Title: A Randomized, Observer-Blind, Placebo-Controlled, Phase 3 Trial to Investigate the Immunogenicity and Safety of a Tetravalent Dengue Vaccine Candidate and a Yellow Fever YF-17D Vaccine Administered Concomitantly and Sequentially in Healthy Subjects Aged 18 to 60 years in Non-Endemic Country(ies)

NCT Number: NCT03342898

SAP Approve Date:

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: DEN-305

A Randomized, Observer-Blind, Placebo-Controlled, Phase 3 Trial to Investigate the Immunogenicity and Safety of a Tetravalent Dengue Vaccine Candidate and a Yellow Fever YF-17D Vaccine Administered Concomitantly and Sequentially in Healthy Subjects Aged 18 to 60 years in Non-Endemic Country(ies)

Immunogenicity and Safety of TDV Administered with a Yellow Fever Vaccine in Adults

PHASE 3

Version**:** Final, 1.0

Date**:** 21 October 2019

Prepared by:

PPD

Based on:

Protocol Version: 4.0
Protocol Date: 28 November 2018

1.1 Approval Signatures

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

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3.0 LIST OF ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of variance
CRF	Case Report Form
FAS	Full Analysis Set
GMT	Geometric mean titer
ICH	International Conference on Harmonization
IP	Investigational product
LLOQ	Lower limit of quantification
LS means	Least squares means
M0, 1, 3, 4, 6, 7, 12	Month 0, 1, 3, 4, 6, 7, 12
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MNT_{50}	Microneutralization test 50%
NI	Non-Inferiority
PPS	Per-Protocol Set
PRNT	Plaque reduction neutralization test
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SOC	System organ class
TDV	Tetravalent dengue vaccine candidate
WHO Drug	World Health Organization Drug Dictionary
YF	Yellow Fever

4.0 OBJECTIVES

4.1 Primary Objective

- To demonstrate non-inferiority (NI) of the Yellow Fever (YF) seroprotection rate response to 1 dose of YF-17D vaccine, 1 month following concomitant administration with 1 dose of a tetravalent dengue vaccine candidate (TDV) compared to placebo.

4.2 Secondary Objectives

Immunogenicity:

- To demonstrate NI of the geometric mean titer (GMT) response to TDV for all 4 dengue serotypes, 1-month post second dose of TDV following concomitant administration of the first dose of TDV with YF-17D vaccine or placebo.
- To demonstrate NI of the GMT response to 1-dose of YF-17D vaccine, 1 month following concomitant administration with 1 dose of TDV compared to placebo.
- To describe the seropositivity rates for all 4 dengue serotypes, 1-month post second dose of TDV following concomitant administration of the first dose of TDV with YF-17D vaccine or placebo.
- To describe the GMTs of neutralizing antibodies and the seropositivity rates for all 4 dengue serotypes, 1-month post first dose of TDV administered concomitantly with YF-17D vaccine or placebo.
- To describe the GMT and seroprotection rate response to YF-17D vaccine, 1 month after sequential administration of a 2-dose regimen of TDV at 0 and 3 months, followed by YF-17D vaccine 3 months later.
- To describe the GMTs of neutralizing antibodies and the seropositivity rates for all 4 dengue serotypes, 1 month after sequential administration of YF-17D vaccine at month 0, followed by a 2-dose regimen of TDV 3 months later at 3 and 6 months.

Safety:

- To assess the safety profile after each vaccine injection in Groups 1, 2 and 3.

4.3 Additional Objectives

Not applicable.

4.4 Study Design

This is a phase 3, observer-blind, randomized, multi-center trial in 900 healthy adults aged 18 to 60 years in non-endemic areas for dengue and YF to investigate the immunogenicity and safety of the concomitant and sequential administration of TDV and YF-17D vaccine [1]. Subjects will be randomized equally (1:1:1 ratio) to one of the following 3 trial groups (300 subjects per trial group) using an interactive response technology:

- Group 1: YF-17D vaccine + placebo concomitantly administered on Day 1 (Month [M0]), first dose of TDV administered on Day 90 (M3) and second dose of TDV administered on Day 180 (M6).
- Group 2: first dose of TDV + placebo concomitantly administered on Day 1 (M0), second dose of TDV administered on Day 90 (M3) and YF-17D vaccine administered on Day 180 (M6).
- Group 3: first dose of TDV + YF-17D vaccine concomitantly administered on Day 1 (M0), second dose of TDV administered on Day 90 (M3) and placebo administered on Day 180 (M6).

Concomitantly administered vaccines will be injected into opposite arms. All subjects will be followed-up for 6 months after the third vaccination (administered approximately 6 months after the first vaccination), so the trial duration will be approximately 360 days (12 months) for each subject.

The total trial population of 900 subjects (300 subjects per trial group) is considered sufficient for the NI assessment of the immune response to the YF-17D vaccine when concomitantly administered with TDV compared to placebo, and for the NI assessment of the immune response to TDV when TDV is concomitantly administered with YF-17D vaccine compared to placebo.

Safety parameters include solicited local (injection site) and solicited systemic adverse events (AE) for 7 days (day of vaccination + 6 days) and 14 days (day of vaccination + 13 days) after each vaccination, respectively, unsolicited AEs for 28 days (day of vaccination + 27 days) after each vaccination, medically attended adverse events (MAAE) and serious adverse events (SAE) throughout the trial.

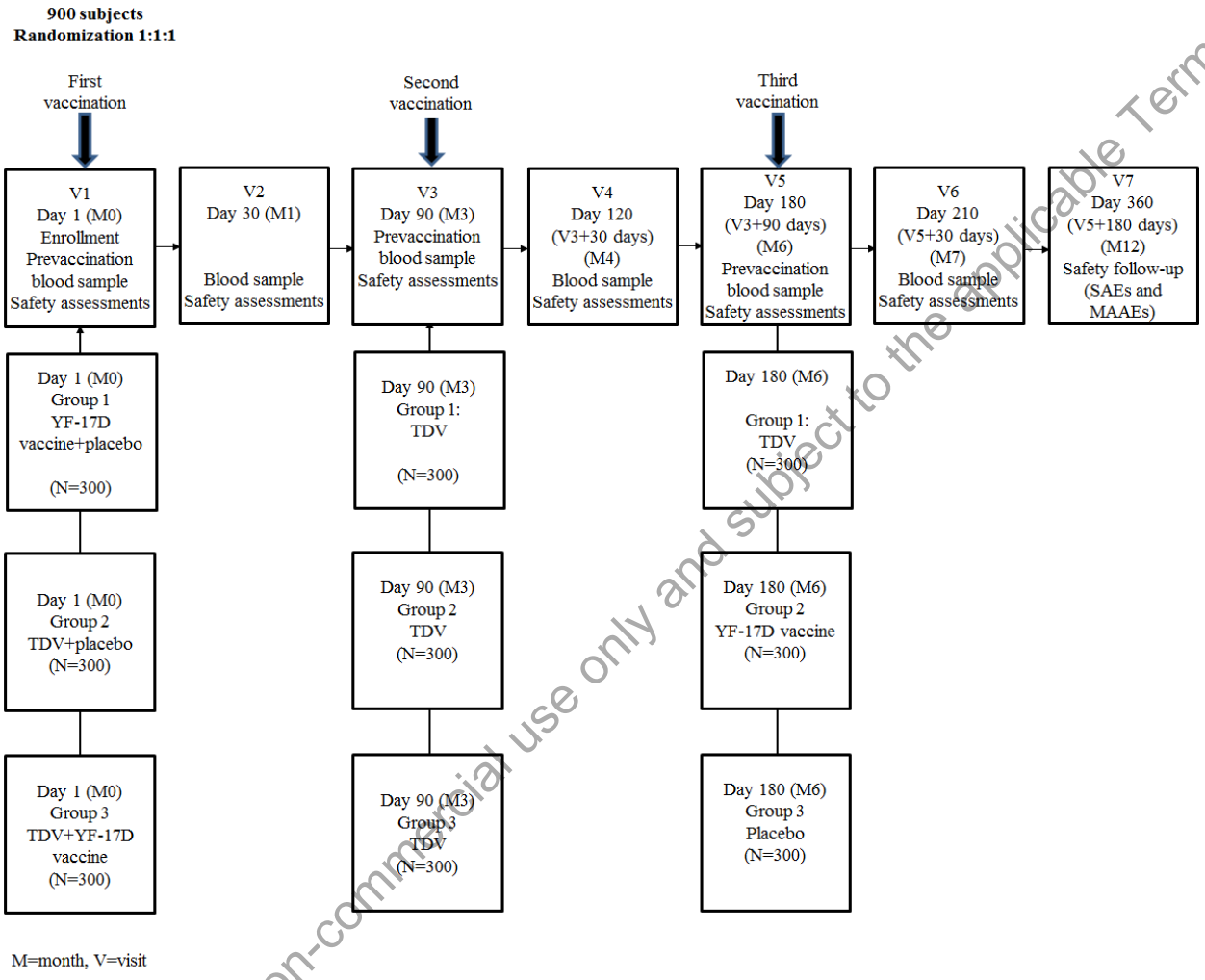
A schematic of the trial design is included as Figure 4.a. The schedule of trial procedures is provided in Appendix A.

Immunogenicity evaluation:

Blood samples for the measurement of dengue neutralizing antibodies (microneutralization test 50% [MNT_{50}]) will be collected at pre-first vaccination (Day 1 [M0]), 1-month post first vaccination (Day 30 [M1]), pre-second vaccination (Day 90 [M3]), 1-month post second vaccination (Day 120 [M4]), pre-third vaccination (Day 180 [M6]), and 1-month post third vaccination (Day 210 [M7]).

Blood samples for the measurement of YF neutralizing antibodies (plaque reduction neutralization test [PRNT]) will be collected at pre-first vaccination (Day 1 [M0]), 1-month post first vaccination (Day 30 [M1]), pre-third vaccination (Day 180 [M6]), and 1-month post third vaccination (Day 210 [M7]).

Figure 4.a Schematic of Trial Design



Safety evaluation:

- Diary cards (paper or electronic) will be distributed to all subjects for the recording of:
  - Solicited local AEs for 7 days following each vaccination (day of vaccination + 6 days). These will include: injection site pain, injection site erythema, and injection site swelling, and will be collected at each injection site.
  - Solicited systemic AEs for 14 days following each vaccination (day of vaccination + 13 days). These will include: fever, headache, asthenia, malaise, and myalgia.
- Unsolicited AEs for 28 days following each vaccination (day of vaccination + 27 days).

- SAEs and MAAEs will be recorded 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, but not fulfilling seriousness criteria.

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

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

- Proportion of subjects YF and DENV-naive at Baseline who are seroprotected against YF on Day 30 (Month-1 [M1]) as measured by PRNT (YF seroprotection rate). YF seroprotection is defined as reciprocal anti-YF neutralizing antibody titer ≥10. Immunological naivety to YF and DENV is defined as Baseline reciprocal neutralizing antibody titers <10 for YF and for the 4 dengue serotypes.

5.2 Secondary Endpoints

Immunogenicity:

- GMT of neutralizing antibodies (as measured by MNT_{50}) for each of the 4 dengue serotypes at pre-second and -third vaccinations (Day 90 [Month 3; M3] and Day 180 [Month 6; M6], respectively); and 1 month post first, second, and third vaccinations (Day 30 [M1], Day 120 [Month 4; M4], and Day 210 [Month 7; M7], respectively) in subjects YF and DENV-naive at Baseline.
- GMTs of anti-YF neutralizing antibodies at 1-month post first and third vaccinations (Day 30 [M1] and Day 210 [M7], respectively) in subjects YF and DENV-naive at Baseline.
- Seropositivity rates (% of subjects seropositive) for each of the 4 dengue serotypes at pre-second and -third vaccinations (Day 90 [M3] and Day 180 [M6], respectively); and 1 month post first, second, and third vaccinations (Day 30 [M1], Day 120 [M4], and Day 210 [M7], respectively) in subjects YF and DENV-naive at Baseline, where seropositivity is defined as a reciprocal neutralizing antibody titer ≥10.
- Seropositivity rates (% of subjects seropositive) for multiple (2, 3 or 4) dengue serotypes at pre-second and -third vaccinations (Day 90 [M3] and Day 180 [M6], respectively); and 1 month post first, second, and third vaccinations (Day 30 [M1], Day 120 [M4], and Day 210 [M7], respectively) in subjects YF and DENV-naive at Baseline, where seropositivity is defined as a reciprocal neutralizing antibody titer ≥10.
- Proportion of subjects YF and DENV-naive at Baseline who are seroprotected against YF at 1-month post third vaccination (Day 210 [M7]) as measured by PRNT.

Safety:

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

6.0 DETERMINATION OF SAMPLE SIZE

The sample size calculation assumes a significance level of 0.025 (one-sided).

For the primary objective of showing NI in YF seroprotection rates, the calculation assumes a NI margin of 5%, and a YF seroprotection rate of 98% at 1 month after YF-17D vaccination in the two trial groups (Group 1 and Group 3).

For the secondary objective of showing NI in GMTs of neutralizing antibodies for all the 4 dengue serotypes, the calculation assumes a NI margin of 2.0, that the true GMT ratio for the two trial groups (Group 2 and Group 3) is 1, and that the natural logarithm of titers are distributed as normal distributions with SDs of 1.35, 0.86, 1.21, and 1.27.

For the secondary objective of showing NI in GMTs of anti-YF neutralizing antibodies, the calculation assumes a NI margin of 2.0, that the true GMT ratio for the two trial groups (Group 1 and Group 3) is 1, and that the natural logarithm of titers are distributed as normal distributions with a SD of 1.31 [1].

A sample size of 300 subjects per trial group, with approximately 255 evaluable subjects per trial group (assuming approximately 15% dropouts and non-evaluable subjects), is sufficient to achieve approximately 90% overall power for showing NI for the above primary and secondary objectives.

A total sample size of 900 subjects also ensures that a sufficient number of healthy YF/DENV-naive adults will be vaccinated 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-305, Version 4.0 dated 28 November 2018 [2] and on International Conference on Harmonization (ICH) E3 [3] and E9 [4] Guidelines.

All statistical analyses 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 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

In general, descriptive summaries will be provided by trial group.

Unless specified otherwise, number of subjects with non-missing observations, mean or geometric mean, SD or geometric SD, median, minimum, and maximum will be presented for continuous data. Frequency and percent will be presented for categorical data. In summary tables for categorical data for which categories are defined on the CRF, all categories will be presented as specified, even if the subject count within that category is zero. For other categorical data (eg, AEs and medications/vaccinations), only categories with at least one subject will be presented.

Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Means, geometric means, and medians will be presented to 1 more decimal place than the recorded data. SD and geometric SD will be presented to 2 more decimal places than the recorded data, with possible exceptions made for derived data. The CI about a parameter estimate will be presented using the same number of decimal places as the parameter estimate (ie, 1 more decimal place than the recorded data). Percentages will be presented to 1 decimal place (eg, 80.3%).

All data collected will be presented in listings, sorted by trial group, site number, subject number, and date/time of the finding, if applicable. If not stated otherwise, screen failure subjects will be grouped and listed at the end.

7.1.2 Study Day, Baseline and Analysis Window Definitions

Study Day 1 is defined as the date of the first vaccination, as recorded in the CRF vaccination page. Other study days are defined relative to Study Day 1, with Day -1 being the day prior to Day 1.

Baseline is defined as the last non-missing measurement taken before the first trial vaccination. Where time is available, the time of the measurement must be prior to the trial vaccination time. Day 1 observations taken after the vaccination are considered 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), analysis windows for each visit will be calculated relative to the day on which each trial dose was administered (Day 1 [M0], Day 90 [M3], and Day 180 [M6]).

The analysis visit windows for each trial visit are displayed in Table 7.a.

Table 7.a Analysis Visit Windows

Visit	Scheduled Visit Day (Month)	Scheduled Vaccination	Analysis Visit Window		
			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 [b] days after Dose 1	2 – 60 [b] days after Dose 1	29 – 37 [b] days after Dose 1
V3	Day 90 (M3)	Dose 2	61 – 115 [b] days after Dose 1; and Prior [≤ 1 day] [a] to Dose 2	61 – 115 [b] days after Dose 1; and Prior [≤ 1 day] [a] to Dose 2	75 – 115 [b] after Dose 1; and Prior [≤ 1 day] [a] to Dose 2
V4	Day 120 (M4)		2 – 60 [b] days after Dose 2; or 116 – 150 [b] days after Dose 1 [c]	2 – 60 [b] days after Dose 2; or 116 – 150 [b] days after Dose 1 [c]	29 – 37 [b] days after Dose 2
V5	Day 180 (M6)	Dose 3	61 – 115 [b] days after Dose 2; and Prior [≤ 1 day] [a] to Dose 3; or 151 – 195 [b] days after Dose 1 [c]	61 – 115 [b] days after Dose 2; and Prior [≤ 1 day] [a] to Dose 3; or 151 – 195 [b] days after Dose 1 [c]	75 – 115 [b] after Dose 2 and Prior [≤ 1 day] [a] to Dose 3
V6	Day 210 (M7)		2 – 105 [b] days after Dose 3; or 116 – 195 [b] days after Dose 2 [d]; or 196 – 285 [b] days after Dose 1 [c]	2 – 105 [b] days after Dose 3; or ≥116 [b] days after Dose 2 [d]; or ≥196 [b] days after Dose 1 [c]	29 – 37 [b] days after Dose 3
V7	Day 360 (M12)		≥106 [b] days after Dose 3; or ≥196 [b] days after Dose 2 [d]; or ≥286 [b] days after Dose 1 [c]	Not applicable (no blood sample is taken at V7)	Not applicable (no blood sample is taken at V7)

(a) Blood draw for immunogenicity assessments and assessments 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) observations taken after the first trial vaccination 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 Dose 2, or both Dose 2 and Dose 3.
(d) Applies to subjects who missed Dose 3.

If several measurements of a variable are obtained for a subject within the same visit window, the measurement with the date closest to the scheduled visit date will be used. In the event that 2 measurements within a given visit window are equidistant to the scheduled visit date, the later observation will be used. Both scheduled and unscheduled visits will be considered equally.

7.1.3 Handling of Missing Data

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

Immunogenicity data

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). If a reported value is between the LLOD and the lower limit of quantification (LLOQ, which differs among serotypes), this value 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.

YF antibody titers (PRNT) which are below the LLOQ (ie, <10) will be imputed with a value of 5 (half of the LLOQ).

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

Adverse event data

Missing information regarding 'relationship to investigational product (IP)' (related/not related) for solicited systemic and unsolicited AEs, and 'severity' (mild/moderate/severe) for unsolicited AEs, will be handled using the worst-case approach. Thus, unsolicited AEs with missing severity will be considered as 'severe' and solicited systemic and unsolicited AEs with missing relationship will be considered as 'related'.

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 allocated with (i.e. Vaccination 1, 2, or 3). An AE should be temporally allocated with the correct dose using the following rules:

- If the AE start and end dates are both completely missing, the AE will be allocated with the first trial vaccination;
- If at least month and/or year of 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 3 trial vaccinations, but an AE end date or 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 or 2 and ongoing on the day of

Vaccination 2 or 3 would be identified during the clinical assessments that are performed before administration of the second or third trial vaccination. If partial end date information indicates possible association with multiple vaccinations, the AE will be allocated with the earliest of these.

Prior/concomitant medication/vaccination data

Missing and partial medication/vaccination dates may be assessed only to distinguish between a prior or a concomitant medication/vaccine. A medication will be considered prior only if the partial end date indicates that it was stopped before 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 the medication or vaccine will be considered concomitant.

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 CRF 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 as defined in Table 7.b will be excluded from respective analyses, but presented as recorded in data listings including a flag that highlights implausible values.

Table 7.b Plausible Data Ranges

	Parameter	Plausible range
Demographic/ Physical examination	Height	110 – 210 cm
	Weight	20 – 200 kg
Solicited AEs	Erythema	≤ 500 mm
	Swelling	≤ 500 mm
	Body Temperature [(a)]	32 – 43ºC
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 signs.

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 was received.

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

Full Analysis Set (FAS): All randomized subjects who received at least 1 dose of IP and for whom a valid pre-dose (Baseline) and at least 1 post-dose measurement are available for immunogenicity assessments.

YF FAS: All randomized subjects who received at least 1 dose of IP and for whom a valid pre-dose (Baseline) and at least 1 post-dose measurement (Day 30) are available for YF immunogenicity assessments.

Per-Protocol Set (PPS): All subjects from the FAS who have no major protocol violations, excluding subjects who are seroprotected for YF virus and/or who are seropositive for any serotype of dengue virus at Baseline.

YF PPS: All subjects from the YF FAS who have no major protocol violations, excluding subjects who are seroprotected for YF virus and/or who are seropositive for any serotype of dengue virus at Baseline.

The criteria described in Table 7.c will be used to identify subjects who will be excluded from the PPS and YF PPS during the blinded data review prior to unblinding of the IP assignment. These criteria are considered to have a potentially significant impact on the immunogenicity results of the subject. Subjects excluded from PPS and YF PPS due to receiving incorrect IP will be identified after unblinding.

Other major protocol violations may be identified during the data review and deviation logs throughout the trial, subject to medical review. Any changes to these criteria after approval of the SAP will be documented and approved prior to database lock.

Analyses using the Randomized Set, FAS sets, and PPS sets will be based on randomized treatment.

Analyses using the Safety Set will be based on the actual treatment. For example, a subject randomized to Group 1 (YF+P/TDV/TDV) but vaccinated with the planned vaccinations of Group 2 (TDV + P/TDV/YF) will be analyzed in Group 2 (TDV + P/TDV/YF). Subjects who received vaccination (or combination of vaccinations) that is not planned for any trial group will be considered together in a separate group. Data for this group will be displayed in selected summaries and all listings generated for the Safety Set.

Analyses based on the Safety Set (except AEs), FAS and PPS sets will only include measurements obtained following the analysis visit windows defined in Table 7.a.

Table 7.c Criteria for Exclusion from the PPS

Criteria for Exclusion	Probable Method of Identification	YF PPS	PPS
Not receiving at least one dose of the IP [(a)]	Identified programmatically using dosing data	X	X
Not having a valid pre-dose (Baseline) and at least 1 valid post-dose measurement for YF immunogenicity assessments at Day 30 [(b)]	Identified programmatically using immunogenicity data	X	NA
Not having a valid pre-dose (Baseline) and at least 1 valid post-dose measurement for immunogenicity assessments [(b)]	Identified programmatically using immunogenicity data	NA	X
Subjects seroprotected for YF virus and/or seropositive to any serotype of dengue neutralizing antibody titers at Baseline (Day 1 [M0])	Identified programmatically using immunogenicity data	X	X
Not receiving all three doses of the IP	Identified programmatically using dosing data	NA	X
Receiving the second trial and/or third vaccination inadmissibly outside of the scheduled visit window (ie, outside Day 90 [-15/+25 days])	Identified programmatically using dosing data	NA	X
Receiving incorrect IP(s) for Vaccination 1, Vaccination 2, and/or Vaccination 3	Identified after unblinding (eg, a subject who was randomized to TDV but received YF or a subject who was randomized to Placebo but received TDV)	X [(c)]	X
Receiving IP using incorrect route of administration	Identified through protocol deviation log	X [(c)]	X
Product preparation error	Identified through protocol deviation log	X	X
Subject meets any of the following exclusion criteria: 5-8, 19-23	Identified programmatically using CRF-recorded data; Identified through protocol deviation review/medical review	X	X
Use of prohibited medications/vaccines	Identified through medical review based on CRF-recorded data	X [(c)]	X

(a) Subjects with this protocol violation will be excluded from the Safety Set, and thus also from the FAS sets and the PPS sets.
(b) Subjects with this protocol violation will be excluded from the YF FAS/FAS, and thus also from the PPS sets.
(c) Applies to Vaccination 1 only.

7.3 Disposition of Subjects

Trial information will be presented for all screened subjects, including date first subject signed the informed consent form, 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, the date of first subject's third vaccination, the date of last subject's third vaccination, the date of the first subject's first visit, the date of the last subject's last visit, the Medical Dictionary for Regulatory Activities (MedDRA) version, the World Health Organization Drug Dictionary (WHO-Drug) version, and the SAS version used for analysis.

Disposition of all screened subjects will be summarized descriptively, including a summary of the number of screened subjects, the number of randomized subjects and the primary reason for not being eligible for randomization. The number of screen failures and their characteristics will also be summarized.

Disposition for all randomized subjects will be summarized by trial group. Disposition categories include:

- Number of subjects randomized by trial site.
- Number of subjects randomized, but not vaccinated (including primary reason for being randomized, but not vaccinated).
- Number of subjects who completed the vaccine regimen/trial visits.
- Number of subjects who prematurely discontinued the vaccine regimen/trial visits.
- Primary reason for premature discontinuation of the vaccine regimen/trial visits.

Number of subjects in the analysis sets will be summarized by trial group. Reasons for exclusion of subjects from the analysis sets will be summarized by trial group based on all randomized subjects. In addition, significant protocol deviations will be summarized by trial group for the Randomized Set.

7.4 Demographic and Other Baseline Characteristics

Age, gender, race, and other Baseline characteristics will be summarized descriptively based on the Safety Set, YF FAS, FAS, YF PPS, and PPS. Baseline characteristics for the FAS sets will also include baseline seropositivity status for dengue (seropositive for at least 1 dengue serotype /seronegative for all dengue serotypes), baseline seropositivity status for each and multiple dengue serotype, and baseline seroprotection status against YF (yes/no).

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded according to the MedDRA coding system.

A medical history is defined as any significant condition/disease that stopped at or prior to 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.

Summary tables will be provided by SOC and PT based on the Safety Set.

7.6 Medication History and Concomitant Medications

Medication history, vaccination history, concomitant medications, and concomitant vaccinations will be coded according to WHO Drug.

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

Summary tables for medication history and concomitant medications will be provided by Anatomical Therapeutic Chemical class level 2 and preferred medication name. Vaccination history and concomitant vaccination will be summarized by vaccination type and name as recorded in the CRF. Summaries and listings will be provided based on the Safety Set.

7.7 Investigational Product Exposure and Compliance

The Investigator records all injections of the IP given to the subject on the CRF.

Investigational product compliance will be summarized for the Safety Set presenting the number and percentage of subjects receiving:

1) First vaccination only;
2) First and second vaccinations only;
3) All three vaccinations.

This summary will be prepared by trial group, including a separate group of subjects who received different IPs (or combination of different IPs) that is not planned for any trial group (if any).

The duration of follow-up [days] after each dose will be summarized for the Safety Set as a continuous variable (number of subjects [n], mean, SD, median, minimum, and maximum), and as categorical variable (frequency and percentage of subjects) for the following categories:

After first vaccination:

- 1 – 30 days,
- 31 – 90 days,
- 91 – 120 days,
- 121 – 180 days,
- 181 – 360 days,
- ≥ 361 days.

After second vaccination:

- 1 – 30 days,
- 31 – 90 days,
- 91 – 120 days,
- 121 – 180 days,
- 181 – 270 days,
- ≥ 271 days.

After third vaccination:

- 1 – 30 days,
- 31 – 90 days,
- 91 – 120 days,
- 121 – 180 days,
- ≥ 181 days.

The duration of follow-up will be calculated as end of trial date – vaccination date (first, second or third, respectively) + 1 day.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

The primary and secondary immunogenicity endpoints are listed in Table 7.d, together with the analyses (descriptive summaries, graphical presentations, or pairwise comparisons) planned for each endpoint/population. The primary population for all immunogenicity summaries and analyses will be the YF-PPS/PPS. Supportive immunogenicity summaries will be provided based on the YF-FAS/FAS.

Descriptive Summaries

Descriptive statistics for the primary and secondary immunogenicity endpoints will be provided by trial group and for each vaccine/serotype, and will include the following:

- Seroprotection/Seropositivity Rate: number and percentage of subjects with seroprotection / seropositivity and corresponding 95% CIs calculated with the exact (Clopper-Pearson) method [5].
- GMT: geometric mean, GSD, median, 95% CIs, minimum, and maximum. The geometric mean, GSD, and the 95% CIs of the geometric mean will be calculated as the anti-logarithm transformation of the mean, standard deviation, and 95% CIs of the log-transformed titers.

Graphical Presentations

Graphical presentations for selected immunogenicity endpoints will be provided by trial group and for each vaccine/serotype, and will include the following:

- Bar graphs presenting the percentage of subjects with seroprotected (YF)/seropositive (for each of the 4 dengue serotypes and for multiple serotypes [at least trivalent and tetravalent only], including error bars for the 95% CIs, for all visits (except baseline).
- Line plots of GMTs, including error bars for the 95% CIs, plotted over time.
- Reverse cumulative distribution curves of antibody titers
    - For YF at Day 30 (Group 1 and Group 3) and Day 210 (Group 2);
    - For Dengue at Day 120 (Group 2 and Group 3) and Day 210 (Group 1).

Table 7.d Planned Analyses and Populations for Immunogenicity Endpoints

	Endpoint			Planned Analyses and Populations		
Vaccine	**Variable**	**Time Point**	**Endpoint Type**	**Descriptive Summaries**	**Graphical Presentations**	**Pairwise Comparisons[a]**
YF	Seroprotection Rate	Day 30	Primary	YF PPS, YF FAS	YF PPS	YF PPS, YF FAS
		Day 180	Secondary	PPS, FAS	PPS	
		Day 210				
	GMT	Day 30	Secondary	YF PPS, YF FAS	YF PPS	YF PPS, YF FAS
		Day 180	Secondary	PPS, FAS	PPS	
		Day 210				
Dengue	Seropositivity Rate (Each serotype[a])	Day 30	Secondary	PPS, FAS	PPS	
		Day 90				
		Day 120				
		Day 180				
		Day 210				
	GMT (Each serotype[b])	Day 30	Secondary	PPS, FAS	PPS	PPS, FAS (Day 120)
		Day 90				
		Day 120				
		Day 180				
		Day 210				
	Seropositivity Rate (Multiple serotypes[c])	Day 30	Secondary	PPS, FAS	PPS	
		Day 90				
		Day 120				
		Day 180				
		Day 210				

(a) Pre-specified comparisons of interest are defined in the following text.
(b) Immunogenicity for each dengue serotype will be summarized /analyzed for: DENV-1, DENV-2, DENV-3, and DENV-4.
(c) Immunogenicity for multiple dengue serotypes will be summarized in the following categories: Monovalent, Bivalent, Trivalent, Tetravalent, at least Bivalent, and at least Trivalent.

Pairwise Comparisons

Pairwise comparison will be performed for the primary endpoint and key secondary endpoints (with the later group as the reference group):

- YF Seroprotection Rate: Group 1 vs Group 3 at Day 30.
- YF GMT: Group 1 vs Group 3 at Day 30.
- TDV GMT: Group 2 vs Group 3 at Day 120.

The following statistics will be provided for the comparison:

- Seroprotection Rate: rate difference and corresponding 95% CIs based on the Newcombe score method [6]; risk ratio and corresponding 95% CIs based on Fisher's exact test.
- GMT: geometric mean ratio and 95% CIs based on an analysis of variance (ANOVA) model, which includes the log-transformed value of titer as the dependent variable, and the trial group as a factor. The geometric mean, geometric mean ratio and 95% CIs are presented in anti-log values of least squares means (LS means) estimated from the ANOVA model.

7.10.1 Primary Immunogenicity Endpoint

The primary endpoint of this trial is the proportion of subjects (YF and DENV-naive at Baseline) who are seroprotected against YF on Day 30 (M1) as measured by PRNT (YF seroprotection rate). YF seroprotection is defined as reciprocal anti-YF neutralizing antibody titer ≥10. Immunological naivety to YF and DENV is defined as Baseline reciprocal neutralizing antibody titers <10 for YF and for the 4 dengue serotypes.

Descriptive summary and graphical presentation will be provided for the primary immunogenicity endpoint based on the YF PPS. Sensitivity analyses will be provided based on the YF FAS. The primary pairwise comparison, i.e. Group 1 vs Group 3 in terms of YF seroprotection rates on Day 30, will be carried out based on the YF PPS, with a sensitivity analysis performed based on the YF FAS.

The NI of the immune response to YF-17D vaccine when concomitantly administered with TDV (Group 3) compared to concomitant administration of YF-17D vaccine with placebo (Group 1) will be assessed in terms of seroprotection rates on Day 30 (M1) based on the YF PPS. NI will be concluded if the upper bound of the 95% CI for the seroprotection rate difference (Group 1 minus Group 3) is less than the NI margin of 5%.

Sensitivity analyses for the primary endpoint based on the YF FAS will include all subjects regardless of their DENV/YF protection status at Baseline.

7.10.2 Secondary Immunogenicity Endpoints

The secondary immunogenicity endpoints of this trial are:

- GMT of neutralizing antibodies (as measured by MNT_{50}) for each of the 4 dengue serotypes at pre-second and -third vaccinations (Day 90 [Month 3; M3] and Day 180 [Month 6; M6], respectively); and 1 month post first, second, and third vaccinations (Day 30 [M1], Day 120 [Month 4; M4], and Day 210 [Month 7; M7], respectively) in subjects YF and DENV-naive at Baseline.
- GMTs of anti-YF neutralizing antibodies at 1-month post first and third vaccinations (Day 30 [M1] and Day 210 [M7], respectively) in subjects YF and DENV-naive at Baseline.
- Seropositivity rates (% of subjects seropositive) for each of the 4 dengue serotypes at pre-second and -third vaccinations (Day 90 [M3] and Day 180 [M6], respectively); and 1 month post first, second, and third vaccinations (Day 30 [M1], Day 120 [M4], and Day 210 [M7],

respectively) in subjects YF and DENV-naive at Baseline, where seropositivity is defined as a reciprocal neutralizing antibody titer ≥10.

- Seropositivity rates (% of subjects seropositive) for multiple (2, 3 or 4) dengue serotypes at pre-second and -third vaccinations (Day 90 [M3] and Day 180 [M6], respectively); and 1 month post first, second, and third vaccinations (Day 30 [M1], Day 120 [M4], and Day 210 [M7], respectively) in subjects YF and DENV-naive at Baseline, where seropositivity is defined as a reciprocal neutralizing antibody titer ≥10.
- Proportion of subjects YF and DENV-naive at Baseline who are seroprotected against YF at 1-month post third vaccination (Day 210 [M7]) as measured by PRNT.

As specified in Table 7.d, descriptive summaries, graphical presentations, and pairwise comparisons will be based on the YF PPS and PPS. Sensitivity analyses will be based on the YF FAS and FAS, respectively.

The NI of the immune response to TDV when concomitantly administered with YF-17D vaccine (Group 3) compared to concomitant administration of TDV with placebo (Group 2) will be assessed in terms of the GMTs of neutralizing antibodies for all 4 dengue serotypes on Day 120 (M4). NI will be concluded if the upper bound of the 95% CI for the GMT ratio (Group 2/Group 3) is less than the NI margin of 2.0. An ANOVA model will be used for this assessment.

The NI of the immune response to YF-17D vaccine when concomitantly administered with TDV (Group 3) compared to concomitant administration of YF-17D with placebo (Group 1) will be assessed in terms of the GMTs of anti-YF neutralizing antibodies on Day 30 (M1). NI will be concluded if the upper bound of the 95% CI for the GMT ratio (Group 1/Group 3) is less than the NI margin of 2.0. An ANOVA model will be used for this assessment.

Sensitivity analyses for secondary endpoints based on the YF FAS or FAS will include all subjects regardless of their DENV/YF protection status at Baseline.

7.11 Safety Analysis

All summaries and analyses of safety data will be based on subjects in the Safety Set.

7.11.1 Adverse Events

Unless otherwise specified, AEs will be summarized by trial group after first trial vaccination, second trial vaccination, third trial vaccination, and any trial vaccination.

Reactogenicity (Solicited AEs)

Solicited AEs are collected for at least 30 min after each vaccination at the site (in-clinic assessment). In addition, subjects are provided with a diary card for the recording of solicited local (injection site) AEs, including injection site pain, injection site erythema, and injection site swelling, for 7 days following vaccination (day of vaccination + 6 days). Subjects are also provided with a diary card for the recording of solicited systemic AEs (fever, headache, asthenia, malaise, and myalgia) for 14 days following vaccination (day of vaccination + 13 days). For the local (injection site) AEs erythema and swelling, the subject/the subject's representative will

record the length of the longest diameter in mm. However, for the analysis these data will be displayed in cm. For the systemic AE fever, the subject/the subject's representative will record the body temperature in either °F or °C. For the analysis, all data will be displayed in °C. Severity grades for erythema and swelling will be derived from the recorded diameters, and fever will be presented using the proposed temperature increments published by the Brighton Collaboration Fever Working Group [7]. Details of solicited local (injection site) and systemic AEs, and severity of solicited safety parameters are given in Appendix B.

Missing data for solicited AEs will not be imputed unless otherwise specified in Section 7.1.3. For each trial group and solicited AE, the denominator for the percentage will exclude subjects with completely missing data (i.e. subject does not have at least 1 recorded results [ie, none, mild, moderate, or severe]) for the solicited AE in the period being summarized.

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

- 30 minutes (in-clinic assessment of solicited local [injection site] and systemic AEs – analyzed separately from diary-recorded solicited AEs);
- Within 7 days (solicited local [injection site] AEs);
- Within 14 days (solicited systemic AEs);
- Days 1 – 7 (daily, solicited local [injection site] AEs);
- Days 1 – 14 (daily, solicited systemic AEs);
- Days 1 – 3 and Days 4 – 7 (solicited local [injection site] AEs);
- Days 1 – 7 and Days 8 – 14 (solicited systemic AEs).

For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Concomitantly administered vaccines (e.g., YF + Placebo) will be injected into opposite arms at Vaccination 1. Solicited local events following Vaccination 1 will be summarized for the two arms respectively, and presented as YF Arm, TDV Arm, or Placebo Arm, by linking left/right arm with kit numbers received after unblinding. Summaries of these solicited local events will be tabulated by each arm and for any arm as describe in Table 7.e.

Table 7.e Summaries of Solicited Local AEs following Vaccination 1

	Vaccination 1	Summary #1 Arm (1)	Summary #2 Arm (2)	Summary #3 Any Arm
Group 1	YF + Placebo	YF arm	Placebo arm	Any
Group 2	TDV + Placebo	Placebo arm	TDV arm	Any
Group 3	TDV + YF	YF arm	TDV arm	Any

For solicited systemic AEs, the number and percentage of subjects will also be summarized by relationship to IP (assessed by the Investigator) for the following intervals post-vaccination:

- 30 minutes;
- Within 14 days.

Subjects will only be counted once if the subject has more than 1 episode of the same event. In the case where the subject has both related and unrelated solicited systemic AEs, the subject will be counted under the related category. All solicited local (injection site) AEs are considered as related to IP.

A summary of the day of first onset of each event and the number of days subjects reported each event will be presented post-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.

Prolonged solicited AEs that continued beyond Day 7 (for local [injection site] AEs) or Day 14 (for systemic AEs) will be captured in the AE CRF page, indicated by the checkbox "Is this event a continuation of a solicited event". These prolonged solicited AEs will be presented in a separate listing and will not be included in any unsolicited AE summary or listing.

An overview table for solicited AEs post-vaccination will be provided including:

- 30 minutes in-clinic assessment (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).

Unsolicited AEs

Unsolicited AEs will be assessed for 28 days following administration of each trial dose (day of vaccination + 27 days). MAAEs, SAEs and AEs leading to IP withdrawal and/or trial discontinuation will be collected from first trial dose until the end of the trial. Unsolicited AEs, MAAEs, SAEs, and AEs leading to IP withdrawal and/or trial discontinuation will be coded according to the current version of MedDRA.

In general, the number of events, number of subjects, and the percentage of subjects will be tabulated by trial group at each of the following levels: overall (any AEs/subjects with any AEs) and by SOC and PT. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once in number/percentage of subjects. Percentages will be based on the number of subjects in the Safety Set who received the respective trial dose. When

relationship or severity is concerned, the AE with the most closely related occurrence or the highest known severity will be counted.

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

- By SOC and PT. This summary will also include a separate group of subjects who received different IPs (or combination of different IPs) that is not planned for any trial group (if any);
- By SOC and PT including events with frequency greater than 2% in any trial group;
- By SOC and PT for IP related events;
- By SOC and PT for IP related events with frequency greater than 2% in any trial group;
- By SOC, PT, and severity (mild, moderate, severe).

MAAEs post-vaccination throughout the trial duration will be summarized as follows:

- By SOC and PT;
- By SOC and PT for IP related events;
- By SOC, PT, and severity (mild, moderate, severe).

SAEs post-vaccination throughout the trial duration will be summarized as follows:

- By SOC and PT. This summary will also include a separate group of subjects who received different IPs (or combination of different IPs) that is not planned for any trial group (if any).
- By SOC and PT for IP related events.

AEs leading to IP withdrawal and/or trial discontinuation post-vaccination throughout the trial duration will be summarized as follows:

- By SOC and PT. This summary will also include a separate group of subjects who received different IPs (or combination of different IPs) that is not planned for any trial group (if any).
- By SOC and PT for IP related events.

Subject mappings (ie, list of subject 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 and/or trial discontinuation.

Based on clinicaltrials.gov results posting requirements another summary table by SOC and PT for AEs after any vaccination is needed including all non-serious events (ie, all non-serious AEs up to 28 days post-vaccination, all MAAEs post-vaccination throughout the trial duration, and all non-serious AEs leading to IP withdrawal and/or trial discontinuation post-vaccination throughout the trial duration) with frequency greater than 2% in any trial group.

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

Table 7.f Overview of Unsolicited Adverse Events

	All AEs (28 days post-vaccination)	SAEs	MAAEs	AEs leading to IP withdrawal and/or trial discontinuation
Relationship to IP	✓	✓	✓	✓
Relationship to 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	✓	✓		✓

7.11.2 Clinical Laboratory Evaluations

Not applicable.

7.11.3 Vital Signs

Vital sign will be summarized descriptively (number of subjects [n], mean, SD, median, minimum, and maximum) at each scheduled visit. The change from Baseline to each scheduled post-Baseline visit will be presented as applicable.

7.11.4 12-Lead ECGs

Not applicable.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Changes in the Statistical Analysis Plan

A separate set of FAS and PPS was defined for the endpoints related to YF at Day 30.

8.0 REFERENCES

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Appendix A Schedule of Trial Procedures

Table 8.a Schedule of Trial Procedures

Visit number		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**
		Day 1	**Day 30**	**Day 90**	**Day 120 (V3+30 days)**	**Day 180 (V3+90 days)**	**Day 210 (V5+30 days)**	**Day 360 (V5+180 days)**
Day/Month		**M0**	**M1**	**M3**	**M4**	**M6**	**M7**	**M12 (ET) [a]**
Visit window (days)		**±0**	**-1/+7**	**-4/+7**	**-1/+7**	**-4/+7**	**-1/+7**	**-7/+14**
Signed informed consent [b]		X						
Assessment of eligibility criteria [c]		X						
Demographics [b]		X						
Medical history [b]		X						
Concomitant medications/ vaccinations [d]		X	X	X	X	X	X	X
Check contraindications to vaccination				X		X		
Check criteria for delay of vaccination				X		X		
Complete physical examination [e]		X		X		X		
Targeted physical examination [f]			X		X		X	X
Vital signs [g]		X	X	X	X	X	X	X
Pregnancy test [h]		X		X		X		
Pregnancy avoidance guidance [i]		X	X	X	X	X	X	
Randomization		X						
Blood Collection	YF neutralizing antibodies (10 mL) [j]	X	X			X	X	
	Dengue neutralizing antibodies (5 mL) [j]	X	X	X	X	X	X	
Vaccine administration		X		X		X		
30 min post-vaccination in-clinic observation		X		X		X		

Visit number		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**
Day/Month		**Day 1 M0**	**Day 30 M1**	**Day 90 M3**	**Day 120 (V3+30 days) M4**	**Day 180 (V3+90 days) M6**	**Day 210 (V5+30 days) M7**	**Day 360 (V5+180 days) M12 (ET) [a]**
Visit window (days)		**±0**	**-1/+7**	**-4/+7**	**-1/+7**	**-4/+7**	**-1/+7**	**-7/+14**
Including injection site evaluation and body temperature measurement [k]								
Diary Card [l]	Distribution	X		X		X		
	Review/collection		X		X		X	
Unsolicited AEs [m]		X	X	X	X	X	X	
SAEs [n]		X	X	X	X	X	X	X
MAAEs [n]		X	X	X	X	X	X	X
AEs leading to discontinuation or withdrawal [n]		X	X	X	X	X	X	X

Note: AE=adverse event, ET=early termination, M=Month, MAAE=medically attended adverse event, SAE=serious adverse event, V=visit, YF=yellow fever
Footnotes:

(a) If the subject terminates early, Day 360 (M12) procedures should be performed.
(b) Prior to the subject entering into the trial, and before any protocol-directed procedures are performed.
(c) Review of inclusion/exclusion criteria will be performed prior to the first trial vaccination at Day 1 (M0). After written informed consent has been obtained and eligibility is assessed, subjects will be randomized to one of the 3 trial groups.
(d) Any other vaccination against any flavivirus (licensed or investigational, including any other dengue vaccine) during the entire trial period, all concomitant medications and vaccine history from 1 month (minimum 28 days) prior to administration of each dose of trial vaccine(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 at Day 1 (M0) including measurement of weight and height; BMI will be calculated automatically. Measurement of height is only required at Day 1 (M0).
(f) 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 electronic Case Report Form (CRF).
(g) Vital signs including (but not limited to) the measurement of systolic blood pressure/diastolic blood pressure, heart rate, and body temperature.
(h) Pregnancy testing (serum or urine) for females of childbearing potential. Results must be confirmed and documented as negative prior to each vaccination. Additional pregnancy tests may be performed during the trial if deemed necessary by the Investigator.
(i) Females of childbearing potential who are sexually active will be provided with information on acceptable methods of contraception and will be asked prior to vaccination on Day 1 (M0) to sign the informed consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova. Subjects will be reminded during trial visits to adhere to acceptable contraceptive methods and not donate ova up to 6 weeks post last trial vaccination at Day 180 (M6).

(j) The blood sample on Day 1 (M0), Day 90 (M3) and Day 180 (M6) should be taken prior to trial vaccination. The blood sample on Day 120 (M4) and Day 210 (M7) should be taken at least 29 days after the vaccination on Day 90 (M3) and Day 180 (M6), respectively.

(k) After each trial vaccination, the subject will be observed for at least 30 minutes including observation for solicited local (injection site) and systemic AEs, unsolicited AEs (non-serious and serious), and body temperature measurement.

(l) Diary (paper or electronic) cards will be used for the collection of:
1) Solicited local (injection site) AEs for 7 days after each vaccination (including the day of vaccination). If solicited local AEs continue on Day 8 following each trial vaccination, record the extended information on the Adverse Event CRF.
2) Solicited systemic AEs for 14 days after each vaccination (including the day of vaccination). If solicited systemic AEs continue on Day 15 following each trial vaccination, record the extended information on the Adverse Event CRF.
The Investigator will categorize events by severity (mild, moderate or severe) and will assess causality to vaccine administration for solicited systemic events (related or not related).

(m) Unsolicited AEs for 28 days (including the day of vaccination) after each vaccination will be collected by interview and recorded for all subjects at Day 30 (M1), Day 120 (M4) and Day 210 (M7). The Investigator will categorize events by severity (mild, moderate or severe) and will assess causality to vaccine administration (related or not related).

(n) AEs leading to discontinuation or withdrawal, MAAEs and SAEs will be collected for the trial duration. The Investigator will categorize events by severity (mild, moderate or severe) and will assess causality to vaccine administration (related or not related).

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 [7].

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

NA = not applicable
(a) Subjects are to record greatest surface diameter in mm on the diary card.
(b) Fever is defined as a body temperature ≥38°C (100.4°F) regardless of the method used [7].

Signature Page for DEN-305 Statistical Analysis Plan, Version 1.0, 21 October 20
Title:

Approval	PPD	
Approval	PPD	

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