Title: Phase III, Double-Blind, Randomized, Placebo-Controlled Trial to Investigate the Efficacy, Safety and Immunogenicity of a Tetravalent Dengue Vaccine (TDV) Administered Subcutaneously in Healthy Children Aged 4 – 16 Years Old

NCT Number: NCT02747927

SAP Approve Date: 24 September 2020

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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.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: DEN-301

Phase III, Double-Blind, Randomized, Placebo-Controlled Trial
to Investigate the Efficacy, Safety and Immunogenicity of a
Tetravalent Dengue Vaccine (TDV) Administered Subcutaneously
in Healthy Children Aged 4 – 16 Years Old

Efficacy, Safety and Immunogenicity of Takeda's TDV in Healthy Children

PHASE III

Version**:** Final, **5.0**

Date: **24 September 2020**

Prepared by:

PPD

Based on:

Protocol Version: 6.0

Protocol Date: 18 May 2020

1.0 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
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CCI [redacted]	
BLA	Biologics License Application
COVID-19	Coronavirus Disease 2019
CRO	Clinical Research Organization
CSR	Clinical Study Report
DHF	Dengue Hemorrhagic Fever
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	Full Analysis Set
CCI [redacted]	
FASI	Full Analysis Set for Immunogenicity
CCI [redacted]	
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HR	Hazard Ratio
IA	Interim Analysis
IEC	Independent Ethics Committee
Ig(s)	Immunoglobulin(s)
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LFT	Liver Function Test
MAV	Markedly Abnormal Value
MedDRA	Medical Dictionary for Regulatory Activities
MNT_{50}	Microneutralization Test 50%
NS1	Nonstructural Protein 1
PCR	Polymerase Chain Reaction
PFU	Plaque Forming Units

PPS	Per-Protocol Set
CCI	[redacted]
PPSI	Per-Protocol Set for Immunogenicity
CCI	[redacted]
PT	Preferred Term
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Set
CCI	[redacted]
TDV	Takeda's Tetravalent Dengue Vaccine Candidate
VCD	Virologically-Confirmed Dengue
VE	Vaccine Efficacy
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objective

To evaluate the efficacy of 2 doses of Takeda's Tetravalent Dengue Vaccine Candidate (TDV) in preventing symptomatic dengue fever of any severity and due to any of the 4 dengue virus serotypes in 4-16 year old subjects.

4.2 Secondary Objectives

To be assessed post-second vaccination:

Efficacy:

- To assess the efficacy of TDV in preventing symptomatic dengue fever of any severity induced by individual dengue serotypes.
- To assess the efficacy of TDV in preventing symptomatic dengue fever of any severity by dengue exposure status at baseline.
- Note: In later sections of the Statistical Analysis Plan (SAP), "dengue exposure status at baseline" (wording as per protocol) is referred to as "dengue baseline seropositivity status".
- To assess the efficacy of TDV in preventing hospitalization due to virologically-confirmed dengue (VCD) fever.
- To assess the efficacy of TDV in preventing severe dengue induced by any dengue serotype.

Safety:

- To describe the safety of TDV.
- To describe the reactogenicity of TDV in a subset of subjects.

Immunogenicity:

- To assess the immunogenicity of TDV in a subset of subjects.

4.3 Exploratory Objectives

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4.4 Study Design

This is a phase III, double-blind, randomized, placebo-controlled trial with 2 parallel groups. The trial includes for all subjects at least 3 time periods (Parts 1, 2, and 3) for surveillance of febrile illness with potential dengue etiology. CCI

4.4.1 Parts 1, 2, and 3

Part 1 constitutes the primary analysis period, including primary efficacy analysis. Part 2 constitutes a period of additional active surveillance for secondary efficacy analyses. Part 3 constitutes modified active surveillance for the assessment of long term safety.

Part 1: Active surveillance for the primary assessment of efficacy in all subjects. During this time subjects will be contacted at least weekly to ensure identification of febrile illness that could

potentially be due to dengue. This part will commence on the day of vaccination and finish once both of the following 2 criteria are fulfilled:

- 120 cases of dengue fever are confirmed
- Minimum duration of subject follow-up of 12 months post-second vaccination

The end of Part 1 will be defined for each subject so that the duration of follow up after the second vaccination will be approximately the same for all subjects. Virologically-confirmed cases in Part 1 count towards the primary efficacy objective if occurring at least 30 days post-second vaccination.

Part 2: Active surveillance for an additional 6 months for each subject following the completion of Part 1. During this time subjects will be contacted at least weekly to ensure identification of febrile illness that could potentially be due to dengue.

Virologically-confirmed cases in Parts 1 and 2 contribute towards the secondary efficacy objectives.

Part 3: Modified active surveillance for the assessment of safety in all subjects following the completion of Part 2 and lasting approximately 3 years for each subject. The modified surveillance during Part 3 will maintain at least weekly contacts through Part 3 of the trial, but the intensity of investigation will be modified based on the need for hospitalization. Surveillance will identify febrile illness of any severity that could potentially be due to dengue.

Subjects may be enrolled into a dry-run to commence and test febrile surveillance methodology. This dry-run will involve pre-vaccination surveillance for dengue and may be conducted for up to 10 months prior to vaccination on Day 1. It may not be required in all sites and may not be applicable to all subjects at the trial sites where it is conducted. The need for and duration of the dry run at an individual site will depend on the experience of the site in conducting similar trials. For ease of terminology, trial time points will use the date of first vaccination (Day 1) as the reference point, so activities occurring prior to the day of first vaccination (Day 1) will be referred to as Day –x to Day-1 (the day before first vaccination).

The target sample of 20,100 healthy children and adolescents aged between 4 and 16 years will be randomized to receive either TDV or placebo in a 2:1 ratio (13,400 TDV; 6,700 placebo). Randomization by using an interactive system (Interactive Web Response System [IWRS] or Interactive Voice Response System [IVRS]) will be stratified by region (Asia Pacific and Latin America) and age range (children aged 4-5 years, 6-11 years, and 12-16 years) to ensure each age range has the appropriate ratio of TDV to placebo in each region. In addition, recruitment will follow an enrollment plan to ensure representative enrollment across the age ranges and regions. This is considered necessary to mitigate the relative difficulty of recruitment of subjects at the extremes of age-ranges in this trial. Each subject will receive TDV or placebo by a subcutaneous injection into the upper arm. A subset of the same subjects (n=4,000) will be included in specific safety and immunogenicity evaluations (safety/immunogenicity subset, hereafter referred to as 'subset'). This subset will be selected randomly using IWRS or IVRS and

stratified by region (Asia Pacific and Latin America) and age range (children aged 4-5 years, 6-11 years, and 12-16 years).

Aspects of active surveillance (dry-run, Parts 1 and 2):

Definition of active surveillance

During active surveillance (dry-run, Parts 1 and 2), any subject with febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) will be asked to return to the site for dengue fever evaluation by the Investigator. Subjects/guardians will be contacted at least weekly to ensure robust identification of febrile illness by reminding subjects/guardians of their obligation to return to the site in case of febrile illness. This contact will be implemented through appropriate methods that may differ in each trial site (eg, phone calls, text messaging, home visits, school-based surveillance). The text messaging system, if used, will be identified and evaluated by the Sponsor before use. Each trial site will have locally-developed Standard Procedures (ie, Internal Operating Procedures) that details the local healthcare map relevant to the trial (as assessed by the trial site), methodology of febrile illness surveillance and case handling.

Duration of active surveillance

Active surveillance for febrile illness will commence at the dry-run or on Day 1 (Part 1) and will continue until the end of Part 2.

Part 1 is designed to support the primary objective of assessment of efficacy of the vaccine candidate in preventing VCD fever induced by any dengue serotype, and will include active surveillance until the 2 conditions described previously are fulfilled.

Part 2 is designed to provide additional data regarding the secondary efficacy objectives detailed in Section 4.2. These analyses involve subsets of dengue cases, such as dengue due to a single serotype, and will therefore be less precise than the primary efficacy endpoint which considers dengue cases regardless of severity or serotype. A longer surveillance period enables the identification of additional dengue cases, thereby improving the precision of the secondary efficacy objectives. For this reason all subjects will continue active surveillance for 6 months following the completion of Part 1.

Aspects of modified active surveillance (Part 3):

Modified active surveillance will start after the completion of Part 2, and will last for approximately 3 years. Modified active surveillance will be implemented to detect dengue cases of any severity in a tiered approach based on the need for hospitalization. Any subject with febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) will be asked to return to the site for evaluation by the Investigator. Subjects presenting with febrile illness not requiring hospitalization will be screened for dengue disease (by reverse transcriptase polymerase chain reaction [RT-PCR]) unless there is alternate laboratory confirmed etiology. They will undergo local laboratory evaluations as per standard medical practice. Subjects with febrile illness requiring hospitalization will be evaluated as during active surveillance (ie, dry-run, Parts 1 and 2). During Part 3, there will be a minimum frequency of 1 contact every week through

appropriate methods that may differ in each trial site (see above). Modified active surveillance will be performed according to locally-developed Standard Procedures as described above.

The trial design (Parts 1, 2, and 3) is presented below in Figure 4.a. Differences between active surveillance (dry-run, Parts 1 and 2) and modified active surveillance (Part 3) are summarized in Table 4.a.

Figure 4.a Schematic Showing Parts 1, 2, and 3

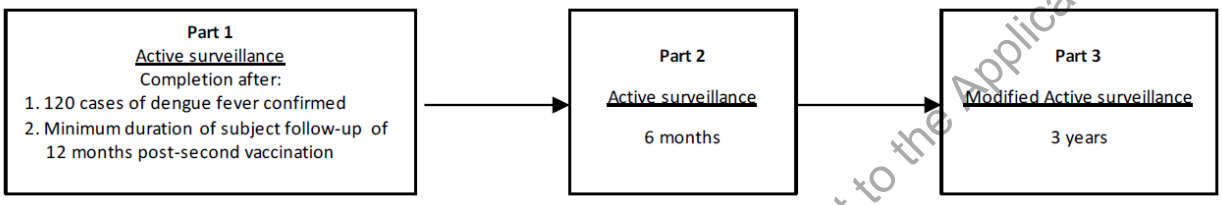


Table 4.a Differences between Active Surveillance (Dry-Run, Parts 1 and 2) and Modified Active Surveillance (Part 3)

	Active Surveillance (dry-run, Parts 1 and 2)	Modified Active Surveillance (Part 3)	
Contact frequency	At least weekly	At least weekly	
Threshold for evaluation	All febrile illness (irrespective of need for hospitalization)	Febrile illness requiring hospitalization	Febrile illness not requiring hospitalization (unless the febrile illness has an alternate laboratory confirmed etiology).
Laboratory evaluations	- Within 5 days: RT-PCR, NS1 antigen, IgM, IgG ELISA (central laboratory); and platelet count, hematocrit, ALT, and AST (locally) - 7-14 days after the acute sample: IgM and IgG ELISA (central laboratory); and platelet count, hematocrit, ALT, and AST (locally) - Other laboratory evaluations as per standard of care (locally)		- Within 5 days: RT-PCR (central laboratory) - Other laboratory evaluations as per standard of care (locally)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ELISA = enzyme-linked immunosorbent assay; IgG/IgM = Immunoglobulin G/M; NS1 = nonstructural protein 1; RT-PCR = reverse transcriptase polymerase chain reaction

Case definition for efficacy objectives:

A virologically-confirmed dengue case is defined as febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or illness clinically suspected to be dengue by the Investigator with a positive serotype-specific RT-PCR. The presence of febrile illness or clinically suspected dengue will be recorded in the electronic Case Report Form (eCRF) by the Investigator.

Handling of febrile illness cases (suspected dengue cases):

Subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or clinically suspected dengue during the dry-run, Parts 1 and 2 or requiring hospitalization during Part 3 will have 2 blood samples taken to confirm dengue infection, in addition to those taken as part of the clinical care of the subject. The first or acute blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after

the onset of fever). Testing will include dengue IgM and IgG enzyme-linked immunosorbent assay (ELISA), dengue NS1 antigen ELISA, dengue RT-PCR, hematocrit, platelet count and liver function tests (LFTs [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]). The second or convalescent blood sample will be taken during the convalescent phase of the disease (ie, between 7 and 14 days after the acute sample) and will be tested for dengue IgM/IgG by ELISA, hematocrit, platelet count, and LFTs (as above).

Local standards of care may require additional tests, based on clinical presentation and at medical discretion. Additional dengue neutralizing antibody and other laboratory tests may be performed. In addition to blood tests, clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms.

In addition, during Part 3, subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or clinically suspected dengue and not requiring hospitalization will have 1 blood sample taken for dengue infection confirmation by RT-PCR unless there is an alternate laboratory confirmed etiology. The blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Febrile illness cases within 30 days after vaccination will be investigated for the presence of WT or vaccine-derived dengue virus. The testing algorithm is described in the serology plan. Clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms. Local standards of care may require additional tests, based on clinical presentation and at medical discretion.

A febrile illness as described above will require an interval of at least 14 days from a previous febrile illness to avoid overlap of acute and convalescent visits from 1 episode with those from a second episode.

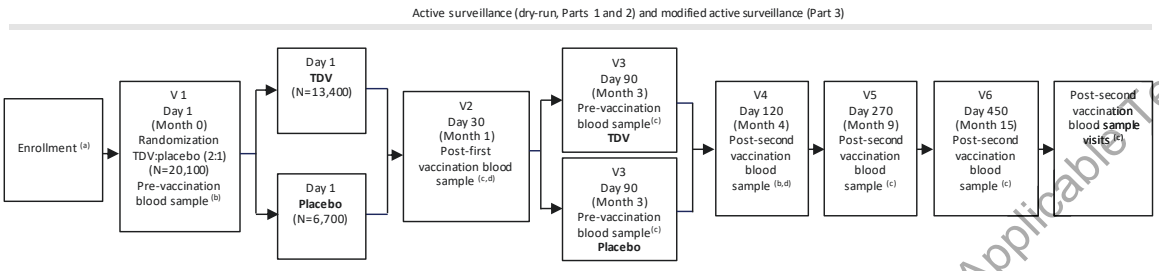
Procedures

After informed consent/assent has been obtained (which may be up to 10 months prior to vaccination on Day 1 [Month 0] as described above and as a result of the dry-run) each subject will be assessed for eligibility to participate in the trial. On Day 1 (Month 0) a pre-vaccination blood sample will be taken, randomization to TDV or placebo, and vaccination will occur. A second vaccination will be administered at Day 90 (Month 3). Subjects included in the subset (see above) will also be randomly selected using the IWRS or IVRS.

Any withdrawals from enrollment until Day 1 will be replaced so that 20,100 subjects are randomized and vaccinated; any withdrawals after randomization will not be replaced.

The trial schedule (subject flow and visits) is presented below in Figure 4.b. A detailed schedule of procedures is listed in Appendix A (Table 8.a).

Figure 4.b Schematic to Show Subject Flow Through the Study (Parts 1, 2, and 3)



Note: (i) Any subjects who withdraw between enrollment and randomization will be replaced so that 20,100 subjects are randomized; subjects who withdraw after randomization will not be replaced.
(ii) Subjects presenting with febrile illness (defined as temperature ≥38°C on any two of three consecutive days) or clinically suspected dengue during the dry-run, Parts 1 and 2, or with febrile illness requiring hospitalization during Part 3 will have two blood samples taken to confirm dengue infection. The first or acute blood sample will be taken during the acute phase of the disease (i.e., as soon as possible and preferably within 5 days after the onset of fever); the second or convalescent blood sample will be taken during the convalescent phase of the disease (i.e., between 7 to 14 days after the acute sample).
(iii) During Part 3, subjects presenting with febrile illness (defined as temperature ≥38°C on any two of three consecutive days) or clinically suspected dengue and not requiring hospitalization will have one blood sample taken during the acute phase of the disease (i.e., as soon as possible and preferably within 5 days after the onset of fever) unless there is an alternate laboratory confirmed etiology.
[a]Prior to entry into the dry-run or Day 1 (Month 0)
[b]Blood sample for dengue neutralizing antibodies for all subjects
[c] Additional blood samples for dengue neutralizing antibodies will be taken in the subset on Day 30 (Month 1), Day 90 (Month 3), Day 270 (Month 9), Day 450 (Month 15), and then every 12 months until the end of Part 3.
[d] Day 30 (Month 1) and Day 120 (Month 4) blood samples should be taken at least 28 days after the first and second vaccination, respectively.
V= Visit

Between 4 years and approximately 4.5 years post-dose 2 in Part 3, the parent/guardian of subjects who are included in the Per-Protocol Set (PPS, for definition refer to Section 7.2.1) CCI [redacted]. Details on data analysis for subjects who do not complete Part 3 of the trial will be described in Section 7.1.

Immunogenicity evaluation (microneutralization test 50% [MNT_{50}]):

All subjects:

- Blood samples will be collected pre-vaccination on Day 1 (Month 0) and post-second vaccination on Day 120 (Month 4).

Subset:

- Additional blood samples will be collected post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3), post-second vaccination on Day 270 (Month 9) and Day 450 (Month 15), and then every 12 months until the end of Part 3.

Safety evaluation:

All subjects:

- Identification of febrile episodes with potential dengue etiology for the trial duration.
- Blood samples will be collected in the event of febrile illness as described above.

- Documentation of all Serious Adverse Events (SAEs) during Parts 1 and 2. During Part 3, investigators will be required to report all deaths as well as SAEs assessed as related, or deemed relevant by the Investigator in the context of vaccine safety.

Subset:

- Subjects will be provided with a diary card for the recording of:
  - Solicited local AEs for 7 days following each vaccination (day of vaccination + 6 subsequent days). These will include:
    - Injection site pain, injection site erythema and injection site swelling.
  - Solicited systemic AEs for 14 days following each vaccination (day of vaccination + 13 subsequent days). These will include:
    - Child <6 years: fever, irritability/fussiness, drowsiness and loss of appetite.
    - Child ≥6 years: asthenia, fever, headache, malaise and myalgia.
- Unsolicited AEs for 28 days following each vaccination (day of vaccination + 27 subsequent days) will be collected by interview (ie, at Day 30 [Month 1] and Day 120 [Month 4], as applicable).

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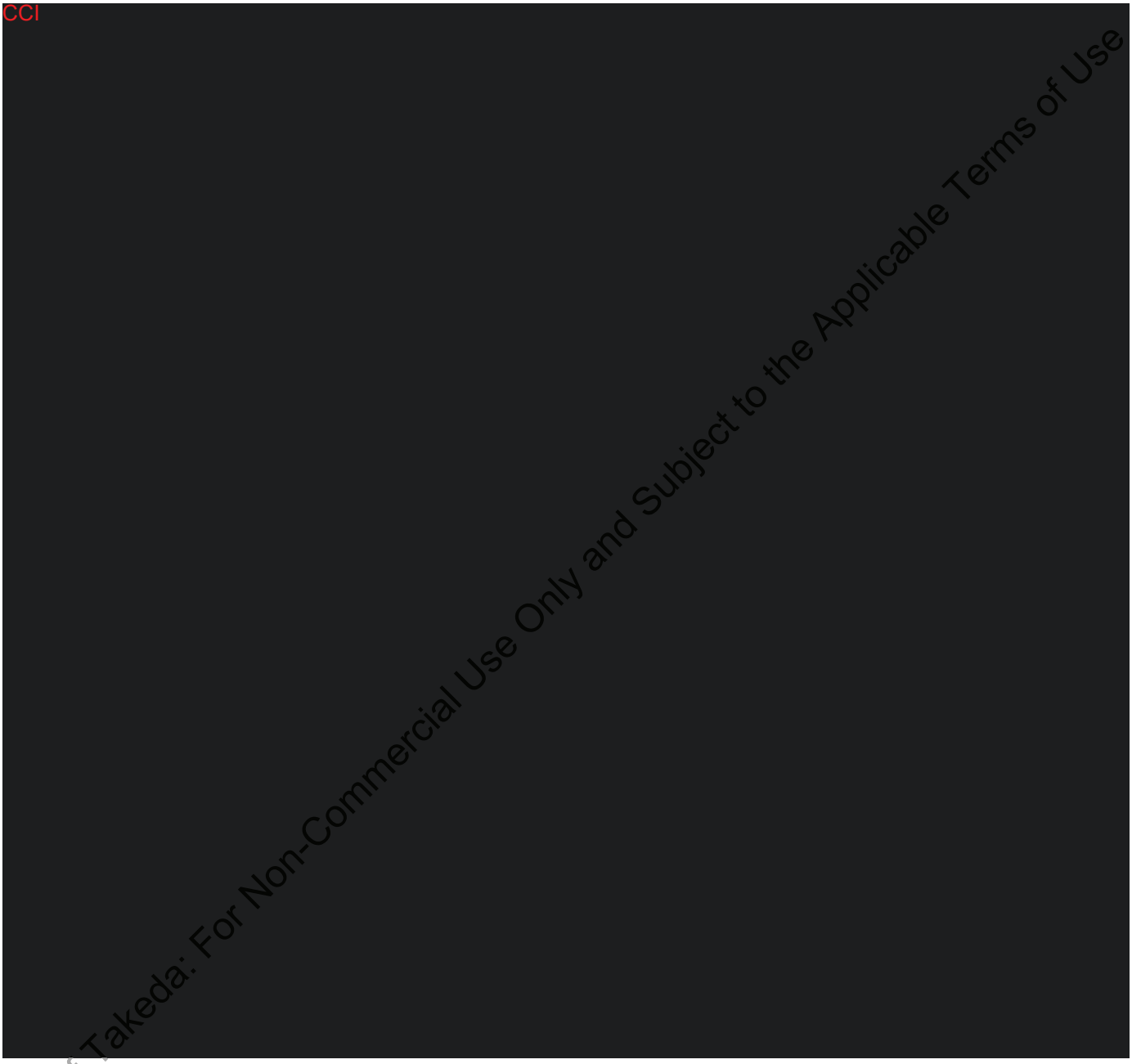

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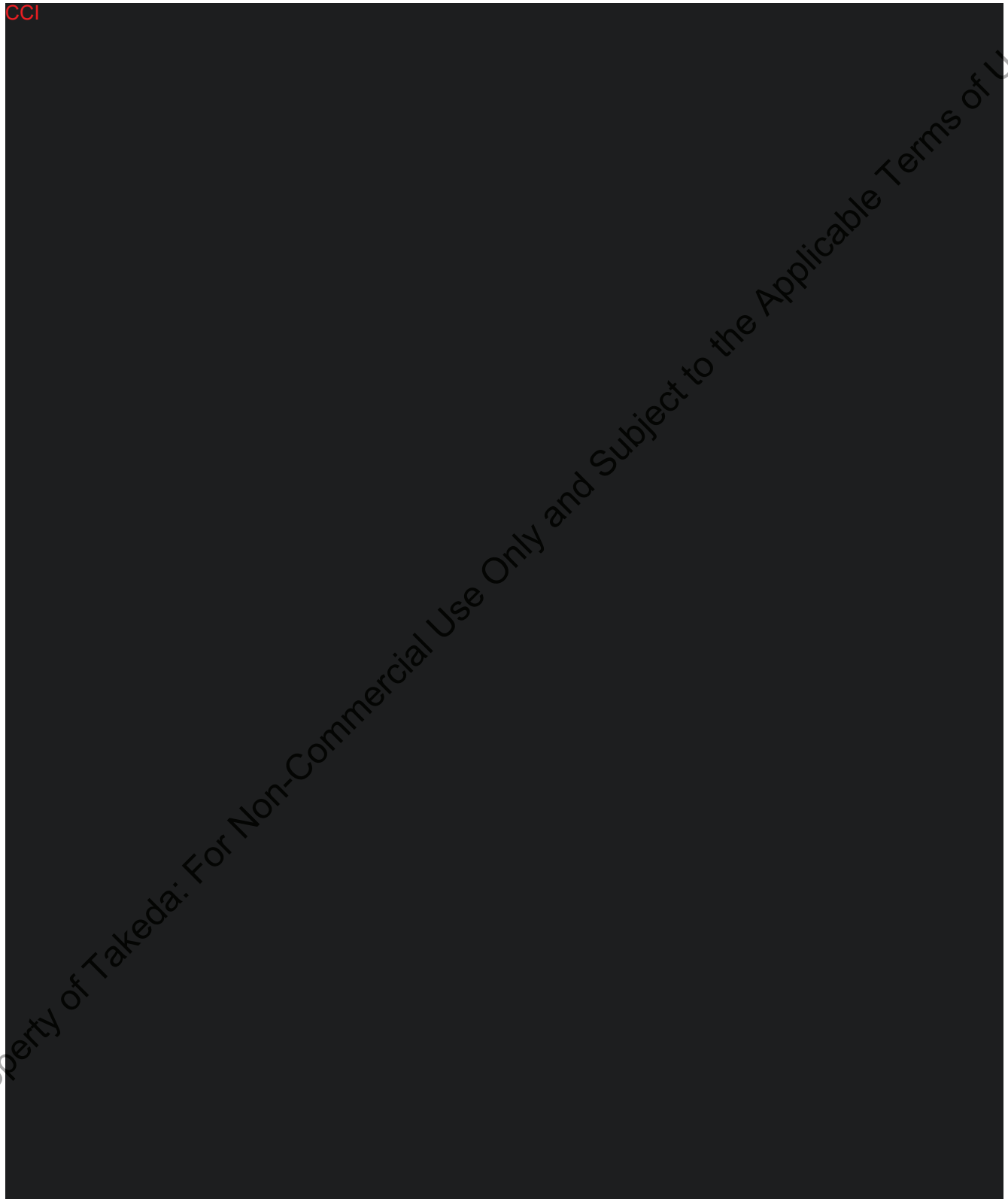

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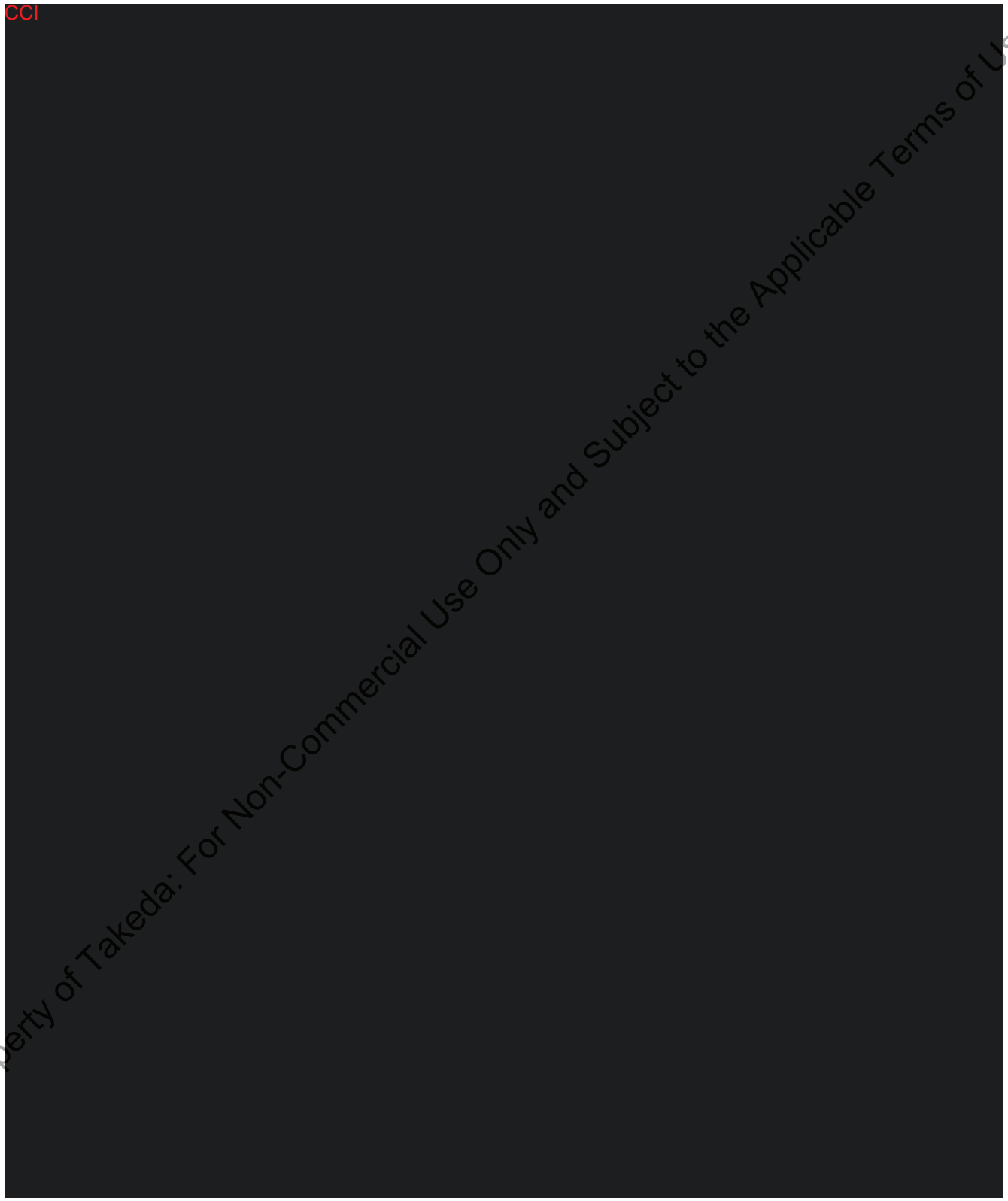

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4.5 Duration of Study

4.5.1 Parts 1, 2, and 3

For each participant, the trial duration will be approximately 42 months after the completion of Part 1 (at least 6 months in Part 2 and approximately 3 years in Part 3). The minimum duration of Part 1 will be approximately 15 months (including minimum 12 months after second vaccination for each subject) but may be longer depending on the time taken to fulfill criteria for the end of Part 1. Hence, it is not explicitly defined. There is a possibility that when end of Part 1 is determined, certain subjects who were randomized earlier might have already completed the 6 months of active surveillance required for Part 2. The transition to Part 3 (ie, modified active surveillance) will occur at that point for those subjects.

CCI

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5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

Efficacy

VE of 2 doses of TDV in preventing VCD fever induced by any dengue serotype occurring from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 1, with VE defined as $1 – (\lambda_V/\lambda_C)$ (where λ_V and λ_C denote the hazard rates for the TDV and placebo arms, respectively).

5.2 Secondary Endpoints

Efficacy

- VE of 2 doses of TDV in preventing VCD fever induced by each dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2.
- VE of 2 doses of TDV in preventing VCD fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2 in subjects dengue seronegative at baseline.
- VE of 2 doses of TDV in preventing VCD fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2 in subjects dengue seropositive at baseline.
- VE of 2 doses of TDV in preventing hospitalization due to VCD fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2.
- VE of 2 doses of TDV in preventing virologically-confirmed severe dengue fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2.

Safety

<u>Subset (post-first and post-second vaccinations):</u>

- Frequency and severity of solicited local (injection site) adverse events (AEs) for 7 days (day of vaccination + 6 subsequent days) and solicited systemic AEs for 14 days (day of vaccination + 13 subsequent days) post-vaccination.
- Percentage of subjects with any unsolicited AEs for 28 days (day of vaccination + 27 subsequent days) post-vaccination.

<u>All subjects:</u>

- Percentage of subjects with SAEs during Part 1, Part 2, and Parts 1 and 2 combined.
- Percentage of subjects with fatal SAEs and related SAEs during first and second half of Part 3.

Immunogenicity

Subset (post-first and post-second vaccination):

- Seropositivity rate (% of seropositive subjects) for each of the 4 dengue serotypes at pre-vaccination on Day 1 (Month 0), post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3), post-second vaccination on Day 120 (Month 4), Day 270 (Month 9), Day 450 (Month 15), and then annually.
- Seropositivity rate (% of seropositive subjects) for any 1 (monovalent), 2 (bivalent), 3 (trivalent), and 4 (tetravalent) dengue serotypes, as well as at least bivalent (seropositive for ≥2 dengue serotypes) and at least trivalent (seropositive for ≥3 dengue serotypes) at pre-vaccination on Day 1 (Month 0), post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3), post-second vaccination on Day 120 (Month 4), Day 270 (Month 9), Day 450 (Month 15), and then annually.
- Note: Seropositivity is defined as a reciprocal neutralizing titer ≥10.
- Geometric mean titers (GMTs) of neutralizing antibodies (MNT50) for each dengue serotype at pre-vaccination on Day 1 (Month 0), post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3), post-second vaccination on Day 120 (Month 4), Day 270 (Month 9), Day 450 (Month 15), and then annually.

5.3 Exploratory Endpoints

5.3.1 Parts 1, 2, and 3

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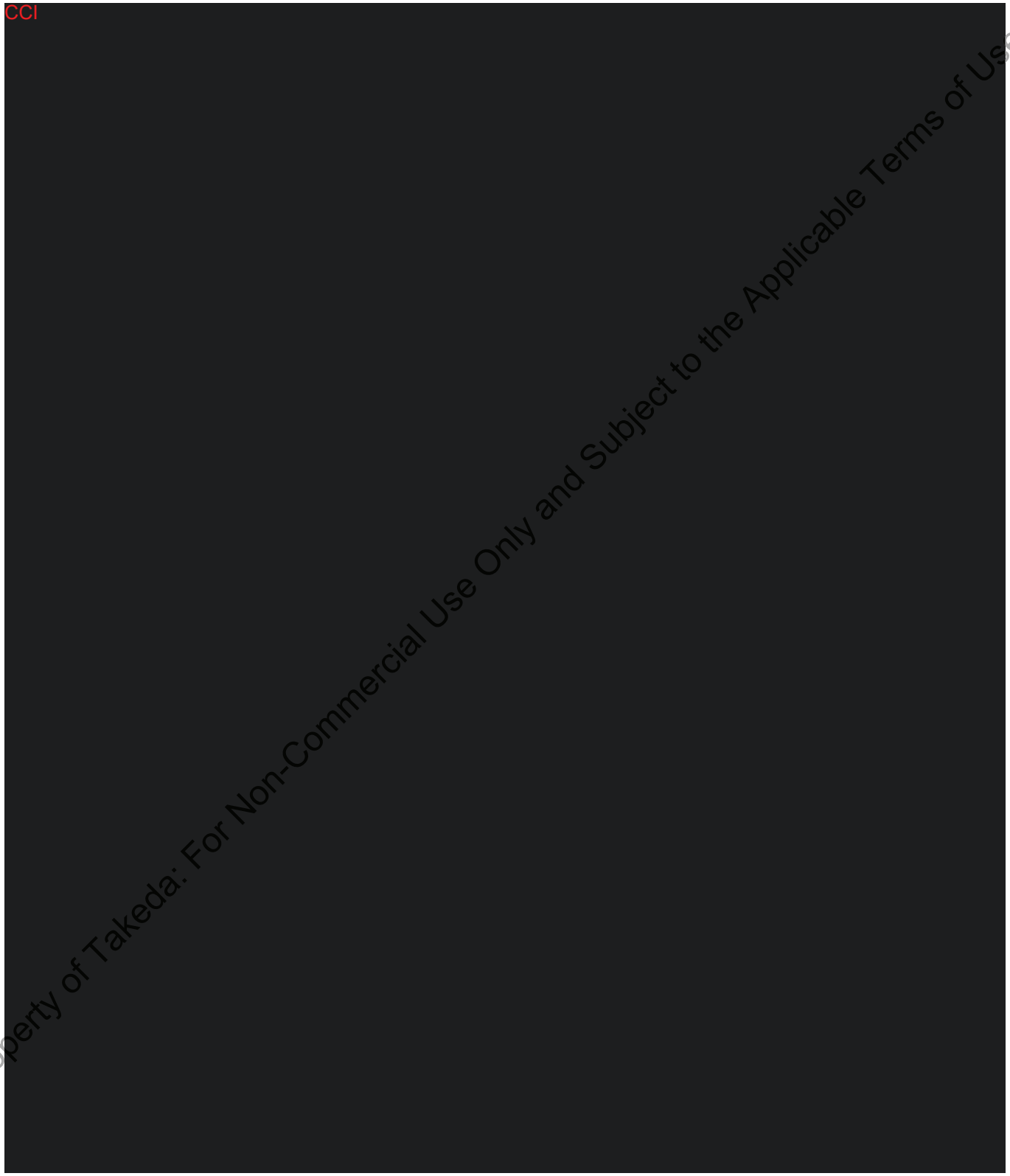

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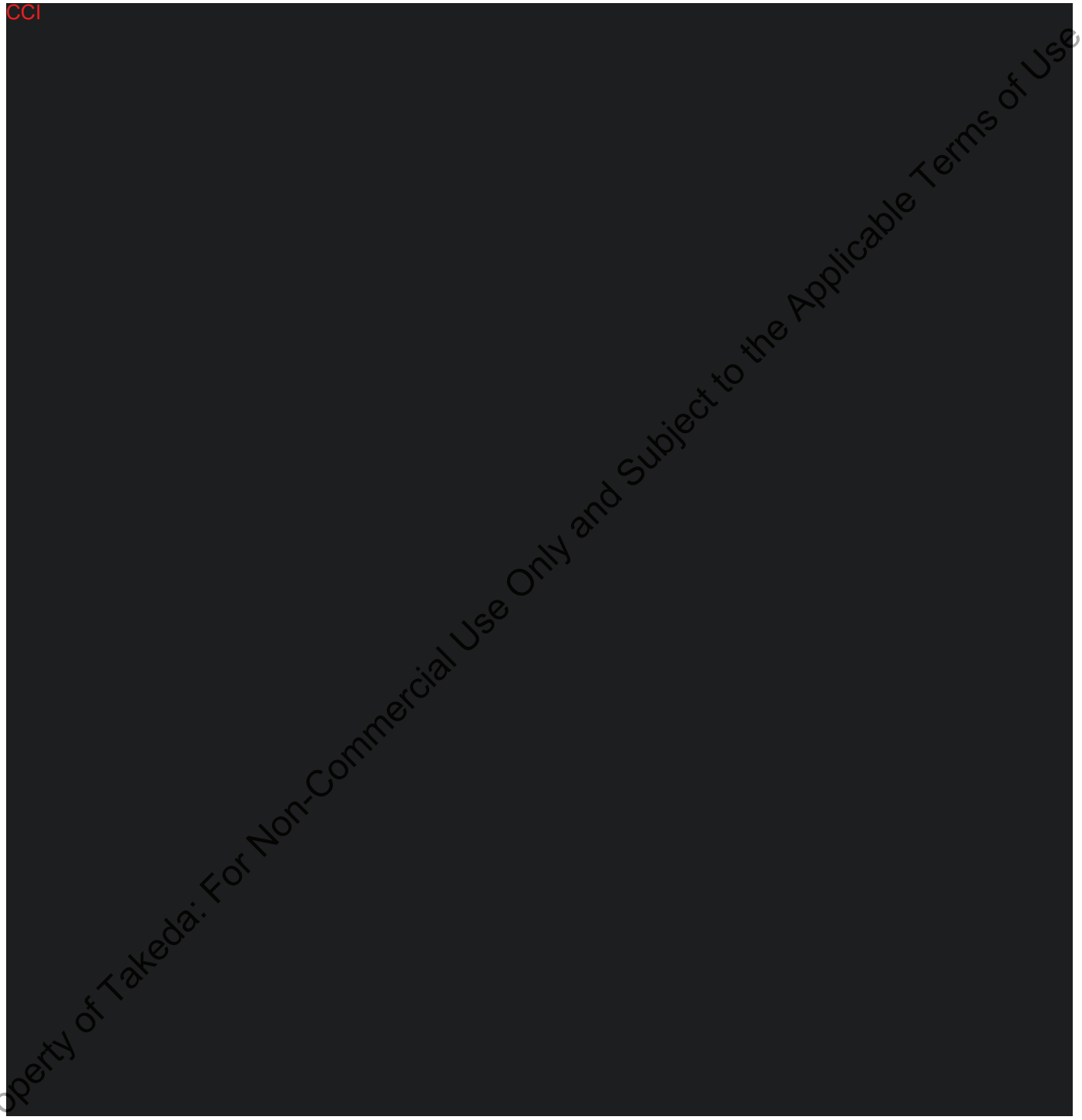

6.0 DETERMINATION OF SAMPLE SIZE

6.1 Parts 1, 2, and 3

This is a partially case-driven trial (ie, Part 1 is case driven).

Assuming true VE of 60% and a randomization ratio of 2:1 (TDV:placebo), a total of 120 virologically-confirmed cases of dengue fever induced by any dengue serotype occurring from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 1 would provide at least 90% power to rule out a vaccine effect of ≤ 25% (with a 2-sided significance level of 0.05). Assuming a background incidence rate of 1.0% by the end of Part 1 (minimum 12 months after the second vaccination for each subject), randomization of 20,100 subjects in a 2:1 ratio with follow-up for a minimum of 12 months would allow accrual of at least 120 dengue fever cases. Exclusion of subjects from the Per-Protocol Set will be compensated by a potentially longer duration of Part 1.

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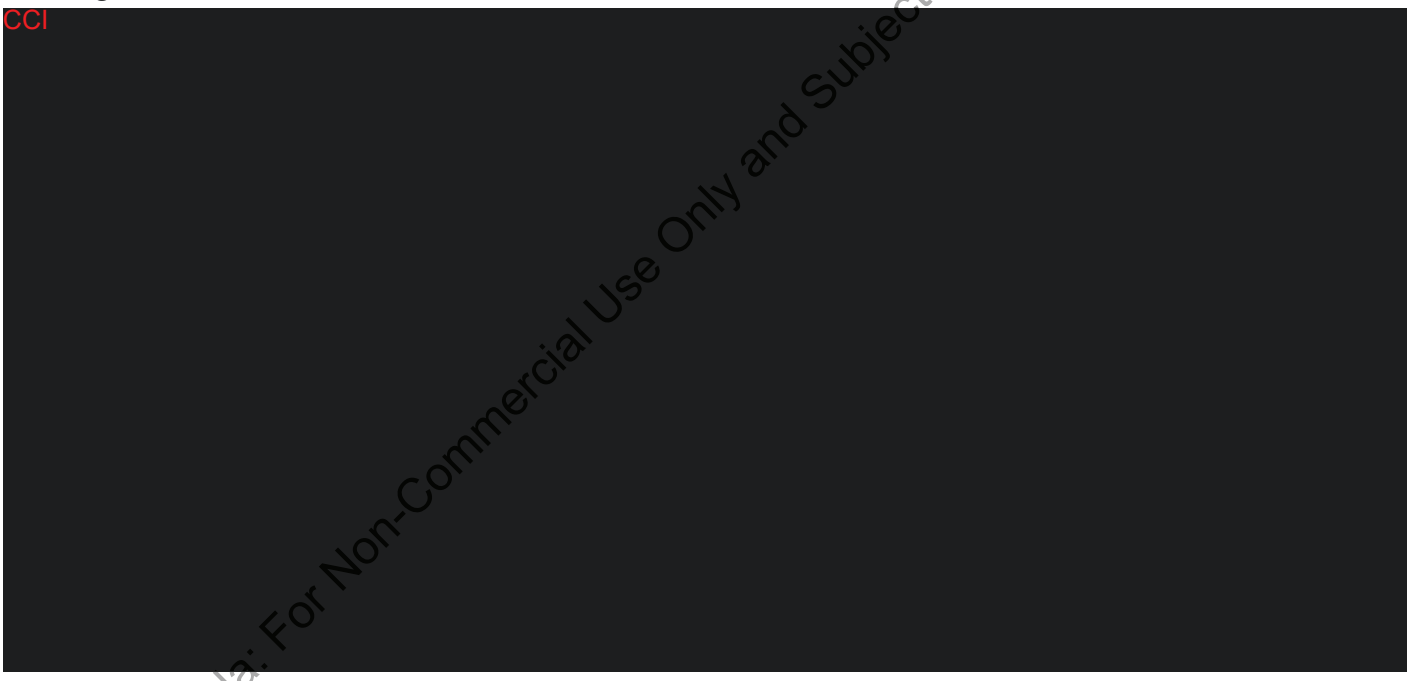

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7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Considerations

This SAP was developed on the International Conference on Harmonization E3 and E9 Guidelines, and information provided in Protocol DEN-301, Version 6.0 dated 18 May 2020 [1]. The shells of tables, listings and graphs will be provided in a separate document.

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

This document will provide details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A blinded data review will be conducted prior to unblinding of subject's assignment to IP. 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 eCRF, all categories will be presented as specified, even if the subject count within that category is zero. For other categorical data (eg, adverse events and medications), only categories with at least one subject will be presented.

For summary tables a value of 5 (midpoint between 0 and the lower limit of detection [ie, 10]) will be used for Dengue Neutralizing Antibody titers which are below the lower limit of detection. If a reported value is between the lower limit of detection and the lower limit of quantification (different for each serotype) this value will be replaced with the mid-point between the two. However, for listings the original reported values will be displayed.

CCI [redacted]

For subjects who received Dengvaxia during the course of the trial data will be handled in the following way:

- Efficacy/Immunogenicity: Subjects' data after receipt of Dengvaxia will be excluded from the "Per-Protocol" and "Full Analysis" analyses. For analyses related to vaccine efficacy subjects will be censored at the time of receipt of Dengvaxia or at Day 1 if receipt of Dengvaxia was before the respective analysis period. This time point will be considered as last contact. CCI [redacted].
- Safety: Safety summaries will be provided on all subjects regardless of the receipt of Dengvaxia. CCI [redacted].

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

Handling of missing and partial start/end dates for unsolicited AEs, medical history/concurrent medical conditions and prior/concomitant medication/vaccination dates:

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 could be allocated with (ie, Vaccination 1 or Vaccination 2). 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 the year of the AE start is/are available, the AE will be allocated with the latest vaccination prior to the AE start date;
- If the AE start date is completely missing, or the available start date information is insufficient to distinguish between the 2 trial vaccinations, but a partial AE end date (ie, month and/or year) is available, the AE end date will be assessed and the AE will be allocated with the vaccination after which the event ends, assuming transient nature of events. If partial end date information indicates possible allocation with both vaccinations, the AE will be allocated with the first trial vaccination.

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

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

CCI [redacted]

Rounding and precision:

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. Standard deviations (SD) and Standard errors (SE) will be presented to 2 more decimal places than the recorded data. Confidence intervals (CI) 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 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". P-values will only be presented for the primary and key secondary efficacy endpoints.

Definition of baseline and study day for immunogenicity and safety:

Baseline is defined as the last non-missing measurement taken before the first dose of IP administration. Study Day 1 is defined to be the date of the first of IP administration, as recorded on the eCRF page. Other trial days are defined relative to the study day 1, with Day -1 being the day prior to Day 1. CCI [redacted] These trial days will be presented in the listings, where applicable.

Windowing of Post Baseline Data:

A windowing convention for the immunogenicity and safety data will be used to determine the analysis value for a given trial visit for observed data analyses. Analysis visit windows will be calculated relative to the days when each trial dose was administered (Day 1 [M0] and Day 90 [M3] in Part 1 CCI [redacted] The window definitions for Parts 1, 2, and 3 are presented in Table 7.a CCI [redacted]

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. Only scheduled visits will be considered for the visit mapping.

Table 7.a Analysis Visit Windows (Parts 1, 2, and 3)

Visit	Scheduled Visit Day (Month)	Scheduled Vaccination	Visit Windows	
			Full Analysis Set & Safety Set	Per-Protocol Set
V1	Day 1 (M0)	Dose 1	Prior [≤1 day] [(a)] to Dose 1	Prior [≤1 day] [(a)] to Dose 1
V2	Day 30 (M1)		2-60 days [(b)] after Dose 1	29-37 days [(b)] after Dose 1
V3	Day 90 (M3)	Dose 2	61-115 days [(b)] after Dose 1 and Prior [≤1 day] [(a)] to Dose 2	75-115 days [(b)] after Dose 1 and Prior [≤1 day] [(a)] to Dose 2
V4	Day 120 (M4)		2-105 days [(b)] after Dose 2 or 116-195 days [(b)] after Dose 1[(c)]	29-37 days [(b)] after Dose 2
V5	Day 270 (M9)		106-270 days [(b)] after Dose 2 or 196-360 days [(b)] after Dose 1[(c)]	159-201 days [(b)] after Dose 2
V6	Day 450 (M15)		271-542 days [(b)] after Dose 2 or 361-632 days [(b)] after Dose 1[(c)]	330-390 days [(b)] after Dose 2

CCI [redacted]

(a) Blood draw for immunogenicity assessments and assessment of vital signs must be prior to the vaccination scheduled for the same visit, and where time is available, the time of the blood/vital signs collection must be prior to the vaccination time. Day 1 (M0) 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 the second dose at V3.

CCI [redacted]

CCI

[redacted]

Definition of end of Part 1 for subjects who didn't receive the second dose or discontinued the trial during Part 1:

For subjects who did not receive a second vaccination, the end of Part 1 will be defined as 455 days (365 days + 90 days) from first vaccination. Note that subjects can be followed for febrile illnesses after trial discontinuation if they consent. For subjects in the Full Analysis Set and Per-Protocol Set (see definitions in Section 7.2) who discontinue from the trial before the defined end of Part 1, Part 1 will end at the time of trial discontinuation, regardless of whether subjects agreed to be followed for febrile illnesses after trial discontinuation. For subjects in the Safety Set (see definition in Section 7.2) whose last febrile surveillance contact date is before the defined end of Part 1, Part 1 will end at the last febrile surveillance contact date; if subjects in the Safety Set did not agree to be followed for febrile illness after trial discontinuation, and trial discontinuation date is before the defined end of Part 1, Part 1 will end at the time of trial discontinuation.

A similar approach will be followed for other trial parts.

CCI

[redacted]

CCI

7.2 Analysis Sets

Dry Run Set: The Dry Run Set will consist of all subjects (regardless of whether they were randomized or not) who participated in the dry-run prior to Part 1.

7.2.1 Parts 1, 2, and 3

Randomized Set: The Randomized Set will consist of all randomized subjects, regardless of whether any dose of the IP (TDV or placebo) was received. Subjects will be summarized according to the IP to which they were assigned.

Safety Set (SS): The SS will consist of all randomized subjects who received at least one dose of the IP (TDV or placebo). For analyses of solicited AEs (reactogenicity) and unsolicited AEs, only subjects in the subset will be included. For all subjects in the SS, SAEs will be assessed during Parts 1, 2, and 3. Subjects will be summarized according to the IP received.

The following approach will be used for subjects with IP misallocations:

- Subjects who received the planned vaccine regimen for the other trial group to the one randomized to (ie, subjects who received TDV/TDV instead of Placebo/Placebo or vice versa) will be displayed in the respective trial group in the summaries based on the Safety Set (according to the IP received).
- Subjects who did not receive the planned vaccine regimen (ie, subjects who received TDV/Placebo or Placebo/TDV) will be considered in a separate group (ie, misallocations). Data for this group will be displayed in selected summary tables and all listings generated based on the Safety Set.

Full Analysis Set (FAS): The FAS will consist of all randomized subjects who received at least one dose of the IP (TDV or placebo). Subjects will be summarized according to the IP to which they were assigned.

Full Analysis Set for Immunogenicity (FASI): The FASI will be based on the FAS and will consist of all randomized subjects in the subset for whom a valid pre-dosing and at least one valid post-dosing blood sample have been received for immunogenicity. Subjects will be summarized according to the IP 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 Section 7.2.3 (Table 7.c).

Per-Protocol Set for Immunogenicity (PPSI): The PPSI will consist of all subjects in the FASI who have no major protocol violations.

CCI

CCI [redacted]

7.2.3 Major Protocol Violations and Evaluability Criteria

A major protocol violation is considered to have a potentially significant impact on the efficacy and immunogenicity results of the subject. All protocol violations will be identified prior to unblinding and a clinical judgment will be necessary to classify each deviation as "major" or not. These violations and the judgment regarding their use will be listed and summarized (for all subjects, by region and country) based on the randomized set and separately for the subset C CI [redacted].

The criteria described in this section will be used to identify subjects with major protocol violations which could impact the primary analysis of efficacy and also the immunogenicity results. Subjects meeting these criteria will be excluded from the PPS, PPSI, CCI [redacted] described above. Subjects meeting these criteria will be identified and approved prior to database lock and unblinding for Part 1 (PPS and PPSI) and the first interim analysis (IA) CCI [redacted] Subjects excluded from the PPS/PPSI CCI [redacted] due to receiving incorrect IP will be identified after unblinding for Part 1 CCI [redacted]. The criteria mentioned in Table 7.c below will be assessed for Part 1 only (primary endpoint

timeframe) and will not be changed for other trial parts. Similarly, the criteria mentioned in Table 7.d below will be assessed prior to the first IA CCI [redacted]

These criteria for exclusion of subjects from the PPS sets will be reviewed, approved and documented (in a separate document) prior to database lock and unblinding as part of the blinded data reviews. Any changes to these criteria after approval of the SAP will be documented and approved in a separate document prior to database lock and unblinding.

Table 7.c Criteria for Exclusion from PPS and PPSI

Criteria for Exclusion	Probable Method of Identification
Not receiving both doses of the IP (TDV or placebo) administration	Identified programmatically using dosing data.
Not receiving both doses in the correct interval (refer to windows defined in Table 7.a)	Identified programmatically using dosing data.
Not receiving the assigned IP/dosing schedule [refers to correct administration of active or placebo on Day 1 or Day 90]	Identified after unblinding [eg, subject A who was randomized to TDV but received Placebo, subject who was randomized to placebo but received TDV]
Product preparation error.	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/vaccines (subject to blinded medical review)	Potential prohibited medications (Appendix C) to be identified by sending a blinded review list of CRF-recorded medication data for medical review to determine evaluability status for each identified subject.

CCI [redacted]

Furthermore, for immunogenicity analyses, samples taken outside the visit windows pre-specified in the trial protocol (see also Table 7.a and Table 7.b) will not be included in the respective visit.

Other major violations may be identified based on blinded data reviews and deviation logs throughout the trial, subject to medical review.

Significant protocol deviations will be summarized based on the randomized set and all CCI [redacted] during Parts 1, 2, and 3 CCI [redacted] respectively. In addition, a listing including all significant protocol deviations will be presented based on all screened and all sCCI [redacted] during Parts 1, 2, and 3 CCI [redacted] respectively.

All protocol deviations related to the Coronavirus Disease 2019 (COVID-19) pandemic will be summarized based on the randomized set up to end of Part 3. CCI [redacted]. CCI [redacted]. An additional listing including all protocol deviations related to the COVID-19 pandemic will be presented by subject number, significance, date of the protocol deviation, deviation type and description of the protocol deviation.

7.3 Disposition of Subjects

Trial information will be presented for all screened subjects, including the date the first subject signed the informed consent form, the date of the first subject's first vaccination, the date of the last subject's first vaccination, the date of the first's subject's second vaccination, the date of the last subject's second vaccination, the date of first subject first visit/contact and the date of last subject's last visit/contact. CCI [redacted]. Finally, the Medical Dictionary for Regulatory Activities (MedDRA) version, the World Health Organization Drug Dictionary (WHODrug) version, and the SAS version used for analysis, will be presented, where applicable.

Number of subjects in all the analysis sets described in Sections 7.2.1 CCI [redacted] will also be summarized.

7.3.1 Parts 1, 2, and 3

The reasons for screen failure will be summarized based on all screened subjects (for all subjects and by region, country and site).

Disposition of all randomized subjects as well as for subjects in the SS will be summarized for each trial group. For the SS disposition will also be summarized by age group, by region, by country, and by combination of region and age group.

Note: Age group is defined as the age at the time of randomization. When age group is mentioned in the SAP this refers to the age group at the time of randomization.

The categories will include:

- Number of subjects who participated in the dry-run
- Number of randomized subjects
- Number of subjects randomized but not vaccinated including primary reason for not being vaccinated
- Number of subjects who received at least 1 dose of the IP
- Number of subjects who received both doses of the IP
- Number of subjects who prematurely discontinued before receiving the second dose of the IP including primary reason for discontinuation prior to receipt of second dose
- Number of subjects who completed the trial (by trial part)
- Number of subjects who prematurely discontinued the trial (by trial part)
- Primary reason for premature discontinuation of the trial (by trial part)
- Number of subjects who agreed to be followed for febrile surveillance

A subject is to be assumed ongoing unless he/she completed the end of trial CRF, indicating either completion or early terminated. Number of subjects screened/enrolled, randomized, and participating in the dry-run and analysis populations by region and country will also be presented. In addition, the number of subjects participated in the dry-run will be summarized.

CCI

7.4 Demographic and Baseline Characteristics

7.4.1 Parts 1, 2, and 3

Demographic and baseline characteristics will include age, age group (4-5 years / 6-11 years / 12-16 years), gender, body weight, height, BMI, race, region (Asia Pacific / Latin America), country, and will be summarized descriptively by trial group based on the Safety Set, Safety Set-Immunogenicity Subset, the PPS and the PPSI. Demographic and baseline characteristics for the dry-run set will also be summarized.

Summary statistics (number of subjects, mean, median, SD, minimum, and maximum) will be generated for continuous variables and the number and percentage of subjects within each category will be presented for categorical variables. Inferential analyses of demographic data and baseline characteristics will not be performed.

CCI

CCI [redacted]

Individual demographic data and baseline characteristics will be presented in the data listing.

Demographic data and baseline characteristics of screen failure subjects will be summarized overall, CCI [redacted] for subjects who are screened, but not randomized in the trial. These individual data as well as the date of informed consent and reason for screen failure will also be presented in the data listing.

CCI [redacted]

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded using the MedDRA coding system. The version of the dictionary used will be specified in the CSR (Clinical Study Report).

In addition, all medical history and concurrent medical condition data will be listed by trial group and subject number and presented based on SS/CCI [redacted], depending on the time of the trial. The listing will also contain system organ class (SOC), preferred term (PT), start and stop dates of the medical history and concurrent medical conditions and the study day/CCI [redacted] when the medical history or concurrent medical condition occurred.

7.5.1 Parts 1, 2, and 3

During Parts 1, 2, and 3, a medical history is defined as any significant condition/disease that stopped at or prior to first dose of IP. Concurrent medical conditions are conditions that are recorded as ongoing at the time the first dose of IP is administered.

CCI

[redacted]

7.6 Medication/Vaccination History and Concomitant Medications/Vaccinations

Medication/vaccination history and concomitant medications/vaccinations will be coded using the WHODrug. The version of the dictionary used will be specified in the CSR.

In addition, all medication/vaccination history and concomitant medications/vaccinations will be listed by trial group and subject number and presented on SS/CCI [redacted] depending on the time of the trial. The listing will also contain Anatomical Therapeutic Chemical (ATC) code, preferred medication name, dose, frequency, unit, route, start/stop date and reason for use.

7.6.1 Parts 1, 2, and 3

During Parts 1, 2, and 3, a prior medication/vaccination (history) is defined as any medication/vaccination that stopped at or prior to first dose of IP. A concomitant medication/ vaccination is any medication/vaccination taken on or after trial vaccination (ie, 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 will be provided by ATC code, preferred medication name, and trial group based on the SS (overall, by region and by country). Summary tables for vaccination history will be provided by vaccination type, vaccination name, and trial group based on the SS (overall, by region and by country). Additional summary tables will contain more details on prior/ concomitant use of Japanese Encephalitis and Yellow Fever Vaccines based on the SS and Safety Set-Immunogenicity Subset (overall, by region, by country, by age group, by combination of region and age group, and by combination of country and age group).

CCI

[redacted]

CCI [redacted]

7.7 Investigational Product Exposure and Compliance

The investigator records all injections of IP (TDV or placebo) given to the subject in the eCRF. The IP administration date/time information will be listed for each subject. The compliance rate will be summarized for the SS by trial group (including a separate group of subjects who received different IPs at the first and second vaccination [if any]) presenting the number and percentage of subjects who received both doses and the number and percentage of subjects who received the first dose only (overall, by region, by country, by combination of region, country and age group). The duration of follow-up during Parts 1, 2, and 3 will be summarized based on the SS as a continuous variable, and also in categories using intervals of 6 months, ie, 1 – 180 days, 181 – 360 days, 361 – 540 days, etc. The follow-up is defined as the number of days from first or second vaccination until end of the respective analysis reporting period. CCI [redacted]

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint in this trial is VE of two doses of TDV in preventing VCD fever induced by any dengue serotype occurring from 30 days post-second vaccination (Day 120 [Month 4]) until end of Part 1 (see Figure 4.a). VE is defined as $1 - (\lambda_V / \lambda_C)$, where λ_V and λ_C denote the hazard rates for the TDV and placebo arms, respectively.

The primary analysis of VE will be done after the 2 criteria for the end of Part 1 are fulfilled: (1) at least 120 cases of VCD have accrued, and (2) the minimum duration of subject follow-up is at least 12 months post-second vaccination.

The primary efficacy objective is considered to be met if the lower bound of the 2-sided 95% CI for the VE is above 25%. The following hypotheses will be tested in a confirmatory manner 2-sided at a significance level of 5%:

$$H_0: 1 - \lambda_V/\lambda_C \leq 0.25$$

$$H_1: 1 - \lambda_V/\lambda_C > 0.25$$

For the primary efficacy evaluation, a case of VCD is defined as febrile illness with a positive serotype-specific RT-PCR (ie, positive dengue detection RT-PCR) and occurring at any time starting from 30 days post-second vaccination (Day 120 [Month 4]) through the end of Part 1. The primary analysis will be performed on the PPS (ie, for the primary analysis the end of Part 1 will be defined based on the PPS).

The primary analysis method will be based on a Cox proportional hazard model with trial vaccine as a factor, adjusted for age, and stratified by region, with two-sided 95% CIs provided for the VE. A p-value associated with the primary objective will also be provided. The p-value can be output directly from SAS or manually calculated from SAS PROC PHREG estimates of the regression coefficient associated with the treatment ($\hat{\beta}$) and the related standard error ($\widehat{SE}$) as shown below.

The above hypotheses can be re-written as follows, given that the hazard ratio HR= λ_V/λ_C:

$$H_0: HR \geq 0.75$$

$$H_1: HR < 0.75$$

The primary objective is considered to be met if the upper bound of the 2-sided 95% CI for $\widehat{HR}$ is below 0.75.

p-value = P(obtaining a sample HR < observed HR| H_0: HR ≥ 0.75)

- If the observed HR<0.75, then the p-value can be obtained by solving the critical value Z in the following equation:

  Upper bound of 1-sided (1-p%) CI of HR=0.75

  $$e^{[\hat{\beta}+Z*\widehat{SE}]} = 0.75$$

  The 1-sided p-value is 1-(area to the left of the critical value Z from a standard normal distribution). Since the hypotheses will be tested in a confirmatory manner 2-sided at a significance level of 5%, the calculated 1-sided p-value should be compared with 0.025.

- If the observed HR ≥ 0.75, then the p-value = P(obtaining a sample HR < observed HR| H_0: HR ≥ 0.75)

  = 1-P(obtaining a sample HR > observed HR| HR ≤ 0.75)

  P(obtaining a sample HR > observed HR| HR ≤ 0.75) can be obtained by solving the critical value Z in the following equation:

  Lower bound of 1-sided (1-p%) CI of HR=0.75

$$e^{\wedge}[\hat{\beta}-Z^{*}\widehat{SE}] = 0.75$$

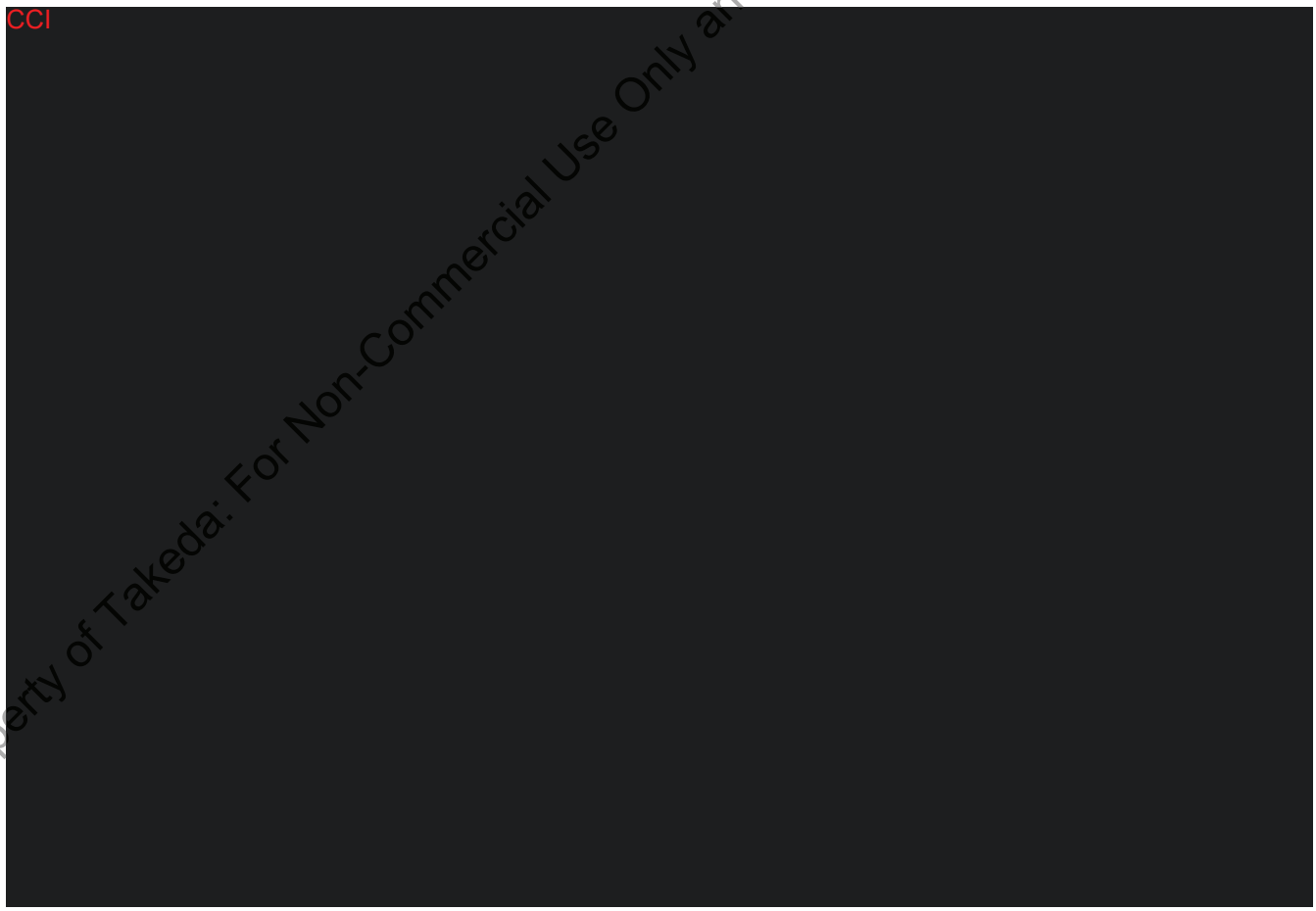
The 1-sided p-value is the area to the left of the critical value Z from a standard normal distribution. Since the hypotheses will be tested in a confirmatory manner 2-sided at a significance level of 5%, the calculated 1-sided p-value should be compared with 0.025.

Days from 30 days after the second vaccination, where 30 days of the second vaccination is considered the first day, will be used as the time scale. Subjects who withdraw consent or are lost to follow-up will be censored at the time of last contact. Subjects with VCD before the first day (as defined above) will be censored on that day.

For the PPS and FAS discontinued subjects will be censored at the day of discontinuation. For exploratory analyses based on the Safety Set, discontinued subjects who consent for febrile illness follow up will be censored after the day of discontinuation.

Sensitivity analyses of the primary endpoint include: (1) analysis using exact 95% CIs calculated as described by Breslow & Day [2], (2) analysis based on the FAS, and (3) analysis in which cases of VCD were observed at any time post-second vaccination (ie, starting on Day 90 [Month 3]).

CCI



Efficacy tables will also include number of subjects with febrile illness, number of febrile illness cases, VCD cases, person-years at risk (defined as cumulative time in years until start of VCD fever, until end of the respective trial part or discontinuation date, whichever comes first), incidence density (defined as the number of cases per 100 person-years at risk), and relative risk (calculated as number of events divided by the number of subjects evaluated in the TDV group, over the number of events divided by the number of subjects evaluated in the placebo group) and corresponding 95% CIs.

Efficacy data CCI will also be presented using Forest plots.

7.8.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint in this trial is VE of two doses of TDV in preventing hospitalization due to VCD fever induced by any dengue serotype occurring from 30 days post-second vaccination (Day 120 [Month 4]) until end of Part 2.

A hierarchical testing strategy will be used and the key secondary efficacy endpoint will only be tested in a confirmatory manner if statistical significance for the primary efficacy endpoint is achieved. Thus, the family wise Type I error rate is strongly controlled for the primary endpoint and the key secondary endpoint.

If statistical significance for the primary endpoint is achieved, the following hypotheses will be tested in a confirmatory manner 2-sided at a significance level of 5%:

$$H_0: 1 - \lambda_V/\lambda_C \leq 0$$

$$H_1: 1 - \lambda_V/\lambda_C > 0$$

The analysis of the key secondary efficacy endpoint will be based on the PPS and will be assessed using data from Parts 1 and 2. A similar approach as for the primary efficacy endpoint as described in Section 7.8.1 will be used, but statistical significance will be concluded if the lower bound of the 95% CI is >0.

CCI

CCI

CCI

7.9 Pharmacokinetic/Pharmacodynamic Analysis

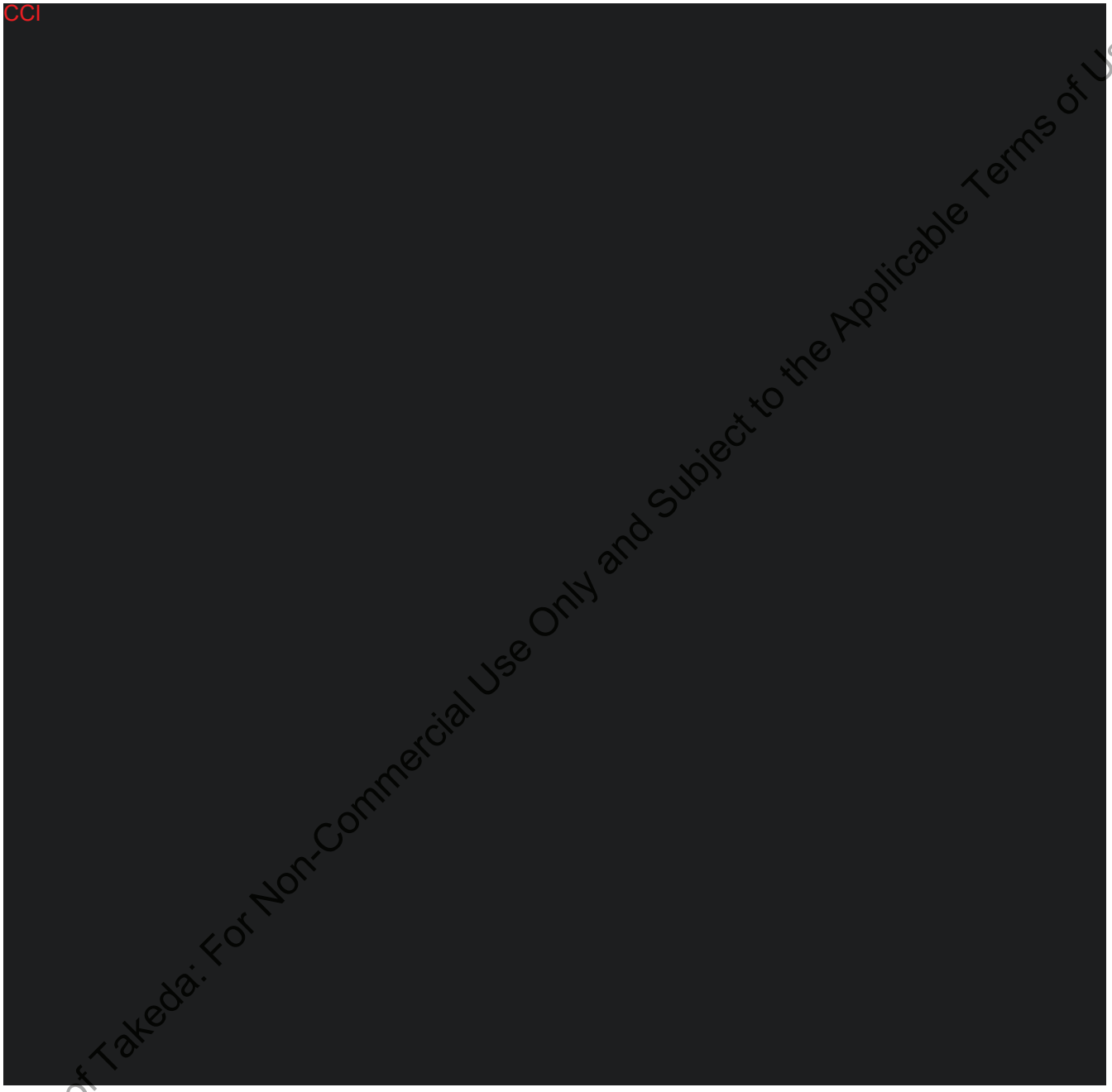
Not applicable.

7.10 Other Outcomes

All analyses described in the next sections will be exploratory only.

CCI

CCI



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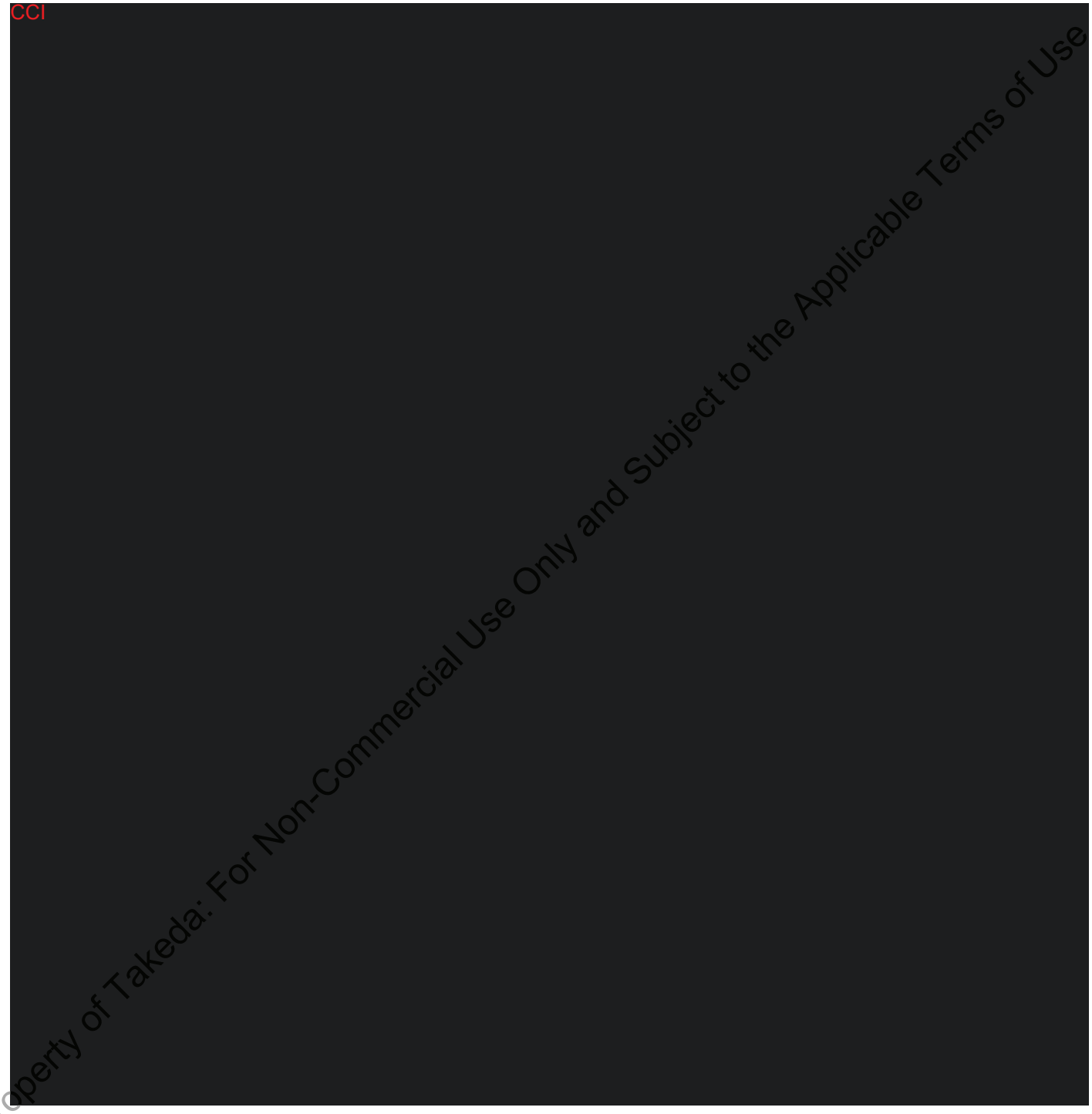

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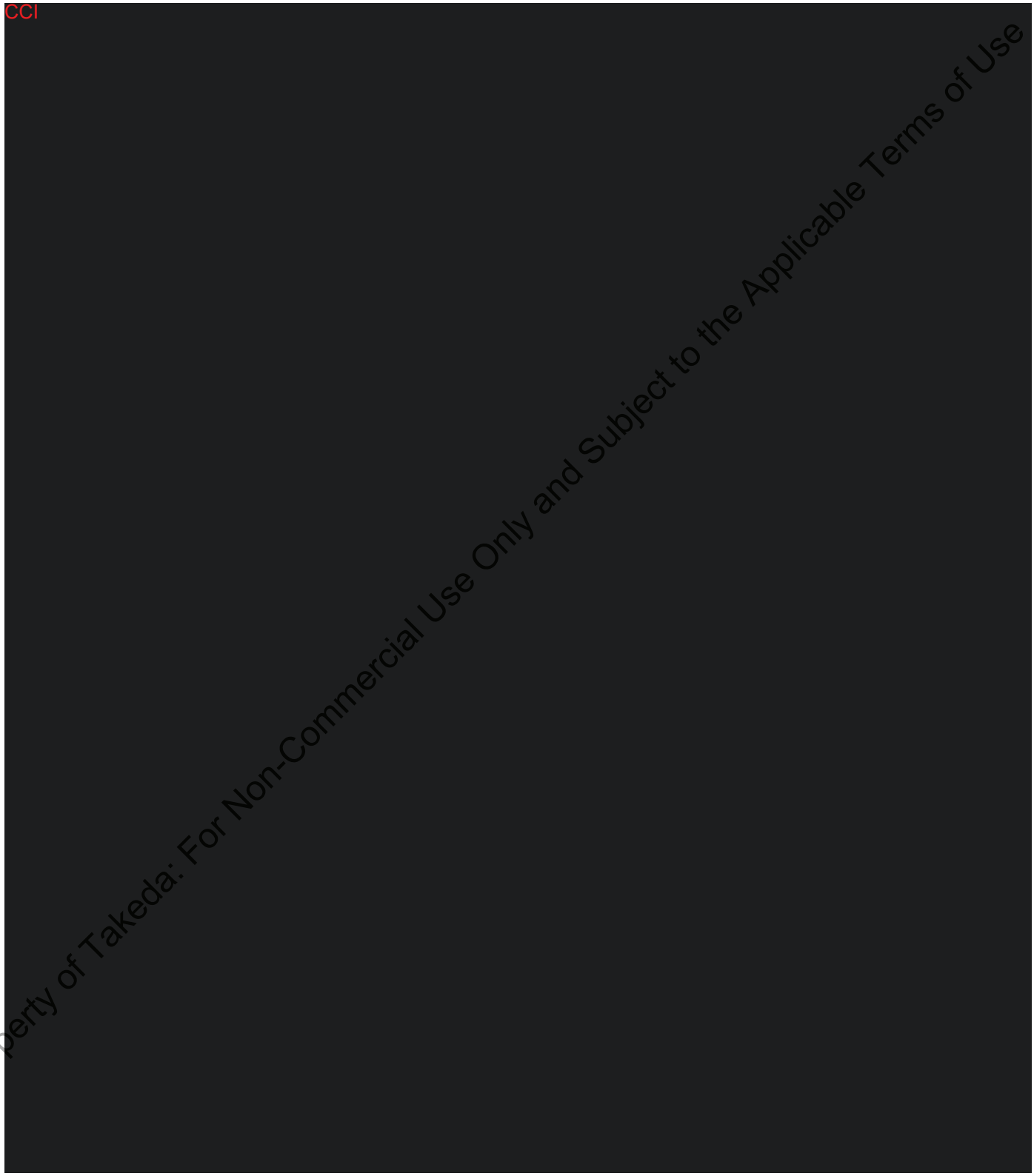

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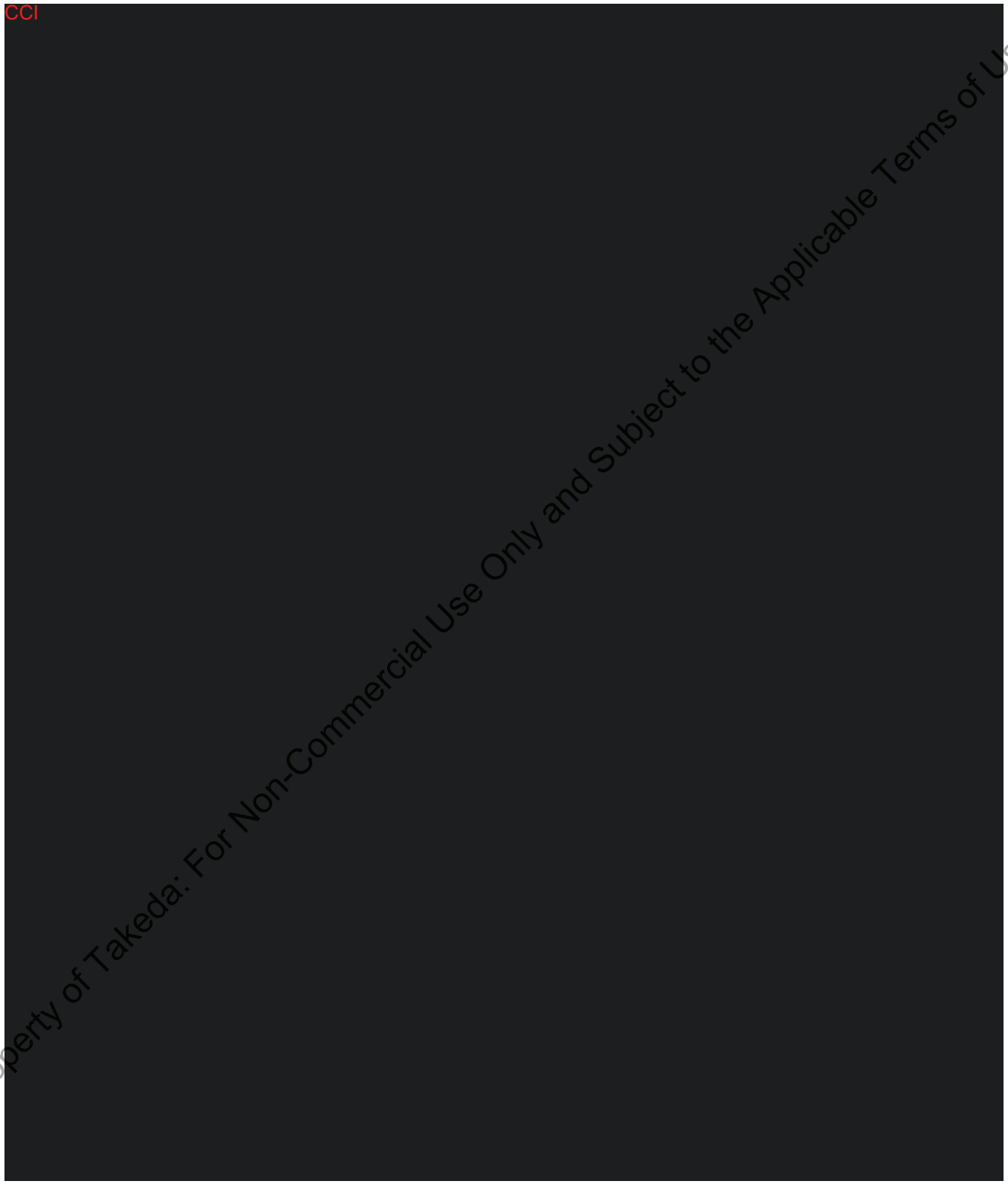

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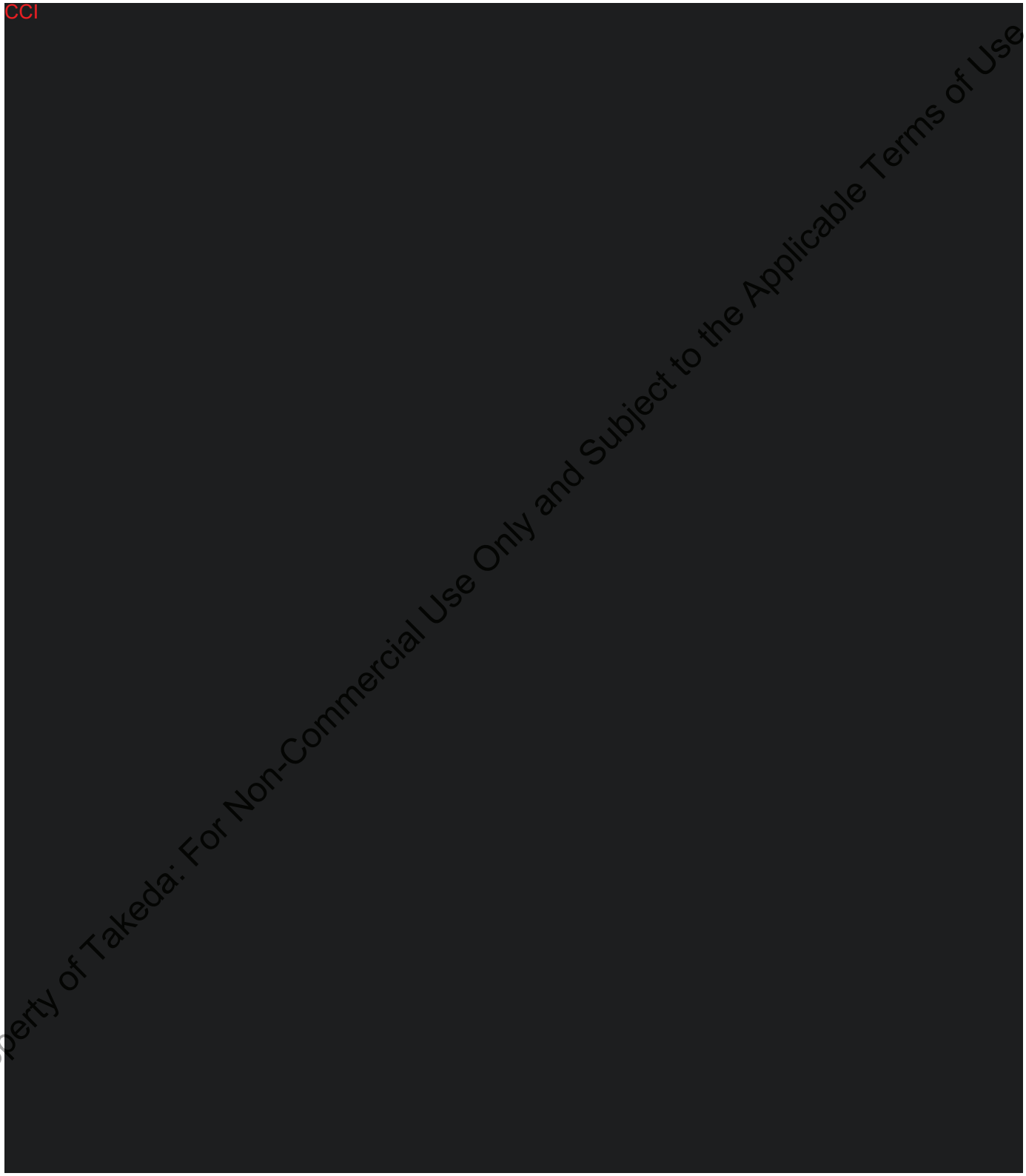

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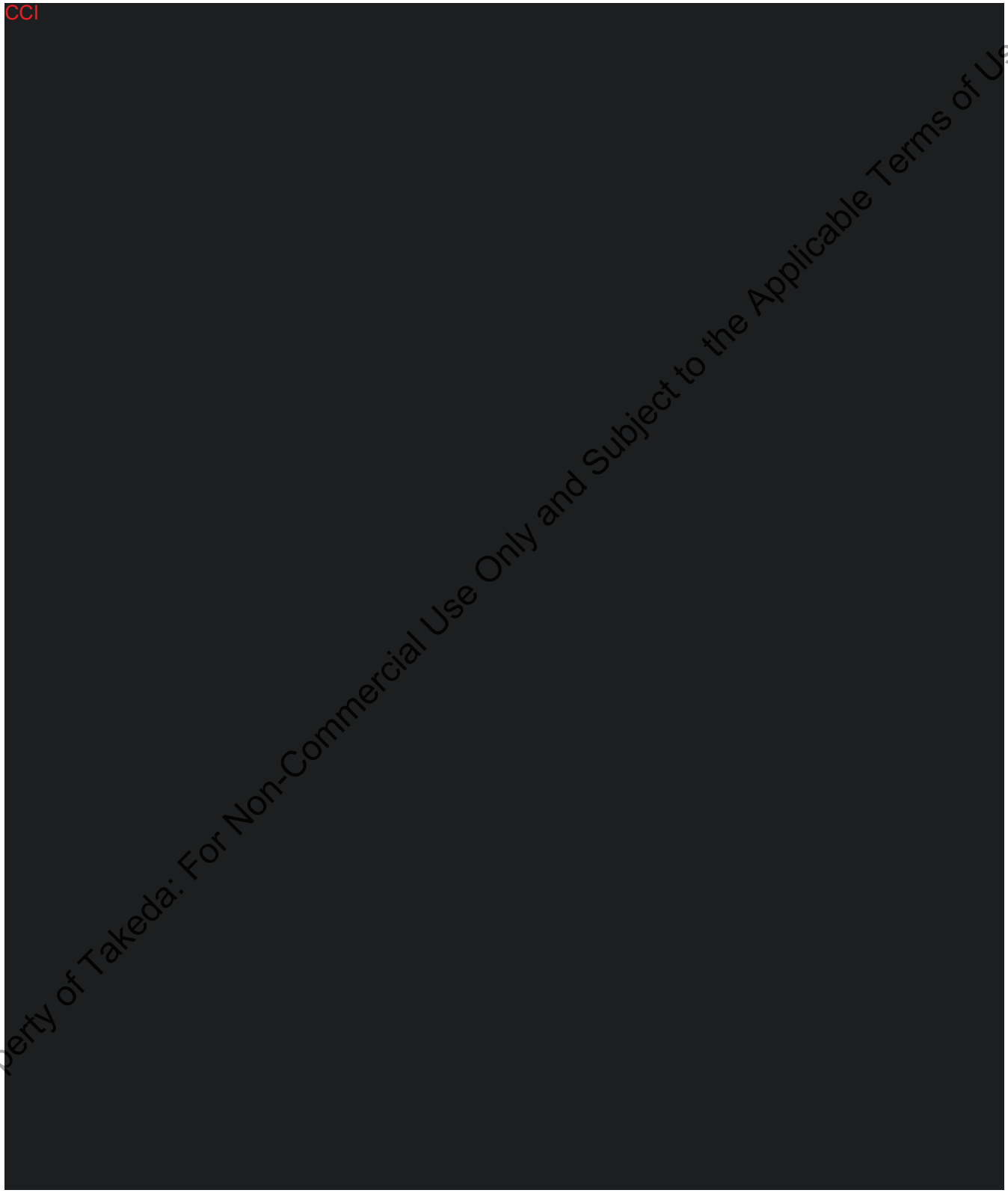

CCI [redacted]

7.10.3.3 Sensitivity Analyses to assess impact of COVID-19 pandemic

Additional sensitivity analyses and/or summary tables will be performed to assess the impact of the COVID-19 pandemic.

Sensitivity analyses for IA of first half of Part 3 (ie, 18 months after end of Part 2)

VE of two doses of TDV in preventing VCD fever induced by any dengue serotype occurring between two and three years post-second vaccination ie, Month 28 to Month 39, and between 30 days post-second vaccination until 18 months after end of Part 2 will be assessed considering a reduced follow-up time due to the pandemic. A modified censoring approach will be applied for subjects participating at sites that were impacted by the COVID-19 by censoring on the WHO pandemic declaration date of March 11, 2020 [5].

Impact on neutralizing antibodies measured by MNT_{50} will also be assessed, presenting the number of MNT_{50} samples that were expected, actually collected within protocol defined visit window, and missing due to COVID-19. CCI [redacted]

Descriptive statistics on surveillance performance metrics (eg, percentage of febrile illness cases in which acute samples were taken within 5 days of febrile illness) will be repeated overall, and

CCI [redacted].

In addition, the follow-up time impacted due to the pandemic will be summarized by trial group. Impacted follow-up time is defined as the amount of time subject could not be followed due to the start of pandemic (ie, regular end of follow-up date – start date of pandemic + 1 day). The regular end of FU date is defined as 3 years post-second vaccination or, if prior to 3 years post-second vaccination, the latest date between trial discontinuation date or last surveillance contact date.

CCI [redacted]

All information on the COVID-19 Impact eCRF will also be presented in a separate data listing.

For IA beyond the 18 months after end of Part 2 (first half of Part 3), and depending on the future impact of the COVID-19 pandemic, additional analyses may be required to assess this impact.

CCI [redacted].

7.11 Safety Analysis

All summaries of safety data will be based on subjects in the SS during Parts 1, 2, and 3 and CCI [redacted] Safety data will be summarized by trial group. No inferential analyses of safety data will be performed. Unless otherwise stated, data imputation will not be performed for any missing safety data.

7.11.1 Adverse Events

In Parts 1, 2, and 3, summaries will be provided post-first dose, post-second dose and post-any dose. For analyses of solicited and unsolicited AEs only subjects from the subset will be included. SAEs, related AEs and AEs leading to vaccine or trial withdrawal will be summarized for all subjects. AEs for subjects in the subset and all SAEs will be collected and analyzed for Part 1 and Part 2. For Part 3, all deaths, related SAEs and SAEs deemed relevant in the context of vaccine safety by the investigator will be analyzed. Summaries will be provided for Part 1, Part 2, Part 1 and Part 2 combined, and for Part 3. In addition, summaries will be provided at 12-month-intervals after completion of Part 1 (ie, Part 2 and the first 6 months of Part 3, months 7-18 within Part 3, months 19-30 within Part 3, and >months 30).

CCI [redacted]

Reactogenicity

For subjects in the immunogenicity subset in Part 1, solicited local AEs (injection site pain, injection site erythema, and injection site swelling) and solicited systemic AEs (child <6 years: fever, irritability/fussiness, drowsiness and loss of appetite; child ≥6 years: asthenia, fever, headache, malaise and myalgia) will be assessed during the first 30 minutes (both local and systemic) by the investigator, and for 7 days (local) and 14 days (systemic) following each vaccination (vaccination day included) via collection of diary cards. CCI [redacted].

The presence and severity of each solicited symptom will be collected using diary cards. The subject/legal guardian 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/legal guardian will record the length of the longest diameter. For the systemic AE fever, the subject/legal guardian will record the body temperature in either degrees Fahrenheit or degrees Celsius. 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 derived from the recorded body temperature measurements and presented using the proposed temperature increments published by the Brighton Collaboration [6].

Details of solicited local and systemic AEs and intensity scales are given in Appendix B. For solicited AEs, missing data will be handled as follows. For each trial group and solicited AE, the denominator for the percentage will exclude subjects with completely missing data (ie, subject does not have at least one recorded result of none, mild, moderate, or severe) and subjects with implausible data for body temperature (ie, <30°C and >45°C) for the solicited AE in the period being summarized.

In Part 1, summary tables will be presented by age category (child <6 years / child ≥6 years). The percentage of subjects will be summarized by event severity: 30 minutes after each dose, for each day after each dose (Days 1 to 7 and after Day 7 for local AEs and Days 1 to 14 and after Day 14 for systemic AEs relative to each dose), and overall. A summary of the day of first onset of each event will also be provided. The number of days subjects experienced each event will also be summarized for each trial group. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.CCI [redacted]

For Part 1, additional summaries will be performed by age group (4-5 years [corresponds to age category "child <6 years"] / 6-11 years / 12-16 years), region (Asia Pacific / Latin America), country, gender, baseline seropositivity status (seropositive for at least 1 Dengue serotype / seronegative for all Dengue serotypes), combination of age group and region (4-5 years and Asia Pacific, 6-11 years and Asia Pacific, 12-16 years and Asia Pacific, 4-5 years and Latin America,

6-11 years and Latin America, and 12-16 years and Latin America), combination of age group and baseline seropositivity status (4-5 years and seropositive for at least 1 Dengue serotype, 6-11 years and seropositive for at least 1 Dengue serotype, 12-16 years and seropositive for at least 1 Dengue serotype, 4-5 years and seronegative for all Dengue serotypes, 6-11 years and seronegative for all Dengue serotypes, and 12-16 years and seronegative for all Dengue serotypes), prior vaccination against Yellow Fever (yes/no), and prior vaccination against Japanese Encephalitis (yes/no) for selected tables. CCI [redacted]

Any AE captured on the AE eCRF that is a prolonged solicited AE (ie, continues beyond Day 7 [for local AEs] or Day 14 [for systemic AEs]) will not be included in any unsolicited AE summary or listing. Prolonged solicited AEs will be presented in a separate listing.

Unsolicited Adverse Events

Unsolicited AEs (immunogenicity subset only) and SAEs (all subjects), will be coded according to MedDRA and summarized by primary SOC and PT for each trial group. Related AEs/SAEs and AEs/SAEs leading to withdrawal from the trial will also be summarized.

All unsolicited AEs up to 28 days after each dose CCI [redacted] will be included in the analyses of all AEs. For SAEs and AEs leading CCI [redacted] 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 SOC or PT being summarized will be counted only once. Percentages will be based on the number of subjects in the Safety Set who received the respective trial dose. Unsolicited AEs will be summarized as follows: by SOC and PT including events with frequency greater than 2% in any trial group; by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to the IP.

Unsolicited AEs during Part 1 will be summarized in the following ways:

- Onset within 28 days after dose 1
- Onset within 28 days after dose 2
- Onset within 28 days after any dose

CCI [redacted]

Additional summaries will be performed by age group (4-5 years / 6-11 years / 12-16 years), region (Asia Pacific / Latin America), country, gender, baseline seropositivity status (seropositive for at least 1 Dengue serotype / seronegative for all Dengue serotypes), combination of age group and region (4-5 years and Asia Pacific, 6-11 years and Asia Pacific, 12-16 years and Asia Pacific, 4-5 years and Latin America, 6-11 years and Latin America, and 12-16 years and Latin America), combination of age group and baseline seropositivity status (4-5 years and seropositive for at least 1 Dengue serotype, 6-11 years and seropositive for at least 1

Dengue serotype, 12-16 years and seropositive for at least 1 Dengue serotype, 4-5 years and seronegative for all Dengue serotypes, 6-11 years and seronegative for all Dengue serotypes, and 12-16 years and seronegative for all Dengue serotypes), prior vaccination against Yellow Fever (yes/no), and prior vaccination against Japanese Encephalitis (yes/no) for selected tables. Similar summaries will be repeated CCI

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% in any trial group to provide this information for Clinicaltrials.gov.

Summary tables including non-serious unsolicited AEs by SOC and PT with frequency greater than 2% in any trial group, SAEs by SOC and PT, as well as AEs leading to IP withdrawal or trial discontinuation by SOC and PT will include a separate group of subjects who received different IPs at first, second vaccination CCI

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, and AEs leading to IP withdrawal or trial discontinuation.

An additional table summarizing the proportion of subjects with SAEs by calendar month from two until three years post-second vaccination overall, and by country, will also be presented to assess the impact of the COVID-19 pandemic. The proportions will be estimated based on the number of subjects followed-up in the trial at the beginning of each month. For IA beyond the 18 months after end of Part 2 (first half of Part 3), and depending on the future impact of the COVID-19 pandemic, additional analyses may be required to assess this impact.

7.11.2 Clinical Laboratory Evaluations

Not applicable.

7.11.3 Vital Signs

7.11.3.1 Parts 1, 2, and 3

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 Day 1 (Month 0) and Day 120 (Months 4) for all subjects and at Day 450 (Months 15) and then yearly in Part 3 for the subset. Vital signs will be summarized descriptively by visit (overall, by region, by country, and by age group), and individual subject data will be presented in the listing by trial group, trial site, subject number, collection date/time, and measurement parameters. For body temperature only values between 30°C and 45°C will be included in the summaries. However, all data will be included in listings.

Measurements are taken for all subjects on Day 30 (Month 1), Day 120 (Month 4) or early termination visit (if applicable), and in the subset at all trial visits subsequent to Visit 4 (Day 120 [Month 4]).

Descriptive statistics (number of subjects, 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 signs measurements at the scheduled visits will be included in the summaries.

CCI

[redacted]

7.11.4 Other Observations Related to Safety

Vaccine viremia (assessed by three PCRs: dengue detection RT-PCR, vaccine screening PCR and TDV sequencing) in subjects with febrile illness within 30 days after each vaccination CCI [redacted] will be presented based on the SS CCI [redacted] (overall, by age group and baseline seropositivity status).

The number of subjects with non-missing assessment, mean, associated 2-sided 95% CI and associated SD, median, minimum, and maximum will be presented for vaccine RNA levels (expressed as $\log_{10}$ [copies/mL]) for each of the four TDV strains (TDV-1, TDV-2, TDV-3, TDV-4).

The proportion of febrile illness cases with vaccine viremia along with exact 2-sided 95% CI, will be presented for each TDV strain. The exact 2-sided 95% CI of incidence rate will be calculated based on the Clopper-Pearson method [7].

Information from replication competent virus propagation and attenuation loci sequencing will be summarized.

All febrile illness cases, febrile illness cases clinically diagnosed as dengue, clinical signs, symptoms and laboratory data of febrile illness cases, solicited AEs and unsolicited AEs within 30 days after each vaccination will be presented according to the presence of vaccine viremia with or without reversion of attenuation loci (based on replication competent virus propagation and attenuation loci sequencing).

7.12 Interim Analysis

7.12.1 Parts 1, 2, and 3

This is a partially case-driven trial with the primary efficacy analysis planned after the 2 criteria for the end of Part 1 have been fulfilled (see Section 4.4).

At the time of primary analysis of VE following the completion of Part 1 of the trial, external vendors (Clinical Research Organizations [CROs]) who are involved in the analyses will be unblinded at an individual subject level in order to analyze and summarize the trial data. Takeda

will receive summary tables containing aggregated data by trial group for the primary analysis of Part 1 and at the time of any subsequent analyses. A small group of Takeda personnel will also have access to individual level unblinded data. In order to maintain the double-blind design, investigators, site staff, subjects, as well as Takeda staff and external vendors advising sites on trial conduct will remain blinded to individual subject level trial group allocation for the trial duration. There will be blinded and unblinded trial teams at Takeda and within the external vendors. The blinded team may have access to group unblinded results (eg, publications) but will remain blinded to subject level data for the duration of the trial and will remain responsible for all further activities during trial conduct after unblinding for the primary analysis.

The number of virologically-confirmed cases of dengue fever identified by the time of the primary endpoint analysis may not be sufficient to assess less common events such as dengue fever due to a specific serotype or severe dengue. Therefore, it is proposed that active surveillance will continue for an additional 6 months after the analysis of the primary endpoint. Consequently, analysis of the secondary efficacy endpoints would then be based on cases occurring at any time from 1 month after the second vaccination (Day 120 [Month 4] until 6 months after the end of Part 1 (ie, until the end of Part 2). As a result, data from the additional 6 months surveillance for secondary efficacy endpoints will not be available at the same time as the primary endpoint.

Assuming a 1.0% incidence rate by the end of Part 1 (minimum 12 months after the second vaccination for each subject), it is estimated that approximately 180 evaluable cases will accrue by the end of the additional 6 months of observation (ie, an additional ~60 cases). These additional cases will improve the power for assessment of secondary endpoints, including serotype-specific efficacy.

In addition, the number and percentage of subjects with VCD, virologically confirmed and hospitalized dengue, as well as subjects with fatal SAEs and related SAEs, will be summarized for the first half (18 months) and second half (18 months) of Part 3 when such data become available.

CCI

7.12.3 Interim Analysis and Reporting

IAs are planned for Part 1, Part 2, 2-year follow-up post-second dose, 3-year follow-up post-second dose, at the end of Part 3, CCI [redacted]

At the time of this SAP amendment, an Interim CSR has been prepared for the results from the dry-run, Part 1, and Part 2. A second Interim CSR will be prepared for data until 6 months after the end of Part 2 (2-year follow-up post-second dose). Additional reports for the results from Parts 3, CCI [redacted] including further Interim CSRs, will be prepared if required for internal use and/or for regulatory submission. A Final CSR will be prepared upon trial completion and will include results for the trial duration.

7.13 Changes in the Statistical Analysis Plan

The SAP describes additional analyses/summaries that may be provided to assess the impact of the COVID-19 pandemic, as compared to the protocol. In addition, some details are added to some sections for further clarification.

7.13.1 Amendment History

Date	Amendment Number
21 May 2015	Initial Analysis Plan
18 Nov 2015	1
04 Oct 2016	2
02 Oct 2018	3
24 Sep 2020	4

7.13.2 Summary of Changes

This section describes major changes to previous SAP versions.

Final Version	Section	Description of Change
2.0	General	The main rationale for this amended SAP was the Amendment to Protocol Version 2.0, dated 17 Dec 2014. Minor grammatical and editorial changes are included for clarification purposes only.
	1.0	Administrative updates
	4.4; 7.1-7.12; Appendix A	Update of study design, study visits, procedures; CCI [redacted] addition of second dose
	4.0; 5.0; 7.8.2-7.11.3	Update of objectives and endpoints
	6.0	Update on sample size justification
	7.8; 7.10; 7.11; 7.12	Update of statistical analyses based on the changed study design
	7.8; 7.10	Change from FAS to PPS for the primary analysis of the efficacy and immunogenicity endpoints due to change from 1 dose to 2 doses
	7.8.1; 7.8.2	Change in handling of multiplicity There is only one key-secondary efficacy endpoint which will be tested in a confirmatory manner only if statistical significance for the primary endpoint is achieved. No adjustment for the significance level of 5% is needed due to this hierarchical testing strategy.
	7.10.3	Update on other exploratory endpoints
2.0	7.11.3 (removal of former APPENDIX C)	Summaries for markedly abnormal values removed 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.
	7.12	Update on Interim Analysis section for further clarity
	Appendix B	Clarification added regarding solicited AE severity/intensity categories

Final Version	Section	Description of Change
3.0	General	The main rationale for this amended SAP was the feedback on the SAP Version 2.0 from the Food and Drug Administration (FDA) received on 23 December 2015. Minor grammatical and editorial changes are included for clarification purposes only.
	1.0	Administrative updates
	3.0	Further abbreviations added
	7.1	Methods for handling of missing data, and of values below the lower limit of quantification were added for immunogenicity. CCI [redacted]
	7.2.3	Addition of an exclusion criterion for the PPSI for immunogenicity analysis regarding samples taken outside the visit windows pre-specified in the study protocol.
	7.8.1; 7.8.3	CCI [redacted]
	7.10.1	Further clarification for analysis of immunogenicity endpoints was added.
3.0	7.10.3	Addition of further exploratory analyses to assess CCI [redacted]
	7.11.1	Addition of summaries for solicited AEs 30 minutes after vaccination. Additional summaries by 12 months intervals after completion of Part 1 were added as for efficacy. Intervals for the analysis of unsolicited AEs have been removed taking into account the timing of vaccine viremia which has been shown in previous studies to have an onset mostly between one to three weeks after vaccination.
	7.11.4	Vaccine viremia analyses were added.
	7.12	Additional CSR addendum was added.
	8.0	Reference #4 was added.
	Appendix B	Fever categories for the summary tables were added.

Final Version	Section	Description of Change
4.0	General	The main rationale for this amended SAP was the feedback on the SAP Version 3.0 from the Food and Drug Administration (FDA) received on 03 April 2017 and the amendment to the study protocol which clarifies that blinded study team members might have access to published group unblinded study data. Minor grammatical and editorial changes are included for clarification purposes only.
	1.0	Administrative updates
	7.1	Clarifications were added on how to handle subjects who received Dengvaxia during the course of the study. Text regarding handling of missing/partial AE/CM dates was updated for consistency across Dengue studies. Clarification was added that p-values will only be calculated for the primary and key-secondary endpoint. Analysis visit windows were updated to ensure visit window calculation is calculated relative to days of IP administration and consistent across dengue studies. Clarifications for the definition of end of Part 1 for subjects who didn't receive the second dose or discontinued the study during Part 1 were added.
	7.2	Handling of possible IP misallocations was added to the Safety Set. The Dry Run Set was added. Clarification that PPS and PPSI will be defined for the primary endpoint timeframe only and kept unchanged for other study parts was added.
	7.3 -7.7	Clarifications regarding definitions, CCI and analysis sets were added.
	7.8.1	Calculation of p-value for the primary endpoint was added. CCI censoring were added.
	7.10.1	CCI cumulative seropositivity were added.
	7.10.2	CCI
	7.10.3	Addition of further exploratory analyses to assess CCI Additional clarifications for exploratory analyses were added.

Final Version	Section	Description of Change
	7.11	Clarifications regarding CCI prolonged solicited AEs, vaccine viremia were added. Handling of implausible values for body temperature was added.
	7.12	Clarifications on blinding/unblinding for Part 1 and subsequent analyses as well as for Clinical Study Report preparation were added based on the Amended Protocol Version 4.0, dated 27 August 2018.
	8.0	The reference to the study protocol was updated.
5.0	General	The main rationale for this amended SAP was the amendment to the trial protocol CCI
	4.2	Wording for one of the secondary objectives was aligned with protocol. No actual change in the objectives.
	4.3	Split into exploratory objectives in Parts 1, 2, and 3 (Section 4.3.1) CCI
	4.4	Split into study design in Parts 1, 2, and 3 (Section 4.4.1) CCI . Additional information added to Parts 1, 2, and 3 relating to the handling of febrile illness cases (suspected dengue cases) and procedures, to align with the protocol.
	4.5	Split into study duration during Parts 1, 2, and 3 (Section 4.5.1) CCI .
	5.3	Split into exploratory endpoints for Parts 1, 2, and 3 (Section 5.3.1) CCI).
	6.0	Split into determination of sample size for Parts 1, 2, and 3 (Section 6.1) CCI
	7.1	Information (e.g. analysis visit window table) was added to CCI A definition of end of Part 3 for subjects who had completed Part 3 already or didn't complete Part 3 CCI
	7.2	Split into analysis sets for Parts 1, 2, and 3 (Section 7.2.1) CCI
	7.2.3	CCI Also, clarifications on the presentation of significant protocol deviations and protocol deviations related to COVID-19 were added.
	7.3	Trial information categories and a summary of all analysis sets were added. Sub-sections 7.3.1 CCI were also created to summarize the disposition of subjects in Parts 1, 2, and 3 CCI .

Final Version	Section	Description of Change
	7.4	Split into demographic and baseline characteristics in Parts 1, 2, and 3 (Section 7.4.1) CCI [redacted]
	7.5	Clarifications on the presentation of medical history and concurrent medical conditions were added, as well as a split by Parts 1, 2, and 3 (Section 7.5.1) CCI [redacted]
	7.6	Clarifications on the presentation of medication/vaccination history and concomitant medications/vaccinations were added, as well as a split by Parts 1, 2, and 3 (Section 7.6.1) CCI [redacted].
	7.7	Duration of follow-up and follow-up duration categories CCI [redacted] were added CCI [redacted].
	7.10.1	Split into other vaccine immunogenicity endpoints for Parts 1, 2, and 3 (Section 7.10.1.1) CCI [redacted]).
	7.10.2	CCI [redacted]
	7.10.3	Split into other exploratory endpoints for Parts 1, 2, and 3 (Section 7.10.3.1) CCI [redacted]).
	7.10.3.3	Sensitivity analyses to assess the impact of the COVID-19 pandemic were added in a separate section.
	7.11	CCI [redacted]
	7.11.1	CCI [redacted]
	7.11.3	CCI [redacted]
	7.11.4	CCI [redacted]
	7.12	Split into an interim analysis description for Parts 1, 2, and 3 (Section 7.12.1) CCI [redacted] A separate section (Section 7.12.3) was included to describe the interim analysis reporting for all parts of the study.
	7.13	Section was updated to state additional analyses for the impact assessment of the COVID-19 pandemic.
	8.0	Clopper-Pearson reference was added.

8.0 REFERENCES

1. Phase III, Double-Blind, Randomized, Placebo-Controlled Trial to Investigate the Efficacy, Safety and Immunogenicity of a Tetravalent Dengue Vaccine (TDV) Administered Subcutaneously in Healthy Children Aged 4 – 16 Years Old. Takeda Vaccines, Inc. Protocol No. DEN-301 Version 6.0 dated 18 May 2020.
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4. World Health Organisation, Dengue haemorrhagic fever, diagnosis, treatment prevention and control (2nd ed.), WHO, Geneva (1997).
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Appendix A Schedule Of Trial Procedures

Table 8.a Schedule of Trial Procedures for Parts 1, 2, and 3

	Possible dry-run for surveillance between enrollment and vaccination	Active surveillance							Modified active surveillance			Follow up visit [d]
		Part 1 [a]						Part 2 [b]	Part 3 [c]			
		Day 1 (Month 0) (Visit 1)	Day 30 (Month 1) (Visit 2)	Day 90 (Month 3) (Visit 3)	Day 120 (Month 4) (Visit 4)	Day 270 (Month 9) (Visit 5)	Day 450 (Month 15) (Visit 6)		Y 1 D815 (M27) (V7)	Y 2 D1180 (M39) (V8)	Y3 D1545 (M51) (V9)	
	Procedure for all subjects											
Visit window			-1 day/ +7 days	±15 days	-1 day/ +7 days	±21 days	±30 days		±45 days		±45 days [e] -45 days/ +180 days [f]	
Visits	X	X	X	X	X			NA				
End of trial phone Contact											X [g]	
Signed informed consent/ assent [h]	X	X										
Assessment of eligibility criteria [h]	X	X										
Check contraindications to vaccination				X								
Check criteria for delay of vaccination				X								
Demographics	X	X										
Medical history	X	X		X								X
Concomitant medications [i]	X	X	X	X	X							X
Complete physical examination [j]	X	X		X								
Targeted physical examination [k]			X		X							X
Pregnancy test [l]	X	X		X								

Continued

Table 8.a Schedule of Trial Procedures for Parts 1, 2, and 3 (Continued)

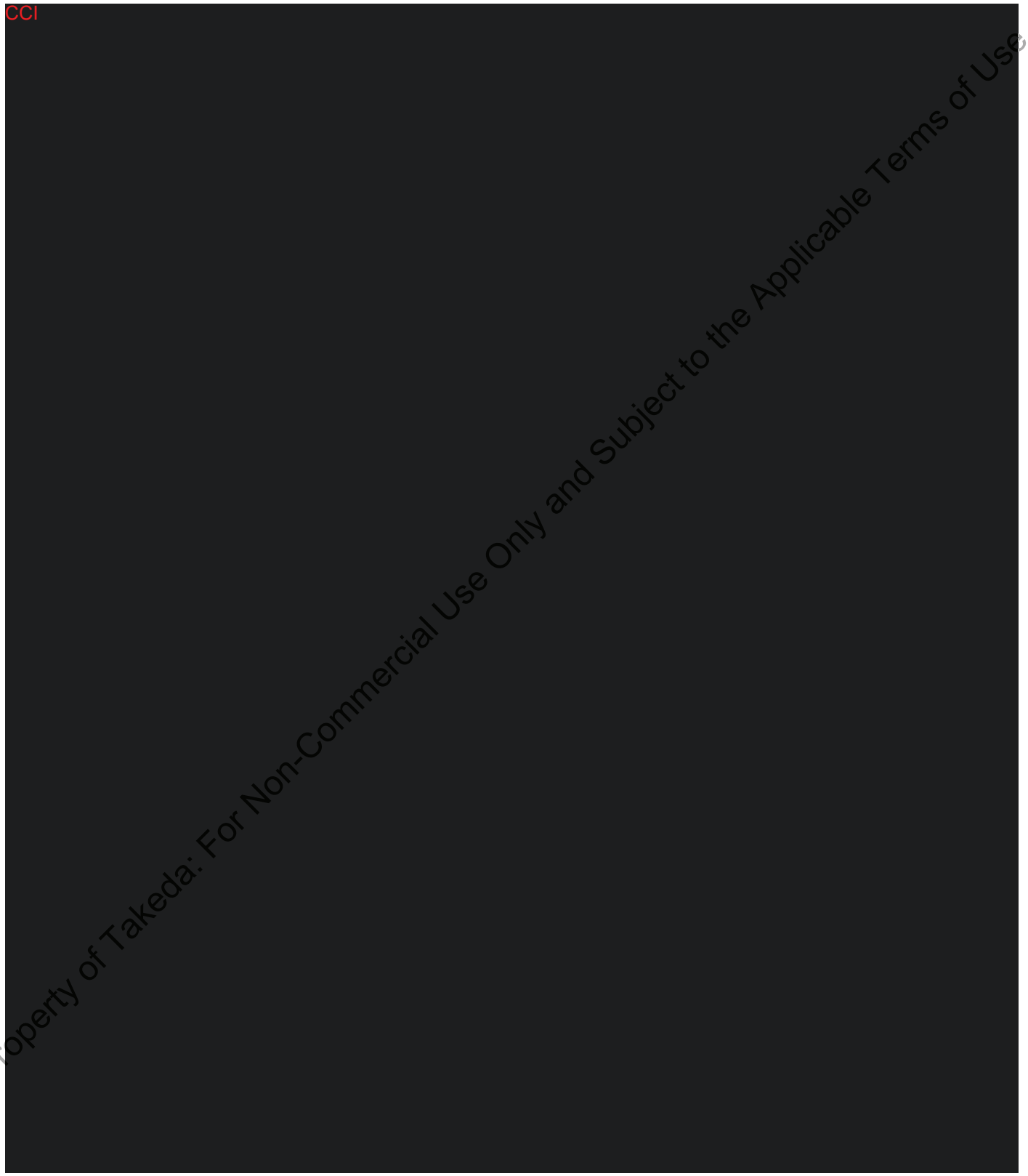
	Possible dry-run for surveillance between enrollment and vaccination	Active surveillance							Modified active surveillance			Follow up visit [d]
		Part 1 [a]						Part 2 [b]	Part 3 [c]			
		Day 1 (Month 0) (Visit 1)	Day 30 (Month 1) (Visit 2)	Day 90 (Month 3) (Visit 3)	Day 120 (Month 4) (Visit 4)	Day 270 (Month 9) (Visit 5)	Day 450 (Month 15) (Visit 6)		Y 1 D815 (M27) (V7)	Y 2 D1180 (M39) (V8)	Y3 D1545 (M51) (V9)	
	Procedure for all subjects											
Visit window			-1 day/ +7 days	±15 days	-1 day/ +7 days	±21 days	±30 days		±45 days		±45 days [e] -45 days/ +180 days [f]	
Visits	X	X	X	X	X			NA				
Randomization [m]		X										
Vaccine administration		X		X								
Surveillance for dengue fever [n]	X											
Blood sample [o] (8 mL)		X			X							
Febrile illness blood sample [p]	X											
SAEs [q]	X											
	Additional procedures for the subset											
Visits						X	X	NA	X	X	X	
Targeted physical examination [k]						X	X		X	X	X	X
Injection site evaluation [r]		X	X	X	X							
Diary card distribution [s]		X		X								
Diary card collection and review			X		X							
Documentation of AEs [s] [t]			X		X							
Blood sample [u] (5 mL)			X	X		X	X		X	X	X [v]	

AEs = adverse events, D = Day, M = Month, NA = not applicable, V = Visit, Y = Year

(a) Part 1 will end once both of the 2 following criteria are fulfilled: (1) 120 cases of dengue fever are confirmed, and (2) a minimum duration of subject follow-up of 12 months post-second vaccination.
(b) Part 2 will start after the completion of Part 1 and will last 6 months.
(c) Part 3 will start after the completion of the active surveillance period (i.e. end of Part 2) and will last for approximately 3 years.
(d) Follow-up visit is only applicable if the subject terminates early.
CCI [redacted]
CCI [redacted]
(g) Between 4 years and approximately 4.5 years post-dose 2 in Part 3, the parent/guardian of subjects who are not included in the subset from Parts 1, 2, and 3 (see footnote 'm') but are included in the PPS and were 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) CCI [redacted] depending on the assignment on Day 1 (Month 0) (see footnote 'm'). CCI [redacted]
(h) Eligibility by review of inclusion/exclusion criteria will be documented before randomization. Eligibility assessment performed prior to the dry-run must be repeated on Day 1 (Month 0). For subjects participating in dry-run, informed consent/assent must be obtained prior to entry into the dry-run.
(i) History of vaccination against Japanese Encephalitis or against Yellow Fever until Day 120 (Month 4) irrespective of time of administration and including the vaccine type as well as any additional supportive documentation for these vaccinations, all concomitant medications and vaccine history from 1 month (minimum 28 days) prior to administration of each dose of TDV or placebo up to 1 month (minimum 28 days) thereafter, steroids and immunostimulants within 60 days prior to Day 1 (Month 0), immunoglobulins and blood products within 3 months prior to Day 1 (Month 0), and immunosuppressive therapy within 6 months prior to Day 1 (Month 0).
(j) Physical examination including measurement of weight and height; body mass index will be calculated automatically. Measurement of height is not required at Day 90 (Month 3).
(k) Vital signs including (but not limited to) the measurement of systolic blood pressure/diastolic blood pressure, heart rate, temperature, height and weight. Measurement of height is not required at Day 30 (Month 1) for all subjects, and at Day 270 (Month 9) for the subset.
(l) Pregnancy testing (serum or urine) for females of childbearing potential. Results must be confirmed and documented as negative prior to trial entry (if dry-run is applicable) and prior to each trial vaccine administration.
(m) After eligibility is assessed and written informed consent/assent has been obtained, subjects will be randomized 1) to receive either 2 doses of Takeda's TDV or placebo by subcutaneous (SC) injection in the upper arm, and 2) to be included in the subset.
(n) The subject AND/OR the subject's parent/guardian will be contacted at least weekly during the dry-run, Parts 1, 2, and 3. Contacts will be made through appropriate methods that may differ in each site (eg, phone calls, text messaging, home visits, school-based surveillance). The text messaging system, if used, will be identified and evaluated by the Sponsor before use.
(o) Blood samples for dengue neutralizing antibodies will be collected for all subjects at pre-vaccination (Day 1 [Month 0]) and post-second vaccination on Day 120 (Month 4). The Day 30 (Month 1) and Day 120 (Month 4) blood samples should be taken at least 28 days after the first and second trial vaccination, respectively.
(p) For subjects presenting with febrile illness (fever ≥38°C on any 2 of 3 consecutive days or clinically suspected dengue) during the dry-run and Parts 1 and 2, or with febrile illness requiring hospitalization during Part 3, a blood sample will be collected during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever) and a convalescent blood sample will be collected between 7 and 14 days after the acute sample. For subjects presenting with febrile illness (fever ≥ 38°C on any 2 of 3 consecutive days or clinically suspected dengue) during Part 3 not requiring hospitalization will have 1 blood sample taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever) unless there is an alternate laboratory confirmed etiology.
(q) Serious adverse events (SAEs) will be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event.
(r) At 30 minutes after vaccine administration on the day of vaccinations.
(s) Diary cards will be distributed for the collection of solicited local adverse events (AEs) until Day 7 (day of vaccination + 6 subsequent days), and of solicited systemic AEs until Day 14 (day of vaccination + 13 subsequent days) after each vaccination.

(t) Unsolicited AEs will be collected up to 28 days after each vaccination by interview.
(u) Additional blood samples for dengue neutralizing antibodies will be collected for subjects in the subset post first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3), post-second vaccination on Day 270 (Month 9), Day 450 (Month 15), and then every 12 months until the end of Part 3.
(v) CCI [redacted]

CCI



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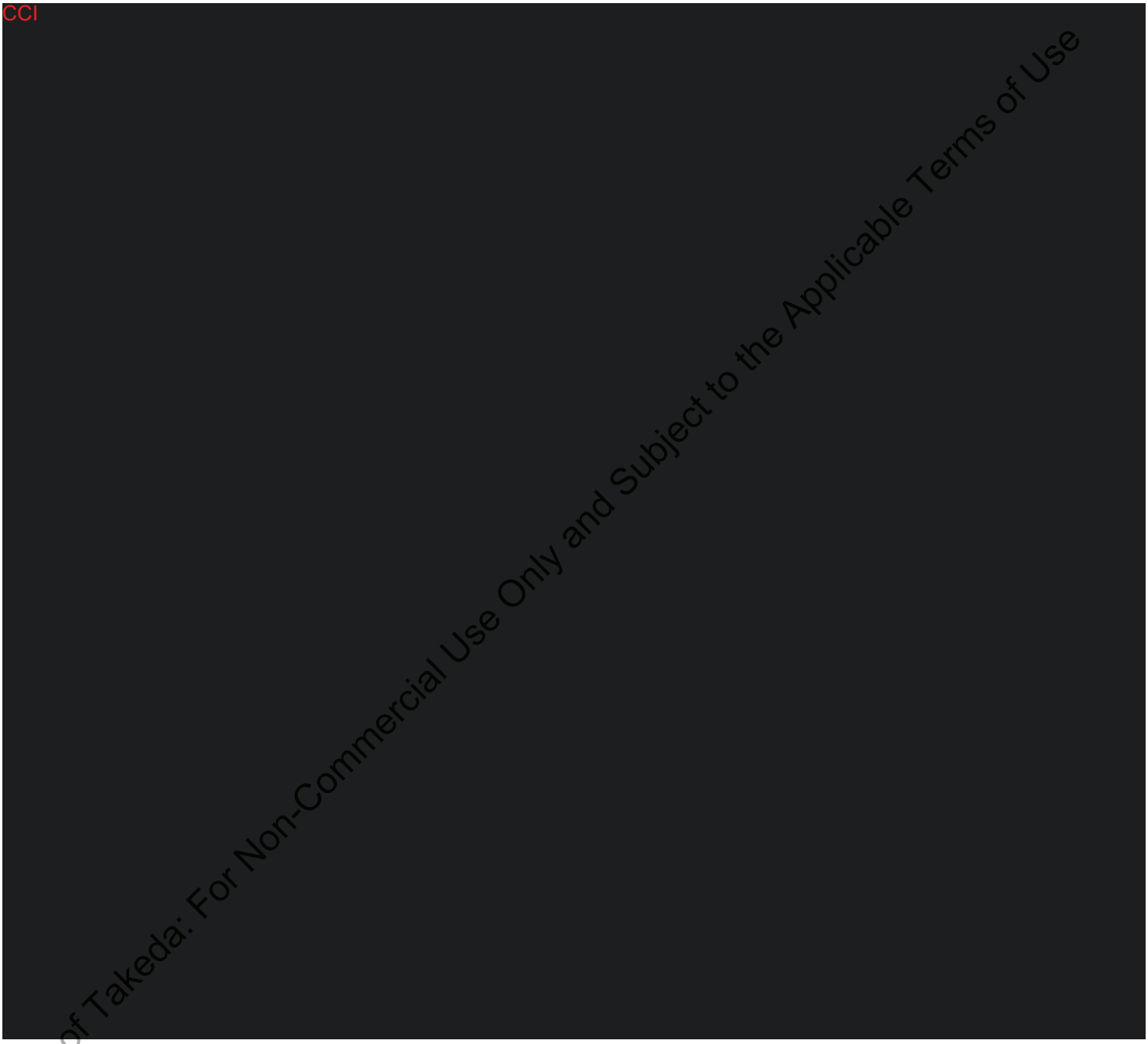

Appendix B Solicited and Systemic Adverse Events and Intensity

Table 8.c 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 [(a)]	Fever [(a)]
	Irritability/fussiness	Asthenia
	Drowsiness	Headache
	Loss of appetite	Malaise
		Myalgia

(a) Body temperature ≥ 38.0°C or 100.4°F is defined as fever irrespective of site of measurement

Table 8.d Intensity Scales for Solicited Safety Parameters (Infant/Toddler/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)]	NA	None
	NA	38.0-<38.5°C
	NA	38.5-<39.0°C
	NA	39.0-<39.5°C
	NA	39.5-<40.0°C
	NA	40.0-<40.5°C
	NA	40.5-<41.0°C
	NA	≥41.0°C

(a) Subjects are to record greatest surface diameter in mm in the Diary
(b) Fever is defined as greater than or equal to 38.0°C (100.4°F) irrespective of site measurement

Table 8.e Intensity Scales for Solicited Safety Parameters (Child ≥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)]	For categories refer to Table 8.c.	

(a) Subjects are to record greatest surface diameter in mm in the Diary
(b) Fever is defined as greater than or equal to 38.0°C (100.4°F) irrespective of site measurement

Appendix C Potential Prohibited Therapies and Vaccines

1. Chronic use of systemic (ie, 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) / Day 1b (Month 0b) or within 1 month prior to Day 90 (Month 3).

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3. Receipt of immunostimulants within 60 days prior to Day 1 (Month 0) / Day 1b (Month 0b).
4. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1 (Month 0) / Day 1b (Month 0b) or within 1 month prior to Day 90 (Month 3).

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6. Receipt of any other clinical trial product within 30 days prior to Day 1 (Month 0) / Day 1b (Month 0b).
7. Subjects who participated in any clinical trial of a dengue candidate vaccine, or previous receipt of a dengue vaccine.

Signature Page for DEN-301 Statistical Analysis Plan, Version 5.0, 24 September
Title:

Approval	PPD

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