. In addition, details will be provided for: versions of the Medical Dictionary for Regulatory Activities (MedDRA), World Health Organization Drug Dictionary (WHODrug), and the SAS® used for analyses.

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 summaries 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 (IP 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 Randomized Set, Randomized Set (Immunogenicity Subset), Safety Set, FAS and PPS. These summaries will include overall dengue seropositivity status (seropositive [reciprocal neutralizing titer ≥10 for at least 1 dengue serotype] or seronegative [reciprocal neutralizing titer <10 for all dengue serotypes]), dengue seropositivity status for each serotype and for multiple serotypes.

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 IP. A concurrent medical condition is defined as any significant condition/disease that is ongoing at the time the first dose of IP 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/vaccination (history) is any medication/vaccination for which intake was stopped before the first trial vaccination is administered. A *concomitant* medication/vaccine is any medication/vaccination ongoing at the time of the first trial vaccination, or taken on or after the first trial vaccination.

Medication history, vaccination history, concomitant medications, and concomitant vaccinations 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 vaccinations 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 Product Exposure and Compliance

The Investigator will record in the eCRF all injections of the IP that were given to the subject. 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 IP; the number of subjects who prematurely discontinued the trial before receiving the second dose of IP; 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 in days 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, percentage) using 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 IP (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 categorical variable for the following intervals: 1 – 30 days, 31 – 90 days, 91 – 180 days, and >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.

For antibody titers these will include:

- Number of subjects with non-missing assessment, GMT with 95% CI, GSD, median, minimum, and maximum. The GMT, 95% CI and GSD will be calculated as the anti-logarithm transformation of the means, 95% CI and standard deviations of the log-transformed titers.

For seropositivity these will include:

- Number and percentage of seropositive 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 subjects and the 95% CIs for all visits (seropositivity for each of the 4 dengue serotypes and seropositivity for multiple dengue serotypes);
- Line plots of GMTs at each visit, including the 95% CIs (for each of the 4 dengue serotypes);
- Reverse cumulative distribution curves of dengue antibody titers for each of the 4 dengue serotypes at all post-Baseline visits.

Pairwise Comparisons

Pairwise comparisons between trial groups will be performed using GMTs and seropositivity rates for each of the 4 dengue serotypes at post-baseline visits, for:

- Group 1 vs Group 2,
- Group 1 vs Group 3,
- Group 2 vs Group 3.

Between group geometric mean ratios or differences in seropositivity rates, together with corresponding 95% CIs, will be reported for each comparison.

7.10.1 Primary Immunogenicity Analysis

The primary immunogenicity endpoint for this trial is GMTs of neutralizing antibodies (by MNT_{50}) for each of the 4 dengue serotypes at Day 120 (M4). This endpoint will be measured for

those subjects included in the immunogenicity subset and will be used to evaluate the lot-to-lot consistency of the 3 TDV lots.

A descriptive summary of the primary immunogenicity endpoint will be provided for each trial group, including placebo.

For each dengue serotype, pairwise mean differences between the 3 TDV lots will be estimated using an analysis of variance (ANOVA) model with natural logarithms of titers as a response variable and trial group as a factor variable. This model will only use data from the subjects in groups 1, 2 and 3. Mean log-titers, mean differences and 95% CIs for all 3 comparisons (ie, Group 1 vs Groups 2, Group 1 vs Group 3, and Group 2 vs Group 3) will be anti-log transformed to obtain group GMTs, between group geometric mean ratios and 95% CIs.

Equivalence between immune responses of 2 trial groups will be established if the 95% CI of the corresponding geometric mean ratio is contained between equivalence margins of 0.5 and 2.0. Lot-to-lot consistency of the 3 TDV lots will be concluded if equivalence of immune responses is established for all pairwise comparisons between 3 lots and for all 4 dengue serotypes. All of these evaluations are considered co-primary, therefore no multiplicity adjustment of 5% significance level is needed.

The primary immunogenicity analysis will be provided for the PPS. The evaluation of primary endpoint will also be repeated for:

- PPS with expanded visit windows for second dose (Day 90 [M3]) and Day 120 (M4) blood draw, please refer to the Table 7.a and Table 7.c;
- PPS including subjects seropositive at baseline. For this analysis, pairwise mean differences between 3 TDV lots will be estimated using an analysis of covariance (ANCOVA) model with natural logarithms of titers as response variable, natural logarithms of baseline titers as a covariate and trial group as a factor.

Number of subjects included in abovementioned analysis populations will be presented in the Analysis Sets summary table.

A supportive analysis will be provided using the FAS. Second line analysis for FAS will be performed, with ANCOVA model including baseline titer as a covariate.

All descriptive summaries will also include Baseline values.

7.10.2 Secondary Immunogenicity Analysis

Secondary immunogenicity endpoints in this trial are

- Seropositivity rates (% of seropositive subjects) for each of the 4 dengue serotypes at Day 120 (M4) and Day 270 (M9);
- Seropositivity rates (% of seropositive subjects) for multiple dengue serotypes at Day 120 (M4) and Day 270 (M9);
- GMTs of neutralizing antibodies (by MNT50) for each of the 4 serotypes at Day 270 (M9).

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

Dengue neutralizing antibody titers at Day 270 (M9) will be analyzed descriptively in the same manner as the primary immunogenicity endpoint, and will be presented for all trial groups. Between group GMT ratios and 95% CIs, estimated using an ANOVA model, will also be provided. Only data from Groups 1, 2 and 3 will be used in this estimation.

Seropositivity will be summarized descriptively by trial group and for each applicable visit. For each of the 4 dengue serotypes, differences in seropositivity rates between TDV lots will be presented together with the 95% CIs calculated by the Newcombe and Wilson method [5].

For multiple dengue serotypes, seropositivity will be assessed descriptively 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).

Secondary immunogenicity endpoints will be summarized for the PPS and the FAS. These summaries will also include Baseline data.

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 AE)

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 AE include headache, asthenia, malaise, myalgia, and fever (defined as a body temperature ≥38°C). The subject can record the body temperature in either °F or °C. However, body temperature measured in °F will be converted to °C for the summaries and listings. Fever will be derived from the recorded temperature measurements and presented using the proposed temperature increments published by the Brighton Collaboration Fever Working Group [6].

Severity grades for solicited safety parameters are defined in the Appendix B.

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

- 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 IP 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 severity will be used in summaries.

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

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

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

If a subject reported more than one 1 episode for the same event, then the strongest relationship will be included in the summaries.

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 AE

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 conservative approach.

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

- By SOC and PT;
- By SOC and PT including events with a frequency greater than 2% in any trial group;
- By SOC and PT including events with a frequency greater than 2% in any trial group, for non-serious unsolicited AE. This summary will also include a group of subjects who received unplanned IP sequence (if any);
- By SOC and PT for IP related AEs;
- By SOC and PT including 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 MAAE only.

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

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

Table 7.d Variables to be Included in the Overview of Unsolicited Adverse Events

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

Subject mappings – list of subject identification numbers in each category of SOC and PT and each trial group – will be provided for 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 1 (M0), Day 30 (M1), Day 90 (M3), 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

The SAP contains no changes to the planned analyses described in the protocol. Seropositivity for multiple dengue serotypes was added as secondary endpoint, for consistency with other phase 3 TDV trials.

7.13.1 Amendment History

Date	Amendment Number
17 January 2018	Initial Analysis Plan
31 January 2019	1

7.13.2 Summary of Changes

This section describes major changes to the SAP Version 1.0, dated 17 January 2018.

Section	Description of Change
7.1	Table 7.a: Different analyses windows defined for Safety Set and FAS, because of no immunogenicity evaluation planned for V3, ie, analysis visit window defined in the previous SAP version is applicable for Safety Set but not applicable for FAS. Analysis with expanded visit window for Day 120 blood draw is added. Column with scheduled visit day removed as redundant (repeats information given in the Appendix A: Schedule of Trial Procedures) Minor edit changes and added clarifications in handling missing data for AEs and medical history/concurrent medical conditions, for consistency across Phase 3 TDV trials. Section 7.1.4 - Implausible values - is added, including Table 7.b. Subsequent tables numbering and references are updated.
7.2	Example of case with subject receiving different IPs at first and second vaccination is added, together with label for such group of cases (if any). Reference to interim analysis removed following protocol amendment. Table 7.c Exclusion criterion referring to Day 120 measurement outside of window is removed, because of the removal of Day 120 interim analysis. Analysis with expanded second dose visit window is added.
7.3	Additional data for trial information table is added, for consistency across Phase 3 TDV trials. Disposition summary for all randomized subjects in the immunogenicity subset is added.
7.4	Demographic summary for all randomized subjects in the immunogenicity subset is added.
7.10	Reference to interim analysis removed following protocol amendment.
7.10.1	Supplementary evaluations of the primary endpoint are added, second line analysis for FAS is detailed.
7.11.1	Three safety summaries added for trial data reporting. Reference to interim analysis removed following protocol amendment. Several edit changes made for clarity and alignment of safety data presentation across Phase 3 TDV trials.

Section	Description of Change
7.11.3	Reference to interim analysis removed following protocol amendment.
7.12	Revised as no interim analysis is planned.

8.0 REFERENCES

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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. 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(5-6): 551-556.

Appendix A Schedule of Trial Procedures

Visit	**1**	**2 [a]**	**3**	**4 [a]**	**5**
Day	**Day 1 M0**	**Day 30 M1**	**Day 90 M3**	**Day 120 M4**	**Day 270 M9 (ET) [b]**
Visit window (days)	**1±n.a**	**30 days (-1/+7) after Visit 1**	**90 days (-4/+7) after Visit 1**	**30 days (-1/+7) after Visit 3**	**180 days (-7/+14) after Visit 3**
Informed consent [c]	X				
Assessment of eligibility criteria [d]	X				
Demographics	X				
Medical history	X				
Concomitant medications/vaccinations [e]	X	X	X	X	X
Check contraindications to trial dose administration	X		X		
Check criteria for delay of trial dose administration			X		
Complete physical examination [f]	X		X		
Targeted physical examination [g]		X		X	X
Vital signs [h]	X	X	X	X	X
Pregnancy test [i]	X		X		
Pregnancy avoidance guidance [j]	X	X	X	X	
Blood sample for dengue neutralizing antibodies (5 mL) [k]	X			X	X
Randomization	X				
Trial vaccine administration [l]	X		X		
Injection site evaluation [m]	X		X		
Diary card – Distribution	X		X		
Diary card – Review/collection of solicited adverse events [n]		X		X	
Adverse events leading to withdrawal or discontinuation	X	X	X	X	X
Unsolicited adverse events [o]	X	X	X	X	
Serious adverse events [p]	X	X	X	X	X
Medically attended adverse events [p]	X	X	X	X	X

ET=early termination, M=month, n.a=not applicable

Footnotes:

(a) Visit 2 and Visit 4 should occur 30 days (at least 29 days) after the 1st and 2nd dose.

(b) If the subject terminates early, Day 270 (M9) procedures should be performed.

(c) Up to 28 days prior to the day of randomization.

(d) Review of inclusion/exclusion criteria will be performed prior to administration of Dose 1 on Day 1 (M0). After eligibility is assessed and written informed consent has been obtained, subjects will be randomized to receive 2 doses of TDV or placebo by subcutaneous injection.
(e) All medications and vaccine history from 1 month (minimum 28 days) prior to administration of each trial dose of TDV or placebo 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). Concomitant medication/vaccination will be collected throughout the trial conduct.
(f) Physical examination including measurement of weight and height; body mass indexwill be calculated. Measurement of height is only required at Day 1 (M0).
(g) Subjects may undergo a brief symptom-directed physical examination. Clinically significant changes from the Baseline examination should be recorded in the subject's source documents and eCRF.
(h) Vital signs including (but not limited to) the measurement of systolic blood pressure/diastolic blood pressure, heart rate, and body temperature.
(i) Pregnancy testing (serum or urine) for females of childbearing potential. Results must be confirmed and documented as negative prior to each trial dose administration. Additional pregnancy tests may be performed during the trial if deemed necessary by the Investigator.
(j) 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). 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 and donation of ova.
(k) Blood samples for immunogenicity assessments for subjects included in the immunogenicity subset. The blood sample on Day 1 (M0) should be taken prior to administration of Dose 1. The blood sample on Day 120 (M4) should be taken at least 29 days (-1, 7 days) after administration of Dose 2. At Day 270 (M9) a final blood sample will be taken.
(l) Subjects will be randomized to receive TDV (Lots 1, 2 or 3) or placebo.
(m) Injection site pain, erythema, and swelling assessed by blinded trial staff for 30 minutes post-vaccination.
(n) Review the diary card and collect solicited AE that occurred after vaccination:
    1) Solicited local (injection site) AE for 7 days following administration of each trial vaccination (day of vaccination + 6 days). If solicited local AE continue on Day 8 following each trial vaccination, record the extended information on the Adverse Event eCRF.
    2) Solicited systemic AE for 14 days following administration of each trial vaccination (day of vaccination + 13 days). The Investigator will categorize events by severity (mild, moderate or severe) and will assess causality to vaccine administration (related or not related). If solicited systemic AE continue on Day 15 following each trial vaccination, record the extended information on the Adverse Event eCRF.
(o) Unsolicited AE for 28 days following each trial vaccination (day of vaccination + 27 days) will be collected by interview and recorded on Day 30 (M1) and Day 120 (M4). The Investigator will categorize events by severity (mild, moderate or severe) and will assess causality to trial dose administration (related or not related).
(p) Medically attended AE and serious AE will be collected for the trial duration.

Appendix B Intensity Grades for Solicited Safety Parameters

Adverse Event	Intensity grade	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 [(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)]	N/A	None
		38.0-<38.5°C
		38.5-<39.0°C
		39.0-<39.5°C
		39.5-<40.0°C
		40.0-<40.5°C
		40.5-<41.0°C
		>=41.0°C

(a) Subjects are to record greatest surface diameter in mm on the diary card.
(b) Fever is defined as greater than or equal to 38°C (100.4°F) [6].

Signature Page for DEN-304 Statistical Analysis Plan, Version 2.0, 31 January 20

Title:

Approval	PPD
Approval	PPD
Approval	PPD

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