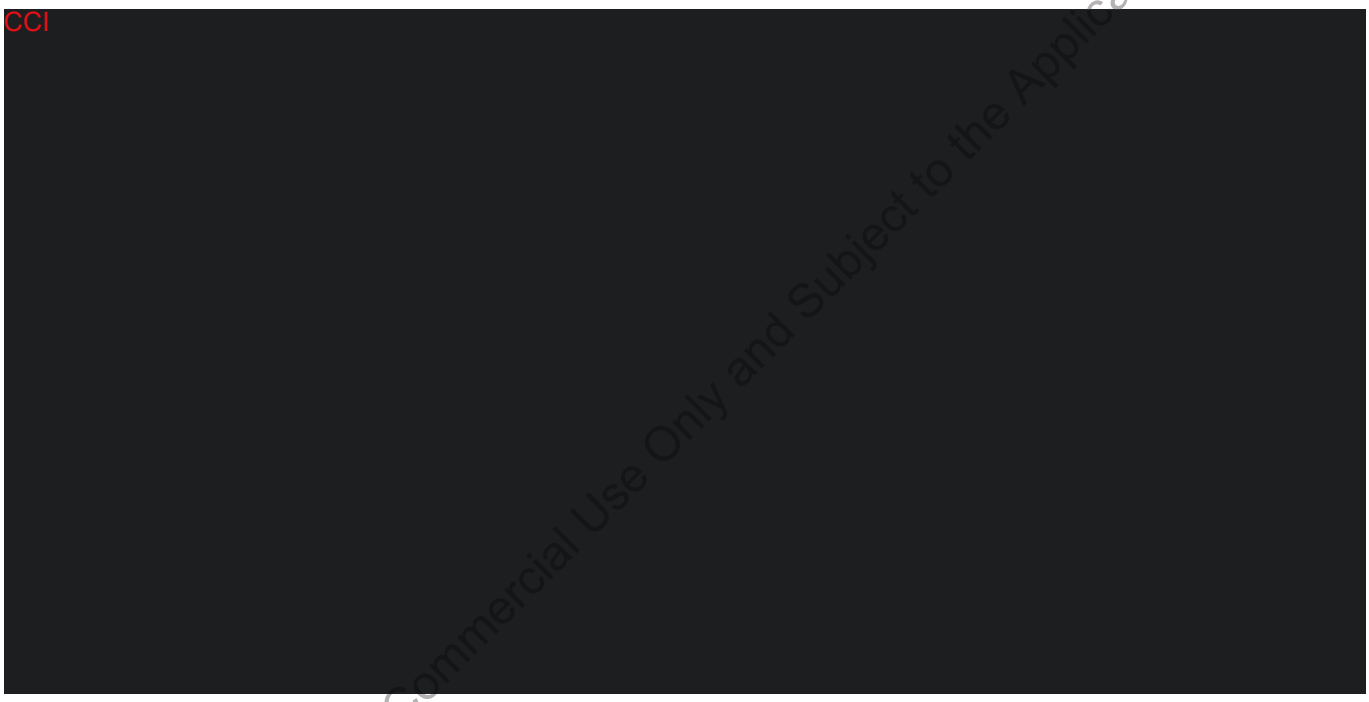
9.1.3 Documentation of Trial Entrance/Randomization

Only subjects for whom a signed informed consent form/assent has been obtained, and meet all of the other inclusion criteria and none of the exclusion criteria are eligible for trial entry/randomization into the vaccination phase. The list of randomization assignments is produced by IVRS/IWRS.

If the subject is found to be not eligible for randomization/trial phase, the Investigator should record the primary reason for failure on the screening log.

CCI



9.1.5 Physical Examination

Physical examinations must be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Site Responsibility Delegation Log.

A complete physical examination includes but is not limited to: auscultation of heart and lungs, palpation of the abdomen, inspection of extremities (including skin over intended vaccination site(s)), and a check of general appearance. Additional physical examinations may be performed if indicated by review of the subject's medical history. The performance of the physical examination must be recorded in the eCRF (Yes/No). The findings should be documented in the subject's source document.

A targeted physical examination includes but is not limited to measurement of vital signs (see Section 9.1.6).

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

9.1.5.1 Parts 1, 2, and 3

Complete physical examination will be performed prior to the dry-run, on Day 1 (Month 0), and on Day 90 (Month 3). A targeted physical examination will be performed for all subjects on Day 30 (Month 1), Day 120 (Month 4), and in the subset at all trial visits subsequent to Visit 4 (Day 120 [Month 4]).

CCI

[redacted]

9.1.6 Vital Signs

9.1.6.1 Parts 1, 2, and 3

During the physical examination (see Section 9.1.5.1), a subject should have their vital signs measured. These will include (but are not limited to) systolic blood pressure/diastolic blood pressure, heart rate, temperature, height and weight.

CCI

[redacted]

9.1.7 Immunogenicity Assessments

9.1.7.1 Vaccine Immunogenicity

9.1.7.1.1 Parts 1, 2, and 3

All subjects will undergo blood sampling for serological immunogenicity testing at pre-vaccination on Day 1 (Month 0) and on Day 120 (post-second vaccination [Month 4]). Additional samples will be collected from 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) and Day 450 (Month 15), and then every 12 months until the end of Part 3.

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood taken for immunogenicity at any single visit is approximately 8 mL at Day 1 (Month 0) and Day 120 (Month 4) for all subjects. The maximum volume of blood

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

taken for immunogenicity at other visits (subset only) is 5 mL. The approximate total volume of blood for the trial is 16 mL for subjects not included in the subset and 51 mL for subjects in the subset. Blood samples will be processed and stored at the trial site according to the Laboratory Guidelines as provided in the Laboratory Manual.

Blood samples taken at pre-vaccination on Day 1 (Month 0) of all subjects will be analyzed for evaluation of dengue serostatus at baseline. Day 120 (Month 4) samples for subjects not in the subset will be stored for future analysis. A higher blood volume for immunogenicity assessment (ie, approximately 8 mL vs. 5 mL) is collected on Day 1 (Month 0) and on Day 120 (Month 4) for all subjects in comparison to additional sampling time points (for the subset) to obtain additional serum to be stored for future analysis. This is considered essential in view of the evolving scientific field around dengue vaccine development (see also Section 9.4).

CCI

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

9.1.7.2 Handling of Febrile Illness Cases (Suspected Dengue Cases)

9.1.7.2.1 Parts 1, 2, and 3

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 as outlined in Figure 6.b and detailed in the Laboratory Manual. 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 ELISA, dengue NS1 antigen ELISA, dengue RT-PCR, hematocrit, platelet count and LFTs (AST and 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 ELISA, hematocrit, platelet count, and LFTs.

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. Approximate blood volumes and analyses for febrile surveillance are presented in Table 9.a.

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.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Table 9.a Blood Volumes and Analyses for Febrile Surveillance

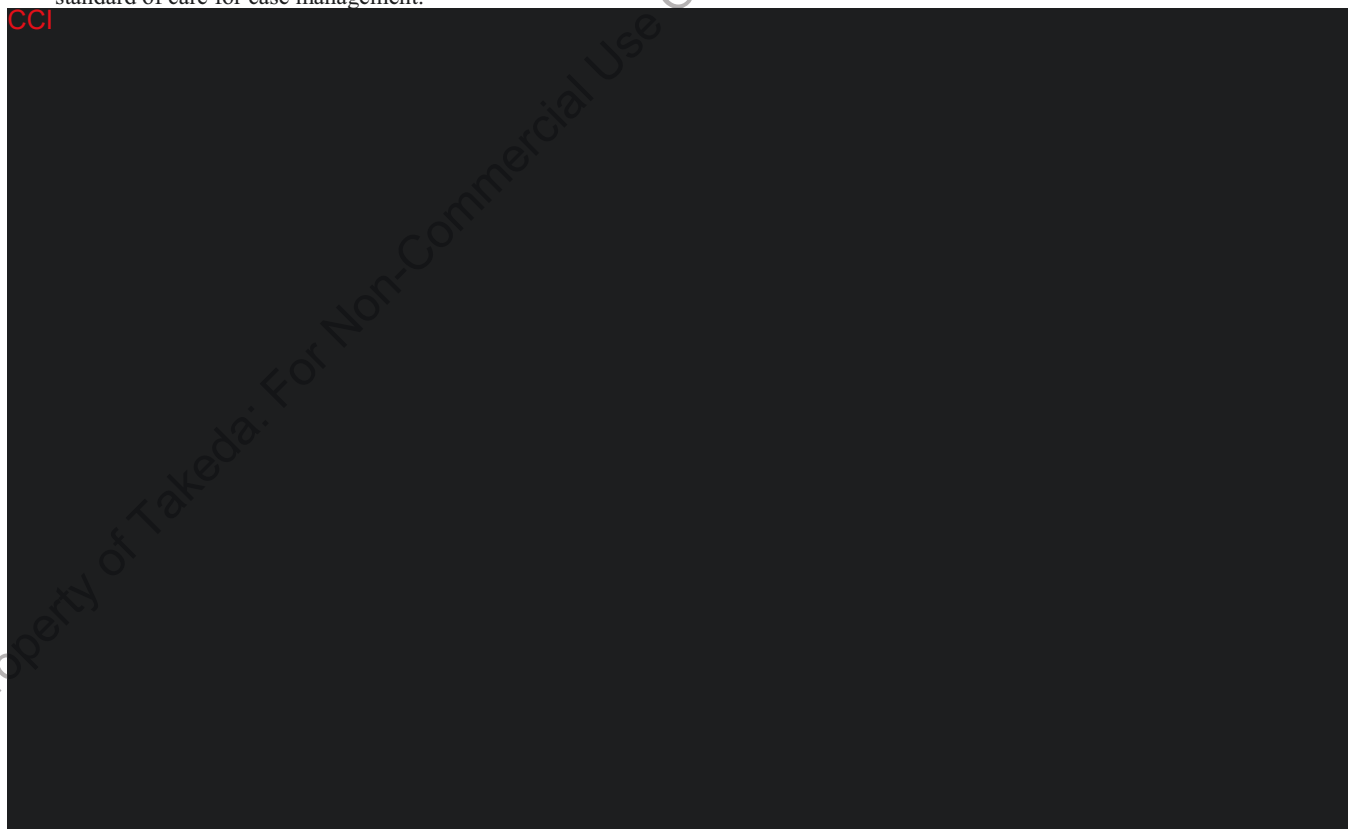
Timing	Blood volume	Assessments
During the dry-run, Parts 1 and 2, and if hospitalization is required during Part 3		
Acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever)	4 mL	RT-PCR, NS1 antigen ELISA, IgM and IgG ELISA
	3-5 mL [(a)]	Hematocrit, platelet count and LFTs (AST and ALT)
Convalescent phase of the disease (ie, between 7 and 14 days after the acute sample)	3 mL	IgM and IgG ELISA
	3-5 mL [(a)]	Hematocrit, platelet count and LFTs (AST and ALT)
During Part 3 without alternate laboratory confirmed etiology and not requiring hospitalization		
Acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever)	3 mL	RT-PCR

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

(a) Blood volume may be different as per local laboratory requirements.

Note: Only samples for RT-PCR, NS1 antigen ELISA, IgM ELISA and IgG ELISA will be sent to the central laboratory. Data from central laboratory will not be available for real time case management. Diagnostic tests are to be performed locally as per standard of care for case management.

CCI



Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

9.1.8 Safety Assessments

Safety assessments will include collection and recording of solicited local (injection site) and systemic AEs, and unsolicited AEs (serious and non-serious). Solicited AEs and non-serious unsolicited AEs will be collected for the subjects in the subset.

CCI [redacted]

Refer to Section 10.1 for safety definitions. Details on collection and reporting of AEs are in Section 10.4.

9.1.9 Contraception and Pregnancy Avoidance Procedure

9.1.9.1 Parts 1, 2, and 3

For female subjects of child bearing potential, urine or serum pregnancy testing will be performed prior to entry into the dry-run and prior to each vaccination. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign an assent/consent form (the same form as signed for trial entry) stating that they understand the requirements for avoidance of pregnancy and donation of ova. Refer also to Section 7.2.

CCI [redacted]

9.1.10 Pregnancy

To ensure subject safety and the safety of the unborn child, each pregnancy in a subject having received the investigational vaccine must be reported to the Sponsor within 24 hours of the site learning of its occurrence. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended.

Any pregnancy occurring following investigational vaccine administration should be reported immediately, using a pregnancy notification form, to the contact listed in the Investigator Site File.

If pregnancy occurs after administration of a blinded investigational vaccine, the Investigator must inform the subject or parent/guardian of their right to receive trial vaccine information. If

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

the subject or parent/guardian chooses to receive unblinded trial vaccine information, the individual blind should be broken by the Investigator and procedures must be followed as described in Section 8.5.

9.1.11 Documentation of Subjects who are not Randomized

Investigators must account for all subjects for whom a signed informed consent/assent has been obtained. If a previously enrolled subject is found to be not eligible at Day 1 (Month 0), the Investigator should complete the eCRF. The IVRS/IWRS should be contacted as a notification of non-randomization.

The primary reason for non-randomization is recorded in the eCRF using the following categories:

- AEs prior to receipt of investigational vaccine.
- Screen failure (did not meet inclusion criteria or did meet exclusion criteria).
- Withdrawal by subject and/or subject's parent/guardian.
- Site terminated by Sponsor.
- Study terminated by Sponsor.
- Other (Note: The specific reason[s] should be recorded in the 'specify' field of the eCRF).

Subject numbers assigned to subjects who fail screening or who are withdrawn or discontinued between enrollment and Day 1 (Month 0) should not be reused.

CCI

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

9.2 Monitoring Subject Trial Vaccine Compliance

The Investigator must record each administration of trial vaccine (TDV or placebo) into the subject's source documents and eCRF.

9.3 Schedule of Observations and Procedures

The schedule for all trial-related procedures for all evaluations is shown in Section 2.1. Assessments should be completed at the designated visit/time point(s).

9.3.1 Parts 1, 2, and 3

When a site visit cannot be carried out due to the COVID-19 pandemic, alternative methods of contact (eg, telephone contact) will be made for subjects who are still under monitoring for safety reporting.

9.3.1.1 Enrollment (Day 1 [Month 0] or Prior to the Dry-Run) and Vaccination Procedures (Day 1 [Month 0] and Day 90 [Month 3])

All subjects:

- Prior to vaccination:
  - Before performing any other trial procedure, the signed informed consent/assent needs to be obtained (*prior to the dry-run or on Day 1 [Month 0]*). Refer to Section 9.1.1.
  - Collect demographic data (prior to the dry-run or Day 1 [Month 0]), medical history (*prior to the dry-run, Day 1 [Month 0], and Day 90 [Month 3]*), and concomitant medication (*prior to the dry-run, Day 1 [Month 0], and Day 90 [Month 3]*). Refer to Section 9.1.2.
  - Perform a complete physical examination (*prior to the dry-run, Day 1 [Month 0] and Day 90 [Month 3]*). Refer to Section 9.1.5.
  - Perform pregnancy testing (serum or urine) for female subjects of childbearing potential (*prior to the dry-run, Day 1 [Month 0], and Day 90 [Month 3]*). Refer to Section 9.1.10.
  - Check inclusion and exclusion criteria (*prior to the dry-run and on Day 1 [Month 0]*). Refer to Sections 7.1.1 and 7.2.1.
  - Check criteria for delay of second trial vaccination on Day 90 (Month 3). Refer to Section 7.3.1.
  - Check contraindications to second vaccination on Day 90 (Month 3). Refer to Section 7.3.1.
- If subject meets all eligibility criteria:
  - Randomize subject (*Day 1 [Month 0] only*). Refer to Section 9.1.3.
  - Collect blood sample (*Day 1 [Month 0]*). Refer to Section 9.1.7.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in Procedures Manuals.

- Vaccinate subject according to the assigned investigational vaccine or placebo (*Day 1 [Month 0] and Day 90 [Month 3]*). Refer to Section 8.1.2.3.
- Observe subject for at least 30 minutes after vaccination (Day 1 [Month 0] and Day 90 [Month 3]).
- The site should schedule the next trial activity clinic visit with the subject and/or the subject's parent/guardian (*Day 1 [Month 0] and Day 90 [Month 3]*).
- The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity (*Day 1 [Month 0] and Day 90 [Month 3]*).

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if the subject experiences febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Refer to Section 9.1.7.2.

The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity. The subject and/or the subject's parent/guardian will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

Additional procedures for the subset (Day 1 [Month 0] and Day 90 [Month 3]):

- Collect blood sample (*Day 90 [Month 3]*) prior to vaccination. Refer to Section 9.1.7.

  Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in Procedures Manuals.
- Perform injection site evaluation. Refer to Section 10.1.2.
- Distribute diary cards and perform following procedures (see also Section 10.4.2):
  - Careful training of the subject and/or the subject's parent/guardian on how to measure local AEs and temperature, how to complete and how often to complete the diary card. Training should be directed at the individual(s) who will perform the measurements of local AEs and those who will enter the information into the diary card. This individual may not be the subject or the subject's parent/guardian, but if a person other than the subject or the subject's parent/guardian enters information into the diary card, this person's identity must be documented in the trial file and this person must receive training on the diary card. Training of the subject or the subject's parent/guardian on how to measure an injection site reaction should be performed while the subject is under observation after vaccination.

Diary card instruction must include the following:

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

– The subject and/or the subject's parent/guardian must understand that timely completion of the diary card on a daily basis is a critical component to trial participation. The subject and/or the subject's parent/guardian should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card that are performed by the person completing the diary card should include a single strikethrough line with a brief explanation for any change and be initialed and dated.

Please note:

Diary cards will be the only source document allowed for remote collection of solicited local and systemic AEs (including body temperature measurements, preferably by the oral route). The following additional rules apply to the documentation of safety information collected by diary card:

- The diary card should be reviewed with the subject and/or the subject's parent/guardian.
- No corrections or additions to the diary card will be allowed after it is reviewed with the investigator/designee.
- Any data that are identified as implausible or incorrect, and confirmed by the subject and/or the subject's parent/guardian to be a transcription error should be corrected by the subject or the subject's parent/guardian on the diary card (the correction should include a single strikethrough line and should be initialed and dated by the subject and/or the subject's parent/guardian).
- Any blank or illegible fields on the diary card not otherwise corrected as above will be missing in the eCRF.
- The site must enter all readable entries on the diary card into the eCRF.
- Any newly described solicited safety information should be added to the diary card by the subject and initialed and dated. Any new unsolicited safety information would be recorded in the subject source document as a verbally reported event and therefore captured as an AE and recorded in the AE eCRF.
- Starting on the day of vaccination, the subject and/or the subject's parent/guardian will check for specific types of reactions at the injection site (solicited local AEs), any specific generalized symptoms (solicited systemic AEs), body temperature (preferably to be taken orally), any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals). These solicited AEs and body temperature will be recorded in the diary. Assessments should preferably take place in the evening at day's end.
- Temperature measurement is to be performed using the thermometer provided by the site, and preferably by the oral route. If the subject feels unusually hot or cold during the day, the subject and/or the subject's parent/guardian should check their temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the diary card.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

- The measurement of solicited local AEs (erythema and swelling) is to be performed using the ruler provided by the site.
- The collection on the diary card of body temperature (preferably oral) and of solicited systemic AEs will continue for a total of 14 days (day of vaccination + 13 subsequent days) following each vaccine administration. Collection of solicited local AEs will continue for a total of 7 days (day of vaccination + 6 subsequent days) following each vaccine administration.

The collection of unsolicited AEs and medications by interview will be done after 28 days (day of vaccination + 27 subsequent days) following each vaccine administration (ie, at Day 30 [Month 1] and Day 120 [Month 4], as applicable).

After each vaccination, the subject will be observed for at least 30 minutes including observation for unsolicited AEs, solicited AEs, and temperature measurement. Please take the opportunity to remind the subject and/or the subject's parent/guardian how to measure solicited AEs and temperature as part of this observation period. Record all safety data collected in the subject's source documents.

The site should schedule the next trial activity reminder call.

The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity. The subject and/or the subject's parent/guardian will be reminded to complete the diary card daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All contact details will be provided to the subject and/or the subject's parent/guardian.

9.3.1.2 Clinic Visit for all Subjects after Vaccination (Day 1 [Month 0] and Day 90 [Month 3]) on (Day 30 [Month 1] and Day 120 [Month 4])

All subjects:

- Perform a targeted physical examination. Refer to Section 9.1.5.
- Collect concomitant medication. Refer to Section 9.1.2.
- Collect blood sample at Day 120 (Month 4). Refer to Section 9.1.7.

Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in Procedures Manuals.

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if their child/ward experience febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Refer to Section 9.1.7.2.

The site should schedule the next trial activity clinic visit with subject and/or the subject's parent/guardian.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity. The subject and/or the subject's parent/guardian will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

Additional procedures for the subset:

- Collect blood sample at Day 30 (Month 1). Refer to Section 9.1.7.
- Perform an evaluation of the injection site.
- The diary card will be reviewed. The healthcare professional reviewing these data will discuss the solicited AEs (if any) reported by the subject and/or the subject's parent/guardian and will determine if any additional diagnoses and/or AEs are present and/or concomitant medications have been used.
- Unsolicited AEs will be collected by interview.

Please note:

Diary cards will be the only source document allowed for solicited local and systemic AEs (including temperature measurements). The following additional rules apply to the documentation of safety information collected by diary card:

1. No corrections or additions to the diary card will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the diary card not otherwise corrected will be missing in the eCRF.
3. The site must enter all readable entries in the diary card into the eCRF.
4. Any illegible or implausible data should be reviewed with the subject or the subject's parent/guardian.

Any newly described solicited safety information should be added to the diary card by the subject and initialed and dated. Any new unsolicited safety information would be recorded in the subject's source document as a verbally reported event and therefore captured as an AE and recorded in the AE eCRF.

Perform brief symptom-directed physical assessment. Corresponding information is documented in the source documents and eCRFs.

9.3.1.3 Clinic Visits After Vaccination (Day 1 [Month 0] and Day 90 [Month 3]) for Subjects in the Subset of Parts 1, 2, and 3 (Day 270 [Month 9], Day 450 [Month 15], and Every 12 Months Until Completion of Part 3)

- Perform a targeted physical examination. Refer to Section 9.1.5.
- Collect blood sample. Refer to Section 9.1.7.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

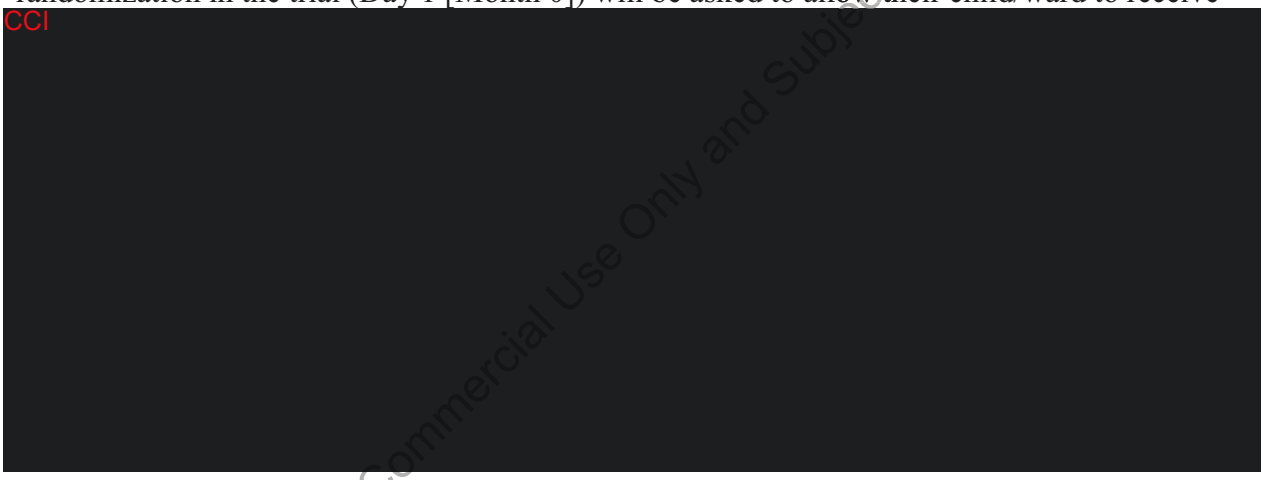
Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in Procedures Manuals.

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if the subject experiences febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Refer to Section 9.1.7.2.

The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity. The subject and/or the subject's parent/guardian will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room 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 (Day 1 [Month 0]) will be asked to allow their child/ward to receive

CCI



9.3.1.4 Contacts During Surveillance (Dry-Run; Parts 1, 2 and 3)

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 with the subject and/or the subject's parent/guardian 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.

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if the subject experiences febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Each site will identify potential healthcare facilities other than the trial site (including those for hospitalization) in the locality where a subject may visit in case of febrile illnesses. This will enable the identification of subjects who present to a non-trial site, maximizing the detection of febrile illnesses satisfying trial criteria, and facilitating the collection of a sample for dengue infection confirmation by RT-PCR (i.e. as soon as possible and preferably within 5 days after onset of fever). Refer to Section 9.1.7.2.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

The subject and/or the subject's parent/guardian will be reminded to contact the trial site if there are any questions and to contact the trial site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to hospitalization or an emergency room visit. All contact details will be given to the subject and/or the subject's parent/guardian.

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 (Day 1 [Month 0]) will be asked to allow their child/ward CCI [redacted].

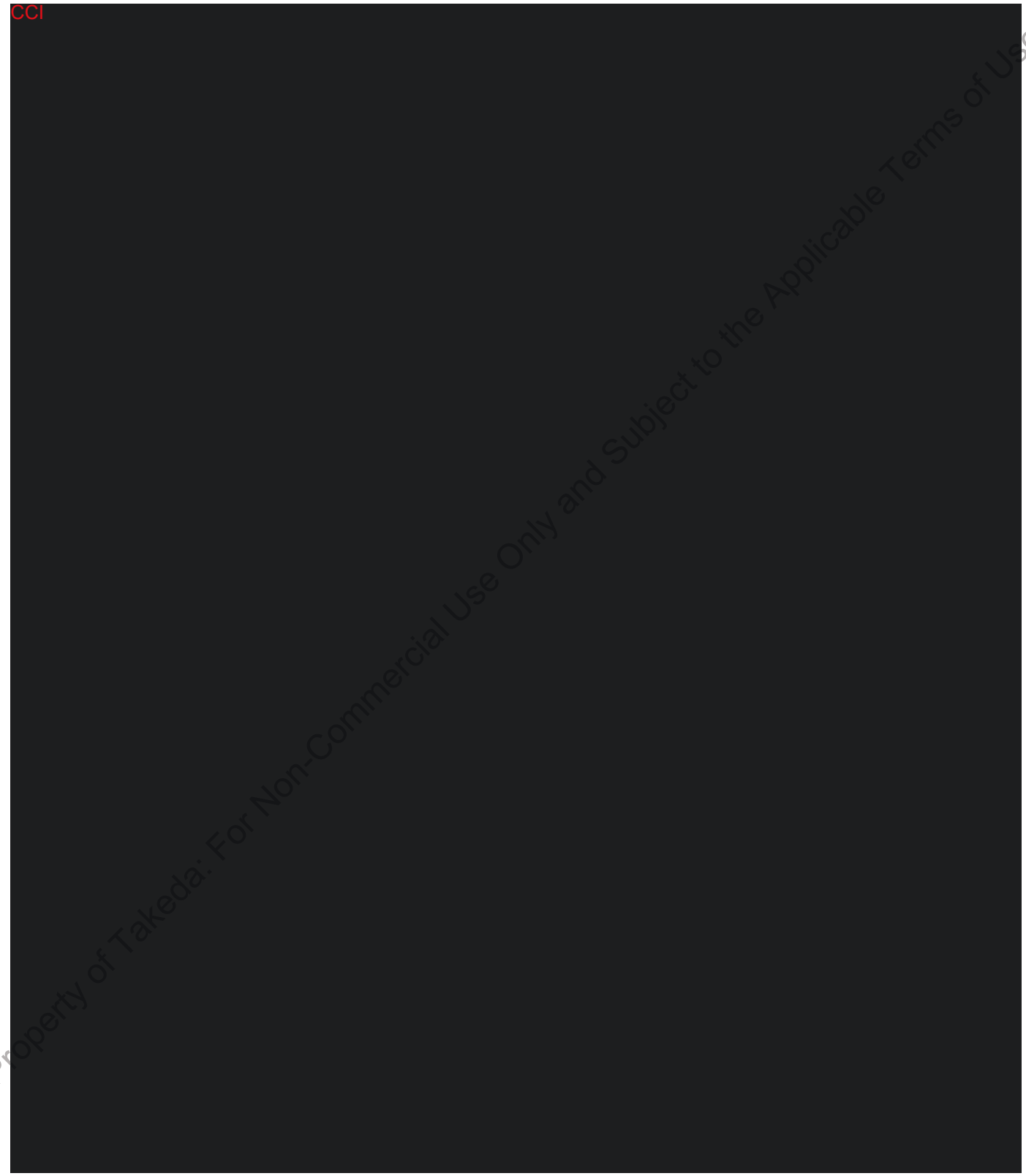
9.3.1.5 Follow-up Visit

If a subject is withdrawn or discontinues after vaccination, standard visit procedures should be performed if possible.

CCI [redacted]

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI



Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI

[redacted]

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI

[redacted]

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI [redacted]

9.3.3 Post-Trial Care

9.3.3.1 Parts 1, 2, and 3

No post-trial care will be provided except for the provision of a licensed vaccine to all subjects irrespective of their full participation in Parts 1, 2, and 3 of this trial. This licensed vaccine will be administered in the time period from at least 6 months after any protocol defined vaccination in Part 1 and before the end of Part 3 CCI [redacted]. 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. CCI [redacted]

CCI [redacted]

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI [redacted]

9.4 Biological Sample Retention and Destruction

In this trial, specimens for immune response testing will be collected as described in Section 9.1.7. After blood draw and serum processing, the serum samples will be preserved and retained at a central laboratory that was contracted by the Sponsor for this purpose for up to but not longer than 20 years or as required by applicable law. CCI [redacted]. Accountability of all samples will be documented from collection until analysis or destruction. The Sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered an investigational vaccine; it does not necessarily have to have a causal relationship with trial vaccine administration.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the administration of an investigational vaccine whether or not it is considered related to the investigational vaccine.

AEs will be graded by the Investigator in the following manner:

Mild	Grade 1	• Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities. Relieved with or without symptomatic treatment.
Moderate	Grade 2	• Sufficient discomfort is present to cause interference with normal activity. Only partially relieved with symptomatic treatment.
Severe	Grade 3	• Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities. Not relieved with symptomatic treatment

10.1.2 Solicited AEs

10.1.2.1 Parts 1, 2, and 3

The occurrence of selected indicators of safety will be measured/collected in the subset until Day 7 (solicited local reactions) and Day 14 (solicited systemic reactions) following each vaccination (vaccination day included) and will be recorded on the relevant sections of the eCRF as applicable as listed in Table 10.a. These will be summarized in the final report under the category "solicited AEs" to differentiate them from other AEs which were not solicited.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Table 10.a Local and Systemic AEs

Local AEs (injection site) (infant/toddler/child <6 years, child ≥6 years):	Pain Erythema Swelling
Systemic AEs (infant/toddler/child <6 years):	Fever [(a)] Irritability/fussiness Drowsiness Loss of appetite
Systemic AEs (child ≥6 years):	Fever [(a)] Headache Asthenia Malaise Myalgia

(a) Fever is defined as body temperature greater than or equal to 38.0°C (100.4°F) regardless of method taken [18].

The intensity of solicited safety parameters will be assessed in the subset as described in Table 10.b and Table 10.c.

Table 10.b Intensity Scales for Solicited Safety Parameters (Infant/Toddler/Child <6 Years)

AE	Intensity grade	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		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever [(a)]		Record temperature in °C/°F
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
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
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

(a) Fever is defined as body temperature greater than or equal to 38.0°C (100.4°F) regardless of method taken [18].

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Table 10.c Intensity Scales for Solicited Safety Parameters (Child ≥6 Years)

AE	Intensity grade	Intensity
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities
	2	Moderate: Painful when limb is moved and interferes with every day activities
	3	Severe: Significant pain at rest. Prevents normal every day activities
Erythema at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever [(a)]		Record body temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Asthenia	0	Normal
	1	Mild: Asthenia that is easily tolerated
	2	Moderate: Asthenia that interferes with normal activity
	3	Severe: Asthenia that prevents normal activity
Malaise	0	No symptoms
	1	Mild: Malaise that is easily tolerated
	2	Moderate: Malaise that interferes with normal activity
	3	Severe: Malaise that prevents normal activity
Myalgia	0	No symptoms
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity

(a) Fever is defined as body temperature greater than or equal to 38.0°C (100.4°F) regardless of method taken [18].

CCI

[redacted]

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI

[redacted]

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence that:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT in the offspring of a subject.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

10.2 Causality of AEs

Relatedness (causality) to vaccine will also be assessed by the Investigator. The relationship of each AE, including solicited systemic AEs (solicited local AEs are considered as related) to trial vaccine(s) will be assessed using the following categories:

Related:	There is suspicion that there is a relationship between the investigational vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that the investigational vaccine contributed to the AE.
Not Related:	There is no suspicion that there is a relationship between the investigational vaccine and the AE; there are other more likely causes and administration of the investigational vaccine is not suspected to have contributed to the AE.

10.2.1 Relationship to Trial Procedures

Relationship (causality) to trial procedures should be determined for all AEs.

The relationship should be assessed as "Yes" if the Investigator considers that there is reasonable possibility that an event is due to a trial procedure. Otherwise, the relationship should be assessed as "No".

10.2.2 Outcome of AEs

Recovered:	The subject has fully recovered from the event or the condition has returned to the level observed at baseline
Recovering:	The event is improving but the subject is still not fully recovered
Not recovered:	The event is ongoing at the time of reporting and the subject has still not recovered
Recovered with sequelae:	As a result of the AE, the subject suffered persistent and significant disability/incapacity (eg, became blind, deaf or paralysed)
Fatal:	The subject died due to the event. If the subject died due to other circumstances than the event, the outcome of the event per se should be stated otherwise (eg, Not Recovered or Recovering)
Unknown:	If outcome is not known or not reported.

10.3 Additional Points to Consider for AEs

An untoward occurrence generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. Intermittent events for pre-existing conditions or underlying disease should not be considered as AEs.
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require vaccine discontinuation or a change in concomitant medication.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

- Be considered unfavorable by the Investigator for any reason.

Diagnoses *vs.* signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, signs or symptoms should be recorded appropriately as an AE(s).

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after starting administration of the trial vaccine, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in trial vaccine, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

10.4 Procedures

10.4.1 Collection and Reporting of AEs

All AEs, whether considered related with the use of the investigational vaccine or not, must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an AE eCRF and on the SAE form, if necessary (see Section 10.4.3). All findings in subjects experiencing AEs must also be reported in the subject's source documents. Any unsolicited AEs will be collected in the subset for 28 days after each vaccination during site visits via interview.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

The following information will be documented for each event:

- Reported term for the AE.
- Start and end date.
- Serious (Y/N).
- Severity.
- Investigator's opinion of the causality (relationship) between the event and administration of trial vaccine(s) ("related" or "not related").
- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure.
- Action taken with the trial treatment (trial vaccine).
- Outcome of event.

10.4.2 Collection and Reporting of Solicited AEs

10.4.2.1 Parts 1, 2, and 3

The occurrence of selected indicators of safety will be collected on diary cards by the subjects in the subset until Day 7 (solicited local reactions) or Day 14 (solicited systemic reactions) following each vaccination (vaccination day included) and will be recorded on the relevant sections of the eCRF, as appropriate. Any solicited local or systemic AE observed as continuing on trial Day 7 (local reactions) or Day 14 (systemic reactions) will be recorded as an unsolicited AE on the AE eCRF. Any solicited local or systemic AE that resolved before that time but which recurs at a later time will be recorded as an unsolicited AE on the AE eCRF.

Any solicited AE that meets any of the following criteria must be entered as an AE on the AE eCRF.

- Solicited local or systemic AEs that lead the subject to withdraw from the trial.
- Solicited local or systemic AEs that lead to the subject being withdrawn from the trial by the Investigator.
- Solicited local and systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.3).

CCI

[redacted]

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI

[redacted]

10.4.3 Collection and Reporting of SAEs

10.4.3.1 Parts 1, 2, and 3

Collection of SAEs will commence from the time that the subject is first administered the investigational vaccine (Day 1 [Month 0]). Routine collection of all SAEs will continue 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.

CCI

[redacted]

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

10.5 Follow-up Procedures

10.5.1 AEs

All AEs will be monitored until resolution or a stable status is reached or until a formal diagnosis can be made. This could potentially be outside of this trial.

10.5.2 SAEs

If information not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, laboratory tests, discharge summary, postmortem results) should be sent to the Sponsor after redaction for privacy.

All SAEs should be followed up until resolution or permanent outcome of the event or is otherwise explained. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.5.3 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The Sponsor or designee will be responsible for the reporting of all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators and IRBs or IECs, as applicable, in accordance with national regulations. Relative to the first awareness of the event by/or further provision to the Sponsor or designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the trial vaccine administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to their IRB or IEC in accordance with national regulations.

10.5.4 Post-Trial Events

Any AE that occurs outside of the protocol-specified observation period or after the end of the trial but considered to be caused by the investigational vaccine(s) must be reported to the Sponsor. These AEs will be processed by the Sponsor's Pharmacovigilance Department. Instructions for how to submit these AEs will be provided in a handout in the Investigator Site File.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

11.0 TRIAL-SPECIFIC REQUIREMENT(S)

11.1 Trial-Specific Committees

11.1.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will have oversight of this trial. The DMC functions at a program level and further information is available in the DMC Charter. Criteria to classify dengue severity will be defined by the DMC and will be documented in an appendix to the DMC Charter. An Adjudication Committee will assess the severity of individual confirmed dengue cases.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

12.0 DATA HANDLING AND RECORD-KEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, System Organ Class [SOC], High Level Group Term, High Level Term, Low Level Term, Preferred Term [PT], and their corresponding descriptive terms). Drugs will be coded using the WHO Drug Dictionary.

12.1 Electronic CRFs (eCRF)

Completed eCRFs are required for each subject for whom a signed informed assent/consent has been obtained.

The Sponsor or its designee will supply investigative sites with access to eCRFs. The Sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These eCRFs are used to transmit the information collected in the performance of this trial to the Sponsor and regulatory authorities. eCRFs must be completed in English. Data are entered directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Sponsor personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The Investigator or designee must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the trial site during periodic visits by trial monitors. The Sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the trial to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

When a site visit cannot be carried out due to the COVID-19 pandemic, alternative methods of contact (eg, telephone contact) will be made for subjects who are still under monitoring for safety reporting. Refer also to Section 14.1.

12.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 12.0 and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records. Temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

and assent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copies of eCRFs, including the audit trail, and detailed records of vaccine disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Furthermore, ICH E6 Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified, or according to local regulation. In addition, ICH E6 Section 4.9.5 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A SAP related to Parts 1, 2, and 3 was prepared and finalized prior to unblinding of subjects' vaccination assignment for the first interim analysis (see Section 13.2.3). This document provides further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

An amendment to the SAP will be prepared and finalized prior to unblinding of subjects' vaccination assignment for the first interim analysis CCI [redacted] This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

Blinded data reviews will be conducted prior to unblinding of subjects' vaccination assignments. These reviews will assess the accuracy and completeness of the trial database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

13.1.1.1 Parts 1, 2, and 3

Safety Set (SS): The SS will consist of all randomized subjects who received at least 1 dose of the trial vaccines (TDV or placebo). For analyses of solicited AEs (reactogenicity) and unsolicited non-serious 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.

Full Analysis Set (FAS): The FAS will include all randomized subjects who received at least 1 dose of the trial vaccines (TDV or placebo).

Full Analysis Set for Immunogenicity (FASI): The FASI will include all randomized subjects in the subset who received at least 1 dose of the trial vaccines (TDV or placebo) and for whom valid pre-dosing and at least 1 post-dosing blood sample have been received for immunogenicity.

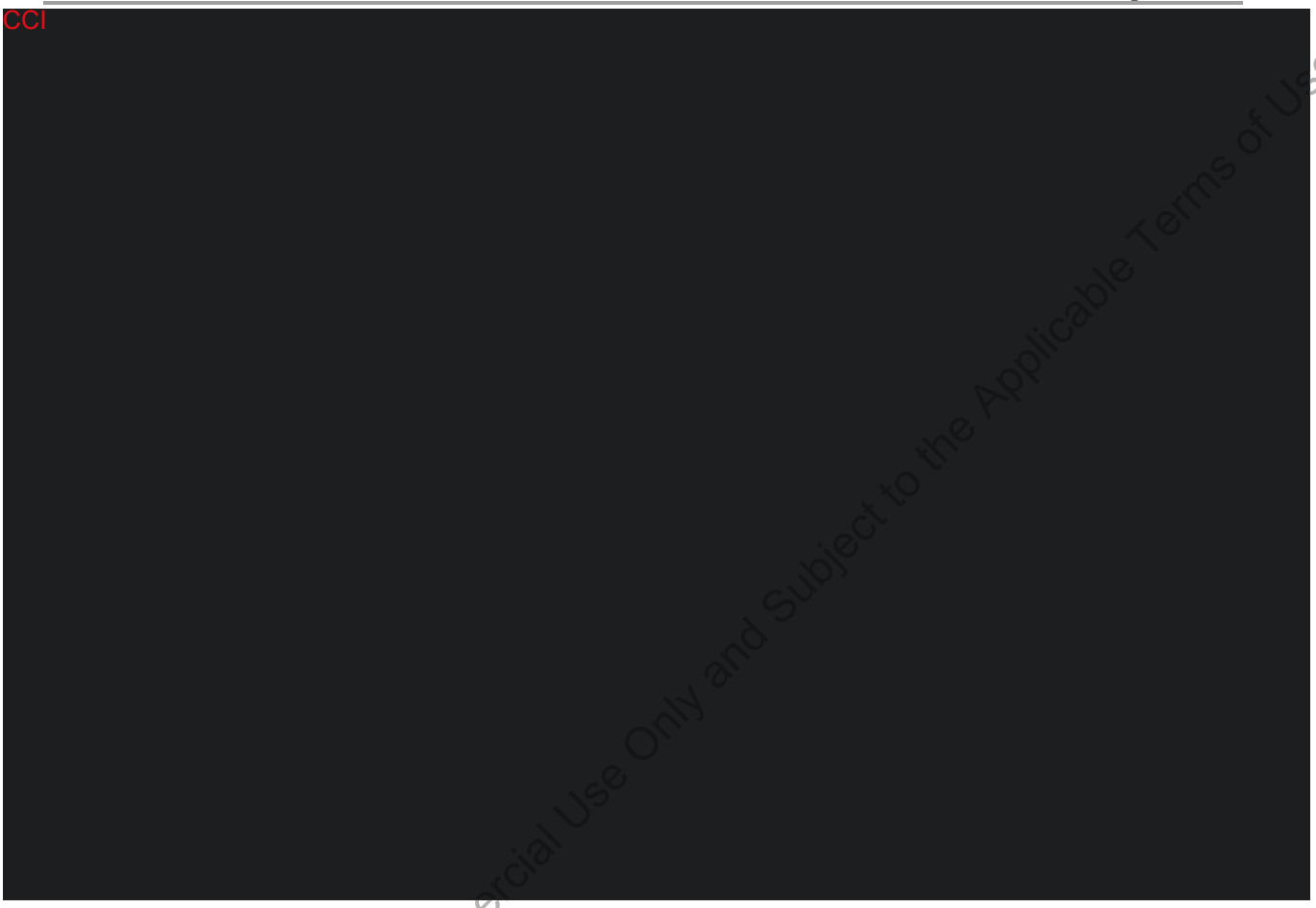
PPS: The PPS will include all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of the subject's trial vaccine assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving the wrong trial vaccine, (3) receiving prohibited therapies, (4) not receiving 2 doses of trial vaccine or receiving the second vaccination inadmissibly outside of the visit window, and (5) other major protocol violations that may be identified during blinded data reviews.

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

The primary analysis of VE of 2 doses of TDV in preventing virologically confirmed dengue fever induced by any dengue serotype and occurring from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 1 will be performed on the PPS.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI



13.1.2 Analysis of Demographics and Other Baseline Characteristics

13.1.2.1 Parts 1, 2, and 3

Age, gender, race, and other baseline characteristics will be summarized descriptively by group for all randomized subjects, and for each of the analysis sets (ie, SS, FAS, FASI, PPS, and PPSI).

CCI

13.1.3 Efficacy Analysis

13.1.3.1 Parts 1, 2, and 3

The primary analysis of VE will occur after both of the following 2 criteria for the end of Part 1 are fulfilled: (1) 120 cases of virologically confirmed dengue have accrued, and (2) a minimum

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

duration of subject follow-up of 12 months post-second vaccination.

For the primary efficacy evaluation, a case of virologically confirmed dengue is defined as febrile illness with a positive serotype-specific 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. The primary analysis method will be based on a Cox proportional hazard model with trial group as a factor, adjusted for age, and stratified by region, with 2-sided 95% confidence intervals (CIs) provided for the estimate of VE. The primary efficacy objective is considered to be met if the lower bound of the 95% CI for the VE is above 25%, where 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. A similar approach will be used to analyze the secondary efficacy endpoints.

Sensitivity analyses of the primary endpoint include: (1) analysis using exact 95% CIs [19], (2) analysis based on the FAS, and (3) analysis including cases of virologically confirmed dengue occurring at any time post-second vaccination (ie, starting on Day 90 ([Month 3]).

Evaluation of secondary efficacy endpoints will be based on the PPS and will be assessed using data from Parts 1 and 2. Secondary VE endpoints will be analyzed using a similar approach as for the primary endpoint described above, except that statistical significance will be concluded if the lower bound of the corresponding CI is > 0. Some of the secondary endpoints will be considered as key secondary endpoints and family-wise type I error will be controlled for these endpoints. These endpoints will only be tested if statistical significance is achieved for the primary endpoint. Details on key secondary endpoints and control of the type I error will be provided in the SAP.

The number and percentage of subjects with virologically confirmed dengue will be summarized in the timeframes post-first vaccination (Day 1 [Month 0]) until the end of Part 2 and between administration of the first vaccination and second vaccination on Day 1 (Month 0) and Day 90 (Month 3), respectively.

CCI

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

13.1.4 Vaccine Immunogenicity Analysis

13.1.4.1 Parts 1, 2, and 3

For immunogenicity endpoints including seropositivity rate and GMTs for dengue neutralizing antibodies, descriptive statistics and 95% CIs will be provided by trial group and visit for subjects in the subset.

Seropositivity is defined as a reciprocal neutralizing titer ≥10.

CCI

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

13.1.6 Safety Analysis

13.1.6.1 Parts 1, 2, and 3

All summaries of safety data will be based on subjects in the SS. Unless otherwise specified, the safety data will be summarized by trial group.

Reactogenicity

For subjects in the subset, 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 for 7 days and 14 days, respectively, following each vaccination (vaccination day included) via collection of diary cards.

For each solicited AE, the percentage of subjects will be summarized by event severity for each day after each vaccination (Days 1 to 7 for local AEs and Days 1 to 14 days for systemic AEs), and overall. A summary of the first onset of each event will also be provided. The number of days subjects experienced each event will also be summarized for each trial group. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs

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

All unsolicited AEs up to 28 days after each vaccination will be included in the analyses of all AEs. For SAEs and AEs leading to subject withdrawal from the trial (Refer to Section 7.5), Parts 1, 2, and 3 will be included.

In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE) and by SOC and PT. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. Unsolicited AEs will be summarized as follows: by PT including events with frequency greater than 2%; by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to the investigational vaccine. Unless otherwise specified, unsolicited AEs will be summarized in the following 3 ways: 1) overall up to 28 days post-vaccination, 2) with onset between 1 and 14 days post-vaccination, and 3) with onset between 15 and 28 days post-vaccination.

CCI

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI

[redacted]

13.2 Interim Analysis and Criteria for Early Termination

13.2.1 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 13.1.3).

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 virologically confirmed dengue, 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.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI [redacted]

13.2.3 Interim Analyses and Reporting

Interim analyses 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, 30 days (1 month) CCI [redacted]

At the time of this protocol amendment, an Interim CSR has been prepared for the results from the dry-run, Part 1, and Part 2 and a second Interim CSR has been prepared for data until 6 months after the end of Part 2 (2-year follow-up post-second dose). A third interim CSR will be prepared for data until 18 months after the end of Part 2 (3-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.

13.3 Determination of Sample Size

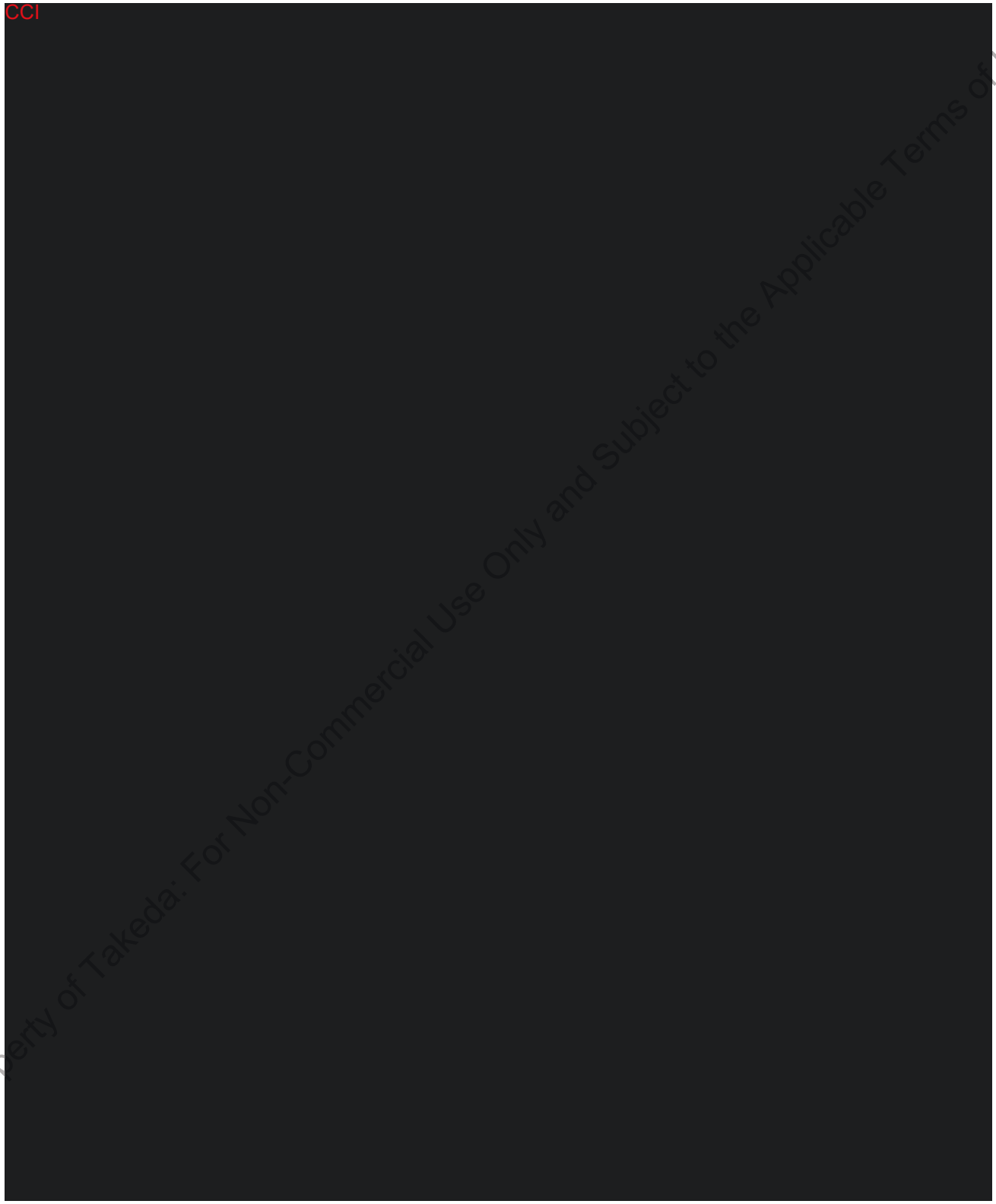
13.3.1 Parts 1, 2, and 3

This is a partially case-driven trial as described above.

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 PPS will be compensated by a potentially longer duration of Part 1.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

CCI



Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Trial-Site Monitoring Visits

Monitoring visits to the trial site will be made periodically during the trial to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The Investigator and institution guarantee access to source documents by the Sponsor or designee (CRO) and by the IRB or IEC.

All aspects of the trial and its documentation will be subject to review by the Sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, investigational vaccine, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the Investigator and other trial personnel are available during the monitoring visits and that sufficient time is devoted to the process.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification (SDV) or telephone contact may be used to ensure data quality and integrity and maintain subject safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and when approved by the IRB/IEC. Site staff will inform each trial participant or designated legal representative and ensure that they do not object to the remote review of their records for trial purposes and document this process in the trial participant's medical records. If a trial participant objects to remote review of their records, no remote SDV will occur for that trial participant. During remote monitoring, the monitor should focus on trial activities that are essential to the safety of trial subjects and/or data reliability.

14.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator should consult with the medical monitor (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the vaccine is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of foreign governments (eg, the US Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical

Property of Takeda - For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Devices Agency of Japan). If the trial site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator and institution guarantee access for quality assurance auditors to all trial documents as described in Section 14.1.

14.4 Trial Risk Management

The ICH E6 addendum (R2) guidance encourages a risk-based approach to the management of clinical trials and includes requirements for risk control and risk reporting. Takeda or designee (CRO) has established Quality Tolerance Limits (QTL), taking into consideration the medical and statistical characteristics of the variables and the statistical design of this trial. This process was performed according to Takeda internal procedures.

At the end of the trial, the quality management approach implemented will be described in the CSR. If applicable, the CSR will summarize important deviations from the predefined QTL and the remedial actions taken.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

15.0 ETHICAL ASPECTS OF THE TRIAL

This trial will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for GCP. Each Investigator will conduct the trial according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained. Those US sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent/assent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent/assent must be obtained and submitted to the Sponsor or designee before commencement of the trial (ie, before shipment of the Sponsor-supplied Vaccine or trial specific screening activity). The IRB or IEC approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The Sponsor will notify the site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from the competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent/assent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB or IEC, and submission of the Investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the Sponsor or designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and Sponsor.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

15.2 Subject Information, Informed Consent/Assent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent/assent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the trial. The informed consent form and the subject information sheet (if applicable) further explain the nature of the trial, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The Investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent/assent form and if applicable, the subject authorization form. The informed consent/assent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

The informed consent/assent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject and/or subject's parent/guardian. It is the responsibility of the Investigator to explain the detailed elements of the informed consent/assent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject and/or subject's parent/guardian. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's parent/guardian may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's parent/guardian, must be given ample opportunity to: (1) inquire about details of the trial and (2) decide whether or not to participate in the trial. If the subject, or the subject's parent/guardian, determines that the subject will participate in the trial, then the informed consent/assent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's parent/guardian, at the time of consent and prior to the subject's entering into the trial. The subject or the subject's parent/guardian should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The Investigator must also sign and date the informed consent/assent form and subject authorization (if applicable) at the time of consent/assent and prior to subject entering into the trial; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent/assent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the subject signs the informed consent/assent in the subject's medical record and eCRF. Copies of the signed informed consent/assent form, the

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent/assent forms must be reviewed and signed by relevant subjects or the relevant subject's parent/guardian in the same manner as the original informed consent/assent. The date the revised consent/assent was obtained should be recorded in the subject's medical record and eCRF, and the subject should receive a copy of the revised informed consent/assent form.

15.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this trial, a subject's source data will only be linked to the Sponsor's clinical trial database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, regulatory authorities of an European / European Economic Area Member State, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, electrocardiogram (ECG) reports, admission and discharge summaries for hospital admissions occurring during a subject's trial participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent/assent process (see Section 15.2).

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain subject safety (refer also to Section 14.1).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The results of this trial are expected to be published in a scientific journal. It is anticipated that clinical and laboratory co-Investigators will participate in authorship. The order of authorship and choice of journal will be determined by the Investigators and the Sponsor. The data analysis

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

center for this trial will provide the analyses needed for publication. Information regarding this trial will be posted on ClinicalTrials.gov and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) websites.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, the Sponsor will, at a minimum register all clinical trials conducted in subjects that it sponsors anywhere in the world on ClinicalTrials.gov, EudraCT or other publicly accessible websites before trial initiation. The Sponsor contact information, along with Investigator's city, country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

The Sponsor will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov, EudraCT or other publicly accessible websites, as required by applicable laws and/or regulations.

Trial completion corresponds to the date on which the final subject was examined or received an intervention for the purposes of final collection of data (Last Subject Last Visit).

In line with EC Regulation N° 1901/2006, the Sponsor will submit a pediatric trial within six months of their completion and irrespective of whether it is part of a pediatric investigational plan (PIP) (completed or not yet completed) or not, or whether it is intended for submission later on as part of a variation, extension or new stand-alone marketing-authorization application or not.

15.5 Insurance and Compensation for Injury

Each subject in the trial must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the Sponsor or designee will obtain clinical trial insurance against the risk of injury to clinical trial subjects. Refer to the Clinical Study Site Agreement regarding the Sponsor's policy on subject compensation and treatment for injury. If the Investigator has questions regarding this policy, he or she should contact the Sponsor or designee.

Property of Takeda. For Non-Commercial use Only and Subject to the Applicable Terms of Use

16.0 REFERENCES

1. Simmons CP, Farrar JJ, Nguyen V, Wills B. Dengue. N Engl J Med 2012; 366:1423-32.
2. Gubler D. Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem for the 21st century. Trends in Microbiology 2002; 10:100-3.
3. Guzman M, Kouri G. Dengue: an update. Lancet Infect Dis 2002; 2:33-42.
4. World Health Organization, Dengue and severe dengue. World Health Organization, Geneva, Switzerland, 2018. (Available at: http://www.who.int/mediacentre/factsheets/fs117/en/) (accessed 20 April 2021).
5. World Health Organization. Dengue hemorrhagic fever: diagnosis, treatment, prevention and control, 2nd Edn. Geneva: World Health Organization. 1997. (Available at: http://www.who.int/csr/resources/publications/dengue/Denguepublication/en/) (accessed 20 April 2021).
6. Dengue - Guidelines for Diagnosis, Treatment, Prevention and Control. World Health Organization; 2009. (ISBN: 978 92 4 154787 1).
7. Halstead S, Deen J. The future of dengue vaccines. Lancet 2002; 360:1243-1245.
8. Wichmann O, Vannice K, Asturias EJ, de Albuquerque Luna EJ, Longini I, Lopez AL, et al. Live-attenuated tetravalent dengue vaccines: The needs and challenges of post-licensure evaluation of vaccine safety and effectiveness. Vaccine. 2017. 35(42):5535-42.
9. Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med 2015; 373(13):1195-206.
10. Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. N Engl J Med. 2018. 379(4):327-40.
11. Revised SAGE recommendation on use of dengue vaccine. April 2018. Available at https://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_dengue_vaccines_apr2018/en/ [Accessed 20 April 2021].
12. World Health Organization. Weekly Epidemiological Record. 2018. 93:329-44. Available at http://www.who.int/wer [Accessed 20 April 2021].
13. Yoksan S, Bhamarapravati N, Halstead SB. Dengue virus vaccine development: study on biological markers of uncloned dengue 1-4 viruses serially passaged in primary kidney cells. In: TD St. George, BH Kay and J Blok (ed.), Arbovirus research in Australia. Proceedings of the 4th Symposium. CSIRO/QIMR, Brisbane, Australia, 1986: 35-8.
14. Huang CYH, Butrapet S, Tsuchiya KR, Bhamarapravati N, Gubler DJ, Kinney RM. Dengue 2 PDK-53 virus as a chimeric carrier for tetravalent dengue vaccine development. J Virol 2003; 77:11436-47.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

15. Biswal S, Borja-Tabora C, Martinez Vargas L, Velásquez H, Alera MT, Sierra V et al. Efficacy of a tetravalent dengue vaccine in healthy children aged 4-16 years: a randomized, placebo-controlled, phase 3 trial. Lancet 2020; 395(10234):1423-33.
16. Lopez-Medina E, Biswal S, Saez-Llorens X, Borja-Tabora C, Bravo L, Sirivichayakul C, et al. Efficacy of a dengue vaccine candidate (TAK-003) in healthy children and adolescents two years after vaccination. J Infect Dis 2020 [Epub ahead of print].
17. Tetravalent Dengue Vaccine Candidate (TDV) Global Investigator's Brochure Edition 11, 26 June 2020.
18. Marcy SM, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004; 22:551-6.
19. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--the design and analysis of cohort studies. Lyon, France: International Agency for Research on Cancer, 1987.
20. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 1989; 8:431– 40.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Appendix A Responsibilities of the Investigator

Clinical research trials sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The Investigator agrees to assume the following responsibilities:

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that trial related procedures, including trial specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
5. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the trial to the IRB/IEC, and issue a final report within 3 months of trial completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 56, ICH, and local regulations, are met.
8. Obtain valid informed consent from each subject's parent/guardian who participates in the trial, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an informed consent form does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject or the subject's parent/guardian.
9. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied vaccines, and return all unused Sponsor-supplied vaccines to the Sponsor.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

12. Report AEs to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.
13. In the event of a pregnancy, notify the Sponsor within 24 hours.
14. Review and provide a signature as approval of the content of the CSRs.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Appendix B Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the Investigator, including his or her name, address, and other personally identifiable information. In addition, the Investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the Investigator for the trial and/or other clinical trials.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other vaccines used in other clinical trials that may contain the same chemical compound present in the investigational vaccine.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting Investigator site contact information, trial details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in Investigator's own country. The Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the trial involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the trial.
7. A description of the subject's responsibilities.
8. A description of the conduct of the trial.
9. A statement describing the vaccination(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects following vaccine administration that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's parent/guardian is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the trial.
17. The anticipated expenses, if any, to the subject for participating in the trial.
18. An explanation of whom to contact for answers to pertinent questions about the research (Investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's parent/guardian will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the Sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the trial. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the investigational vaccine(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical trials;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the trial to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

e) that the subject's identity will remain confidential in the event that trial results are published.

25. CCI [redacted]

26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Approval	PPD
Approval	
Approval	
Approval	

Document Number: TAK-003-00495 v8.0

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use