# 3.0 TRIAL REFERENCE INFORMATION

## 3.1 Trial-Related Responsibilities

The Sponsor will perform all trial-related activities with the exception of those identified in the Trial-Related Responsibilities template. The identified vendors in the template for specific trial-related activities will perform these activities in full or in partnership with the Sponsor.

## 3.2 Principal Investigators/Coordinating Investigators

Selection criteria for the principal investigators and coordinating investigators will include significant knowledge of the trial protocol, the investigational vaccine, their expertise in the therapeutic area and the conduct of clinical research as well as trial participation. Takeda will select one or more signatory/signatories from the investigators who participate in the study. The signatory coordinating investigator(s) will be required to review and sign the clinical protocol. The signatory coordinating investigator(s) will also be required to review and sign the Clinical Study Report(s) (CSR[s]) and by doing so agree(s) that it accurately describes the results of the trial.

### 3.3 List of Abbreviations

| | |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| CI | Confidence interval |
| CRO(s) | Clinical Research Organization(s) |
| CSR(s) | Clinical Study Report(s) |
| CYD-TDV | Chimeric yellow fever virus-dengue virus tetravalent dengue vaccine |
| DEN | Dengue serotype |
| DENV | Dengue virus (wild type virus strain) |
| DHF | Dengue hemorrhagic fever |
| DMC | Data Monitoring Committee |
| DSS | Dengue shock syndrome |
| E | Envelope |
| eCRF | electronic Case Report Form |
| ELISA | Enzyme-linked immunosorbent assay |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| FAS | Full Analysis Set |
| CCI [redacted] | |
| FASI | Full Analysis Set for Immunogenicity |
| CCI [redacted] | |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GMR | Geometric mean ratio |
| GMT | Geometric mean titer |
| HIV | Human immunodeficiency virus |
| ICH | International Council for Harmonisation of technical requirements for pharmaceuticals for human use |
| IEC | Independent Ethics Committee |
| Ig(s) | Immunoglobulin(s) |
| Inc | Incorporated |
| IRB | Institutional Review Board |
| IWRS | Interactive Web Response System |
| IVRS | Interactive Voice Response System |
| LFTs | Liver function tests |

| | |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| $MNT_{50}$ | Microneutralization test 50% |
| N | Number |
| NS1 | Nonstructural protein 1 |
| PDK | Primary Dog Kidney |
| PFU | Plaque forming units |
| PPS | Per-Protocol Set |
| CCI [redacted] | |
| PPSI | Per-Protocol Set for Immunogenicity |
| CCI [redacted] | |
| prM | pre-membrane |
| PT | Preferred Term |
| QTL | Quality Tolerance Limits |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcriptase polymerase chain reaction |
| SAE | Serious adverse event |
| SAGE | Strategic Advisory Group of Experts on Immunization |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SDV | Source data verification |
| SOC | System Organ Class |
| SS | Safety Set |
| CCI [redacted] | |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TDV | Tetravalent Dengue Vaccine Candidate |
| VE | Vaccine efficacy |
| WHO | World Health Organization |
| WT | Wild type |

## 3.4 Corporate Identification

TV Takeda Vaccines, Inc.

# 4.0 INTRODUCTION

## 4.1 Background

Dengue fever is caused by infection with the dengue virus (DENV), a ribonucleic acid (RNA) virus that occurs as 4 recognized serotypes, DENV-1, DENV-2, DENV-3 or DENV-4. These dengue viruses are transmitted from human to human by mosquitoes (primarily *Aedes aegypti*). The 4 dengue viruses have spread worldwide and are endemic in Asia, Central and South America, the Caribbean, the Pacific Islands, parts of Australia, and parts of Africa. An estimated 50 - 100 million cases of dengue fever occur annually, which results in around 500,000 cases of dengue hemorrhagic fever (DHF) and an estimated 22,000 deaths, primarily in children. It is estimated that 2.5 billion people (40% of the world's population) live in areas at risk of dengue virus transmission [1-4].

Dengue fever is clinically defined as an acute febrile illness with 2 or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leucopenia) and occurrence at the same location and time as other confirmed cases of dengue fever. The most severe forms of dengue infection – DHF and dengue shock syndrome (DSS) – are life threatening. Primary infection with any 1 of the 4 dengue serotypes is thought to result in life-long protection from re-infection by the same serotype, but does not protect against a secondary infection by 1 of the other 3 dengue serotypes and may lead to an increased risk of severe disease (DHF/DSS) [3-6].

Treatment of dengue fever is based solely on symptoms and signs, with fluid replacement required for hemorrhagic or shock cases. No antiviral therapy for dengue virus infection is available. Preventive measures that rely on mosquito control and individual protection, are of limited efficacy, complex to implement and questionable in terms of cost-effectiveness. There is a great unmet global public health need for a safe and effective vaccine that will protect against all serotypes of dengue infection, and thereby reduce the morbidity and mortality associated with dengue disease [1-7]. A first recombinant dengue vaccine (chimeric yellow fever virus-dengue virus tetravalent dengue vaccine [CYD-TDV]) has been approved since 2015 in several Asian and Latin American countries [8] as well as in the United States and in the European Union. Clinical data indicate an unfavorable risk-benefit profile for children aged <9 years with this first approved vaccine. Additionally, vaccine efficacy was different between serotypes and depended on dengue pre-exposure status [9]. More recent analyses found that people who had not been infected by dengue virus before vaccination had a higher risk of getting severe disease when they were infected with dengue virus after vaccination with CYD-TDV [10]. In a revised Strategic Advisory Group of Experts on Immunization (SAGE) recommendation in April 2018, the SAGE concluded that for countries considering CYD-TDV vaccination as part of their dengue control program, a "pre-vaccination screening strategy" would be the preferred option, in which only dengue-seropositive persons are vaccinated [11].

Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines [12].

### Takeda's Tetravalent Dengue Vaccine Candidate (TDV) Background:

TDV consists of a mixture of 4 live, attenuated recombinant dengue virus strains expressing surface antigens corresponding to the 4 recognized dengue serotypes 1-4. The serotype 2 strain is based upon the attenuated laboratory-derived virus, DEN-2 Primary Dog Kidney (PDK)-53, originally isolated at Mahidol University, Bangkok, Thailand [13]. The chimeric, attenuated vaccine strains for dengue serotypes 1, 3 and 4 were engineered by replacing the DEN-2 structural genes, pre-membrane (prM) and envelope (E), with the prM and E genes of the wild-type (WT) virus strains, DENV-1 16007, DENV-3 16562 or DENV-4 1036 virus, respectively [14]. TDV is thus comprised of 4 recombinant, live attenuated dengue virus strains: a molecularly characterized, attenuated DEN-2 strain (TDV-2), a DEN-2/1 chimera (TDV-1), a DEN-2/3 chimera (TDV-3) and a DEN-2/4 chimera (TDV-4).

Nonclinical studies carried out in mice and nonhuman primates demonstrated an acceptable safety, immunogenicity, and efficacy profile of Takeda's TDV.

Data from 3 phase I trials and a phase II trial have shown satisfactory reactogenicity, safety and immunogenicity of Takeda's TDV in adults in non-endemic areas as well as in adults and children in endemic areas in Asia and Latin America. At the time of the current protocol amendment, the phase II trial that has enabled the selection of a final TDV dose formulation for use in the pivotal program has been finalized.

In Part 1 of the present ongoing Phase III trial, the primary endpoint was achieved with an overall vaccine efficacy (VE) of 80.2% (95% CI: 73.3 to 85.3). In Part 2, the analysis of secondary endpoints showed efficacies of 76.1% (95%CI: 68.5 to 81.9) in subjects who were seropositive at baseline, 66.2% (95% CI: 49.1 to 77.5) in subjects who were seronegative at baseline, 90.4% (95% CI: 82.6 to 94.7) against hospitalized dengue, and 85.9% (95% CI: 31.9 to 97.1) against dengue hemorrhagic fever. Vaccine efficacy varied by individual serotypes. Cumulative rates of serious adverse events (SAEs) were similar in TDV (4.0%) and placebo (4.8%) recipients, and were consistent with expected medical disorders in the trial population [15].

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The current Investigator Brochure of Takeda's TDV contains additional product information and a more detailed review of pre-clinical and clinical trials [17].

## 4.2 Rationale for the Proposed Phase III Efficacy Trial

Given the accelerating spread of dengue in the world, there is an urgent need for an effective dengue vaccine, not only for those who live in dengue endemic areas, but also for those who travel to those areas. In the absence of a correlate of protection, the World Health Organization (WHO) recommends that phase III dengue trials are performed in dengue endemic areas, where vaccinated and control individuals are at equal risk of acquiring the disease allowing assessment of VE.

Although the ultimate goal of a dengue vaccine is to protect against all 4 serotypes, it is unlikely that a single trial will be sufficiently powered to demonstrate VE against each dengue serotype. Therefore, the WHO recommends a primary objective of VE measured against laboratory-confirmed dengue illness caused by any of the 4 serotypes.

The trial will be conducted in accordance with the protocol, the International Council for Harmonisation of technical requirements for pharmaceuticals for human use - Good Clinical Practice (ICH-GCP) Guidelines and any applicable regulatory requirements.

### 4.2.1 Parts 1, 2, and 3

This phase III trial is comprised of at least 3 parts for all subjects. Part 1 will assess VE against symptomatic dengue illness due to any serotype, and will provide data to support licensure based on WHO recommendations outlined above. An extended follow-up is planned in Part 2, aimed at providing additional data to allow a more precise assessment of VE against each serotype. Part 3 fulfils the WHO recommendation of long-term follow-up to evaluate safety.

In order to maintain the double-blind design, a placebo (Normal Saline) was used in this trial. A placebo had been chosen to avoid the use of a number of active vaccine comparators that would be required due to the wide age range of subjects (4 to 16 years of age) and the diverse countries participating. As no active comparator was possible as part of the trial design, a licensed vaccine will be offered to all subjects, irrespective of their full participation in this trial and at least 6 months after any protocol defined vaccination. The choice of this vaccine was discussed between the Sponsor and the Investigator, and was approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country (see also Section 9.3.3).

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[redacted]

(Day 1 [Month 0]) (see also Section 6.2.2) [redacted]

As no active comparator was possible as part of the trial design, a licensed vaccine will be offered to all subjects at least 6 months after any protocol defined vaccination. A[redacted] The choice of this vaccine will be discussed between the Sponsor and the Investigator, and will be approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.

# 5.0 TRIAL OBJECTIVES AND ENDPOINTS

## 5.1 Objectives

### 5.1.1 Primary Objective

To evaluate the efficacy of 2 doses of 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.

### 5.1.2 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.
- To assess the efficacy of TDV in preventing hospitalization due to virologically confirmed dengue 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.

### 5.1.3 Exploratory Objectives

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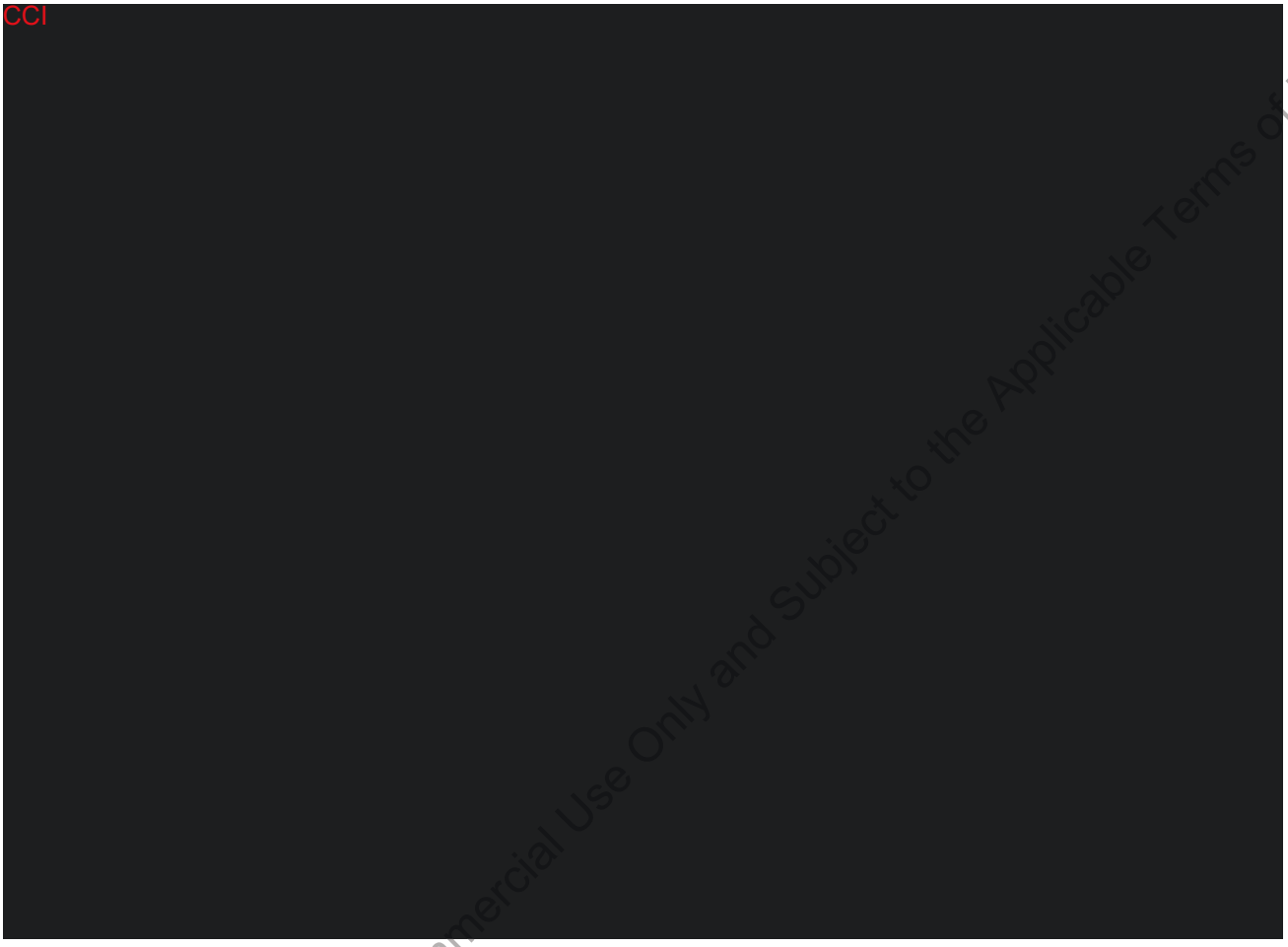



## 5.2 Endpoints

### 5.2.1 Primary Endpoint

***Efficacy***

VE of 2 doses of TDV in preventing virologically confirmed dengue 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 $\lambda_V$ and $\lambda_C$ denote the hazard rates for the TDV and placebo arms, respectively).

### 5.2.2 Secondary Endpoints

***Efficacy***

- VE of 2 doses of TDV in preventing virologically-confirmed dengue 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 virologically-confirmed dengue 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 virologically-confirmed dengue 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 virologically-confirmed dengue 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***

*Subset (post-first and post-second vaccinations):*

- Frequency and severity of solicited local (injection site) 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.

*All subjects:*

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

***Immunogenicity***

*Subset (post-first and post-second vaccinations):*

- 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 at Day 120 (Month 4), Day 270 (Month 9), Day 450 (Month 15), and then annually.
- Seropositivity rate (% of seropositive subjects) for multiple (any 2, 3 or 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 at 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 (microneutralization test 50% [$MNT_{50}$]) 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 at Day 120 (Month 4), Day 270 (Month 9), Day 450 (Month 15), and then annually.

### 5.2.3 Exploratory Endpoints

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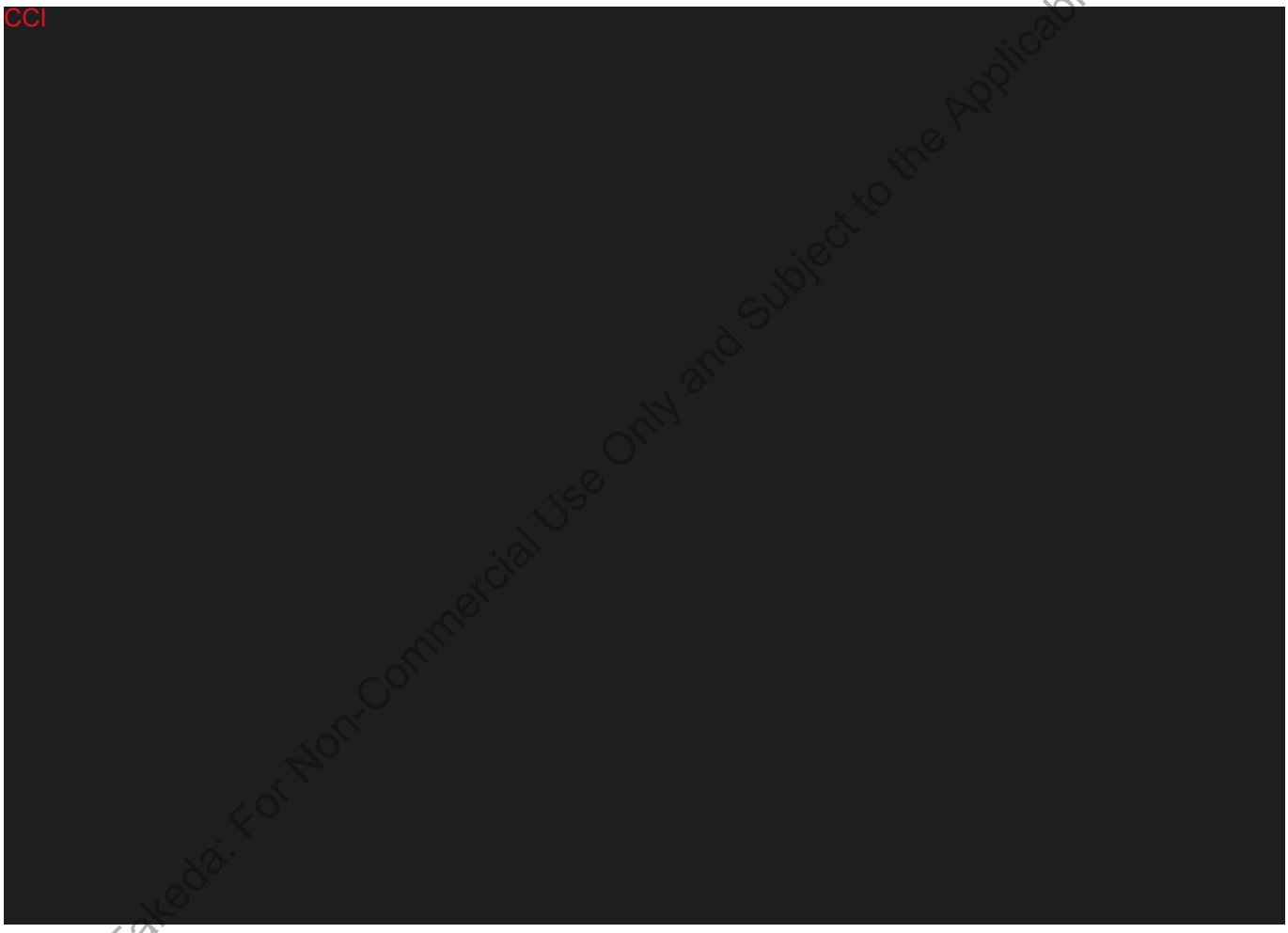

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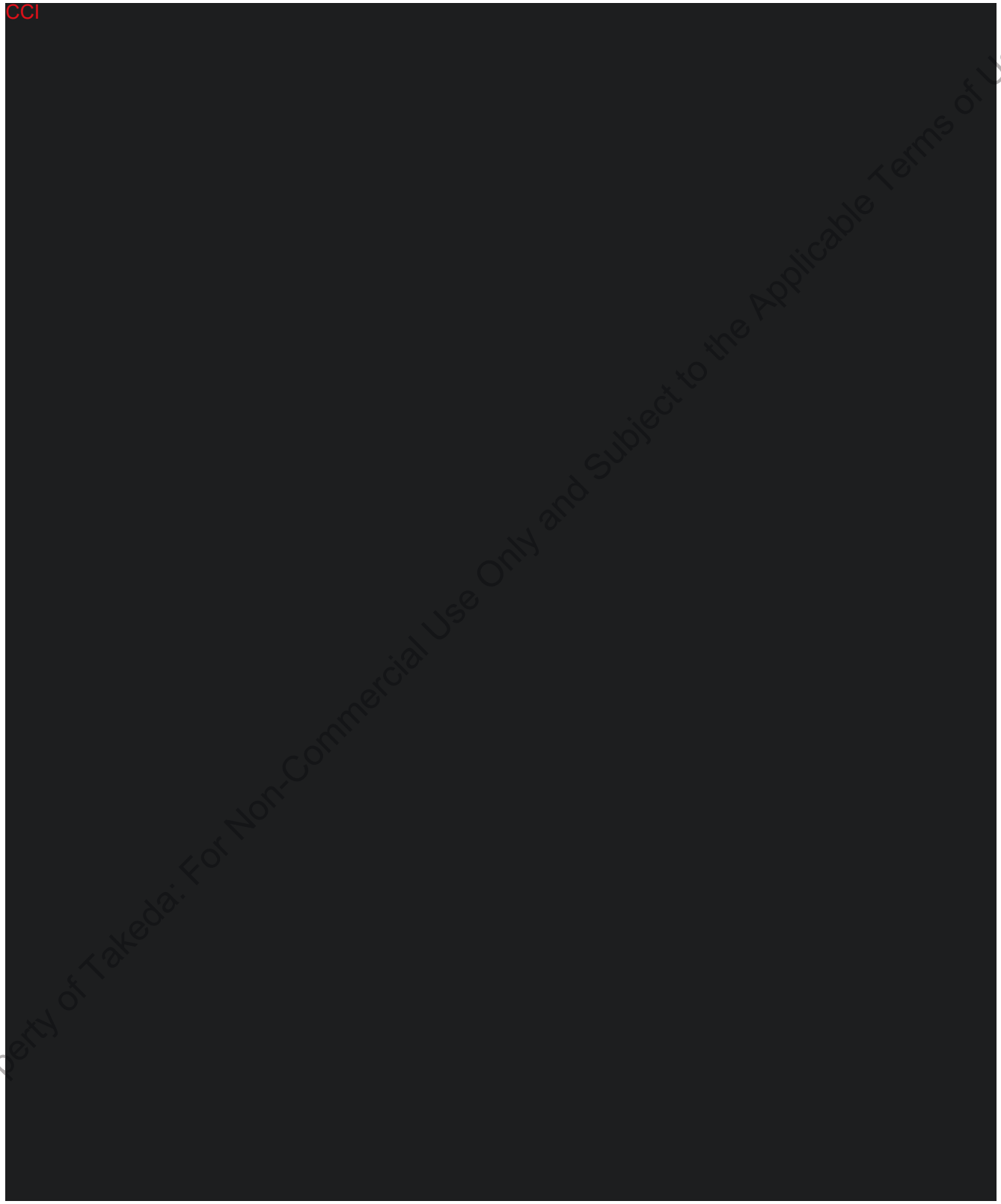

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# 6.0 TRIAL DESIGN AND DESCRIPTION

## 6.1 Trial 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 [redacted]

The trial design and subject population for Parts 1, 2, and 3 of the trial CCI [redacted] are in Section 6.1.1 CCI [redacted].

### 6.1.1 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:
  1. 120 cases of dengue fever are confirmed.
  2. 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 active 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; 6700 placebo). Randomization by using an interactive system (Interactive Web Response System [IWRS] or Interactive Voice Response System [IVRS]) will be stratified by region 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 the age-ranges in this trial. Each subject will receive TDV or placebo by a subcutaneous (SC) injection into the upper arm. A subset of the same subjects (number [N]=4,000) will be included in specific safety and immunogenicity evaluations (safety/ immunogenicity subset, hereafter referred to as 'subset'). This subset will also be selected randomly using IWRS or IVRS and stratified by region 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 virologically confirmed dengue fever induced by any dengue serotype, and will include active surveillance until the 2 conditions described above are fulfilled.

Part 2 is designed to provide additional data regarding the secondary efficacy objectives detailed in Section 5.1.2. 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 6.a. Differences between active surveillance (dry-run, Parts 1 and 2) and modified active surveillance (Part 3) are summarized in Table 6.a.

**Figure 6.a Schematic Showing Parts 1, 2, 3**

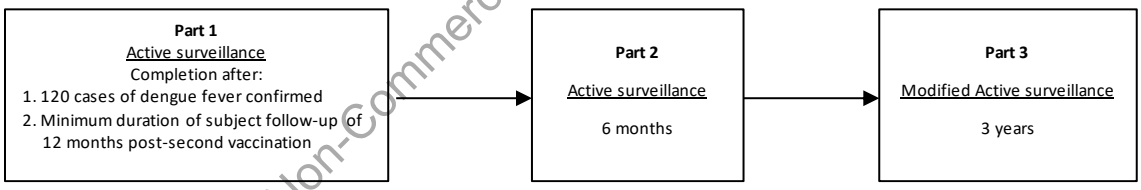


**Table 6.a Differences between Active Surveillance (Dry-Run, Parts 1 and 2) and Modified Active Surveillance (Part 3)**

| | 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)<br>- 7-14 days after the acute sample: IgM and IgG ELISA (central laboratory); and platelet count, hematocrit, ALT, and AST (locally)<br>- Other laboratory evaluations as per standard of care (locally) | | - Within 5 days: RT-PCR (central laboratory)<br>- 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.

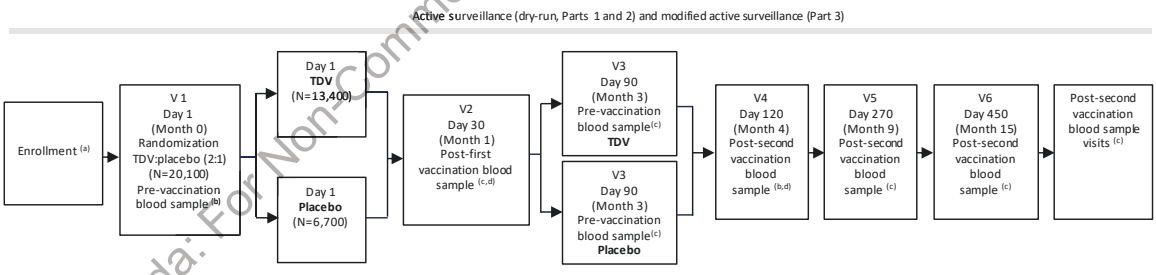
**Procedures**

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 6.b.

**Figure 6.b Schematic to Show Subject Flow Through the Trial (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 PPS and who were 4 to 11 years of age at the time of randomization in the trial on Day 1 (Month 0) will be asked to allow their child/ward to receive

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Immunogenicity evaluation ($MNT_{50}$):

*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 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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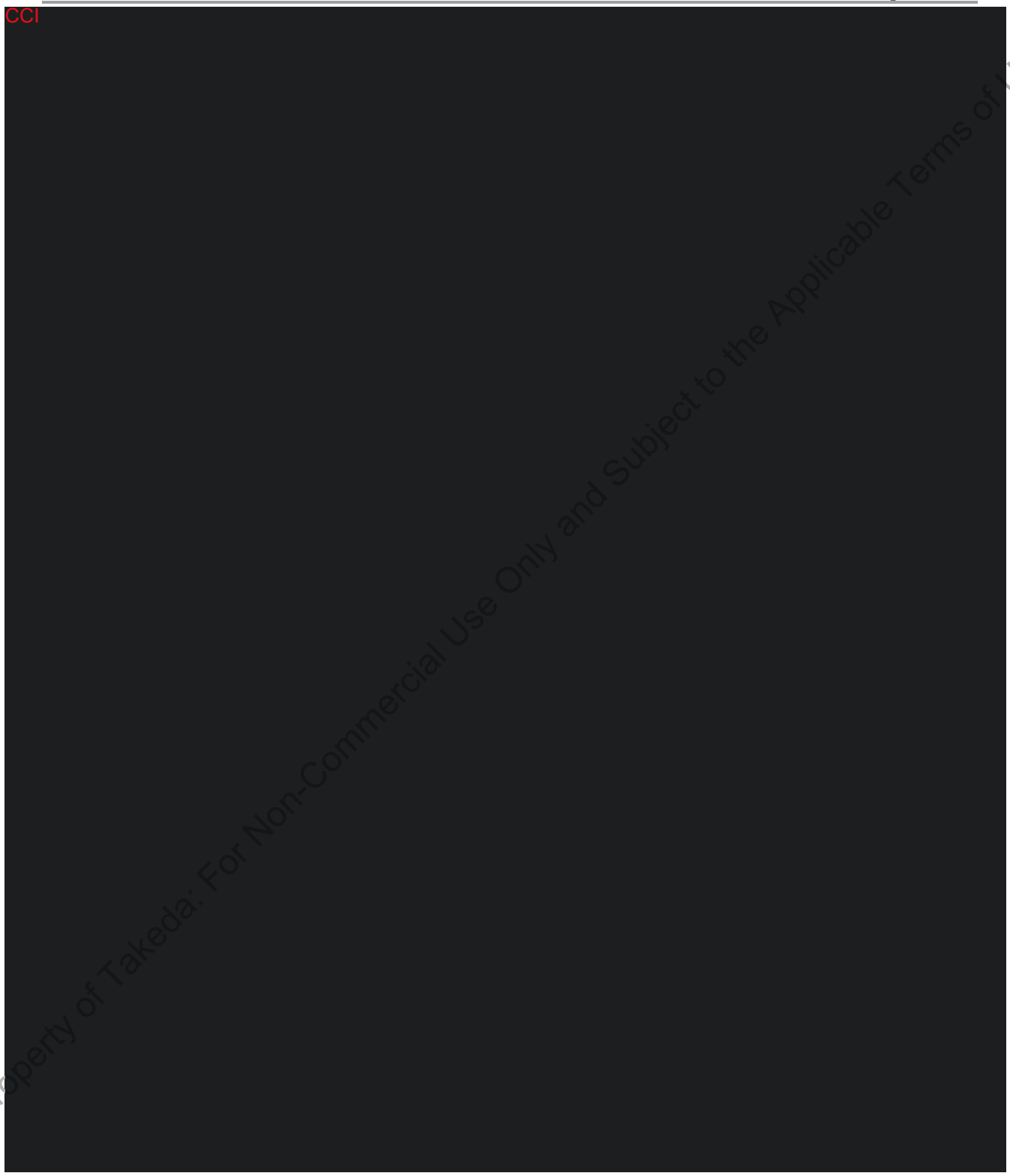

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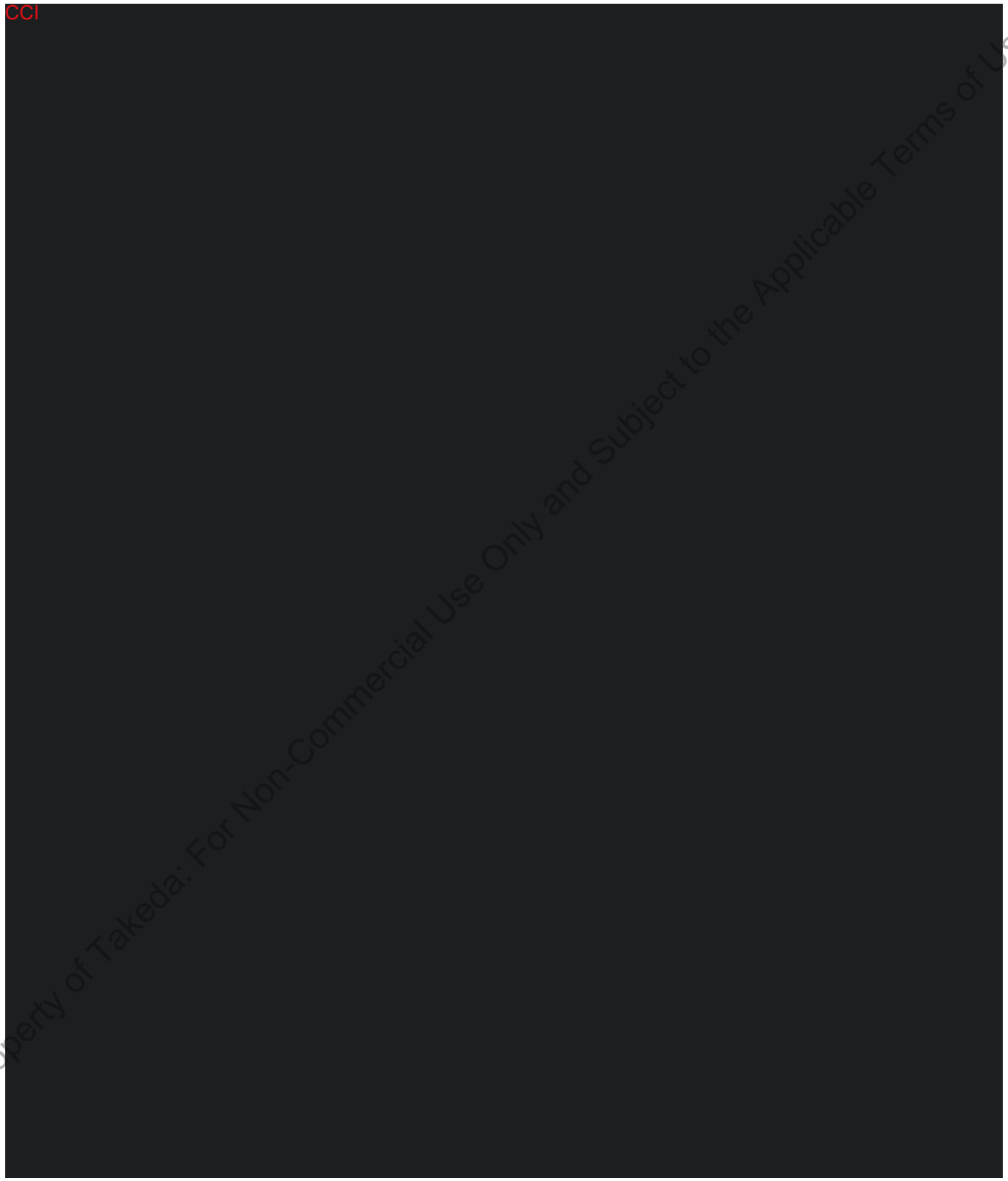

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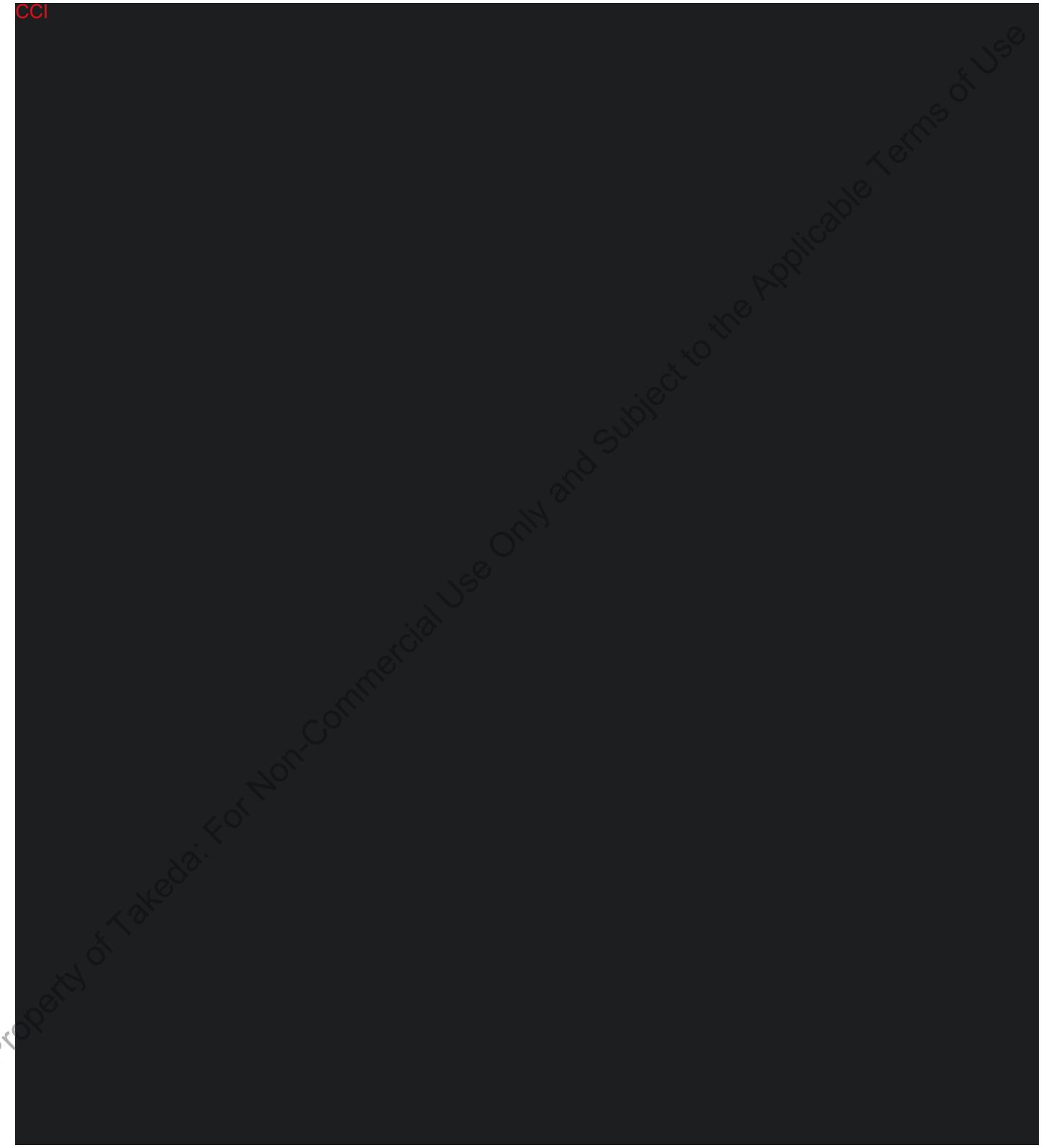

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## 6.2 Justification for Trial Design, Dose, and Endpoints

An efficacy trial is required due to the absence of a correlate of protection, so the primary objective of this trial is to assess the efficacy of 2 doses of TDV in preventing dengue fever of any severity and any serotype in subjects 4 to 16 years of age. This is consistent with WHO recommendations. CCI [redacted] The trial is split into 5 main parts for the reasons described in Section 6.2.1 and 6.2.2.

### 6.2.1 Parts 1, 2, and 3

- Part 1 is designed to support the primary objective through active surveillance of febrile illness intended to detect dengue fever. The duration of Part 1 will ensure that there are

sufficient cases of dengue identified to enable a powered assessment of VE while also ensuring an adequate duration of surveillance following vaccination, both at an individual and a group level.

- Part 2 adds an extra 6 months of active surveillance in order to provide additional data for the secondary objective of assessment of efficacy of the vaccine candidate (see Section 5.1.2). As dengue cases due to individual serotypes are both less common and less predictable in epidemiological terms than a composite assessment of dengue regardless of serotype, it is likely a surveillance duration that supports the later will be inadequate for the former. Part 2 will identify additional cases of dengue to minimize this risk.
- Part 3 fulfils the WHO recommendation of long-term safety follow-up by continuing surveillance for approximately 3 years. The modified active surveillance aims to capture dengue fever of any severity with higher focus on hospitalized dengue fever which has more clinical relevance and societal impact than mild dengue fever managed as an outpatient. Identification of all symptomatic dengue cases will allow monitoring of disease severity over time. However, the surveillance mechanism is modified to lessen burden on subjects and parent/guardian, with the potential to ensure greater compliance to longer term active follow-up. Febrile illness with an alternate laboratory confirmed etiology and not requiring hospitalization will be of lesser clinical relevance in the context of long-term safety assessment of the trial vaccine.

The age range of 4 to 16 years of age has been chosen based on the epidemiology of dengue in the Asian and Latin American countries included in the trial. Symptomatic dengue is most common during a second infection, less common during a primary infection and unusual during a third or fourth infection. Efficacy assessment based on detection of symptomatic dengue is therefore best performed in age groups for which a secondary infection is likely. The peak of symptomatic dengue tends to be younger in Asia (where dengue incidence is higher) and older in Latin America (where incidence is lower, leading to 'delayed' secondary and symptomatic infections). An age range of 4 to 16 years enables some overlap of this epidemiology in the 2 regions and is also an age range for which febrile surveillance and long-term follow-up is more successful.

For the efficacy endpoint, case detection will be supported by a combination of a highly sensitive clinical case definition and a highly specific confirmation method. Febrile episodes will be confirmed virologically by specific RT-PCR to detect specific serotypes and distinguish vaccine-derived from WT viruses. Serological diagnosis will be performed as part of the standard of care but will not be used to confirm cases because the vaccine and other flavivirus infections may induce IgM and IgG responses thereby reducing specificity.

All efforts will be made to detect any possible febrile case as early as possible to optimize the chances of virological confirmation in a timely fashion. However, there may be situations where fever is not documented or may not persist for 2 consecutive days, or atypical presentations trigger the Investigator's suspicion of dengue. To increase the likelihood of capturing more dengue cases, a more flexible criteria that specifies fever on 'any 2 of 3 consecutive days' rather

than '2 consecutive days' and the addition of the Investigator's suspicion of dengue will be used. These cases will be unambiguously recorded by the Investigator using a check box in the eCRF.

In order to maintain the double-blind design, a placebo (Normal Saline) was used in this trial. A placebo had been chosen to avoid the use of a number of active vaccine comparators that would be required due to the wide age range of subjects (4 to 16 years of age) and the diverse countries participating. As no active comparator was possible as part of the trial design, a licensed vaccine will be offered to all subjects, irrespective of their full participation in this trial and at least 6 months after any protocol defined vaccination. The choice of this vaccine was discussed between the Sponsor and the Investigator, and was approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.

The collection of solicited and unsolicited AEs following each vaccination is consistent with vaccine evaluation trials, and with those collected in earlier trials with TDV.

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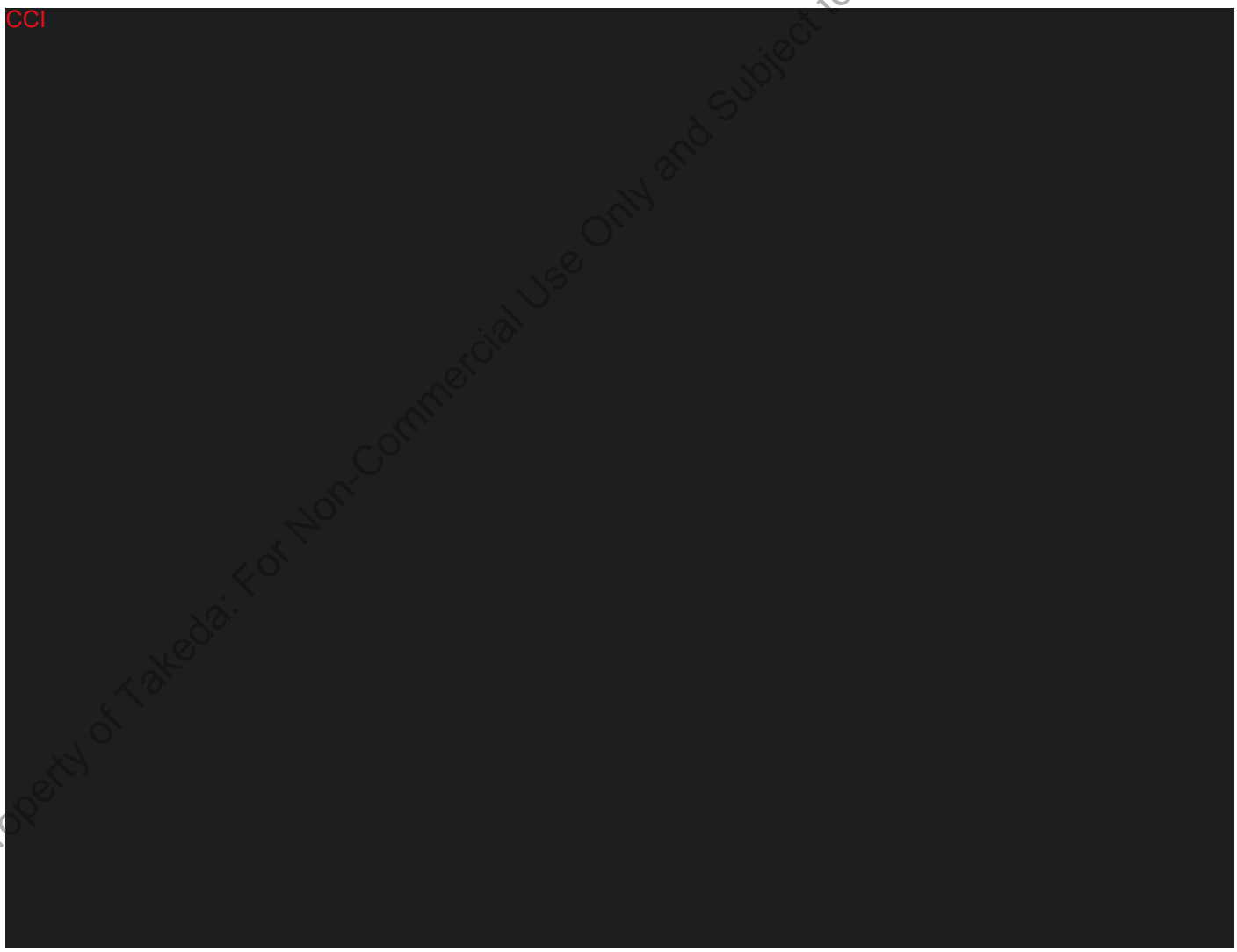

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[redacted]

## 6.3 Duration of Subject's Expected Participation in the Entire Trial

### 6.3.1 Parts 1, 2, and 3

For each participant, at least 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 the 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.

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[redacted]

## 6.4 Premature Termination or Suspension of Trial or Investigational Site

### 6.4.1 Criteria for Premature Termination or Suspension of the Trial

The trial will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the trial.

- New information or other evaluation regarding the safety or efficacy of the investigational vaccine that indicates a change in the known risk/benefit profile, such that the risk/benefit is no longer acceptable for subjects participating in the trial.
- Significant violation of GCP that compromises the ability to achieve the primary trial objectives or compromises subject safety.

### 6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

A trial site may be terminated prematurely or suspended if the site (including the Investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the trial, or as otherwise permitted by the contractual agreement.

A trial site that enrolls subjects prior to randomization may not be able to continue participation in the trial. Examples of reason for non-continuation include failure to adequately implement febrile surveillance or a change in the local standard of care such as availability of a licensed dengue vaccine.

### 6.4.3 Procedures for Premature Termination or Suspension of the Trial or the Participation of Investigational Site(s)

In the event that the Sponsor, IRB/IEC or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or trial suspension.

# 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including pregnancy test results (if applicable), need to be confirmed prior to randomization.

Note that enrollment into the trial could occur up to 10 months prior to Day 1 (Month 0) (ie, as a result of the dry-run for pre-vaccination surveillance for dengue) (see Section 6.1), and that entry criteria will be re-confirmed at Day 1 (Month 0) prior to vaccination.

## 7.1 Inclusion Criteria

### 7.1.1 Trial Entry

Subject eligibility is determined according to the following criteria:

1. The subject is aged 4 to 16 years, inclusive, at the time of randomization.
2. Individuals who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the Investigator.
3. The subject and/or the subject's parent/guardian signs and dates an assent/written informed consent form where applicable, and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements (Appendix C).
4. Individuals who can comply with trial procedures and are available for the duration of follow-up.

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## 7.2 Exclusion Criteria

### 7.2.1 Trial Entry

Any subject who meets any of the following criteria will not qualify for entry into the trial:

1. Febrile illness (temperature ≥38°C) or moderate or severe acute illness or infection at the time of randomization.
2. History or any illness that, in the opinion of the Investigator, might interfere with the results of the trial or pose an additional risk to the subject due to participation in the trial, including but not limited to:
    a. Known hypersensitivity or allergy to any of the vaccine components.
    b. Female subjects (post-menarche) who are pregnant or breastfeeding.
    c. Individuals with any serious chronic or progressive disease according to judgment of the Investigator (eg, neoplasm, insulin-dependent diabetes, cardiac, renal or hepatic disease, neurologic or seizure disorder or Guillain-Barré syndrome).
    d. Known or suspected impairment/alteration of immune function, including:
        i. Chronic use of oral steroids (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) (use of inhaled, intranasal, or topical corticosteroids is allowed).
        ii. Receipt of parenteral steroids (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).
        iii. Administration of immunoglobulins and/or any blood products within the 3 months prior to Day 1 (Month 0) or planned administration during the trial.
        iv. Receipt of immunostimulants within 60 days prior to Day 1 (Month 0).
        v. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1 (Month 0).
        vi. Human immunodeficiency virus (HIV) infection or HIV-related disease.
        vii. Genetic immunodeficiency.
3. Receipt of any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1 (Month 0) or planning to receive any vaccine within 28 days after Day 1 (Month 0).
4. Participation in any clinical trial with another investigational product 30 days prior to Day 1 (Month 0) or intent to participate in another clinical trial at any time during the conduct of this trial.

5. Previous participation in any clinical trial of a dengue candidate vaccine, or previous receipt of a dengue vaccine.
6. First degree relatives of individuals involved in trial conduct.
7. Females of childbearing potential who are sexually active, and who have not used any of the acceptable contraceptive methods for at least 2 months prior to Day 1 (Month 0).
    a. Of childbearing potential is defined as status post onset of menarche and not meeting any of the following conditions: bilateral tubal ligation (at least 1 year previously), bilateral oophorectomy (at least 1 year previously) or hysterectomy.
    b. Acceptable birth control methods are defined as 1 or more of the following:
        i. Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring).
        ii. Barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse.
        iii. Intrauterine device (IUD).
        iv. Monogamous relationship with vasectomized partner (partner must have been vasectomized for at least six months prior to Day 1 [Month 0]).

    Other contraceptive methods may be considered in agreement with the Sponsor and will be approved by the appropriate ethics committee.
8. Females of childbearing potential who are sexually active, and who refuse to use an acceptable contraceptive method up to 6 weeks post-second vaccination.
9. Deprived of freedom by administrative or court order, or in an emergency setting, or hospitalized involuntarily.
10. Current alcohol abuse or drug addiction that may interfere with the subject's ability to comply with trial procedures.
11. Identified as an employee of the Investigator or trial center, with direct involvement in the proposed trial or other trials under the direction of that Investigator or trial center.

There may be instances when individuals meet all entry criteria except one that relates to transient clinical circumstances (eg, temperature elevation or recent use of excluded medication or vaccine). Under these circumstances, a subject may be considered eligible for trial entry or first vaccination, as applicable, if the appropriate window for delay has passed, inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

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[redacted]

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## 7.3 Criteria for Delay of Vaccination and Contraindications

### 7.3.1 Second Vaccination (Day 90 [Month 3])

If any of the below criteria occur at the time scheduled for second vaccination, the subject may be vaccinated at a later date as long the subject is otherwise eligible to continue trial participation. In certain situations, the period of delay may lead to deviations from the time window for second vaccination. The decision to vaccinate in those situations will be taken by the Investigator. The following clinical circumstances warrant a delay for administration of the second trial vaccination:

1. Body temperature ≥38.0°C within 3 days of intended trial vaccination.
2. Receipt of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation within 2 weeks of intended trial vaccination.
3. Receipt of any vaccine other than the trial vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) of intended trial vaccination.
4. Receipt of oral or parenteral steroids or immunosuppressive therapy within 1 month of intended trial vaccination; dosage and duration of treatments for steroids are specified under the exclusion criteria.

There are also circumstances under which receipt of second vaccination is a contraindication in this trial. These circumstances include anaphylaxis or severe hypersensitivity reactions following the first vaccination. If these reactions occur, the subject must not receive second vaccination but

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## 7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the trial should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.11. CCI .

1. Protocol violation: The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety or rights.
2. AE: The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue and/or subject's parent/guardian is unwilling for the subject to continue because of the AE.
3. Lost to follow-up: The subject did not return to the clinic and attempts to contact the subject and/or subject's parent/guardian were unsuccessful. Attempts to contact the subject and/or subject's parent/guardian must be documented. Lost to follow up status will only be confirmed at the time of Last Subject Last Visit at the particular trial site.
4. Withdrawal by subject and/or subject's parent/guardian: The subject wishes to withdraw and/or subject's parent/guardian wishes to withdraw the subject from the trial. The reason for withdrawal, if provided, should be recorded in the eCRF.
    a. Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be

recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

b. Note: subjects will be considered as participating in the trial until the end of Part 3 unless they explicitly withdraw their consent (febrile surveillance will continue and febrile episodes will be recorded in the eCRF per protocol definition).

5. Study terminated by Sponsor.
6. Pregnancy: Any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further investigational vaccines and trial interventions except for febrile surveillance and safety follow-up if the subject and/or the subject's parent/guardian agrees. The site should maintain contact with the pregnant subject and should complete a "Clinical Trial Pregnancy Form" as soon as possible. In addition, the subject should be followed-up until the birth of the child, or spontaneous or voluntary termination; when pregnancy outcome information becomes available, the information should be captured using the same form. The subject should be reported as a withdrawal from trial and the reason for withdrawal (ie, pregnancy) recorded in detail on the Trial Termination eCRF and subject' medical records.
7. Other. (Note: The specific reasons should be recorded in the "specify" field of the eCRF).

## 7.5 Procedures for Discontinuation or Withdrawal of a Subject

### 7.5.1 Parts 1, 2, and 3

The Investigator may terminate a subject's trial participation at any time during the trial when the subject meets trial termination criteria described in Section 7.4. In addition, a subject and/or the subject's parent/guardian may discontinue the subject's trial participation at any time during the trial without giving a reason. Should a subject's participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures as scheduled for the Follow-up Visit (see Table 2.d).

Until the time of randomization, discontinued or withdrawn subjects will be replaced; after that time, discontinued or withdrawn subjects will not be replaced.

All withdrawn and discontinued subjects after vaccination on Day 1 (Month 0) will be followed for safety monitoring until the end of Part 3 CCI [redacted] unless subjects are lost to follow up or specifically withdrawn from febrile surveillance and safety follow up. Those withdrawn or discontinued prior to vaccination will not be followed up for safety.

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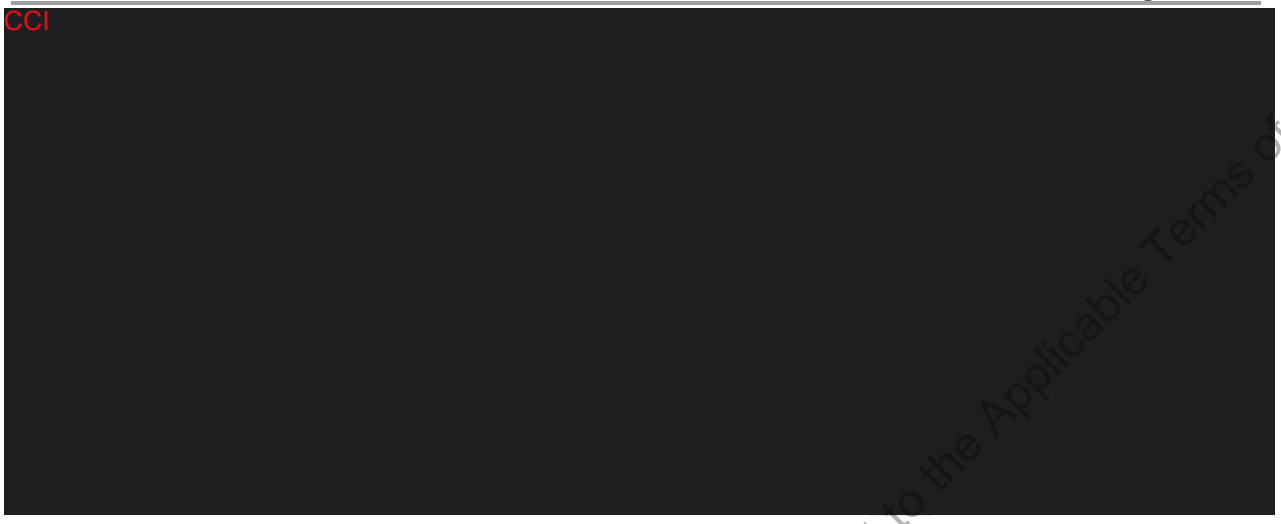

# 8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all vaccines and materials provided directly by the Sponsor, and/or sourced by other means, that are required by the trial protocol, including important sections describing the management of clinical trial material.

## 8.1 Investigational Vaccine(s) and Materials

### 8.1.1 Parts 1, 2, and 3

The Investigational Product is TDV, a tetravalent dengue vaccine comprised of 4 recombinant, live attenuated dengue virus strains: ~2 x $10^4$, 5 x $10^3$, 1 x $10^5$ and 3 x $10^5$ plaque forming units (PFU) per dose of TDV-1, TDV-2, TDV-3 and TDV-4, respectively.

All doses should be prepared at the time of administration by the unblinded pharmacist (or administrator) per the Pharmacy Manual. Each vial and carton will contain a label that includes pertinent trial information and caution statements. The label text will be in the specific country language, depending on local requirements.

CCI [redacted]

*8.1.2.1.1 Parts 1, 2, and 3*

- **Investigational TDV**

TDV is lyophilized and presented in a labeled, single-use, CCI [redacted] liquid dose for SC injection. TDV will be reconstituted CCI [redacted].

The doses should be prepared at the time of administration by the unblinded pharmacist (or administrator) per the Pharmacy Manual. TDV will be provided by the Sponsor in a uniquely numbered carton and will be dispensed in a blinded manner by the IWRS/IVRS.

- **Placeholder (Normal Saline) control**

The placebo was normal saline for injection (0.9% sodium chloride solution). Placebo will be presented in a CCI SC injection. Placebo will be provided by the Sponsor in a uniquely numbered carton and will be dispensed in a blinded manner by the IWRS/IVRS.

Refer to Section 8.6 for accountability of Sponsor-supplied vaccines.

*8.1.2.1.2* CCI

- **Investigational TDV**

TDV is lyophilized and presented in a labeled, single-use, CCI iquid dose for SC injection. TDV will be reconstituted CCI .

The doses should be prepared at the time of administration by the unblinded pharmacist (or administrator) per the Pharmacy Manual.

TDV will be provided by the Sponsor in a uniquely numbered carton and will be dispensed in a blinded manner by the IWRS/IVRS.

- **Placebo (Normal Saline) control**

Normal saline for injection (0.9% sodium chloride solution) will be used as placebo. The placebo is presented as single dose units for PPD® dosing. Placebo will be provided by the Sponsor in a uniquely numbered carton and will be dispensed in a blinded manner by the IWRS/IVRS.

*8.1.2.2 Storage*

*8.1.2.2.1 Parts 1, 2, and 3*

The placebo, TDV and diluent will be shipped in refrigerated containers at 2 to 8°C. From receipt and prior to use, lyophilized TDV kits must be protected from light and stored at 2°C to 8°C in a refrigerator.

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container until dispensed. A daily temperature log of the vaccine storage area must be maintained every working day.

*8.1.2.3 Dose and Regimen*

*8.1.2.3.1 Parts 1, 2, and 3*

Subjects will receive a 2-dose regimen (Day 1 [Month 0]) and Day 90 [Month 3]) with either TDV or placebo according to their random assignment on Day 1 (Month 0).

CCI [redacted]

## 8.2 Investigational Vaccine Assignment and Dispensing Procedures

At Day 1 (Month 0), the Investigator or designee will access the IWRS/IVRS at subject enrollment to obtain the subject number. This number will be used throughout the trial.

The Investigator or designee will utilize the IWRS/IVRS to randomize the subject into the trial on the day of first dosing. During this contact, the Investigator or designee will provide the necessary subject identifying information.

CCI [redacted]

The investigator or the investigator's designee will access the IWRS or IVRS at each dispensing visit to obtain the Vaccination Identification number for the vaccine dose. The vaccines will be prepared and administered by the unblinded pharmacist or unblinded administrator according to the instructions in the Pharmacy Manual or per manufacturer's instructions.

The Investigator or designee will be responsible for overseeing the administration of vaccine to subjects randomized in the trial according to the procedures stipulated in this trial protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable laws and regulations for that specific trial. The unblinded personnel who administer the vaccine will not assess AEs.

If Sponsor-supplied vaccine is lost or damaged, the site can request a replacement. Expired vaccines must not be administered.

## 8.3 Randomization Code Creation and Storage

### 8.3.1 Parts 1, 2, and 3

Randomization personnel of the Sponsor or designee will generate the randomization schedule(s). Randomization information will be stored in a secured area, accessible only by authorized personnel.

Randomization will be stratified by region and age range (children aged 4-5 years, 6-11 years, and 12-16 years). Subjects included in the subset will be randomly selected using the IWRS/IVRS.

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## 8.4 Investigational Vaccine Blind Maintenance.

The investigational vaccine blind will be maintained using the IWRS/IVRS. The subjects, data collectors (eg, Investigator), and data evaluators (eg, trial statisticians) are blinded. One or more designated pharmacists/ vaccine administrators will be unblinded at the site. These unblinded designees will maintain the investigational vaccine blind and will have no role in the assessment of subject safety.

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## 8.5 Unblinding Procedure

The investigational vaccine blind shall not be broken by the Investigator unless information concerning the investigational vaccine is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational vaccine blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational vaccine blind can be obtained by the Investigator, by accessing the IVRS/IWRS.

The Sponsor's Pharmacovigilance Department must be notified as soon as possible if the investigational vaccine blind is broken by the Investigator and the completed SAE form must be sent within 24 hours (Refer to Section 10.4.3). The date, time, and reason the blind is broken must be recorded in the source document and the same information (except the time) must be recorded on the eCRF.

In the event of accidental unblinding of the investigational vaccine, the Sponsor shall be immediately contacted for further decision about the subjects' eligibility to continue in the trial.

Further details regarding the unblinding procedure for the primary analysis after Part 1 can be found in Section 13.2.

## 8.6 Accountability and Destruction of Sponsor-Supplied Vaccine(s)

Vaccine supplies will be counted and reconciled at the site before being destroyed or returned to the Sponsor or designee as noted below. Sites will maintain source documents in addition to entering data in the IVRS/IWRS.

The Investigator or designee must ensure that the Sponsor-supplied vaccines are used in accordance with the approved protocol and is administered only to subjects randomized in the trial. To document appropriate use of Sponsor-supplied vaccine(s) (TDV, diluent and placebo), the Investigator must maintain records of all Sponsor-supplied vaccine delivery to the site, site inventory, administration and use by each subject, and destruction or return to the Sponsor or designee.

Upon receipt of Sponsor-supplied vaccine(s), the Investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the investigational vaccine is received within the labeled storage conditions, and is in good condition. If quantity and conditions are acceptable, the Investigator or designee will acknowledge receipt of the shipment by recording in IVRS/IWRS.

If there are any discrepancies between the packing list versus the actual product received, the Sponsor or designee must be contacted to resolve the issue. The packing list should be filed in the Investigator's essential document file.

The Investigator must maintain 100% accountability for all Sponsor-supplied vaccines received and administered during his or her entire participation in the trial. Proper vaccine accountability includes, but is not limited to:

- Verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the vaccine lot number used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

The Investigator or designee must record the current inventory of all Sponsor-supplied vaccines (TDV and placebo) on a Sponsor-approved vaccine accountability log. The following information will be recorded at a minimum: protocol number and title, name of the Investigator, site identifier and number, description of Sponsor-supplied vaccine(s), expiry date and/or retest date and amount. The IVRS/IWRS should include all required information as a separate entry for each subject to whom Sponsor-supplied vaccine is administered.

Prior to site closure or at appropriate intervals throughout the trial, before any clinical trial materials are returned to the Sponsor or its designee for destruction, a representative from the

Sponsor or its designee will perform clinical trial material accountability and reconciliation. The Investigator will retain a copy of the documentation regarding clinical trial material accountability, return, and/or destruction, and originals will be sent to the Sponsor or designee.

The pharmacist (or designated individual) at each site will be responsible for vaccine accountability and will document receipt, use, return, or destruction of TDV and placebo. Vaccine accountability documentation will be reviewed by the unblinded monitor during clinical monitoring visits.

# 9.0 TRIAL PLAN

## 9.1 Trial Procedures

The following sections describe the trial procedures and data to be collected. For each procedure, subjects are to be assessed by the same Investigator or site personnel whenever possible. The Schedule of Trial Procedures is located in Section 2.1.

### 9.1.1 Informed Consent/Assent

The requirements of the informed consent/assent are described in Section 15.2.

#### *9.1.1.1 Parts 1, 2, and 3*

Informed consent/assent must be obtained prior to the subject entering into the trial, and before any protocol-directed procedures are performed. Note that this may be up to 10 months prior to first vaccination as a result of the dry-run for pre-vaccination surveillance for dengue or prior to Day 1 (Month 0). Informed consent/assent already obtained prior to the dry-run will not need to be repeated on Day 1 (Month 0) unless there is an amendment to the informed consent/assent forms.

After informed assent/consent has been obtained, the IVRS/IWRS will assign a unique identification number (screening number) to each subject. If all eligibility criteria are fulfilled, this will become the definitive subject number to be used throughout the trial. Subject numbers assigned to subjects who fail screening should not be reused (Section 9.1.11), and similarly subject numbers assigned to subjects who withdraw or are discontinued between enrollment and Day 1 (Month 0) should not be reused.

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### 9.1.2 Demographics, Medical History and Prior Medications

#### *9.1.2.1 Parts 1, 2, and 3*

Demographic information to be obtained will include date of birth, gender, and race as described by the subject and/or the subject's parent/guardian.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for trial participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also

include any medical history that contributes to the understanding of an AE that occurs during trial participation, if it represents an exacerbation of an underlying disease/preexisting problem.

History of vaccination against Japanese Encephalitis or against Yellow Fever until Day 120 (Month 4) will be recorded in the eCRF irrespective of time of administration and including the vaccine type (Japanese Encephalitis: inactivated, live-attenuated, live recombinant or other; Yellow fever: live-attenuated or other). Additionally, any supportive documentation for these vaccinations will be recorded in the eCRF.

All concomitant medications and any vaccine taken/received during the period starting 1 month (minimum 28 days) prior to administration of trial vaccine (Day 1 [Month 0] and Day 90 [Month 3]) and ending 1 month (minimum 28 days) after each trial vaccination are to be recorded on the relevant sections of the eCRF. Medications/treatments specifically contraindicated at trial entry and time of first vaccination including 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) are to be recorded on the relevant sections of the eCRF (See also Section 7.2). The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source documents. Trial vaccination should be delayed if subjects have used antipyretics and/or analgesic medication within 24 hours prior to vaccine administration.

Medications taken for prophylaxis are those intended to prevent the onset of AEs following vaccination. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Prohibited therapies (see also Section 7.2):

- Parenteral immunoglobulin preparation, blood products, and/or blood-derived products within the 3 months prior to Day 1 (Month 0).
- Immunosuppressive therapy within 6 months or systemic (eg, oral or parenteral) corticosteroid treatment within 60 days prior to Day 1 (Month 0) or immunostimulants within 60 days prior to Day 1 (Month 0).
- Any vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1 (Month 0) and Day 90 (Month 3), and 28 days after each trial vaccination.
- Receipt of any other clinical trial product within 30 days prior to Day 1 (Month 0).

These data must be written in the source documents.

Medical history (including corresponding medication) to be obtained will include any significant conditions or diseases that have disappeared or resolved at or prior to signing of informed consent/assent. Additionally, reasons for delay of second trial vaccination and contraindications for second vaccination must be recorded in the eCRF (see Section 7.3).

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