Title: A Phase II, double-blind, controlled trial to assess the Safety and Immunogenicity of different schedules of Takeda's Tetravalent Dengue Vaccine Candidate (TDV) in healthy subjects aged between 2 and <18 years and living in dengue endemic countries in Asia and Latin America

NCT Number: NCT02302066

SAP Approve Date: 31 May 2016

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

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

TAKEDA VACCINES, INC.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: DEN-204

A PHASE II, DOUBLE-BLIND, CONTROLLED TRIAL TO ASSESS THE SAFETY AND IMMUNOGENICITY OF DIFFERENT SCHEDULES OF TAKEDA'S TETRAVALENT DENGUE VACCINE CANDIDATE (TDV) IN HEALTHY SUBJECTS AGED BETWEEN 2 AND <18 YEARS AND LIVING IN DENGUE ENDEMIC COUNTRIES IN ASIA AND LATIN AMERICA

Safety and Immunogenicity of different schedules of TDV in healthy subjects

PHASE II

Version**:** Final, Version 2.0

Date**:** 31 May 2016

Prepared by: PPD

PPD

1.1 Approval Signatures

Study Title: A Phase II, double-blind, controlled trial to assess the Safety and Immunogenicity of different schedules of Takeda's Tetravalent Dengue Vaccine Candidate (TDV) in healthy subjects aged between 2 and <18 years and living in dengue endemic countries in Asia and Latin America

Safety and Immunogenicity of different schedules of TDV in healthy subjects

Approvals:

PPD

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
CCI	[redacted]
CI	Confidence Interval
DENV	Dengue Virus
eCRF	electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	Full Analysis Set
GMT	Geometric Mean Titer
GSD	Geometric Standard Deviation
HCT	Hematocrit
IA	Interim Analysis
LS	Least Squares
MAV	Markedly Abnormal Value
MedDRA	Medical Dictionary for Regulatory Activities
MNT_{50}	Microneutralization Test 50%
PBS	Phosphate Buffered Saline
PCC	Platelet Cell Count
PCR	Polymerase Chain Reaction
PFU	Plaque Forming Units
PPS	Per-Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SS	Safety Set
SOC	System Organ Class
TDV	Takeda's Tetravalent Dengue Vaccine Candidate
WCC	White Cell Count
WHO Drug	World Health Organization Drug

4.0 OBJECTIVES

4.1 Primary Objectives

To assess the humoral immune responses to subcutaneously administered Takeda's Tetravalent Dengue Vaccine Candidate (TDV) in a subset of healthy subjects aged between 2 and <18 years and living in dengue endemic countries.

4.2 Secondary Objectives

4.2.1 Immunogenicity

To assess seropositivity rates following subcutaneously administered TDV in a subset of healthy subjects aged 2≥ to <18 years and living in dengue endemic countries.

4.2.2 Safety

To evaluate the safety of subcutaneously administered TDV in healthy subjects aged 2≥ to <18 years and living in dengue endemic countries.

4.3 Exploratory Objectives

CCI [redacted]

4.4 Trial Design

This is a Phase II, double-blind, controlled, randomized trial that will enroll 1,800 healthy children aged 2 ≥ to <18 years old into 1 of the following 4 groups:

- **Group 1 (TDV 2-dose)**: receiving a two-dose primary vaccination at Day 1 (M0:Month 0) and Day 91 (M3:Month 3) with the trial vaccine. These subjects will also receive a placebo injection at Day 365 (M12:Month 12).
- **Group 2 (TDV 1-dose)**: receiving a one-dose primary vaccination at Day 1 (M0) with the trial vaccine. These subjects will also receive a placebo injection at Day 91 (M3) and Day 365 (M12).
- **Group 3 (TDV 1-dose with booster)**: receiving a one-dose primary vaccination at Day 1 (M0) and booster vaccination at Day 365 (M12) with the trial vaccine. These subjects will also receive a placebo injection at Day 91 (M3).
- **Group 4 (Placebo Control)**: receiving injections of placebo at Day 1 (M0), Day 91 (M3), and at Day 365 (M12).

Subjects will be randomized to these 4 groups in a 1:2:5:1 ratio as shown in Table 4.a.

Table 4.a Number of Subjects per Group

Group	No. of Subjects	No. of Subjects in the Immunogenicity Subset
Group 1	200	100
Group 2	400	200
Group 3	1,000	200
Group 4	200	100
Total	1,800	600

Randomization will be stratified by age group based on the age at the time of informed consent:

1. 2 to 5 years of age, inclusive,
2. 6 to 11 years of age, inclusive, and
3. 12 ≥ to <18 years of age

CCI [redacted]

Safety evaluation will include documentation of Serious Adverse Events (SAEs) and identification of febrile episodes of potential dengue etiology in all subjects for the trial duration. In addition, all subjects in the immunogenicity subset will be provided with a diary card and will be instructed to record:

- Solicited local adverse events (AEs) for 7 days following vaccination (day of vaccination + 6 days). These will include:
  - infant/toddler/child < 6 years: injection site pain, injection site erythema and injection site swelling.
  - adult and child (≥ 6 years): injection site pain, injection site erythema and injection site swelling.
- Solicited systemic AEs for 14 days following vaccination (day of vaccination + 13 days). These will include:
  - infant/toddler/child < 6 years: fever, irritability/fussiness, drowsiness and loss of appetite.
  - adult and child (≥ 6 years): asthenia, fever, headache, malaise, myalgia.
- Unsolicited AEs for 28 days following vaccination (day of vaccination + 27 days).

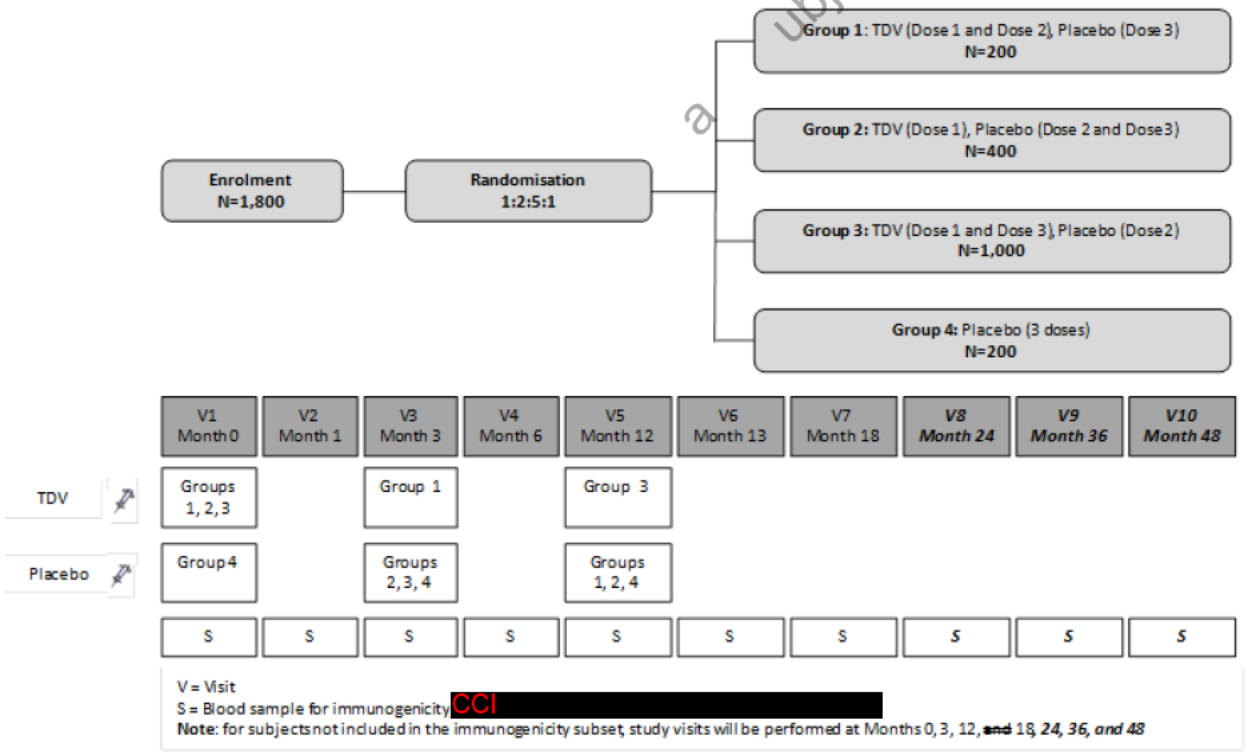
Any subject with febrile illness (defined as temperature ≥ 38°C on 2 consecutive days) will be asked to return to the site for dengue fever evaluation. A dengue infection will be considered virologically confirmed by either positive polymerase chain reaction (PCR) or NS1 enzyme-linked immunosorbent assay (ELISA). A blood sample will be collected within ≤ 5 days after the

onset of fever to perform virological confirmation of dengue and for hematology and for biochemistry to assess the severity of infection.

Blood samples for the measurement of neutralizing antibodies (immunogenicity) will be collected from a randomly selected subset of 600 subjects (100 subjects in group 1 and group 4 and 200 subjects in group 2 and group 3). CCI [redacted]. Samples for immunogenicity will be taken prior to vaccination and at intervals of 1, 3, 6, 12, 13, 18, 24, 36, and 48 months following the first vaccination. CCI [redacted]

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

Figure 4.a Schematic of Trial DEN-204



Investigational Vaccine(s):

The Investigational Product is TDV, a tetravalent dengue vaccine comprised of four recombinant, live attenuated dengue virus strains:

CCI [redacted]

Control Vaccine:

The placebo vaccine is Phosphate Buffered Saline (PBS).

Takeda's TDV and placebo vaccines will be administered by subcutaneous injection.

Visit Schedule:

Clinical trial visits will be performed on Day 1 (Month 0), Day 28 (Month 1), Day 91 (Month 3), Day 180 (Month 6), Day 365 (Month 12), Day 393 (Month 13), Day 540 (Month 18), Day 730 (Month 24), Day 1095 (Month 36), and Day 1460 (Month 48).

A schedule of procedures is listed in Appendix A.

Duration of Trial:

For each subject, the duration of the trial will be 48 months and will include a total of 10 protocol-scheduled visits for subjects included in the immunogenicity subset and a total of 7 protocol-scheduled visits for subjects not included in the immunogenicity subset.

Interim analyses on cleaned safety and immunogenicity data CCI [redacted] are planned on data up to Month 6, and on data up to Month 18 (see Section 7.13).

5.0 ANALYSIS ENDPOINT

5.1 Primary Endpoint

Geometric Mean Titers (GMTs) of neutralizing antibodies (Microneutralization Test 50% [MNT_{50}]) for each of the four DENV serotypes at Months 1, 3, 6, 12, 13, 18, 24, 36, and 48.

5.2 Secondary Endpoint

The secondary endpoints for this trial are as follows:

Immunogenicity Endpoints:

Seropositivity rates (%) for each of the four DENV serotypes where seropositivity is defined as a reciprocal neutralizing titer ≥ 10 at Months 1, 3, 6, 12, 13, 18, 24, 36, and 48.

Safety Endpoints:

Immunogenicity Subset:

- Frequency and severity of solicited local (injection site) and systemic AEs for 7 and 14 days after each vaccination, respectively.
- Percentage of subjects with any unsolicited AEs for 28 days after each vaccination.

All Subjects:

- Percentage of subjects with SAEs throughout the trial.
- Percentage of subjects with febrile episodes of virologically confirmed dengue throughout the trial.

5.3 Exploratory Endpoints

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

This trial is designed to be primarily descriptive and is not based on testing formal null hypotheses. Therefore the sample size was not determined based on formal statistical power calculations. The number of subjects will provide a reasonable sample size for the evaluation of the persistence of immune responses following administration of a single TDV dose, and of the effect of a TDV booster dose, and to provide an adequate safety database prior to initiating Phase III studies.

6.1 Immunogenicity

For illustrative purposes, Table 6.a provides approximate 95% confidence interval (CI) for various different seropositivity rate estimates, given the planned sample size per group in the immunogenicity subset.

Table 6.a Approximate 95% Confidence Interval in Seropositivity Rates ($MNT_{50} \geq 10$) for the Planned Sample Size in the Treatment Groups

	(95% CI) N=100		(95% CI) N=200	
Response Rate	**LL**	**UL**	**LL**	**UL**
50%	39.8%	60.1%	42.9%	57.1%
60%	49.7%	69.7%	52.9%	66.9%
85%	76.5%	91.4%	79.3%	89.6%

LL = Lower Limit, UL = Upper Limit

Table 6.b provides approximate 95% CI for various different GMT and Geometric Standard Deviation (GSD), given the planned sample size per group in the immunogenicity subset.

Table 6.b Approximate 95% Confidence Interval in GMT of Dengue Neutralizing Antibodies for the Planned Sample Size in the Treatment Group

	(95% CI) N=100		(95% CI) N=200	
GMT (GSD)	**LL**	**UL**	**LL**	**UL**
500 (6)	351.9	710.4	390.1	640.9
1500 (6)	1,055.8	2,131.1	1,170.2	1,922.8
200 (8)	133.1	300.6	149.9	266.8
50 (7)	34.1	73.2	38.2	65.5

LL = Lower Limit, UL = Upper Limit

6.2 Safety

Table 6.c illustrates the probability of observing 1 or more event, (e.g., any specific type of AE related to vaccine) for a range of assumed true but unknown event rates in the range of 0.33% to 4.0% (without considering the background incidence), for events that are assessed in all subjects.

Therefore, even with an event rate as low as 0.33%, there is a 99.5% chance that at least 1 such event will be observed in the trial. For AEs with event rate higher than 4.00%, there is a >99.9% chance to observe at least one such event.

Table 6.c Probability of Observing 1 or More Events for Assumed "True" Event Rate and Given Sample Size

	Sample Sizes		
"True" Unknown Event Rate	**N=1,600**	**N=1,000**	**N=200**
0.33%	99.5%	96.3%	48.4%
0.50%	>99.9%	99.3%	63.3%
1.00%	>99.9%	>99.9%	86.6%
2.00%	>99.9%	>99.9%	98.2%
3.00%	>99.9%	>99.9%	99.8%
4.00%	>99.9%	>99 9%	>99.9%

N=number of subjects

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

This Statistical Analysis Plan (SAP) was developed based on International Conference on Harmonization E3 and E9 Guidelines, and information provided in Protocol DEN-204, Version 3.0 dated 23JUL 2015 [1].

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

This document will provide the details regarding the definition of analysis variables and analysis methodology to address all trial objectives. No inferential analyses will be performed for this trial.

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

Immunogenicity and safety endpoints will be summarized descriptively (frequency and percent for categorical data; and number of subjects with non-missing observation, mean, standard deviation (SD), median, minimum and maximum for continuous data) by all relevant trial visits, if appropriate. In summary tables for categorical data for which categories are defined on the electronic Case Report File (eCRF), all categories will be presented as specified, even if the subject count within that category is zero. For other categorical data (e.g. adverse events and medications), only categories with at least one subject will be presented.

All data collected will be presented in the listings, sorted by trial group, site number, subject number, and date/time of the finding if applicable.

There will be no imputation for missing data with the exception of missing or partial dates (i.e. start and stop dates for AEs) and as specified in Section 7.12. Partial dates will be presented as they are in the listings. The partial dates of AEs will be imputed only to determine the relationship between the start date of those partial dates and the informed consent date, as well as the first dose date of the double-blind vaccination. The following methods will be used to impute missing or partial dates of the start date of AEs.

Month/year available and day missing:

If the month and year are the same as those in the first dose date, and the event is not indicated as a pre-treatment event, the first dose date is to be used to impute the AE start date.

If the month and year are the same as those in the first dose date, and the event is indicated as a pre-treatment event, the date prior to the first dose date is to be used to impute the AE start date.

If the month and year are different from those in the first dose date, then the first day of the month will be used for the start date.

Year available and month/day missing:

If the year is the same as the year of the first dose, and the event is not indicated as a pre-treatment event, the first dose date is to be used to impute the AE start date. If the year is the same as the year of the first dose date, and the event is indicated as a pre-treatment event, the date prior to the first dose date is to be used to impute the AE start date. If the year is the same as the year of the first dose date, then set the start date as January 1st.

The imputation of partial end dates for AEs will consider information such as the last dose date, and whether the AEs are ongoing by the end of trial.

Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Means, the least squares means (LS Means), and medians will be presented to 1 more decimal place than the recorded data. SD and SE will be presented to 2 more decimal places than the recorded 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 (e.g., 80.3%). All p-values will be rounded to 3 decimal places. If a p-value is less than 0.001, it will be reported as "<0.001"; if a p-value is greater than 0.999, it will be reported as ">0.999".

Definition of Baseline and Windowing of Post Baseline Data:

Baseline is defined as the last non-missing measurement taken before the first dose of vaccination. Trial Day 1 is defined to be the date of the first vaccination, as recorded on the CRF vaccination page. Other trial days are defined relative to the trial day 1, with Day -1 being the day prior to Day 1.

A windowing convention will be used to determine the analysis value for a given trial visit for observed data analyses and will be applied to immunogenicity data, vital signs, CCI [redacted]. The window definitions are defined below in Table 7.a by trial visit. The window conventions are consecutive and contiguous; that is, the lower or upper bound of the windows is the midpoint between 2 consecutive trial visits and all data are included.

If more than one result for a variable is obtained for a subject in a visit window, the result with the date closest to the scheduled/expected visit date will be used. In the event that two measurements within a given visit window are equidistant to the scheduled visit date, the later observation will be used.

Table 7.a Visit Windows for Immunogenicity and Safety Analyses by Visit

		Visit Window (Trial Day)		
Visit	**Scheduled Trial Day**	**Vital Signs[b]**	**Immunogenicity**	CCI
Baseline[a]	≤ 1	≤ 1	≤ 1	C
Day 28 (Month 1)	28	2-59	2-59	
Day 91 (Month 3)	91	60-135	60-135	CCI
Day 180 (Month 6)	180	136-272	136-272	CCI
Day 365 (Month 12)	365	273-379	273-379	CCI
Day 393 (Month 13)	393	380-466	380-466	
Day 540 (Month 18)	540	≥ 467	467-635	CCI
Day 730 (Month 24)	730		636-912	
Day 1095 (Month 36)	1095		913-1277	
Day 1460 (Month 48)	1460		≥ 1278	

(a) Where time is available, the time of the collection must be prior to the first vaccination of trial drug. Day 1 observations taken after the first vaccination are considered post-baseline values
(b) Vital signs include: systolic blood pressure, diastolic blood pressure, heart rate, body temperature, height and weight.

7.2 Analysis Sets

Randomized Set: The Randomized Set will consist of all randomized subjects, regardless of whether IP was received (any vaccine administered).

Safety Set (SS): The SS will consist of all randomized subjects who received at least one dose of the trial vaccine (including control vaccine). For analyses of solicited AEs and unsolicited non-serious AEs, only subjects in the immunogenicity subset will be included (600 subjects in total [groups 1 and 4: 100 subjects each; groups 2 and 3: 200 subjects each]). SAEs, virologically confirmed dengue and AEs leading to trial or vaccine withdrawal will be assessed for all subjects in the SS. Subjects will be summarized according to the vaccine received.

Full Analysis Set (FAS): The FAS will consist of all randomized subjects who received the trial vaccine (including control vaccine) and for whom valid pre-dosing and at least one valid post-dosing blood sample have been received. Subjects will be analyzed according to the group to which they were assigned.

Per-Protocol Set (PPS): The PPS will consist of all subjects in the FAS who have no major protocol violations as presented in Table 7.b. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of individual subject's treatment assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving wrong trial treatment (3) receiving prohibited therapies, and (4) other major protocol violations that may be identified during blinded data reviews.

Both the FAS and PPS will include only subjects from the immunogenicity subset (600 subjects in total [groups 1 and 4: 100 subjects each; groups 2 and 3: 200 subjects each]), i.e., subjects for whom blood samples for assessment of dengue neutralizing antibodies are collected.

The primary analysis of immunogenicity will be based on the PPS, and other supportive analysis will be provided for the FAS.

7.2.1 Major Protocol Violations

A major protocol violation is considered to have a significant impact on the immunogenicity results of the subject. All protocol deviations will be identified prior to unblinding and a clinical judgment will be necessary to classify each deviation as "major" or not. These deviations and the judgment regarding their use will be listed and summarized in the final clinical trial report.

The criteria described in this section will be used to identify subjects with major protocol violations which could impact the analysis of the primary endpoint. Subjects meeting these criteria will be excluded from the PPS described above. Subjects meeting these criteria will be identified and approved prior to database lock and unblinding

Table 7.b Criteria for Exclusion from the PPS

Criteria for exclusion	Probable Method of identification
Missing Dengue-neutralizing titers for all 4 serotypes at baseline.	Identified programmatically using immunogenicity data
Missing Dengue-neutralizing titers for all 4 serotypes at Months 1, 3, 6, 12, 13 and 18.	Identified programmatically using immunogenicity data.
Month one immunogenicity sample is NOT collected within ± 5 days of the scheduled Month 1 (Day 30) visit.	Identified programmatically using immunogenicity data.
Not receiving all investigational vaccine administrations [Day 1 (M0), Day 91 (M3) and Day 365 (M12)].	Identified programmatically using dosing data.
Not receiving the assigned treatment/dosing schedule [refers to correct administration of active or placebo into the correct arm on Day 1 (M0), Day 91 (M3) or Day 365 (M12)].	Identified programmatically using blinded IVRS data and/or through source documents provided in blinded fashion to the statistician
Not receiving the correct dosage of the investigational vaccine. This refers to improperly prepared syringes at the site pharmacy.	Identified through source documents and provided in blinded fashion to the statistician.
Subject meets any of exclusion criteria 2d, 3, 4 or 5 (subject to blinded medical review).	Subjects identified programmatically using CRF-recorded data. Subjects will be identified before unblinding, and a blinded review list sent for clinical science review to determine evaluability status for each identified subject. Note that exclusion criteria 2d and 3 identify subjects' use of prohibited medications prior to enrollment.
Use of prohibited medications during the trial (subject to blinded medical review).	Potential prohibited medications (Appendix C) to be identified by sending a blinded review list of CRF-recorded concomitant medication data for clinical science review to determine evaluability status for each identified subject.

Other major violations may be identified based on blind data reviews of deviation log subject to medical review.

7.3 Disposition of Subjects

Disposition of all screened subjects will be summarized descriptively, which includes a summary of the number of screened subjects, the number of randomized subjects, the number of subjects completing all planned vaccine regimen and the number of subjects completing all planned trial visits. Disposition of non-randomized subjects will be summarized according to screen failure reason, including primary reason for screen failure [adverse event, screen failure (did not meet inclusion/did meet exclusion criteria), withdrawal by subject, trial terminated by sponsor, and other].

Disposition of all randomized subjects will be summarized by the 4 groups overall and within each age stratum. The categories will include:

- Number of randomized subjects
- Number of subjects completing the trial vaccine
- Number of subjects who prematurely discontinue trial vaccine
- Primary reason for premature discontinuation of trial vaccine
- Number of subjects completing all planned trial visits
- Number of subjects prematurely discontinue all planned trial visits
- Primary reason for premature discontinuation of all planned trial visits

A subject is to be assumed ongoing unless he/she completed the end of trial CRF, indicating either completion or early terminated. The Primary reasons for discontinuation of trial medication/visits will be summarized, and the categories include adverse event, lost to follow-up, protocol violation, trial terminated by sponsor, withdrawal by subject, and other. Number of screened/enrolled, randomized and analysis populations will also be presented.

7.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will include age, sex, race, weight, height and BMI, which is calculated based on both weight and height measurements from baseline, and will be summarized descriptively by group overall and within each age stratum based on the randomized set and PPS.

In addition, the same tables will be produced based on the baseline seropositive status (seropositive or seronegative). A sample is considered seropositive, if $MNT_{50} \geq 10$. A subject who is positive for at least one of four DENV serotypes is categorized as a seropositive subject.

Summary statistics (number of subjects [N], mean, median, SD, minimum, and maximum) will be generated for continuous variables (age, height, weight, BMI and other), and the number and percentage of subjects within each category will be presented for categorical variables (sex, race and other).

Individual demographic data will be presented in the data listing.

Demographic and baseline characteristics of screen failure subjects and reasons for screen failures will be summarized total overall for subjects who are screened, but not enrolled in the trial. Individual demographic data, date of informed consent, any available safety data and reason for screen failure will also be presented in the data listing.

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, Version 16.1, or higher) coding system.

All medical history and concurrent medical condition data will be listed by trial site, and subject number. The listing will contain subject identifier, treatment arm, system organ class (SOC),

whether there was any significant medical history or concurrent condition, and if yes, a detail of the medical history or concurrent condition.

7.6 Medication History and Concomitant Medications

Medication history and concomitant medications will be coded using the World Health Organization DRUG dictionary (WHO Drug Version March 2013, or higher).

Separate listings for medication history and concomitant medications will be produced by trial center and subject number. The listings will contain subject identifier, treatment, WHO Drug preferred term (PT), dose, frequency, unit, route, stop date, and reason for use.

7.7 Investigational Product Exposure and Compliance

The investigator records all injections of investigational vaccine given to the subject in the eCRF. Compliance rate will be summarized by the 4 trial vaccination groups, by presenting the number and percentage of subjects receiving all three doses of vaccination and the number and percentage of those receiving only the first and first two doses of vaccination. The vaccination date/time information will be listed for each subject. The duration of follow-up will be summarized as a continuous variable, and also in the following categories: (1) 1 – 180 days, (2) 181 - 365 days, (3) 366 - 540 days, (4) 541 - 730 days, (5) 731 - 1095 days, and (5) > 1096 days. The follow-up is defined as the number of days since the first vaccination to the end of trial visit. For interim analysis, if the end of trial visit dates are not reported, the date of data cutoff will be used for calculation.

7.8 Efficacy Analysis

Not applicable

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable

7.10 Other Outcomes

7.10.1 Immunogenicity

The primary immunogenicity endpoint in the trial is GMTs of neutralizing antibodies (MNT_{50}) for each of the four DENV serotypes. The secondary endpoint is seropositivity rates (%) for each of the four DENV serotypes where seropositivity is defined as a reciprocal neutralizing titer ≥ 10. A value of 5 (midpoint between 0 and the lower limit of detection) will be used for Dengue Neutralizing Antibody titers which are below the lower limit of detection (10).

Subjects included in the immunogenicity subset (100 subjects in group 1 and group 4 and 200 subjects in group 2 and group 3) will undergo blood sampling for serological immunogenicity testing at Months 0, 1, 3, 6, 12, 13, 18, 24, 36, and 48.

For the immunogenicity subset of subjects, descriptive statistics and 95% CIs for GMTs and seropositivity rates will be computed by treatment group at Months 0, 1, 3, 6, 12, 13, 18, 24, 36, and 48. The 95% CI of seropositivity rate will be calculated based on Clopper-Pearson method. GMTs will be calculated, for each relevant time point as anti-logarithm of ∑(log transformed titer/n), where n is the number of subjects with titer information. The 95% CI for GMTs will be calculated as the anti-log transformation of upper and lower limits for a two-sided CI of the mean of the log-transformed titers. In addition, the percent of subjects with monovalent (seropositive for only one of the four DENV serotypes), bivalent (seropositive for any two of the four DENV serotypes), trivalent (seropositive for any three of the four DENV serotypes), and tetravalent (seropositive for all four DENV serotypes) seropositivity, as well as at least bivalent (seropositive for ≥2 DENV serotypes) and at least trivalent (seropositive for ≥3 DENV serotypes) seropositivity will be summarized by treatment group at each visit. Additional summaries of immunogenicity endpoints by baseline seropositive status (seropositive or seronegative) will also be provided.

The primary immunogenicity analysis will be performed on the PPS. A supportive analysis will be provided using the FAS.

GMTs will also be presented graphically for each serotype overall and by baseline seropositive status. In addition, reverse cumulative distribution curves will be plotted separately for each trial group and serotype by baseline seropositive status for all the time points except the baseline.

7.10.2 CCI

CCI

7.11 Safety Analysis

All summaries of safety data are based on subjects in the Safety Analysis Set. Unless otherwise specified, the safety data will be summarized by trial group. Unless otherwise stated, data imputation will not be performed for any missing safety data.

7.11.1 Adverse Events

For summaries of solicited and unsolicited AEs only subjects from the immunogenicity subset will be included. SAEs will be summarized for all subjects.

Reactogenicity (Solicited AEs)

Solicited local AEs (infant/toddler/child < 6 years: injection site pain, injection site erythema and injection site swelling; adult and child ≥ 6 years: injection site pain, injection site erythema and injection site swelling) and solicited systemic AEs (infant/toddler/child < 6 years: fever, irritability/fussiness, drowsiness and loss of appetite; adult and child ≥ 6 years: asthenia, body temperature, headache, malaise, myalgia) will be assessed for 7 and 14 days following each vaccination (vaccination day included), respectively, via collection of diary cards.

The presence and severity of each solicited symptom will be collected using diary cards. The subject will record the severity of each AE (except erythema, swelling and temperature) according to the diary card instruction as none, mild, moderate, or severe. These grades will be entered onto the eCRF. For the local AEs erythema and swelling, the subject will record the length of the longest diameter. For the systemic AE fever, the subject will record the temperature in either degrees Fahrenheit or degrees Celsius. Severity grades for erythema and swelling will be derived from the recorded lengths, and fever will be derived from the recorded temperature measurements using guidance published by the Brighton Collaboration[2].

The details of Solicited local and systemic AEs, Intensity scales for solicited AEs in infants/toddlers (15-24 months)/child (< 6 years) and Intensity scales for solicited AEs in adults/children (≥ 6 years) are given in Appendix B.

For each solicited AE, the summary tables will be presented by each age category, infants/toddlers (15-24 months)/child (< 6 years) and adults/children (≥ 6 years). The percentage of subjects will be summarized by event severity for each day (Days 1 to 7 and Days 1 to 14 after each vaccination for local and systemic AEs, respectively) and overall.

For solicited AEs, missing data will be handled as follows. For each group and solicited AE, the denominator for the percentage will exclude subjects with completely missing data (i.e. subject does not have at least one recorded results of none, mild, moderate, or severe) for the solicited AE in the period being summarized.

A summary of the first onset of each event will also be provided. The number of days subjects experienced each event will also be summarized for each group. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs

Unsolicited AEs and SAEs, will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for each treatment arm. AEs leading to trial or vaccine withdrawal will also be summarized.

All unsolicited AEs up to 28 days after the last vaccination will be included in the analyses of all AEs. For SAEs and AEs leading to subject withdrawal from the trial, any AE collected during the trial will be included. In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE) and by SOC and PT. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. Unsolicited AEs will be summarized as follows: by PT including events with frequency greater

than 2%; by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to the investigational vaccine. Unsolicited AEs will be summarized as described above for the following periods:

1. Onset within 28 days after vaccination 1
2. Onset within 28 days after vaccination 2
3. Onset within 28 days after vaccination 3
4. Onset within 28 days after any vaccination
5. Onset between 1 and 14 days after vaccination 1
6. Onset between 1 and 14 days after vaccination 2
7. Onset between 1 and 14 days after vaccination 3
8. Onset between 1 and 14 days after any vaccination
9. Onset between 15 and 28 days after vaccination 1
10. Onset between 15 and 28 days after vaccination 2
11. Onset between 15 and 28 days after vaccination 3
12. Onset between 15 and 28 days after any vaccination

Similar summaries by baseline seropositive status will also be included.

In addition, a summary of most frequent non-serious unsolicited AEs will be prepared by SOC and PT including events with frequency greater than 2% to provide this information for Clinicaltrials.gov.

7.11.2 Clinical Laboratory Evaluations

Not applicable

7.11.3 Vital Signs

The vital signs collected in the trial include systolic and diastolic blood pressure, heart rate, body temperature, and weight and height. Note that height will only be measured at Visit 1 [Day 1 (M0)]). Vital signs will be summarized descriptively with windowed visits, and individual subject data will be presented in the listing by group, site, subject number, collection date/time, and measurement parameters. The measurement parameters will be sorted or grouped in a clinically meaningful order.

Measurements are taken at Day 1 (M0), Day 28 (M1), Day 91 (M3), Day 180 (M6), Day 365 (M12), Day 393 (M13), Day 540 (M18), Day 730 (M24), Day 1095 (M36), and Day 1460 (M48).

Descriptive statistics (N, mean, median, SD, minimum and maximum) of vital sign parameters (observed and change from baseline) except the height will be summarized by trial group at each visit. Only vital sign measurements at the scheduled visits will be included in the summaries.

7.11.4 12-Lead ECGs

Not applicable

7.11.5 Other Observations Related to Safety

Febrile Illness Follow-Up

Any subject with febrile illness (defined as temperature ≥ 38°C on 2 consecutive days) will be asked to return to the site for dengue fever evaluation. A dengue infection will be considered virologically confirmed by either PCR or NS1 ELISA.

The percentage of subjects with virologically confirmed dengue (based on the febrile illness cases) will be summarized by group and by baseline seropositive status. Frequency tables will show the following three categories: (1) number of virologically confirmed dengue cases with onset before Day 30, (2) number of virologically confirmed dengue cases with onset on or after Day 30 and (3) total number of virologically confirmed dengue cases.

A blood sample will be collected within (≤) 5 days after the onset of fever to perform virological confirmation of dengue and for haematology (white cell count and differential (WCC), platelet cell count (PCC) and hematocrit (HCT)) and biochemistry (Aspartate Transaminase (AST) and Alanine Transaminase (ALT)) to assess the severity of infection. Haematology and biochemistry will be performed by local laboratories. The subject's medical condition will be recorded in the eCRF, including but not limited to headache, rash, abdominal pain, myalgia, arthralgia, signs of bleeding (including petechiae), signs of plasma leakage. WCC and differential, PCC, HCT, AST and ALT will also be recorded, even if values are normal. Summary tables for subjects with virologically confirmed dengue will be provided by group and by baseline seropositive status.

All individual laboratory data will be presented in both SI and conventional (CV) units in the subject data listings by group, site, subject number, collection date/time, and measurement parameter. The measurement parameters will be sorted or grouped in a clinically meaningful order.

For the subset of subjects with virologically confirmed dengue the main summary tables for GMTs and seropositivity rates will be repeated based on the PPS.

7.12 Interim Analysis

Interim analyses on cleaned safety and immunogenicity data CCI are planned on data up to Month 6, and on data up to Month 18. In order to ensure the trial blind is maintained for the sponsor, these analyses will be performed by an independent third party at CCI The unblinded statisticians and programmers at CCI will have access to individual treatment assignments but will not be involved in subsequent trial conduct. The rest of the personnel involved in the conduct of the trial, including those at Takeda, CCI blinded

trial team, and the trial sites, will remain blinded to the individual subject data (including treatment assignments) until unblinding after trial completion (database lock for data through the Month 48 Follow Up visit). These analyses will not be used to alter the trial conduct but rather to provide data to support the planning and execution of other trials in the development plan of Takeda's TDV. The interim analyses will include descriptive summary tables (containing only aggregate data by treatment assignment) for demographic and baseline characteristics, immunogenicity data, CCI [redacted] solicited and unsolicited AEs, SAEs, febrile illness assessment (if available), and vital signs. The methodology for these tables will generally be as described in the respective sections of the SAP, with the exception that only data through the time of the interim data cut will be included.

7.13 Changes in the Statistical Analysis Plan

7.13.1 Amendment History

Date	Amendment Number
29 May 2015	Initial Analysis Plan
31 May 2016	1

7.13.2 Summary of Changes

This section describes changes to the Statistical Analysis Plan Version 1.0, dated 29 May 2015.

The main rationale for this amendment is the Protocol amendment Version 3.0, dated 23 July 2015. Minor grammatical and editorial changes are included for clarification purposes only.

Section	Description of Change
1.1	Administrative updates.
3.0	$PRNT_{50}$ (Plaque Reduction Neutralization Test 50%) was replaced by MNT_{50} (Microneutralization Test 50%).
5.1; 6.1; 7.10.1	$PRNT_{50}$ was replaced by MNT_{50}.
4.4; 5.0; 7.1; 7.7; 7.10.1; 7.11.3; 7.12; Appendix A	Extension of the trial duration up to Month 48 including the addition of three study visits at Months 24, 36, and 48 for safety follow-up of all subjects, and with blood sampling in the immunogenicity subset.
7.1	Table 7.a was updated.
4.4; 7.12	Addition of a second interim analysis at Month 18.
4.4; 7.12	Addition of safety data analysis for the interim analysis.

Section	Description of Change
5.1; 5.2	Month 0 removed from the primary and secondary immunogenicity endpoints.
7.7	Section title was changed from "Trial Treatment Exposure and Compliance" to "Investigational Product Exposure and Compliance". Updated "the duration of follow-up"
7.10.1	Added the phrase "A value of 5 (midpoint between 0 and the lower limit of detection) will be used for Dengue Neutralizing Antibody titers which are below the lower limit of detection (10)" and "GMTs will also be presented graphically for each serotype overall and by baseline seropositive status. In addition, reverse cumulative distribution curves will be plotted separately for each trial group and serotype by baseline seropositive status for all the time points except the baseline."
7.11.3 (Appendix D was deleted)	Removal of summaries based on markedly abnormal values For this study in healthy subjects, marked abnormal values for vital signs are not applicable, as vital signs are being collected only at selected visits to confirm the healthy status of study participants.
7.11.5	Clarification added for analysis of febrile illness cases.
Appendix B	Clarification added regarding solicited AE severity/intensity categories.

8.0 REFERENCES

1. A Phase II, double-blind, controlled trial to assess the Safety and Immunogenicity of different schedules of Takeda's Tetravalent Dengue Vaccine Candidate (TDV) in healthy subjects aged between 2 and <18 years and living in dengue endemic countries in Asia and Latin America,, Takeda Vaccines, Inc., Protocol No. DEN-204, Version 3.0, dated 23 July 2015.
2. Marcy, M. et a. (2004): Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis and presentation. Vaccine 22: 551-556.

Appendix A Schedule of Trial Procedures

Table A-1 Schedule Trial Procedures for Immunogenicity Subset

Procedure	**Vacc 1**	**Post Vacc 1**	**Vacc 2**	**Post Vacc 2**	**Vacc 3**	**Post Vacc 3**	**Follow-up**	***Follow-up***	***Follow-up***	***Follow-up/ET***	**Unscheduled**
Visit	1	2	3	4	5	6	7	*8*	*9*	*10*	NA
Trial Timelines	D1 (M0)	D28 (M1)	D91[a] (M3)	D180 (M6)	D365 (M12)[b]	D393 (M13)[c]	D540 (M18)[d]	*D730 (M24)[e]*	*D1095 (M36)[f]*	*D1460 (M48)[g]*	
Time window		+5 days	± 15 days	± 15 days	± 15 days	+5 days	± 15 days	*± 15 days*	*± 15 days*	*± 15 days*	
Signed Informed Consent/Assent	X										
Medical History	X										
Demographics	X										
Assessment of eligibility criteria[i]	X										
Complete Physical Examination[j]	X										
Pregnancy Test[k]	X		X		X						
Brief symptom-directed physical assessment[l]		X	X	X	X	X	X	*X*	*X*	*X*	
Randomization	X										
Blood Sampling[h]	X	X	X	X	X	X	X	*X*	*X*	*X*	
Vaccine administration	X		X		X						
Injection site evaluation[m]	X		X		X						
Diary card[n] distribution	X[k]	X	X[k]		X[k]						
Diary card Collection and Review[o]		X[l]		X[l]		X[l]					
Safety Review Call[p]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	
Concomitant medication[q]	X	X	X	X	X	X	X	*X*	*X*	*X*	X
Febrile illness assessment											X
Blood sample febrile illness[r] (4 ml)											X

Note: The double-line border following Month 6 *and Month 18* indicates the interim *analyses* which will be performed on cleaned *safety and* immunogenicity data [CCI] up to Month 6 *and up to Month 18, respectively*; NA: not applicable; D: Day; M: Month; ET: Early termination; Vacc: vaccination.

a. 28 days Post Vacc 2, home visits may be done by the site staff in order to collect the diary card. Optionally, a phone call may be made to remind the subject to keep the diary card secure and bring to the site on the Month 6 visit.

b. D1 + 364 days

c. 28 days Post Vacc 3 (Day 365 + 28 days)
d. D1 + 539 days
e. D1 + 729 days
f. D1 + 1094 days
g. D1 + 1459 days
h. Blood sampling before vaccination for immunogenicity[CCI] (Protocol Section 9.1.6).
i. Review of inclusion/exclusion criteria will be documented before first vaccination.
j. Physical examination at Day 1 (Protocol Section 9.1.4). Weight and height will also be measured and BMI calculated. Includes Vital Signs.
k. In women of childbearing potential, urine or serum pregnancy test will be performed before each vaccination (within one day prior).
l. Including (but not limited to) the measurement of vital signs.
m. At 30 minutes after vaccine administration.
n. Diary cards will be distributed for the collection of
  1) solicited local AEs occurring on the day of vaccination and the 6 subsequent days for a total of 7 days,
  2) solicited systemic AEs occurring on the day of vaccination and the 13 subsequent days for a total of 14 days (Days 1 to 7 and Days 8 to 14), and
  3) unsolicited AEs occurring on the day of vaccination and the 27 subsequent days for a total of 28 days.
o. The investigator will categorize events by severity (mild, moderate or severe) and will assess causality to vaccine administration (related or not related).
p. Monthly safety phone calls (M2, M4, M5, M7 to M11, M14 to M17*, M19 to M23, M25 to M35, M37 to M47*) when no study visit is scheduled. Safety phone calls (M2, M4, M5, M7 to M11, M14 to M17*, M19 to M23, M25 to M35, M37 to M47*) must be 30 days (-7/+14 days) after the last visit/call.
q Collected at clinic visits or phone contact, as applicable. Concomitant therapy and vaccine history from 4 weeks prior to administration of each dose of TDV or placebo, as applicable, and ending one month (minimum 28 days) after the last dose of TDV or placebo.
r Blood sample to be collected from any subject with febrile illness (defined as temperature ≥ 38°C for 2 consecutive days).

Table A-2 Schedule Trial Procedures for Subjects Not Included in the Immunogenicity Subset

Procedure	**Vacc 1**	**Vacc 2**	**Vacc 3**	**Follow-up**	***Follow-up***	***Follow-up***	***Follow-up/ET***	**Unscheduled**
Visit	1	2	3	4	*5*	*6*	*7*	NA
Trial Timelines	D1 (M0)	D91 (M3)	D365 (M12)[a]	D540 (M18)[b]	*D730 (M24)[c]*	*D1095 (M36)[d]*	*D1460 (M48)[e]*	
Time window		± 15 days	± 15 days	± 15 days	*± 15 days*	*± 15 days*	*± 15 days*	
Signed Informed Consent/Assent	X							
Medical History	X							
Demographics	X							
Assessment of eligibility criteria[f]	X							
Complete Physical Examination[g]	X							
Pregnancy Test[h]	X	X	X					
Brief symptom-directed physical assessment[i]	X	X	X	X	*X*	*X*	*X*	
Randomization	X							
Vaccine administration	X	X	X					
Safety Review at the Site[j]		X	X	X				X
Safety Review Call[k]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	
Concomitant medication[l]	X	X	X	X	*X*	*X*	*X*	X
Febrile illness assessment								X
Blood sample febrile illness[m] (4 ml)								X

NA: not applicable; D: Day; M: Month; ET: Early termination; Vacc: vaccination

a. D1 + 364 days
b. D1 + 539 days
c. *D1 + 729 days*
d. *D1 + 1094 days*
e. *D1 + 1459 days*
f. Review of inclusion/exclusion criteria will be documented before first vaccination.
g. Physical examination at Day 1 (Protocol Section 9.1.4). Weight and height will also be measured and BMI calculated.
h. In women of childbearing potential, urine or serum pregnancy test will be performed before each vaccination (within one day prior).
i. Including (but not limited to) the measurement of vital signs.
j. Review of SAEs/AEs (including Febrile Episodes) at Site. SAEs will be reported to the Sponsor within 24 hours of the investigator becoming aware of the event. The investigator will categorize events by severity (mild, moderate or severe) and will assess causality to vaccine administration (related or not related).
k. Monthly safety phone calls (M1, M2, M4 to M11, M13 to M17*, M19 to M23, M25 to M35, M37 to M47*). Safety phone calls (M1, M2, M4 to M11, M13 to M17*, M19 to M23, M25 to M35, M37 to M47*) must be 30 days (-7/+14 days) after the last visit/call.
l. Collected at clinic visits or monthly phone contact, as applicable. Concomitant therapy and vaccine history from 4 weeks prior to administration of each dose of TDV or placebo, as applicable, and ending one month (minimum 28 days) after the last dose of TDV or placebo.
m. Blood sample to be collected from any subject with febrile illness (defined as fever ≥ 38°C for 2 consecutive days).

Appendix B Solicited and Systemic Adverse Events and Intensity

Table B-1 Solicited Local and Systemic AEs

	Infant/Toddler (15–24 months)/Child (< 6 years)	**Adult and child (≥ 6 years)**
Local AEs (injection site)	Pain	Pain
	Erythema	Erythema
	Swelling	Swelling
Systemic AEs	Fever[b]	Fever[b]
	Irritability/fussiness	Asthenia
	Drowsiness	Headache
	Loss of appetite	Malaise
		Myalgia

(b) Body temperature ≥ 38°C or 100.4°F is defined as fever irrespective of site of measurement

Table B-2 Intensity Scales for Solicited AEs in Infants/Toddlers/Child (< 6 years)

Adverse Event	Intensity Grade	Severity/Intensity
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Erythema at injection site [(a)]	0	<10 mm
	1	Mild: ≥10 – ≤ 20 mm
	2	Moderate: > 20 – ≤ 40 mm
	3	Severe: > 40 mm
Swelling at injection site [(a)]	0	<10 mm
	1	Mild: ≥10 – ≤ 20 mm
	2	Moderate: > 20 – ≤ 40 mm
	3	Severe: > 40 mm
Drowsiness	0	Behavior as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Irritability/fussiness	0	Behavior as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all
Fever[b]	Record body temperature in °C/°F	

(a) Subjects are to record greatest surface diameter in mm in the Diary
(b) = Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method taken

Table B-3 Intensity Scales for Solicited AEs in Adults/Children (≥ 6 years)

Adverse Event	Intensity Grade	Severity/Intensity
Pain at injection site	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without treatment
	3	Severe: Prevents daily activity with or without treatment
Erythema at injection site[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]	Record body temperature in °C/°F	

(a) Subjects are to record greatest surface diameter in mm in the Diary
(b) = Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method taken

Appendix C Potential Prohibited Therapies

1. Chronic use of systemic (i.e. oral or parenteral) corticosteroid treatment (equivalent to 20 mg/day prednisone ≥ 12 weeks ≥ 2 mg/kg body weight/day prednisone ≥ 2 weeks) within 60 days prior to Day 1 (Month 0).
2. Administration of immunoglobulins and/or any blood products within the 3 months prior to Day 1 (Month 0) or planned administration during the trial.
3. Receipt of immunostimulants within 60 days prior to Day 1 (Month 0).
4. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1 (Month 0).
5. Receipt of a vaccine outside of the conditions:
    - Subjects who received any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior Day 1 (Month 0) or who planned to receive any vaccine within 28 days Day 1 (Month 0).
    - Subjects participating in any clinical trial with another investigational product 30 days prior to first trial visit or intent to participate in another clinical trial at any time during the conduct of this trial.
    - Subjects who participated in any clinical trial of a dengue candidate vaccine, or previous receipt of a dengue vaccine.