



EU RISK MANAGEMENT PLAN (RMP)
for
Dengue Tetraivalent Vaccine (Live, Attenuated)

RMP Version number: 4.0

Date: 9 July 2026



EU Risk Management Plan for Dengue Tetravalent Vaccine (Live, Attenuated)

Administrative Information

RMP version to be assessed as part of this application:

RMP Version number: 4.0

Data lock point for this RMP: 18 February 2025

Date of final sign off: 15 July 2026

Rationale for submitting an updated RMP:

The RMP for the EU MA and Article 58 is updated from the approved version 3.0 (dated 11 October 2024) to RMP Version 4.0.

The update is triggered by completion of Trials DEN-303 and DEN-301 Part 4 to remove these Category 3 additional pharmacovigilance activities milestones of DEN-303 CSR and DEN-301 Part 4 interim CSR submissions. The RMP update reflects the results of Trials DEN-303 and DEN-301 Part 4 in relevant sections.

Results of Trials DEN-303 and DEN-301 Part 4 provide missing information to characterize reactogenicity of a TDV booster dose. The missing information previously classified as "Safety and reactogenicity of a booster dose" (RMP Version 3.0 and previous versions) is reclassified to "Safety of a booster dose".

Results of Trials DEN-303 and DEN-301 Part 4 are incorporated into RMP Section SVII.3.1 to further characterize the important potential risks "Dengue disease due to waning protection against dengue over time" and "Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus". No new safety concerns were identified in the Trials DEN-303 and DEN-301 Part 4.

With the completion of Trial DEN-303, the trial has been removed from ongoing additional pharmacovigilance activities. With the new data lock point (DLP) of 18 February 2025, updates to epidemiology, clinical and post-marketing data have been made without any impact on the safety profile of TDV.

Summary of significant changes in RMP v4.0:

RMP Part/Module	Significant changes
Part I – Product overview	Not applicable.
Part II – Safety specifications	
Module SI Epidemiology of the indication(s) and target population(s)	Updated to include the 2023-2024 dengue epidemic in the Americas.
Module SII Non-clinical part of the safety specification	Not applicable.

RMP Part/Module	Significant changes
Module SIII Clinical trial exposure	Content and Formatting of Tables SIII.1 to S.III.3 were updated to align with PSUR data and data presentation. Thereby, previous Tables SIII.2.B and SIII.2.C were merged into a single table. Table content was updated to add TDV booster doses from Trials DEN-303 and DEN-301 Part 4.
Module SIV Populations not studied in clinical trials	Section SIV.2 updated to include current number of subjects, observation period, as well as number of ongoing and completed trials at the DLP of 18 February 2025. Section SIV.3 revised to update number of pregnancies and number of exposures during breast-feeding, percentage of population with relevant ethnic origin and corrected the subject numbers from Trial DEN-204. A disclaimer was added to indicate that some participants receiving a booster dose were >60 years at the time of booster administration.
Module SV Post-authorisation experience	Updates to exposure data to incorporate post-authorisation exposure at the DLP of 18 February 2025. Addition of estimated use in children and adolescents in national immunization programme in Brazil in Section SV.1.2.1. Addition of current exposure on use in patients outside indicated age range to Section SV.1.2.2.
Module SVI Additional EU requirements	Addition of relevant data from completed Trial DEN-210 to sub-section "Reversion to virulence". Updated to reflect date of current paediatric investigation plan (PIP) EMA Decision for TDV. Trial DEN-210 and DEN-301 results on vaccine viremia added. A sentence was completed in the reversion to virulence paragraph.

RMP Part/Module	Significant changes
Module SVII – Identified and potential risks	Update to Section SVII.2 to describe reclassification of reactogenicity of a booster dose as being no longer considered missing information. Removal of previous text that described the update to RMP 3.0. Section SVII.3.1 is updated to include results from Trials DEN-301 Part 4 and DEN-303 to characterise both important potential risks. The section is also updated to include current data at the DLP where applicable. Section SVII.3.2 is updated to include the current evidence source for the missing information categories “Safety profile of inadvertent use in pregnant or lactating women”, “Safety and immunogenicity in immunocompromised individuals” and “Safety and immunogenicity of concomitant administration with other vaccines, other than HAV, YF and HPV vaccines”. Section SVII.3.2 is updated to reclassify “Safety and Reactogenicity of a booster dose” to “Safety of a booster dose”. The available evidence on safety and reactogenicity from Trials DEN-301 Part 4 and DEN-303 is added. The section is also updated to include current data at the DLP where applicable. Removal of completed Trial DEN-303 from information on currently ongoing studies in the same section.
Module SVIII – Summary of the safety concerns	Update of missing information from “Safety and Reactogenicity of a booster dose” to “Safety of a booster dose”.
Part III – Pharmacovigilance activities	Section III.1 Removal of anaphylaxis including anaphylactic shock, as well as vaccination failure, which are no safety concerns, from section describing other forms routine pharmacovigilance activities. The frequency of cumulative reviews is updated from half-yearly to yearly. Section III.2 Removal of Trial DEN-303 from additional pharmacovigilance activities. The milestone of interim CSR for Trial DEN-301 Part 4 is updated to completed. Section III.3 Removal of Trial DEN-303 from summary table of additional pharmacovigilance activities. The milestone of interim CSR for Trial DEN-301 Part 4 is updated to completed.
Part IV – Plans for post-authorisation efficacy studies	Not applicable.
Part V – Risk minimisation measures	Update of missing information from “Safety and Reactogenicity of a booster dose” to “Safety of a booster dose”. Removal of completed Trial DEN-303 from Table Part V.3.
Part VI – Summary of the risk management plan	Reactogenicity of a booster dose removed from missing information. Completed Trial DEN-303 removed from additional pharmacovigilance activities.

RMP Part/Module	Significant changes
Part VII – Annexes	Annex 2: Milestone of Part 4 of Trial DEN-301 (Interim CSR) marked as completed. Trial DEN-303 moved to completed pharmacovigilance studies Annex 7: List of references updated to include new references Annex 8: Changes from RMP v2.0 to v3.0 added to table, v1.0 declared as “Initial version” in table Annex 9: Ad-hoc clinical trial exposure tables removed

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

RMP Version number: 3.0

Approved with procedure: EMEA/H/C/005155/WS2695/0016 (Qdenga)
EMEA/H/W/005362/WS2695/0015 (Dengue Tetravalent
Vaccine (Live, Attenuated) Takeda)

Date of approval (opinion date): 31 October 2024

EU/UK QPPV name: Jean-Marie Heim

Please note that the e-signature may also be performed by Deputy EU QPPV [REDACTED],
Deputy EU QPPV [REDACTED], Deputy EU QPPV [REDACTED] or Deputy EU QPPV [REDACTED]
[REDACTED] on behalf of the EU and UK QPPV (i.e., 'per procuration').

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the
marketing authorisation holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

Abbreviation	Definition/Description
ADE	Antibody-dependent disease enhancement
AEFI	Adverse event following immunisation
AR	Assessment report
ATC code	Anatomical therapeutic chemical classification system
CFR	Case fatality rate
CNS	Central nervous system
CSR	Clinical study report
CTD	Common technical document
DCAC	Dengue case adjudication committee
DENV	Dengue virus serotype (wild type)
DHF	Dengue haemorrhagic fever
DLP	Data lock point
DNA	Deoxyribonucleic acid
DSS	Dengue shock syndrome
ECDC	European Centre for Disease Prevention and Control
EEA	European economic area
EMA	European Medicines Agency
EPAR	European public assessment report
EU	European Union
FTA	Buffer containing Pluronic F127, trehalose and human albumin, used for stabilization of TDV viruses
FV	Flavivirus
GLP	Good Laboratory Practice
GMO	Genetically modified organism
GSDB	Global Safety Database
HAV	Hepatitis A virus
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IBD	International birth date
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IMP	Investigational medicinal product
INN	International non-proprietary names
IR	Incidence rate
JE	Japanese encephalitis

Abbreviation	Definition/Description
log	Logarithm
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MID ₅₀	Minimum Infectious Dose 50: Level of viral RNA required to infect half of fed mosquitoes
ml	Millilitre
NCR	Noncoding region
NOAEL	No-observed-adverse-effect level
NIP	National immunisation program
NS	Nonstructural
PAHO	Pan American Health Organization
PBRER	Periodic benefit-risk evaluation report
PDK	Primary dog kidney
PFU	Plaque forming units
PI	Product information
PIP	Paediatric investigation plan
PL	Package leaflet
PSUR	Periodic safety update report
PV	Pharmacovigilance
QPPV	Qualified person responsible for pharmacovigilance (in the European Union)
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious adverse event
SC	Subcutaneous(ly)
SmPC	Summary of product characteristics
TBD	To be determined
TDV	"Dengue Tetravalent Vaccine (Live, Attenuated)" is referred to as TDV, the Takeda dengue vaccine also known as TAK-003
TFUQ	Targeted follow up questionnaires
US	United States
VCD	Virologically confirmed dengue
VE	Vaccine efficacy
vRNA	viral ribonucleic acid
WHO	World Health Organization
YF	Yellow fever

Part I: Product(s) Overview

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	Dengue virus serotype 1 (live, attenuated)* Dengue virus serotype 2 (live, attenuated)# Dengue virus serotype 3 (live, attenuated)* Dengue virus serotype 4 (live, attenuated)* <i>*Produced in Vero cells by recombinant DNA technology. Genes of serotype-specific surface proteins engineered into dengue virus serotype 2 backbone.</i> <i>#Produced in Vero cells by recombinant DNA technology.</i>
Pharmacotherapeutic group(s) (ATC Code)	J07BX04 dengue virus vaccines
Marketing Authorisation Applicant	Takeda GmbH Byk-Gulden-Strasse 2 78467 Konstanz Germany
Medicinal products to which this RMP refers	Dengue Tetravalent Vaccine (Live, Attenuated) "Dengue Tetravalent Vaccine (Live, Attenuated)" is referred to as TDV through this document, the Takeda dengue vaccine also known as TAK-003.
Invented name(s) in the European Economic Area (EEA)	Qdenga
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Vaccines
	Summary of mode of action: TDV contains live attenuated dengue viruses. The primary mechanism of action of TDV is to replicate locally and elicit humoral and cellular immune responses against the four dengue virus serotypes.
	Important information about its composition: Dengue tetravalent vaccine is a live attenuated vaccine. The vaccine serotype, TDV-2, was derived from attenuated wild type dengue serotype 2 virus strain (16681) which forms the common genetic backbone for the other three serotypes. Using recombinant deoxyribonucleic acid (DNA) technology, the genetic sequence encoding for pre-membrane (prM) and envelope (E) proteins in the attenuated TDV-2 genome were replaced with the corresponding genes of the wild-type serotype 1 (16007), serotype 3 (16562) and serotype 4 (1036). The four viruses are cultured in Vero cells. The purified active substance is stabilized in a solution containing various salts, Poloxamer 407, Trehalose, and human serum albumin. There is no adjuvant or preservative in dengue vaccine. Each dose of vaccine will

	contain a minimum of the specified amount of each serotype expressed in PFU/dose (TDV-1 $\geq 3.3 \log_{10}$ PFU/dose, TDV-2 $\geq 2.7 \log_{10}$ PFU/dose, TDV-3 $\geq 4.0 \log_{10}$ PFU/dose, TDV-4 $\geq 4.5 \log_{10}$ PFU/dose).
Hyperlink to the Product Information (PI)	Refer to CTD Module 1.3.1 for the PI.
Indication(s) in the EEA	Current: Qdenga is indicated for the prevention of dengue disease in individuals from 4 years of age.
	Proposed: Not applicable.
Dosage in the EEA	Current: Qdenga should be administered as a 0.5 ml dose at a two-dose (0 and 3 months) schedule. The need for a booster dose has not been established.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Powder and solvent for solution for injection. After reconstitution, 1 dose (0.5 ml) contains: Active ingredients: Dengue virus serotype 1 (live, attenuated)*: $\geq 3.3 \log_{10}$ PFU**/dose Dengue virus serotype 2 (live, attenuated)#: $\geq 2.7 \log_{10}$ PFU**/dose Dengue virus serotype 3 (live, attenuated)*: $\geq 4.0 \log_{10}$ PFU**/dose Dengue virus serotype 4 (live, attenuated)*: $\geq 4.5 \log_{10}$ PFU**/dose <i>*Produced in Vero cells by recombinant DNA technology. Genes of serotype-specific surface proteins engineered into dengue virus serotype 2 backbone.</i> <i>#Produced in Vero cells by recombinant DNA technology.</i> <i>**PFU = Plaque-forming units</i>
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Qdenga is indicated for the prevention of dengue disease in individuals from 4 years of age.	
Incidence:	Due to under-recognition, under-reporting, and passive surveillance systems at the national level, the actual global burden of dengue is difficult to quantify. Access to and the reliability of national data poses additional challenges for estimating the dengue burden [1]. According to the World Health Organization (WHO) about half of the world's population is at risk of dengue, and approximately 100-400 million infections occur annually [2]. Over the past 20 years, the number of dengue cases reported to the WHO increased more than 8-fold, from less than 505,430 cases in 2000 to 5.2 million in 2019 [2]. From a sub-regional perspective, Southeast Asia has the highest age-standardized incidence rate (IR) with 18.2 cases/1000 people [1]. The geographical range of dengue is expected to further expand due to ongoing global phenomena including climate change and urbanization [3]. In 2023-2024 Latin America and the Caribbean experienced the largest dengue epidemic since records began in 1980. Pan American Health Organization (PAHO) countries reported more than 12.6 million cases, nearly three times more than in 2023, including 21,000 severe cases and over 7700 deaths. All four serotypes of the dengue virus circulated during 2024. Brazil, Colombia and Mexico reported simultaneous circulation of the four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). Additionally, Argentina reported simultaneous circulation of DENV-1, DENV-2, and DENV-3 [4]. Argentina, Brazil, Colombia, and Mexico accounted for 90% of cases and 88% of deaths, with Brazil having the largest share [5]. Details for some of the highest burdened countries are below: Indonesia Indonesia, which is comprised of more than 17,000 islands and 260 million people, is the most populous country in Southeast Asia. It is hyperendemic for dengue and is consistently estimated to be among the three countries in the world with the largest dengue burden [6]. In Indonesia, outbreaks of Dengue haemorrhagic fever (DHF) appear to be cyclical, occurring every 6 to 8 years. Since 2000, outbreaks of DHF in Indonesia occurred in 2009 (IR = 66/100k) and 2016 (IR = 78/100k), which coincided with a shift in the dominant serotype from DENV-3 to DENV-1 and DENV-2 [7, 8]. In 2019, Indonesia reported 138,127 dengue cases and 919 deaths attributed to dengue (case fatality rate [CFR] = 0.67) and in 2020, Indonesia reported 95,971 cases and 663 deaths (CFR=0.69) [9]. However, dengue surveillance throughout Indonesia is known to be highly variable and incomplete [10]. A 2013 cartographical based model estimated that 7.6 million dengue cases occurred in Indonesia in 2010 [11]. A seroprevalence study in 2014 of 30 geographically dispersed clusters found 53.1% of 5 to 9 year olds had previously been exposed to at least one dengue infection, with a median age of seroconversion estimated at 4.8 years [12].

	Malaysia Malaysia, a country of 31.6 million inhabitants, is spread across the Malay Peninsula and Borneo. Over the past 10 years, the burden of dengue in Malaysia has fluctuated considerably. From 2009 to 2019, there were on average 72,339 suspected cases reported to the national surveillance system annually, ranging from 19,884 cases in 2011 to 130,101 cases in 2019 [13]. In 2022, Malaysia reported 56,305 cases and 37 deaths due to dengue through epidemiological week 47 [14]. All four dengue serotypes circulate in Malaysia, with shifts in dominance. Between 2014 and 2017, DENV-1 and DENV-2 were most prominent [15], and DENV-4 cases have been increasing in prevalence since 2021 [16]. A seroprevalence survey among 9 to 12-years old in Penang and Kuala Lumpur in 2011 found 34% of children had previously been exposed to dengue [17]. While the majority of dengue cases in Malaysia are among children, in recent years there has been a shift in the age profile of cases to individuals older than 15 years [18]. A retrospective observational study of dengue mortality in Malaysia in 2013-2014 found 10% of fatal dengue cases to be among children less than 15 years, while the majority of deaths were adults from the working age group [19]. Singapore Singapore is an equatorial city-state with approximately 5.6 million inhabitants. For the past 30 years, Singapore has experienced periodic dengue epidemics of increasing frequency and magnitude, despite a strong vector control program which has reduced the percentage of houses infested with <i>Aedes</i> larvae to below 1% [20]. Between 2009 and 2019, an average of 9,704 laboratory confirmed dengue cases were reported in Singapore, ranging from 2,767 in 2017 to a record high of 22,170 in 2013. During this time period, DENV-1 and DENV-2 predominated [21]. In 2020, Singapore experienced its largest dengue outbreak on record, with more than 35,300 cases reported [22]. This record year was driven in part by a serotype switch to DENV-3, which had not predominated in Singapore for more than 30 years [23]. In 2022, as DENV-3 continued to predominate, there were 32,097 cases reported [23]. However, by the second quarter of 2023, DENV-1 again gained dominance, with more than 60% of serotyped cases reported to be DENV-1 in June 2023 [24]. A 2017 seroprevalence survey among Singaporean residents 16 to 74 years found a dengue IgG prevalence of 45.7% among persons sampled. Seropositivity ranged from 13.8% among residents aged 16 to 20 years to 85% among those over 60 years [25]. Sri Lanka Sri Lanka is an island nation of 21.4 million inhabitants. From 2010-2016, Sri Lanka reported an average of 38,802 annual suspected dengue cases. In 2017, Sri Lanka experienced its largest outbreak on record, with more than 186,000 suspected cases. Before the 2017 epidemic, the largest outbreak that occurred in Sri Lanka was in 2014, with 47,502 reported suspected cases [26]. All four serotypes circulate in Sri Lanka annually, but the 2017 outbreak was predominated by DENV-2 [27]. The majority of cases reported during the 2017 outbreak were among working-age adults [28]. Sustained dengue transmission has occurred since the outbreak in Sri Lanka, with 30,620 dengue cases reported in 2020, 25,084 cases of dengue reported in 2021 [29], and 63,409 dengue cases reported in 2022 [30]. To September 2023, there have been 59,527 cases of dengue reported [31]. A 2007 seroprevalence study in Southern Sri Lanka found that dengue seroprevalence reached 70% by 40 years of age. However, an updated study conducted in the same area in 2012, found nearly 70% of 20 years olds to be seropositive, and seropositivity reached 90% among 60 to 65 years olds [32].
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	Thailand Across Thailand's 76 provinces, 13 health regions, and 69.4 million people, there is considerable geographic and annual variation in the burden of dengue. Between 2019 and 2022, Thailand reported approximately 131,157 cases of dengue fever nationwide in 2019, 72,578 cases in 2020, 10,617 cases in 2021 and 46,755 cases in 2022 [33]. As DENV-1 predominated in 2019 and 2020, there were 128,964 and 72,519 cases of dengue reported, respectively [34]. Dengue has been hyperendemic in Thailand since 1958 [33], and a recent study found a high incidence of DENV serotype and genotype co-circulation, particularly in urban areas [35]. Over the past few decades, the age of first infection has increased in Thailand. This increase in average age of first infection may in part be due to a significant shift in the demographics of the Thai population over the past few decades [36]. However, children are still significantly impacted by dengue in Thailand. A dengue seroprevalence survey in Ratchaburi and Kamphaeng Phet conducted in 2011 found nearly 80% of 9 to 12 years old had already been exposed to dengue [17]. Argentina Argentina, a country of 44.5 million inhabitants, remained free from dengue for more than 80 years before the disease was reintroduced in 1997 in Salta Province. Since then, locally acquired dengue cases have only been reported from the northern provinces of the country, though the <i>Aedes aegypti</i> mosquito has spread southward to latitude 35°S, near Buenos Aires [37]. Between 2009 and 2019 the average number of reported cases in Argentina was 17,413, ranging from 213 cases in 2011 to 79,455 cases (41,211 confirmed) in 2016. In 2020, Argentina reported a then record dengue season, with at least 58,415 dengue cases reported, in 2023, Argentina experienced an increase in reported dengue cases, with 146,876 cases [38]. In 2024, 579,955 cases were reported in Argentina with 408 deaths [39]. During the 2020 outbreak, the 20 to 34-year-old age group had the highest number of cases and highest incidence rate, followed by 35 to 44 and 10 to 19. A 2016 seroprevalence survey among 266 affiliates at the Universidad Nacional de Misiones and Universidad Católica de las Misiones found 6.6% to be seropositive for dengue [40]. Brazil Brazil is home to 209.5 million people and is hyperendemic for dengue. Between 2009 and 2019, an average of 986,053 suspected dengue cases were reported annually, ranging from 252,054 in 2017 to 2.25 million in 2019 [41]. Brazil has continued to experience a high level of dengue transmission, with nearly 1.5 million cases reported in 2020, 975,474 cases in 2021, 2.4 million cases in 2022, 3.06 million cases in 2023 and 10.25 million cases in 2024 [39]. By far, Brazil has the largest dengue burden in Latin America. Among all dengue cases that were reported in the Americas in 2024, more than 79% were from Brazil. Even still, dengue is under reported in Brazil, with one notification estimated for every twenty cases of dengue fever [42]. Every year for the past 10 years, Brazil has reported the cocirculation of all four dengue serotypes [41]. Epidemics occurred in 2010, 2013, 2015, 2016 and 2019, marked by reintroduction of new serotypes (in 2010 and 2013) as well as the introduction of new arboviruses (Chikungunya and Zika virus in 2015 and 2016) [43].
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	A recent dengue seroprevalence study conducted in Fortaleza, Natal, Vitoria, Goiania, and Campo Grande found 68% of 9 to 12-year olds to be seropositive for dengue [17]. Colombia Colombia has a population of 49.7 million people and has historically been among the highest dengue burden countries in the Americas. Between 2009 and 2019, Colombia's dengue surveillance system reported an average of 79,634 suspected cases, ranging from 25,284 in 2017 to 138,188 in 2010. The number of dengue cases reported in recent years has remained relatively stable until 2023, with 78,979 cases in 2020, 53,334 cases in 2021, 69,497 cases in 2022, 130,070 in 2023 and 317,993 in 2024 [39]. A dengue seroprevalence study conducted in Bucaramanga, Armenia, Tebaida, Calarca, Montenegro, Giarardot, Acacias, Yopal and Aguazul found 91% of 9 to 12-year olds to be seropositive for dengue [17]. Mexico Dengue transmission in Mexico, a country of 126.2 million inhabitants, is heterogenous between and within regions. Sustained dengue transmission occurs on both coasts, as well as in some central states, namely Morelos and Huasteca [44]. Between 2009 and 2019, the average number of suspected dengue cases reported by the national surveillance system was 151,094, ranging from 51,635 in 2010 to 268,458 in 2019 [41]. In 2020, there were 120,639 cases reported, 1,058 of which were severe. In 2023, there were 277,963 cases reported, of which 1,653 were reported as severe. In 2024, 558,846 cases were reported with 4,214 reported as severe [39]. A dengue seroprevalence study conducted in Temixco, Veracruz, Valladolid, Ciudad Mante, and Tizimin Mexico found 48% of 9 to 12-year olds to be seropositive for dengue [17]. Travellers Travel-acquired dengue cases have been increasing as the overall global dengue burden has expanded. Among travellers returning from Southeast Asia, dengue is a more frequent cause of febrile illness than malaria [45], and accounts for an estimated 2% of all febrile illnesses in travellers returning from the tropics [19, 46]. However, the true burden of dengue among travellers is likely much higher due to variability in reporting, misdiagnosis, and the methodological challenges involved in tracking self-limiting illnesses among travellers [45]. A prospective seroconversion study of travellers to dengue endemic countries estimated an incidence of 2.9% in Dutch travellers who spent approximately 1 month in Asia [47]. Travellers returning home with dengue also contribute to the spread of the disease to non-endemic areas where <i>Aedes aegypti</i> and <i>Aedes albopictus</i> mosquitoes are present [48]. Dengue in Europe Dengue cases have been recorded in continental Europe in recent years. From 2017 to 2019, the number of reported cases in the EU ranged from 1,563 in 2017 to 3,743 in 2019. In 2021, 27 EU/EEA countries reported a total of 428 cases of dengue, 96% of which were laboratory confirmed [49]. The majority (54%) of cases were reported by France, followed by Germany (14%) and Spain (11%). An outbreak on the Madeira island (Portugal) in 2012 resulted in over 2,000 cases and imported cases were detected in mainland Portugal and 10 other European countries. In many European countries, autochthonous cases are observed on an almost annual basis [50].
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	Dengue in European territories Several European territories report dengue transmission: Reunion Island, a French department in the Indian Ocean of about 840,000 inhabitants, experienced an outbreak of dengue in 2018 with more than 6,000 reported suspected infections. Since then, annual outbreaks have occurred, resulting in a now constant presence of the virus [51]. <i>Aedes albopictus</i>, the primary vector of this outbreak, are also widely established in the European Union [52]. Mayotte is a French territory between Madagascar and Mozambique with 256,000 inhabitants. In the first 4 months of 2020, Mayotte experienced a DENV-1 outbreak with 3,533 confirmed cases, 339 of which were hospitalized, 21 required intensive care and 16 died. Prior to the outbreak in 2020, Mayotte had reported four dengue outbreaks - 1993 and 2010 caused by DENV-3, 2013 and 2014 caused by DENV-2 [53]. French Guiana is an overseas department of France with nearly 300,000 inhabitants. French Guiana first reported a case of DHF in 1992. Over the past decade, French Guiana has experienced dengue hyperendemicity, and reported outbreaks in 2009, 2010, 2013 2020 and 2023 [54]. Madeira, an autonomous region of Portugal with a population of 289,000, reported 2,168 probable dengue cases during its first dengue outbreak from September 2012 to March 2013. Of the suspected cases, 1,080 were confirmed. The dengue outbreak in Madeira led to many cases of imported cases in other European countries including 11 in Portugal, 19 in Germany, 7 in Finland, 5 in Sweden, 3 in France, 2 in Denmark, 2 in Austria, 2 in Norway, 1 in Croatia, 1 in Slovenia, 1 in Spain, and 1 in Switzerland [55]. In Martinique and Guadeloupe, overseas regions of France, dengue is highly endemic. A 2011 serosurvey conducted among 783 adult blood donors in Guadeloupe and Martinique found 93.5% [91.5; 95.1] samples were positive for dengue antibodies, 90.7% (350 of 386) in Martinique and 96.2% (382 of 397) in Guadeloupe. Of the adults who tested positive, only 30% recalled having had dengue [56]. In 2023, the region experienced an epidemic level of dengue, primarily DENV-2 – with significant intensity in the municipalities of Saint-François and Trois-Rivières of Guadeloupe and throughout Martinique [57]. In New Caledonia, a special collectivity of France with a population of 278,000, dengue occurs regularly. In 2018, 2,030 dengue cases including two deaths were reported. DENV-2 was the predominant circulating serotype, comprising 1,149 of the 1,336 (86%) typed cases [58]. To end of March 2021, 54 cases had been reported in New Caledonia, with DENV-2 identified as the predominant serotype [59]. French Polynesia, the only overseas country of France, with 118 islands in the South Pacific Ocean, has 276,000 inhabitants. A 2014-2015 serosurvey across the islands using a cluster sampling approach found the majority of the general population (96%±3%) had been exposed to more than one dengue serotype in 2014. Among schoolchildren, the seroprevalence was 60%±5%. These rates of seroprevalence are indicative of high transmission rates throughout French Polynesia [60]. In Wallis and Futuna, a French island collectivity in the South Pacific with about 12,000 people, 225 cases were confirmed since November 2017, putting the islands above the epidemic threshold. Young people between 5 and 20 years represented more than half of all confirmed cases. The death of an 8 year old girl due to dengue was also reported during this epidemic [61]. Saint Barthelemy, an overseas collectivity of France with about 10,000 inhabitants, is endemic for dengue. In 2015, Saint Barthelemy reported 428 cases of dengue to PAHO, an incidence rate of 4,280/100,000 [62].
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	Saint Martin is divided between the French Republic and the Kingdom of the Netherlands, with about 77,000 inhabitants. The first dengue outbreak identified on Saint Martin occurred in 1997. Since then, many outbreaks have occurred, most recently in 2013 and 2014, with 4,020 reported cases, 40 hospitalizations, 2 deaths. In Saint Martin, three serotypes co-circulated during this outbreak: DENV-1, DENV-2 and DENV-4, with serotype 1 predominating [63]. Aruba is a constituent country of the Kingdom of the Netherlands with 105,000 inhabitants. In 2011, 2,850 cases of dengue were reported. Over the past decade, outbreaks were reported in 2009 (3,210 reported cases) and 2011 (2,850 cases). In 2014, 833 cases were reported [64]. Curaçao is a constituent country of the Kingdom of the Netherlands with a population of 160,000. In 2014, Curacao health authorities reported 194 suspected dengue cases (IR = 131/100,000) and 20 confirmed cases. No information on the number of dengue cases reported in subsequent years has been reported [65].
Prevalence:	Dengue is an acute disease and therefore the burden is best characterized by incidence. Seroprevalence rates, however, are informative as a measure of past exposure in a specific population at a given time. Dengue seroprevalence data from studies in Latin America and Asia in 2011 found more than 75% of 9 to 12-year-old children participating in the study have previously been exposed to dengue [17]. However, dengue transmission is spatially heterogenous, and the force of infection can be highly variable within and across countries. In Singapore, for example, only 16% of 16 to 20 year olds have previously been exposed, and in Thailand, schools located within the same municipality have been shown to have significantly different transmission intensities [36, 66].
Demographics of the target population in the indication:	<u>Age:</u> People of all ages are at risk of dengue infection [67]. Though the data are limited, the results of some studies suggest that elderly dengue patients have the highest dengue case-fatality rates [68-70]. In Southeast Asia, dengue has historically been a paediatric disease and clinical dengue in adults has been rare [71]. Throughout the region, the majority of children in endemic areas have already had a primary dengue infection before the age of 9 years [17]. In Asia, DHF and Dengue shock syndrome (DSS) mostly occur in children aged 2 to 15 years [72]. However, data from Singapore, Malaysia, Indonesia, Thailand, and Bangladesh point to a recent increase in dengue incidence among older age groups [36, 73-76]. A study from Thailand indicated that this shift in age profile is, in part, driven by changes in the age structure of the Thai population over the last 30 years [36, 77, 78]. Other factors contributing to this shift in the age burden include increased urbanization, a decrease in mean household size, improvements in sanitation and water, increases in socioeconomics, increases in vector control, and educational campaigns against dengue [79, 80]. In Latin America, first infections have generally been among young adults and severe disease occurs in a significant number of adults [81]. Recently, however, Latin America has seen an important increase in dengue incidence among children, leading to an epidemiological shift that is beginning to resemble the historical age profile seen in Southeast Asia [82]. In Brazil, this shift has been shown to be partly attributed to an increase in multitypic immunity in adults over time following the re-emergence of DENV-1 in 1986, DENV-2 in 1990, and DENV-3 in 2002. As such, the probability of being dengue naive into adulthood has been reduced, resulting in a decrease in the average age of infection [83, 84]. Increases in multitypic immunity among adults may also

	explain the recent increase in severe dengue observed among children in Colombia, Venezuela, Nicaragua, and Mexico [85-87]. <u>Gender:</u> Data regarding differences in dengue vulnerability by gender are mixed and vary by time, place, and study methodology. Whether differences observed are due to the pathogenesis process, immune response, exposure to the vector, or related to treatment seeking behaviour remains unclear [88-91]. <u>Racial and/or ethnic origin:</u> Some association has been described for people of African genetic ancestry who are less affected by severe dengue outcomes [92, 93]. No other ethnic groups have been identified as being at higher or lower risk of severe disease.
Risk factors for the disease:	Variations in risk of dengue are influenced by rainfall, temperature, population density, urbanization, poverty, poor sanitary conditions, domestic water supplies, and vector control. Globalization, migration, international travel and climate change also play a role in the geographic expansion of dengue [94, 95]. At the individual level, the relative risk of developing severe dengue has been shown to be significantly higher among persons with a secondary dengue infection of a heterologous DENV serotype compared to those who have a primary infection [87, 96-101]. Numerous factors are also known to influence the severity of disease, including: co-morbidities, nutritional status, the two extremes of age, genetic composition, pregnancy, and the time interval since primary infection [85, 99, 102-108].
The main existing treatment options:	There is no specific treatment for dengue. Treatment of dengue is based solely on symptoms and signs, with maintenance of the patient's body fluid volume critical for haemorrhagic or shock cases [109]. Dengvaxia is the only dengue vaccine to have been commercialized to date, with licensure by regulatory authorities in multiple endemic countries [110]. In December 2018, Dengvaxia received approval in the EU [111].
Natural history of the indicated condition in the unvaccinated population, including mortality and morbidity:	Twenty-five percent of dengue infections are thought to be symptomatic [11]. Clinically, infection with a dengue virus can result in a range of symptoms, often with unpredictable clinical progression and outcome [112]. The 2009 WHO clinical classification for dengue diagnosis and management divides dengue into two groups: uncomplicated and severe. Uncomplicated dengue is clinically defined as an acute febrile illness with two or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, or haemorrhagic manifestations) [109]. Severe dengue occurs in a small fraction of cases (<5%), and is associated with severe bleeding, severe organ dysfunction, and/or severe plasma leakage [109, 113]. Illness rarely lasts beyond 10 days, though some symptoms can be persistent and debilitating [109, 114]. Without appropriate treatment, fatality rates can exceed 20%, however, with proper case management, the rate can be less than 1% [50]. The WHO estimates about 500,000 people with severe dengue require hospitalization annually, and about 2.5% of those affected die [2].
Important co-morbidities:	Everyone in dengue endemic areas is deemed to be susceptible to dengue infection and disease. There are no known risk groups for uncomplicated dengue. Comorbidities that may predispose individuals to severe forms of dengue include cardiovascular disease, hypertension, stroke, diabetes, respiratory disease, renal disease, hepatitis B or C, and Human immunodeficiency virus (HIV) [115-117]. Obesity and advanced age are also associated with more severe forms of dengue [115, 118].

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Toxicity All toxicity studies were Good Laboratory Practice (GLP) compliant except for the Pilot toxicology study (DEN-001).	
- <u>Single-dose toxicity study (DEN-001)</u> In a non-GLP pilot toxicology study, toxicity of a single subcutaneous (SC) dose of TDV was compared with that of wild type DENV-2 virus, vehicle control (vaccine diluent FTA containing 1% F-127, 15% trehalose, and 0.1% human serum albumin) or saline placebo. No effect on weight or appearance was observed in mice dosed with TDV, while mice receiving DENV-2 had weight loss and poor appearance. Toxicological findings for both DENV-2 and TDV included a generalized inflammatory response, reduction in alkaline phosphatase and splenic extramedullary haematopoiesis. An increase in the number of platelets was observed on Days 7, 9, and 11 in the DENV-2 group, and on Days 7 and 9 in the TDV group. Adverse findings were of lesser severity and shorter duration in TDV treated animals compared with DENV-2-treated animals. Viraemia was of lower magnitude and shorter duration in TDV treated animals compared with DENV-2-treated animals. The results of this pilot toxicology study supported use of the AG129 mouse model based on susceptibility to the parental wild type DENV-2 16681 strain and TDV strains.	There were no tox-related effects observed that would be translatable to the human population.
- <u>Repeat-dose toxicity studies</u> 1/ DEN-004 In a GLP study, repeated administration of TDV by SC injection was well tolerated at a target dose (sum of all 4 components) of 5.5 log₁₀ PFU/dose (actual minimal dose administered 5.9 log₁₀ PFU per back titration) in AG129 mice. Mice were administered TDV up to three occasions on Days 1, 31, and 46. Study animals were then observed after dosing to evaluate the potential toxicity of TDV until scheduled necropsy on Day 8/9, 53, or 61. All 4 vaccine strains replicated after the first TDV dose, but not after the second or third doses of TDV. A single dose of TDV resulted in seroconversion to DENV-1, -2 and -3 by Day 16, while two TDV doses were required for substantial seroconversion to DENV-4. Transient test article-related effects, including some changes in clinical chemistry, hematology, spleen weight and some histopathological effects, were observed after the first dose. The majority of changes were no longer observed on Day 61, 15 days after the third administration of TDV. Minimal increases in the number of platelets were observed in the TDV group throughout the study. No treatment-related or toxicologically significant findings on any coagulation parameters were observed throughout the study. Mixed cell infiltrates persisted at the	Most treatment-related effects were reversible as they were no longer observed on study Day 61. No human safety concerns have been identified from this study.

injection site through study Days 53 and 61 but were deemed related to the vaccine diluent at these later time points. Administration of the first dose of TDV did not result in enhanced infectivity of subsequent doses of the vaccine viruses. In contrast, injection with wild type DENV-2 resulted in a rough fur coat and organ weight changes at necropsy in addition to histopathology and hematology observations associated with a more severe generalized inflammatory state. Injection with wild type DENV-2 resulted in histologic evidence of dengue virus-associated encephalitis. The observations of this GLP toxicology study supported the findings of the pilot toxicology study in supporting tolerability of TDV and immunogenicity against all 4 DENV serotypes.	
2/ Study 5001446 In a GLP toxicity study, repeated administration of TDV when given up to 3 occasions by SC injection to AG129 mice at levels of 7.0 log₁₀ PFU/dose was well tolerated. Reversible target organ effects were observed on Day 8 in the bone marrow (increased myeloid cellularity), spleen (increased hematopoiesis), thymus (decreased weight), skin and injections site (mixed cell infiltration, skin degeneration/necrosis and/or hemorrhage) at 7.0 log₁₀ PFU/dose. Associated changes in organ weights and in clinical pathology parameters were observed. All changes were considered expected observations following vaccine administration and/or non-adverse and reversible based on nature, relative severity and/or reversibility (or partial reversibility). Based on these results, the No-observed-adverse-effect level (NOAEL) was considered to be 7.0 log₁₀ PFU/dose (1.07 x 10⁷ PFU/dose), which exceeds the maximum manufacturing release specification for TDV.	No human safety concerns have been identified from this study. Based on these results, the NOAEL was considered to be 1.07 x 10⁷ PFU/dose. The dose level shown to be well tolerated in this study was 22.8 times higher than the viral content of the TDV high dose tested in clinical studies.
3/ Study 5001168 In a GLP toxicity study, repeated administration of TDV when given up to 3 occasions by SC injection to AG129 mice at levels of 6.8 log₁₀ PFU/dose was well tolerated. Vaccine vRNA from TDV-1, TDV-2 and TDV-3 was detected in the serum of animals given TDV at 6.8 log₁₀ PFU/dose after the first vaccination only. Target organ effects were observed in the bone marrow (increased myeloid cellularity), spleen (increased hematopoiesis), thymus (decreased weight), skin and injection site (mixed cell inflammation) at 6.8 log₁₀ PFU/dose. Associated changes in organ weights and in clinical pathology parameters were observed. Increases in platelets were observed in TDV-vaccinated females throughout the study. In contrast, platelet counts in vaccinated males were not different from control animals. All changes were considered expected observations following vaccine administration. They were non-adverse and reversible based on nature, relative severity, and reversibility or partial reversibility. Based on these results, the NOAEL was considered to be 6.8 log₁₀ PFU/dose (5.93 x 10⁶ PFU/dose).	There were no tox-related effects observed that would be translatable to the human population. Based on these results, the NOAEL was considered to be 5.93 x 10⁶ PFU/dose. The dose level shown to be well tolerated in this study was 12.6 times higher than the viral content of the TDV high dose formulation (i.e., 4.7 x 10⁵ PFU/dose) tested in clinical studies.

– <u>Reproductive and Developmental Toxicity (Study 20129939)</u> The objective of this study was to assess the potential toxicity of TDV on fertility, development of the embryo and fetus, and postnatal development in New Zealand White rabbits. This study was designed to evaluate International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline S5 stages A to E of the reproductive process. F0 generation female rabbits in Groups 1 and 2 were given 2 dose administrations per day (once every 3 weeks) of TDV (containing 5.4 log PFU/mL; TDV-2: 4.8 log PFU/mL; TDV-3: 5.7 log PFU/mL; TDV-4: 6.2 log PFU/mL) or saline control article prior to mating on Days 1, 21 and 42 of study, and on Days 7 and 28 of gestation (GDs 7 and 28). The first day of dosing was considered Day 1 of study (DS 1). Administration of TDV on study DS 1, 21 and 42 and GD 7 and 28 did not increase the incidence of clinical signs, dermal scoring, or maternal gross lesions or have an effect on body weights, food consumption, and mating, fertility, or reproduction in the F0 generation, as compared with the group administered the saline control article. There were no TDV-related mortalities. In addition, there were no effects on any ovarian, uterine, or litter parameters following administration of TDV. Maternal treatment with TDV did not cause any vaccine-related effects on clinical observations, body weights, organ weights, or gross pathology observations in the F1 generation kits. There were no TDV-related mortalities. There were no fetal gross external, soft tissue, or skeletal abnormalities attributed to administration of the vaccine. TDV elicited an immune response in 100% of the rabbits on DS 48 prior to mating. The F1 generation from Group 2 Caesarean-sectioned fetuses were 100% seropositive while the natural delivery kits were 95%, 100%, 83% and 93% seropositive to DENV-1, -2, -3 and -4, respectively. In summary, TDV was well tolerated and did not produce any detectable maternal or developmental toxicity in New Zealand White rabbits.	Non-clinical safety data revealed no special hazard for humans based on toxicity to reproduction and development.
– <u>Genotoxicity</u> Studies investigating genotoxicity have not been conducted. Genotoxicity studies were not conducted as TDV is a live viral vaccine consisting of normal metabolizable components. No novel excipients or compounds of concern are used in the product.	The absence of genotoxicity and carcinogenicity studies is considered acceptable based on the type of product and in line with current guidelines on non-clinical evaluation of vaccines.
– <u>Carcinogenicity</u> Studies investigating carcinogenicity have not been conducted. Carcinogenicity studies were not conducted as TDV consists of attenuated dengue viruses, which are RNA viruses and are not oncogenic. TDV consists of normal metabolizable components. No novel excipients or compounds of concern are used in the product.	

Safety pharmacology	
Studies investigating safety pharmacology have not been conducted. As there were no adverse safety issues related to TDV identified in the toxicology studies, specific safety pharmacology studies were not conducted. This type of study is generally not performed for vaccines. Central nervous system (CNS) effects were evaluated in the neurovirulence studies [Report DEN-014]. CNS-associated organs (brain and spinal cord) were assessed histopathologically as part of the biodistribution [Report 5002340] and toxicology [Reports DEN-004, 5001168 and 5001446] studies with no adverse findings reported.	Separate safety pharmacology studies were not conducted, which is acceptable according to the EMA and the WHO guidelines.
Other toxicity-related information or data	
– <u>Neurovirulence (DEN-014)</u> As a part of the characterization of the attenuation of TDV strains, a mouse neurovirulence study was conducted. This study evaluated the neurovirulence of TDV Master Virus Seeds (MVS) in new-born ICR mice challenged intracranially with a dose of approximately 10^3 and/or 10^4 PFU of TDV MVS, recombinant DEN-2 PDK-53-based viruses or wild type dengue viruses. TDV-1 and TDV-3 MVS exhibited fully attenuated neurovirulence phenotypes (no illness or mortality) at 10^4 PFU. At viral dose levels of $\sim 10^3$ PFU, TDV-2 and DEN-2 PDK-53 as well as TDV-4 and the research grade D2/4 recombinant were significantly less neurovirulent than DEN-2 (16681 DEN-2) indicating attenuation of the recombinant and MVS stocks compared to DEN-2, albeit at a lower dose than used in earlier studies. TDV showed significantly lower mortality after intracranial injection in suckling mice compared with DEN-2 and similar neurovirulence to the original homologue recombinant dengue research strains.	Virus replication in the central nervous system after passage through the blood–brain barrier has been investigated by direct intracerebral injection of the vaccine in new-born mice brains and TDV has showed significantly lower mortality compared with DEN-2 and similar neurovirulence to the original homologous recombinant dengue research strains. Therefore, TDV is considered to have an acceptable neurotoxic profile and no human safety concern has arisen from this study.
– <u>Biodistribution and Shedding (Study 5002340)</u> Biodistribution and shedding of TDV by single SC injection was assessed in AG129 mice at levels of TDV-1: 5.1, TDV-2: 4.5, TDV-3: 5.4 and TDV-4: 5.9 $\log_{10}$ PFU/dose. RT-qPCR and histopathology in 16 tissues, saliva, feces, and urine were evaluated at terminal timepoints (Day 2, 6, 14 and 42). TDV was well tolerated (mortality, clinical signs, body weights, food consumption, macroscopic findings, organ weights, and microscopic findings) and no adverse effects related to TDV administration were observed. On Day 2, viral RNA (vRNA) from the four TDV serotypes was detected at low levels at the injection site. By Day 6, vRNA was distributed broadly, and was detectable in most tissues. By Day 14, vRNA had been reduced to below the level of detection in most tissues, including serum. By Day 42, most tissues were negative for vRNA, but low levels of TDV-2 vRNA were detected in one skin sample from the injection site, one thymus sample, and one brain sample. There were no TDV-associated clinical observations or histopathological findings in the brain or thymus at any timepoint, or in the injection site on Day 42, including in those	Biodistribution and shedding assessment of TDV in AG129 mice demonstrated that vRNA distribution could be detected and was cleared from the majority of tissues. There was no shedding of TDV vRNA in feces and urine and a low level of vRNA detected in saliva of one animal early in the study (Day 6), indicating a low risk for vaccine shedding to the environment or transmission from vaccinees.

animals with detectable vRNA. One mandibular lymph node was positive for TDV-3 vRNA on Day 42 and minimal increased lymphoid cellularity was present in the mandibular lymph node in a few animals, including the one animal with detectable vRNA. With these data in mind, the potential mechanism of vRNA distributing to brain of AG129 mice, and potential risk associated with this finding, was investigated. Review of all nonclinical studies of TDV in AG129 mice showed no TDV-related neurological manifestations. TDV was demonstrated to be less neurovirulent than wild-type DENV-2 in newborn mice. Both DENV-2 16681 (the wild-type parental strain of PDK-53) and DENV-2 PDK-53 (the attenuated parental strain of TDV-2) were reported to have little or no neurovirulence in immune-competent rhesus macaques when injected into the brain or spinal cord, and no clinical signs were observed. It may be that the immunocompromised AG129 mouse model chosen for biodistribution and shedding assessment may be sensitive to distribution or persistence of vRNA in brain due to lack of interferon responses and increased vascular permeability. Overall, in a single dose TDV nonclinical biodistribution and shedding study in AG129 mice, the maximal detection of vRNA in serum was observed on Day 6 and clearance from the majority of samples was noted by Day 42. TDV was well tolerated, and there was no measurable level of vRNA in feces and urine, and a low level of vRNA detected in saliva of one animal early in the study (Day 6), confirming a low risk for vaccine shedding to the environment or transmission from vaccinees.	
– Dengue Antibody-dependent disease enhancement (ADE) Nonclinical studies to evaluate (ADE) were not performed because nonclinical models are not highly predictive of the risk of severe dengue disease in humans. The available models use either immunocompromised animals, or if immunocompetent the animals are not susceptible to symptomatic dengue disease.	Takeda has compiled supportive immunological data that confirms a broad, multicomponent immune response is generated by TDV, which indicates that the risk for ADE is less than that found in waning monovalent infections, or from vaccination with formulations that are unable to activate multiple layers of protection (e.g., dengue specific cellular responses against all 4 serotypes in addition to that afforded by antibodies).

Part II: Module SIII - Clinical trial exposure

Table SIII.1: Cumulative Number of Subjects Exposed to TDV by Age and Gender

N = Number (%) of Subjects Exposed			
Age Range (years)	Male	Female	Total
<4	199 (2.0)	192 (1.9)	391 (1.9)
4 - 5	1105 (10.9)	1023 (10.1)	2128 (10.5)
6 - 11	4236 (41.7)	4215 (41.6)	8451 (41.7)
12 - 17	2486 (24.5)	2552 (25.2)	5038 (24.8)
18 - 45	1630 (16.1)	1611 (15.9)	3241 (16.0)
46 - 60	492 (4.8)	547 (5.4)	1039 (5.1)
>60	0	0	0
Total	10,148 (100)	10,140 (100)	20,288 (100)

Note 1: Includes data from completed clinical trials, ongoing trials with available interim analysis and ongoing trials with available open-label exposure data; Studies included: [DEN-101](#), [DEN-102](#), [DEN-103](#), [DEN-104](#), [DEN-105](#), [DEN-106](#), [DEN-203](#), [DEN-204](#), [DEN-205](#), [DEN-210](#), [DEN-301](#), [DEN-303](#), [DEN-304](#), [DEN-305](#), [DEN-307](#), [DEN-308](#), [DEN-313](#), [DEN-314](#) and [DEN-315](#).

Note 2: In column headings, N = number of subjects in the safety set.

Note 3: Table includes subjects who received any TDV dose.

Table SIII.2.A: Number of subjects exposed during completed and ongoing Phase 1, Phase 2 and Phase 3 trials and overall exposure.

N = Number of Subjects Exposed						
Trial ID	Placebo	TDV	YFv	HAVv	HPVv	Total
INV_DEN_101 ^(a)	24	48	0	0	0	72
INV_DEN_102	17	79	0	0	0	96
INV_DEN_103	16	67	0	0	0	67
INV_DEN_104	24	140	0	0	0	140
INV_DEN_105	0	80	0	0	0	80
DEN-106	162	996	0	0	0	996
INV_DEN_203	111	249	0	0	0	360
DEN-204	1747	1597	0	0	0	1794
DEN-205	0	351	0	0	0	351
DEN-210	0	30	0	0	0	30
DEN-301 ^(b)	6691	13,384	0	0	0	20,071
DEN-301 Booster ^(c)	2986	5991	0	0	0	8977
DEN-303 Booster	118	115	0	0	0	233
DEN-304	131	788	0	0	0	919
DEN-305	233	873	841	0	0	900
DEN-307	0	200	0	0	0	200
DEN-308	0	307	0	0	614	614
DEN-313	0	200	0	0	0	200
DEN-314	270	598	0	597	0	897
DEN-315	100	300	0	0	0	400
Total	9645	20,288	841	597	614	28,187

Abbreviations: HAVv: Hepatitis A vaccine; HPVv: Human Papillomavirus vaccine; IMP: Investigational medicinal product; TDV: Dengue Tetravalent Vaccine (Live, Attenuated); YFv: Yellow Fever vaccine.

(a) Trial was conducted by the Division of Microbiology and Infectious Diseases (DMID) under IND 014317.

(b) Ongoing trial. Exposure data is for Parts 1 to 3 of the trial, for which last subject out (LSO) occurred on 11 January 2022.

(c) Ongoing trial. Exposure data is for Parts 4 and 5 of the trial; LSO for Part 4 occurred on 29 July 2023 and LSO for Part 5 occurred on 28 June 2024.

Note 1: Studies included: [DEN-101](#), [DEN-102](#), [DEN-103](#), [DEN-104](#), [DEN-105](#), [DEN-106](#), [DEN-203](#), [DEN-204](#), [DEN-205](#), [DEN-210](#), [DEN-301](#), [DEN-303](#), [DEN-304](#), [DEN-305](#), [DEN-307](#), [DEN-308](#), [DEN-313](#), [DEN-314](#) and [DEN-315](#). In DEN-303, the first and second dose were administered in the parent trials (DEN-304 and DEN-315), only the booster dose is counted.

Note 2: In column headings, N = number of subjects in the safety set.

Note 3: Subjects who received more than one dose are counted once for each IMP administered.

Note 4: Subjects who received more than one IMP (including those receiving both Placebo and TDV in the same study) are counted only once in the Total column.

Note 5: All studies labelled DEN-1xx are Phase I studies, DEN-2xx are Phase II and DEN-3xx are Phase III studies, with the exception of DEN-106 and DEN-313, which are Phase II studies.

Table SIII.2.B: Subjects Exposed to Different TDV Formulations

N = Number of Subjects who received 1, 2, 3, or 4 Doses and Booster of TDV							
Formulation	1 dose	2 doses	3 doses	4 doses	Booster	Total subjects	Total Doses
Early Investigational Formulations of TDV:							
LD TDV ^(a)	9	187	15	0	0	211	428
HD TDV ^(b)	478	1057	23	0	0	1558	2661
HD/10 TDV ^(c)	3	21	0	0	0	24	45
HD2 TDV ^(c)	2	24	0	16	0	42	114
Corresponds to Authorized Formulation of TDV:							
TDV ^(d)	1099	17,353	0	0	6106	18,453	41,911
Total	1591	18,642	38	16	6106	20,288	45,159

Abbreviations: LD: low dose, HD: high dose, HD/10: 1/10 dilution of high dose, HD2: high dose 2 (increased relative content of vaccine strain TDV-4), TDV: Dengue Tetravalent Vaccine (Live, Attenuated).

(a) Used in DEN-101, DEN-102, DEN-103, and DEN-105.

(b) Used in DEN-101, DEN-102, DEN-104, DEN-106, DEN-203, and DEN-205.

(c) Used in DEN-104.

(d) Used in DEN-204, DEN-205, DEN-210, DEN-301, DEN-303, DEN-304, DEN-305, DEN-307, DEN-308, DEN-313, DEN-314, and DEN-315.

Note 1: Studies included: DEN-101, DEN-102, DEN-103, DEN-104, DEN-105, DEN-106, DEN-203, DEN-204, DEN-205, DEN-210, DEN-301, DEN-303, DEN-304, DEN-305, DEN-307, DEN-308, DEN-313, DEN-314 and DEN-315. For Trial DEN-301 Part 4 interim analysis data is used. In Trial DEN-303, the first and second dose were administered in the parent trials (DEN-304 and DEN-315), only the booster dose is counted.

Note 2: In column headings, N = number of subjects in the safety set.

Note 3: Column "Total Subjects" includes subjects who received any TDV dose.

Table SIII.3: Ethnic origin (safety set)

Racial Group	N = Number (%) of Subjects Exposed to TDV
American Indian or Alaska Native	6299 (31.0)
Asian	7243 (35.7)
Black or African American	2688 (13.2)
Native Hawaiian or Other Pacific Islander	17 (<0.1)
White	3204 (15.8)
Multiracial or Other	664 (3.3)
Not Reported	15 (<0.1)
Unknown	158 (0.8)
Total	20,288 (100)

Note 1: Studies included: DEN-101, DEN-102, DEN-103, DEN-104, DEN-105, DEN-106, DEN-203, DEN-204, DEN-205, DEN-210, DEN-301, DEN-303, DEN-304, DEN-305, DEN-307, DEN-308, DEN-313, DEN-314 and DEN-315.

Note 2: In column headings, N = number of subjects in the safety set.

Note 3: Table includes subjects who received any TDV dose.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1. Exclusion criteria in pivotal clinical studies within the development programme

Female subjects (post-menarche) who were pregnant or breastfeeding.	
Females of childbearing potential, who are sexually active, and who have not used any of the acceptable contraceptive methods for at least 2 months prior to study entry or who refuse to use an acceptable contraceptive method or avoid donation of ova up to 6 weeks post second vaccination.	
Reason for exclusion	These subjects were excluded to ensure vaccinee and fetus safety. Most live attenuated vaccines are not recommended or contraindicated during pregnancy as theoretically, live attenuated virus vaccines administered to pregnant women might, be capable of crossing the placenta and infecting the foetus [119]. There are conflicting data in the literature regarding the association between wild type dengue infection during pregnancy and increased risks of both a more severe course of disease and adverse pregnancy outcome [120-122]. Pre-clinical data for TDV were not available when most of the studies started (including the pivotal Trial DEN-301). Moreover, it was unknown whether TDV was excreted in human milk and data on excretion of wild type dengue via breastfeeding are limited.
Is it considered to be included as missing information?	Yes
Rationale	Not applicable. Safety profile of inadvertent use in pregnant or lactating women is included as missing information.

History of hypersensitivity or allergy to any of the vaccine components.	
Reason for exclusion	These subjects were excluded to ensure vaccinee safety.
Is it considered to be included as missing information?	No
Rationale	There was no evidence TDV was associated with an increased risk of serious anaphylactic shock or hypersensitivity events. However, subjects who are allergic to any vaccine component are at risk to develop anaphylactic reactions. Moreover, hypersensitivity to the active substances or to any of the excipients of the vaccine or to a previous dose of TDV are listed as contraindications for TDV in the Summary of product characteristics (SmPC) in Section 4.3 and Package Leaflet (PL) Section 2.

Receipt of any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to study entry or planned receipt of any vaccine within 28 days after study entry.	
Reason for exclusion	These subjects were excluded to avoid confounding the assessment of emerging immune response and safety profile of TDV. Based on general vaccination guidelines, intervals of 2 or 4 weeks between administration with inactivated or live vaccines, respectively, should be respected to avoid interactions with other vaccines.
Is it considered to be included as missing information?	Yes
Rationale	Not applicable. Safety and immunogenicity of concomitant administration with other vaccines is included as missing information, except yellow fever (YF), Hepatitis A virus (HAV) and Human papillomavirus (HPV) vaccines for which data from the development program are included in the marketing authorisation application.

Known or suspected impairment/alteration of immune function:	
– Chronic use of oral steroids or receipt of parenteral steroids or immunostimulants within 60 days before study entry, – Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 6 months, – HIV or HIV-related disease, – Genetic immunodeficiency	
Reason for exclusion	These subjects were excluded to ensure vaccinee safety and to not confound assessment of TDV immunogenicity and safety profile. Immunocompromised participants may have a higher risk of occurrence of dengue disease and of impaired immune response to the vaccine limiting the availability to demonstrate efficacy and safety of TDV during clinical trials.
Is it considered to be included as missing information?	Yes
Rationale	Not applicable. Safety and immunogenicity in immunocompromised individuals is included as missing information.

Receipt of blood products and/or immunoglobulins within the 6 months before study entry.	
Reason for exclusion	These subjects were excluded to avoid confounding the assessment of TDV immunogenicity in the study population as live-attenuated viruses contained in TDV may be neutralized by circulating antibodies in immunoglobulin therapy or blood products (such as blood or plasma).
Is it considered to be included as missing information?	No
Rationale	As per general vaccination guidelines, for patients receiving treatment with immunoglobulins or blood products containing immunoglobulins, it is recommended to defer the administration of live attenuated viral vaccines for at least 6 weeks and preferably for 3 months, following the end of the treatment before administering TDV, in order to avoid neutralization of the attenuated viruses contained in the vaccine. This information is mentioned in the SmPC Section 4.5 and PL Section 2 .

Febrile illness (temperature $\geq 38^{\circ}\text{C}$) or moderate or severe acute illness or infection at the time of randomization.	
Reason for exclusion	These subjects were excluded to ensure vaccinee safety and not confound the assessment of emerging immunogenicity and safety profile of TDV.
Is it considered to be included as missing information?	No
Rationale	As per established vaccination guidelines, administration of vaccines must be postponed in individuals who present febrile illness or moderate to severe acute disease.

SIV.2. Limitations to detect adverse reactions in clinical trial development programmes

Overall, data from 28,187 subjects, from 19 ongoing or completed trials, as of the overall safety data cut-off date, contributed to the safety evaluation of TDV (20,071 subjects from the pivotal Trial [DEN-301](#)). These trials covered an age range from 1.5 to 60 years and safety surveillance up to 54 months after the second dose of trial vaccine in Trial DEN-301 and up to 67 months after second dose of the primary 2-dose vaccination for participants receiving booster doses (TDV or placebo) in Part 4 of Trial DEN-301. Overall, 20,288 subjects are estimated to have received 45,159 doses of TDV (any formulation). Of the total, 6,106 participants received a booster dose of TDV.

The clinical development program is likely to provide data concerning serious rare adverse events due to size of population and address long-term risks as the follow-up period covers up to 4.5 years after the last TDV injection. Available follow-up data are 67 months after second TDV injection for DEN-301 and 4 years after first TDV injection for [DEN-204](#).

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women Breastfeeding women	This population was not included in the clinical development program and is considered as missing information (see SIV.1). Cumulatively, 34 pregnancies have been identified as exposed to TDV in clinical trials as of the DLP of 18 February 2025. Cumulatively, 82 cases (1 serious, 81 non-serious) of exposure during breastfeeding and 57 cases (6 serious, 51 non-serious) of exposure during pregnancy have been reported post-marketing (refer to CTD M5.3.5.3. Pregnancy analysis Table 3). These limited data are insufficient to conclude on the absence of potential effects of TDV on pregnancy, embryo-foetal development, parturition, and post-natal development.
Immunocompromised patients	This population was not included in the clinical development program and is considered as missing information (see SIV.1).
Patients with hepatic, renal or cardiovascular impairment	These conditions were not evaluated during the clinical development program.
Population with relevant different ethnic origin	Populations with different ethnic origin were included in the clinical trials (see Table SIII.3). Most of them were Asian, American Indian or Alaska native (67%). Data for other ethnic origins are limited, however no clinically significant differences were observed between the different ethnicities.
Subpopulations carrying relevant genetic polymorphisms	This condition was not evaluated during the clinical development program.

Children (<4 years)	The overall clinical development of TDV comprised a population aged 1.5 to 60 years for the initial vaccination regimen (i.e. 2 doses, at Month 0 and Month 3) and up to 63 years for the booster dose; TDV is indicated for the prevention of dengue disease in individuals from 4 years of age. Number of subjects aged <4 years in the clinical development program: - 401 subjects from phase 2 Trial DEN-204 - 54 subjects from phase 2 Trial DEN-203 The evaluation of the safety profile of TDV in children aged <4 years is limited to 401 subjects aged 2 to 3 years from phase 2 Trial DEN-204, comprising 354 subjects exposed to TDV and 47 subjects exposed to placebo only. The 401 children aged <4 years from Trial DEN-204 were followed up until 48 months after the first vaccine dose. All subjects in Trial DEN-204 were enrolled in dengue-endemic countries: The Philippines, Dominican Republic and Panama (Refer to CTD Module 2.7.4). The 54 subjects aged <4 years from Trial DEN-203, comprise 37 subjects exposed to HD TDV and 17 subjects exposed to placebo (none received the final TDV formulation) (Refer to CTD Module 2.7.4). For children aged <4 years (not part of the currently approved age indication), the evaluation of the long-term safety data of the 401 subjects from Trial DEN-204 up to 48 months after the first vaccine dose did not identify any important safety risks.
Elderly (>60 years)	This population was not included in the clinical development programme for the initial vaccination regimen. Six participants aged >60 years up to 63 years of age received a booster dose.

Part II: Module SV - Post-authorisation experience

SV.1. Post-authorisation exposure

SV.1.1. Method used to calculate exposure

For TDV, the exposure was estimated based on available sales data (number of vaccine doses distributed until 28 February 2025). The estimated number of individuals receiving a full vaccination schedule of 2 doses was calculated based on the number of vaccine doses distributed as described below:

Estimated number of individuals having received a full vaccination schedule of 2 doses = number of vaccine doses distributed/2.

SV.1.2. Exposure

TDV was first placed on the market on 06 February 2023. Based on the above methodology, the global cumulative post-marketing exposure to TDV since launch up to 28 February 2025 is estimated to be approximately 12,342,619 doses, corresponding to an estimated 6,171,310 individuals having received a full vaccination schedule.

The estimated post-marketing exposure for TDV is presented in the Table SV.1.2.

Table SV.1.2: Estimated Post-Marketing Exposure for TDV

Region	Cumulative doses distributed since International Birth Date (IBD) (19 August 2022 to 28 February 2025) ^(a)
Asia	1,338,752
Europe^(b) and Middle East	541,108
European Union	480,388
Latin America	10,462,759
Total	12,342,619

Note: IBD is 19 August 2022 (Indonesia).

(a) Exposure data included from 01 February 2023 to 28 February 2025 (no exposure data reported from 19 August 2022 to 31 January 2023).

(b) Includes EU member states, European Economic Area and United Kingdom.

SV.1.2.1 Post-approval use in special populations

Since the post-marketing exposure is estimated based on sales/shipment data, it is not currently possible to present the exposure by gender, age, dose, dosage form or other factors. In addition, the Company has not conducted any non-interventional studies (including registries) investigating post-approval use in special populations.

However, exposure data regarding children and adolescents is available for a national immunization program in Brazil, which started on 9 February 2024. The target population for this vaccination program were children and adolescents aged 10 to 14 years. A rough estimate of doses administered to target age groups can be determined based on doses distributed to the public market intended for use in public vaccination campaigns. Exposure in the Brazilian immunization program is estimated to be 6,819,101 doses cumulatively, corresponding to approximately 3,409,551 individuals having received a full vaccination schedule.

SV.1.2.2 Other Post-approval (Non-clinical Trial) Exposure

No discernible pattern of use, outside the terms in the reference product information could be identified.

The most frequently reported inadvertent use was product administration to patients of inappropriate age, i.e. ages outside the indicated age range.

A search of the global safety database (GSDB) up to the DLP of 18 February 2025 resulted in a cumulative exposure of 300 reported cases in which the product was administered to patients outside the indicated range. Most cases involve administration to patients above 60 years. While TDV is indicated without an upper age limit in most countries, the upper limit of the indicated age range is 60 years in Brazil and Colombia and 45 years in Indonesia. A minority of cases were reported for administration in children under 4 years.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no indication that TDV has potential to be a medicinal product of abuse.

TDV is indicated for the prevention of dengue disease in individuals from 4 years of age and there is no known illegal marketplace. In summary, it is highly unlikely that TDV will be misused for illegal purposes.

Potential for overdose

TDV is administered by a healthcare professional and using single-dose vials. Therefore, overdosing is not anticipated. No cases of overdose have been reported in clinical trials with TDV.

Potential for transmission of infectious agents

Transmission of the vaccine viruses to susceptible people or other organisms

A range of organisms may be exposed directly or indirectly to TDV. Vaccinated individuals are intentionally exposed. Clinical staff administering the vaccine or other staff handling the vaccine during transport may be unintentionally exposed through a spill or needle stick. During the course of the release, access to the dengue vaccine will be limited to pharmacy staff, medical practitioners and health care professionals. Therefore, there is very little potential for unintended exposure to TDV. Standard blood donation screening practices would prevent vaccine recipients from donating blood during their expected periods of viraemia. However, wild type dengue infections resulting from needle stick injuries during the care of febrile patients have been reported [123, 124]. In the worst case, a needle stick or other unintended exposure to TDV would be expected to result in the symptoms seen during intentional vaccination.

Waste management workers, insects, birds and animals may be unintentionally exposed through inadvertent disposal of unused vaccine to landfill. But due to the instability of dengue viruses and the vaccine in the environment, there is little risk of waste management workers, insects, birds and animals being unintentionally exposed to infectious vaccine waste through inadvertent disposal of unused vaccine.

Theoretically accidental exposure could also occur if a mosquito feeds on a vaccinated subject during a period of high TDV replication. TDV uptake by the mosquito and subsequent biting of another person could transmit TDV unintentionally. Takeda has conducted studies in mosquitoes to evaluate the potential of TDV to be transmitted by these vectors. Dengue virus transmission occurs through the bite of an infected mosquito vector. TDV monovalent vaccine strains were shown to have a reduced ability to replicate and disseminate in *Aedes aegypti* and *Aedes albopictus* mosquitoes [125].

Environmental escape of TDV by mosquito transmission could only occur if (i) a mosquito vector feeds on a vaccinee with a sufficient viraemia titer to infect the mosquito midgut, (ii) the virus is capable of replicating in the midgut epithelium, (iii) replicated virus is able to subsequently disseminate out of the midgut, and (iv) the disseminated virus can replicate in the mosquito salivary gland and release

sufficient virus in saliva for transmission. In the Phase 1 and 2 clinical trials, TDV (mostly TDV-2) replicated in only a portion of the subjects and, the vaccine viral RNA levels were 1 to 2 logs lower than the wild type dengue MID₅₀ for both *Aedes aegypti* and *Aedes albopictus* mosquitoes [126, 127]. With the very low mosquito infection, dissemination and transmission capacity of TDV in *Aedes aegypti* and *Aedes albopictus* and the low levels of TDV viraemia seen in vaccinees, it is highly unlikely that the vaccine viruses would be transmitted by mosquitoes through the natural infection route. In addition, TDV has an attenuated phenotype for replication in C6/36 *Aedes albopictus* mosquito cells. Although very unlikely given the above considerations, it is expected that TDV transmission from an infected mosquito's bite would at worst result in the mild symptoms seen during intentional vaccination.

The TDV viruses have been shown to be attenuated in humans, non-human primates and mice [128, 129]. In the worst case, unintended exposure to TDV is expected to result in the same response as intentional inoculation with the vaccine.

Shedding

Dengue viruses are transmitted in blood and are not known to spread to other people by shedding [10, 130]. Although dengue virus RNA and NS1 protein have been found in the urine and saliva in wild type infections of humans, live dengue viruses have not been isolated [130, 131]. In a study, dengue virus has not been detected in the semen in five patients with acute dengue virus infection [132]. Cases of likely sexual transmission and cases of presence of dengue virus in semen or vaginal secretions have been reported but are considered anecdotal [133-135]. There is limited data on the excretion of wild type dengue via breast milk. In a small study, DENV was detected in breast milk samples from 9 (75%) of 12 infected breastfeeding mothers [136].

Like other flaviviruses, dengue virus, has low environmental stability. Thus, if TDV would be shed into the environment, it would likely be unstable. In a single dose TDV nonclinical biodistribution and shedding study in AG129 mice (Study 5002340), there was no shedding of TDV RNA in feces and urine. These results suggest a low risk for TDV shedding to the environment or transmission from vaccinees by shedding.

Maternal-fetal transmission of the vaccine viruses

In studies of dengue in pregnancy, where maternal-fetal transmission of wild type dengue viruses has been demonstrated by the detection of dengue specific IgM in cord blood, rates of transmission were low [137, 138] (vertical transmission 1.6% and 5.6% respectively). In addition, cases of dengue disease in neonates following transmission of the virus between an infected mother and the fetus in utero or as a result of transmission to her infant during labour and delivery, have also been reported rarely [137-141]. Intrauterine transmission of dengue has been associated with high maternal serum viraemia titers [141] and may be related to endothelial damage and increased vascular permeability caused by the wild type dengue virus infection [131]. TDV is attenuated and replication of the vaccine virus is limited relative to wild type dengue viruses.

Pregnant women were not included in the clinical development program (See [Part II: Module SIV - Populations not studied in clinical trials](#)) and therefore there is limited amount of data from the use of TDV in pregnant women. These data are not sufficient to conclude on the absence of potential effects of TDV on pregnancy, embryo-fetal development, parturition and post-natal development. A study in rabbits did not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Although, live attenuated virus vaccines given to pregnant women might be capable of crossing the placenta and infecting the fetus, no evidence of increased adverse pregnancy outcomes has been identified from inadvertent immunisation of women in early pregnancy with the first marketed dengue vaccine at this time [142].

Potential for infections caused by residuals of biological material used in the manufacturing process as well as contaminations introduced by the manufacturing process

The four TDV viruses are purified. The purified active substance is stabilized in a solution containing various salts, Poloxamer 407, Trehalose, and human serum albumin. Both TDV presentations, vial - vial presentation or vial - pre-filled syringe, are sterile. Therefore, no potential infectious contaminants from the manufacturing process are expected.

Reversion to virulence

Vaccine viraemia and potential reversions in the presence of replication-competent vaccine virus only were assessed in several Phase 1 and Phase 2 clinical trials conducted in endemic and non-endemic areas ([DEN-101](#), [DEN-102](#), [DEN-103](#), [DEN-104](#), and [DEN-203](#) Part 1). Furthermore, vaccine viraemia and potential reversions independent of the presence of replication-competent vaccine virus was determined in [DEN-205](#). The proportion of subjects with vaccine viraemia varied from one trial to another likely because of the different trial settings and the different earlier TDV formulations with different viral content. In the TDV group of Trial DEN-205, vaccine viraemia was observed in 30.9% of subjects and occurred mainly after the first dose and peaked 10 to 12 days after vaccination. In the vast majority of cases, vaccine viraemia occurred for vaccine strain TDV-2.

In total, 423/775 (54.6%) of subjects exposed to TDV had detectable vaccine strain RNA. Reversions were detected in 67 subjects; all affected only a single attenuation locus. This included 23 reversions detected in Trial DEN-205 for which the presence of replication competent material was not determined, and 44 reversions detected in Trials DEN-101, DEN-102, DEN-103, DEN-104, and DEN-203 Part 1. The majority of reversions (n = 65) were found in the 5'NCR locus, two affected the NS1 locus (a single partial reversion in subject from Trial DEN-104 and a single reversion in subject from HD TDV group of Trial DEN-205) and none were found for the NS3 locus.

Apart from a numerical increase and temporal association of mostly mild and transient solicited and unsolicited AEs, no major safety findings were identified for subjects with vaccine viraemia. Subjects with vaccine viraemia may develop systemic symptoms such as headache, arthralgia, or myalgia that can also occur in the absence of viraemia, illustrating the non-specific nature of such events. While rashes were rather infrequent (up to 10.2% in vaccine recipients), their occurrence showed a close temporal relationship with viraemia.

The AE profile in the 67 subjects with reversions was not indicative of an increased severity of symptoms. The 2 reversions observed in the NS1 locus (partial reversion in subject from Trial DEN-104, second reversion in subject from the HD TDV group of Trial DEN-205) did not result in increased virulence: the subject from Trial DEN-104 reported fatigue, rash, and headache (all non-serious and graded as mild) and no fever; the second subject from Trial DEN-205 did not report any AEs (refer to CTD [Module 2.7.4](#)).

In Trial DEN-210, vaccine viremia was observed. Most subjects with vaccine viremia had no loci with possible reversion and no subject had more than 1 locus with possible reversion. Possible reversions at 1 locus were detected in 2 flavivirus (FV) naive subjects (TDV-2: n = 2 at Day 9 and n = 1 at Day 12, and TDV-4: n = 1 at Days 9 and 12). One FV naive subject had possible reversions at 1 locus for both TDV-2 and TDV-4. No possible reversions were detected in baseline dengue seropositive subjects. All possible reversions were detected in the 5' noncoding region (NCR)-57 locus. No reversions were detected in the other two attenuation loci.

The results were consistent with previous observations. No important safety findings in subjects with viremia or reversions were identified. No subject with viremia developed clinically diagnosed dengue or required hospitalization due to viremia symptoms.

In the pivotal efficacy Trial [DEN-301](#), reversions were determined in subjects who reported a febrile illness starting within 30 days of vaccination and who had replication competent vaccine virus detected. Single reversions (all in the 5'NCR locus) were identified in 4 out of 15 subjects with replication-competent vaccine viraemia. All four subjects reported headache; two experienced in addition rash and vomiting. One of the subjects was hospitalized due to dehydration; however, there was no evidence of bleeding, low platelet counts or plasma leakage in any of the affected subjects. Overall, no important safety risk was identified.

In Trial DEN-301, vaccine viremia was not detected in any participant with a febrile illness within 30 days after the booster dose in Part 4.

The presence of two attenuation determinants is sufficient to maintain the attenuation phenotype of TDV. Thus, it is unlikely that reversion of only one of the three attenuation loci of TDV would yield more virulent viruses that persist for a long time and cause dengue disease [[143](#)].

Of note, reversion to virulence theoretically may occur by a mechanism other than mutation during replication: when two dengue viruses infect a single cell, it is theoretically possible for recombination to occur if the RNA polymerase switches between genomes during viral replication. Since all four of the

TDV viruses share the identical attenuating mutations, recombination between vaccine strains cannot generate more pathogenic viruses. However, recombination with wild type dengue viruses is theoretically possible in TDV recipients if that person is bitten by a mosquito transmitting wild type dengue viruses during the brief period when vaccine virus replication occurs after vaccination. Recombination between two DENV genomes has been observed, though at a lower frequency than with other RNA viruses such as poliovirus and human immunodeficiency virus. In these studies, there was no evidence of recombination leading to viruses with greater pathogenicity. The life cycle of DENV requires propagation in both humans and mosquitoes, which may restrict the virus' ability to mutate [144]. Thus, the genome tends to be relatively fixed [145-148]. As the attenuated parental virus DENV-2 PDK-53 does not exist in nature, there are no studies of natural recombination with wild type DENV-2 viruses available. However, recombination would require co-infection of the same cell with 2 DENVs. The attenuated phenotype DENV-2 PDK53 results in less replication, reducing the opportunities for co-infection and therefore of recombination. Even if recombination theoretically occurred, the resulting virus would likely be attenuated (Refer to CTD [Module 1.6.2](#)).

Potential for immunisation errors

Clinical trials:

During the clinical trial development of TDV, no systematic immunisation errors were found that would indicate misinterpretation of the product labelling/handling instructions. However, the ability to predict post authorisation immunisation errors from experience during the clinical phase is limited and an effect on the safety and/or immunogenicity of TDV cannot be excluded. In order to minimise immunisation errors in the post-marketing setting, the specific handling, storage and administration requirements are described in the SmPC [Section 6.4](#) Special precautions for storage and [Section 6.6](#) Special precautions for disposal and other handling and have been taken into account during packaging design.

The potential sources of immunisation errors with TDV are related to the following elements:

1. TDV must be stored at +2°C to +8°C and not frozen.

Drug product stability data indicate that the lyophilized drug product will remain within the potency specification for at least 18 months when stored at +2°C to +8°C, depending on the target starting potency titer used to manufacture a given lot (refer to SmPC [Section 6.3](#)).

After reconstitution with the solvent provided, in general, Qdenga should be used immediately. If not used immediately the reconstituted vaccine must be used within 2 hours (refer to SmPC [Section 6.3](#)).

Safety concerns relating to inappropriate storage are theoretical at this point in time.

The SmPC (Sections 6.3 and 6.4) includes the recommendations to store the vaccine.

2. The vaccine is a lyophilized product that needs to be reconstituted in the appropriate solvent prior to administration.

Potential errors include use of the wrong solvent, wrong volume of solvent, administration of solvent alone (without reconstituted vaccine), prolonged storage of reconstituted product before vaccination or not injecting all 0.5 mL of the reconstituted vaccine. All specific requirements are described in the instructions for reconstitution (refer to SmPC [Section 6.6](#)).

3. TDV is indicated for subcutaneous administration in the deltoid region as two doses, three months apart.

The SmPC [Section 4.2](#) includes the recommendations to carry out the administration correctly (Method of administration).

4. Syringes and needles.

TDV is provided as a:

- Vial/vial presentation: Vial containing lyophilized vaccine packed with vial containing solvent; no syringe/needles in the pack.
- Vial/pre-filled syringe presentation: Vial containing lyophilized vaccine packed with pre-filled syringe containing solvent; with or without 2 separate needles in the pack, but none attached to the syringe.

The SmPC Section 6.6 includes the recommendations to carry out the administration correctly.

5. Use of expired vaccine or solvent.

The vaccine should not be used after the expiry date which is stated on the carton.

6. Confusion with another licensed dengue vaccine (i.e. Dengvaxia®) in countries where both vaccines are licensed which may result in incomplete or wrong vaccination schedules.

There are no data available on interchangeability of the two vaccines and whether the immune response may be impacted. In addition, the separate labelling for each product provides instructions on correct usage.

Post-marketing:

As of the DLP, post-marketing data did not raise any new relevant safety concerns for TDV.

As recommended by the WHO, errors in immunisation is considered in the initial evaluation of all adverse event following immunisation (AEFI) [149]. Correct usage is monitored within routine pharmacovigilance activities and any changes in the safety profile of TDV related to immunisation errors is followed via periodic safety update reports/periodic benefit-risk evaluation report (PSURs/PBRERs).

Specific paediatric issues identified in paediatric investigation plans (PIP)

In the current PIP Opinion/EMA Decision for TDV (EMA Decision dated 5 December 2024), the following potential long-term safety/efficacy issues were identified as particular causes of concern in the paediatric population for consideration in the Risk Management Plan/Pharmacovigilance activities:

- Potential Antibody-dependent Disease Enhancement (ADE) in subjects not yet immune to all four serotypes.
- Possible interaction between the vaccine and other flavivirus vaccines.
- Any possible enhancement of severity of other flavivirus diseases.

Assessment of potential ADE in subjects not yet immune to all four serotypes:

The totality of data on virologically confirmed dengue (VCD), hospitalized VCD, and severe forms of dengue, along with the clinical characteristics of these cases, as assessed in Trials [DEN-301](#), [DEN-313](#), and [DEN-204](#), did not reveal an identified risk of increased disease severity or disease enhancement attributable to vaccination in the post-vaccination follow-up period. In baseline seronegative subjects, an increased risk of hospitalization due to dengue and/or clinically severe forms of dengue caused by DENV-3 and DENV-4 is considered an important potential safety risk. This potential risk is under continued monitoring and safety evaluation, based on the ongoing long-term follow-up in Trial DEN-301 (Refer to CTD [Module 2.5](#) and [Module 2.7.4](#)).

Assessment of possible interaction between the vaccine and other flavivirus vaccines:

Co-administration of TDV with yellow fever (YF) and Hepatitis A virus (HAV) vaccines has been evaluated in two phase 3 trials, [DEN-305](#) and [DEN-314](#). In both trials, the co-administration of TDV with YF or HAV vaccines was generally well tolerated and had no negative effect on the safety and reactogenicity of either vaccine. The trials revealed no identified or potential safety risks in case of co-administration. YF vaccine immunogenicity was not affected when administered concomitantly with TDV. However, dengue antibody responses were decreased to some extent following concomitant administration of TDV with the YF vaccine compared with separately administered vaccines, with non-inferiority shown for DENV-2, DENV-3, and DENV-4, but not for DENV-1. The clinical significance of this finding is unknown. Co-administration of the HAV vaccine with TDV has no negative impact on the immune response to either vaccine. The effect of co-administration of TDV with other vaccines currently remains unknown. (Refer to CTD [Module 2.5](#)).

Assessment of any possible enhancement of severity of other flavivirus diseases:

Overall, the data from the TDV clinical development program do not suggest an increased risk for a possible enhancement in severity of non-dengue flavivirus infections following TDV vaccination.

Part II: Module SVII - Identified and potential risks

SVII.1. Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated): upper respiratory tract infection, nasopharyngitis, pharyngotonsillitis, bronchitis, rhinitis, decreased appetite, irritability, headache, somnolence, dizziness, diarrhoea, nausea, abdominal pain, vomiting, rash, pruritus, urticaria, angioedema, myalgia, arthralgia, injection site pain, injection site erythema, malaise, asthenia, fever, injection site swelling, injection site bruising, injection site pruritus, influenza like illness, injection site haemorrhage, fatigue and injection site discolouration.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated: not applicable

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised): not applicable

Known risks that do not impact the risk-benefit profile: not applicable

Other reasons for considering the risks not important: not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks	Risk-benefit impact
No important risk identified	Not applicable

Important Potential Risks	Risk-benefit impact
Dengue disease due to waning protection against dengue over time	Vaccines are not anticipated to be 100% efficacious. In addition, most vaccines are not anticipated to provide lifelong immunity. Vaccine effectiveness may wane with increasing time since vaccination. Waning immunity may lead to a risk for wild type dengue infection unless there is pre-existing immunity for the serotype/prior natural infection.
Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus	For TDV, the data assessed in clinical Trials DEN-301, DEN-313 and DEN-204, the totality of clinical data did not reveal an identified risk of increased disease severity or disease enhancement attributable to vaccination in the post-vaccination follow-up period. An exploratory subgroup analysis of Trial DEN-301, in baseline dengue seronegative subjects suggests a potential risk of hospitalization due to dengue caused by DENV-3 and/or clinically severe forms of dengue. The evaluation of the VE against VCD caused by DENV-4 in baseline seronegative subjects was limited by the overall small number cases reflective of the generally lowest prevalence for this dengue serotype worldwide.

Missing Information	Risk-benefit impact
Safety profile of inadvertent use in pregnant or lactating women	Theoretically the live attenuated virus in the vaccine could cross the placenta and result in viral infection of the foetus. Owing to this concern, most live attenuated vaccines are either contraindicated or not recommended during pregnancy. There is limited amount of data from the use of TDV in pregnant women. These data are not sufficient to conclude on the absence of potential effects of TDV on pregnancy, embryo-foetal development, parturition and post-natal development. It is not known whether TDV is excreted in human milk.
Safety and immunogenicity in immunocompromised individuals	Immunocompromised individuals may not respond adequately to vaccination and potentially the live attenuated virus in the vaccine may become pathogenic. Therefore, as per guidelines on vaccination, live-attenuated virus vaccines are not recommended for use in severely immunocompromised individuals. The safety of TDV in immunocompromised individuals is not known as they were excluded from the clinical development program.
Safety and immunogenicity of concomitant administration with other vaccines, other than HAV, YF and HPV vaccines	Potential interactions between concomitantly administered vaccines may compromise the effectiveness and/or safety.
Safety and reactogenicity of a booster dose	A protective immune response with TDV may decline over time. It is currently unknown whether a lack of protection could result in an increased severity of dengue. The effect of a booster dose is being investigated in 2 ongoing clinical trials (DEN-301 and DEN-303).

SVII.2. New safety concerns and reclassification with a submission of an updated RMP

Missing information previously classified as "Safety and reactogenicity of a booster dose" (RMP Version 3.0 and previous versions) is reclassified to "Safety of a booster dose" as the additional Category 3 pharmacovigilance activities milestones Trials DEN-301 Part 4 and DEN-303 are completed and results from these trials provide information to characterize reactogenicity of a TDV booster dose (DEN-301 Part 4, DEN-303). Details are provided in RMP Section [SVII.3](#).

The booster period of Trial DEN-301 Part 5 is currently ongoing. Long-term safety data from Trial DEN-301 Part 4 will be analysed with data from DEN-301 Part 5 to comprehensively assess the safety profile of a TDV booster dose. As such, the missing information category "Safety of a booster dose" is retained upon completion of the additional pharmacovigilance milestone: submission of the final DEN-301 CSR Report (Parts 1, 2, 3, 4 and 5).

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk: Dengue disease due to waning protection against dengue over time	
<u>Potential mechanisms:</u>	Waning protection against dengue over time may leave the vaccinee susceptible to wild type dengue infection, a potentially life-threatening illness. Waning protection also may render vaccinees at risk for ADE of infection.
<u>Evidence source(s) and strength of evidence:</u>	Efficacy analyses in pivotal Trial DEN-301 demonstrated the Vaccine Efficacy (VE) of TDV in the primary endpoint of preventing VCD fever caused by any dengue serotype from 30 days to 12 months post second vaccine dose, i.e., until end of Part 1 (VE: 80.2%; 95% CI: 73.3%, 85.3%) and also for the secondary endpoint period from 30 days to 18 months post second vaccine dose (VE: 73.3%; 95% CI: 66.5%, 78.8%). VE was also seen for hospitalizations due to VCD by all dengue serotypes combined. From 30 days to 18 months post second vaccine dose, the VE for VCD leading to hospitalization was 90.4% (95% CI: 82.6%, 94.7%). From first dose to 4.5 years after second dose, the VE in preventing VCD fever by any serotype was 62.5% (95% CI: 56.0%, 65.8%) and hospitalization due to VCD fever caused by any serotype was 84.1% (95% CI: 77.8%, 88.6%). In an exploratory analysis at 54 months post second dose (end of Part 3), VE in preventing VCD was shown for all four serotypes in baseline dengue seropositive subjects. In baseline seronegative subjects, VE was shown for DENV-1 and DENV-2, but not suggested for DENV-3 and could not be shown robustly for DENV-4 due to lower incidence of cases. VE varied in exploratory analysis by study intervals: during the third year, although some decline in efficacy compared with Year 2 was observed, largely driven by non-hospitalized VCD cases, efficacy against VCD was demonstrated overall, as well as in both baseline seronegative and seropositive subjects. Efficacy against VCD leading to hospitalization remained robust with little change compared with Year 2. The data obtained in the last 18 months of follow-up following Year 3 showed continued long-term protection against overall VCD and a sustained high level of protection against hospitalized VCD regardless of baseline serostatus. Waning immunity resulting in a loss of protection over time is applicable to all vaccines. The maximum duration of protection with TDV is not known currently.
<u>Characterisation of the risk:</u>	Clinical trials data: In the Trial DEN-301, the exploratory year-by-year analysis of efficacy by serotype and serostatus, TDV efficacy against DENV-3 was seen in baseline seropositive subjects in Year 1, Year 2 and Year 3, while in baseline seronegative subjects, the efficacy against DENV-3 was not suggested. There is not enough data to make an assessment against DENV-4 in baseline seronegative subjects. The relative risk of VCD (TDV <i>versus</i> placebo, irrespective of hospitalization) caused by DENV-3 in baseline seronegative subjects up to 54 months after the second vaccine dose was close to 1 (1.11 [95% CI: 0.62, 1.99]). The relative risk of VCD

	caused by DENV-3 in baseline seronegative subjects declined over time, with a relative risk point estimate of <1 during Year 3 (relative risk 0.91 [95% CI: 0.34, 2.45]) and Year 4 (relative risk 0 [95% CI: not estimable]); no VCD caused by DENV-3 occurred after Year 4 up to the end of Part 3. Over the years, a meaningful long-term protection was observed against VCD despite a pattern of some waning driven by outpatient cases. However, protection against hospitalized VCD was high and sustained. The data obtained in the last 18 months of follow-up up to Month 54 showed continued long-term protection against overall VCD and a sustained high level of protection against hospitalized VCD regardless of baseline serostatus. In year-by-year analysis until four years after the second dose, VE in preventing VCD was shown for all four serotypes in baseline dengue seropositive subjects. In baseline seronegative subjects, VE was shown for DENV-1 and DENV-2, but not suggested for DENV-3 and could not be shown for DENV-4 due to lower incidence of cases. The long-term persistence of neutralising antibodies was shown in Study DEN-301, with titers remaining well above the pre-vaccination levels for all four serotypes, up to 51 months after the first dose. In Part 4 of Trial DEN-301, the neutralising antibodies remained above baseline (i.e. pre-first TDV dose) prior to the booster dose for all four serotypes. Following the booster vaccination, the neutralising antibodies increased for each serotype at 1 month after the booster dose and subsequently declined 12 months after but remained above pre-booster levels (CTD Module 2.5 Addendum for DEN-301 Part 4 and DEN-303). In Part 4 of Trial DEN-301, the overall efficacy after TDV booster vaccination up to 13 months post-dose was similar to that of the first year following the primary vaccination (79.4% vs 80.9%). In baseline seropositive subjects, efficacy was seen for all serotypes. In baseline seronegative subjects, efficacy was seen for DENV-1, DENV-2, and DENV_4 serotypes. Efficacy against DENV-3 was suggested (VE estimate of 42.7% [95% CI: -307.5, 92.0]) but inconclusive. The relative risk (95% CI) of VCD (TDV vs placebo, irrespective of hospitalization) caused by DENV-3 in baseline seronegative subjects up to 13 months after the booster vaccine dose was 0.51 (0.07, 3.62). The relative risk (95% CI) of VCD caused by DENV-4 was 0.41 (0.11, 1.52) (CTD Module 2.7.4 Addendum for DEN-301 Part 4 and DEN-303). Protection against hospitalized VCD remained high and durable throughout the post booster phase regardless of baseline serostatus. In Trial DEN-303, antibody persistence was observed in the pre-booster phase for each serotype up to 33 months (subjects from parent Trial DEN-304) and 60 months (subjects from parent Trial DEN-315) after the second vaccination in the primary vaccination series. Following TDV booster vaccination at Month 33 (subjects from Trial DEN-304) and Month 60 (subjects from Trial DEN-315), neutralizing antibody titers for all serotypes, at 1 month after booster, went up above pre-booster levels and subsequently declined but remained above pre-booster levels at 6 months post booster vaccination. After placebo vaccination at Month 33 (subjects from Trial DEN-304) and Month 60 (subjects from Trial DEN-315), neutralizing antibodies generally declined over time but persisted at varying levels for each serotype for a further 6 months (i.e., until 39 months and 66 months, respectively, after the second vaccination in the parent trial) (CTD Module 2.7.3 Addendum for DEN-301 Part 4 and DEN-303).
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	Post-marketing data: A review of cases received up to 18 February 2025, did not suggest any pattern or trend indicative of waning protection over time. The majority of cases reported, had onset of events which occurred either <30 days from TDV vaccination (and not indicative of waning protection) or the latency was not reported.
<u>Risk factors and risk groups:</u>	In general, lack of response to vaccination can occur in subjects with immunodeficiency (leading to suboptimal or even absent immune response), elderly age and related senescence of immune responsiveness, interference due to wild type infectious agents, acute or chronic disease and suboptimal health and nutritional status, immunological interference (e.g., administration of immunoglobulins, or immunosuppressive medications). In addition, there may be failure to respond due to the normal expected variation in immune response across healthy individuals (i.e., a “low responder” or “non-responder”) [150]. A comprehensive subgroup analysis showed efficacy across the evaluated subgroups by age group, region, country and prior vaccination against YF or JE, with the varying magnitude of VE per subgroup to a large extent attributable to the serotype distribution in the respective subgroup. No risk factors have been identified for TDV vaccination failure. In general, vaccine effectiveness may wane with increasing time since vaccination. Depending on the vaccine, rates of decline may vary across antigens. A number of variables, including subject age, serostatus at vaccination, presence or absence of exposures to circulating wild type virus (natural boosting), possible evolution of the wild type virus away from the targets of vaccine antigens, as well as unknown factors, influence duration of vaccine protection.
Preventability:	The SmPC includes in Section 4.4 the following Special warning and Precaution for use: “A protective immune response with Qdenga may not be elicited in all vaccinees against all serotypes of dengue virus and may decline over time (see Section 5.1). It is currently unknown whether a lack of protection could result in an increased severity of dengue. It is recommended to continue personal protection measures against mosquito bites after vaccination. Individuals should seek medical care if they develop dengue symptoms or dengue warning signs. There are no data on the use of Qdenga in subjects above 60 years of age and limited data in patients with chronic medical conditions”. Information is also provided in PL Section 2.
<u>Impact on the risk-benefit balance of the product:</u>	The impact of waning protection against dengue over time on the risk-benefit balance is expected to be minimal.
<u>Public health impact:</u>	This potential risk is not expected to have a serious impact on public health.

Important Potential Risk: Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus

Potential mechanisms:

The 2009 WHO criteria classify dengue infection according to levels of severity: dengue without warning signs, dengue with warning signs and severe dengue. Severe dengue is defined by one or more of the following criteria: severe plasma leakage that may lead to shock and/or fluid accumulation with or without respiratory distress and/or severe bleeding and/or severe organ impairment [109]. The most severe forms of dengue infection, dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) [67], are life threatening. Primary infection with any of the 4 dengue serotypes is thought to result in life-long protection from re-infection by the same serotype but does not protect against a secondary infection by 1 of the 3 other dengue serotype and may lead to an increased risk of severe disease over the course of secondary infection (DHF/DSS) [151].

In wild type dengue, severe disease is mainly observed after secondary infections, typically with a different serotype.

There are 4 distinct, but closely related, serotypes of the virus that cause dengue. Following a primary infection with one dengue virus (DENV) serotype, protection against the infecting serotype (homotypic protection) is considered long-lasting. Temporary cross-protection is induced to the other serotypes (heterotypic protection), lasting 2 years on average. Following waning of cross-neutralizing antibodies, the host-immune response may increase the severity of subsequent DENV infections with different serotypes. Following recovery from a second infection, broadly cross-neutralizing antibodies are induced (multitypic protection), such that severe disease with tertiary and quaternary infections is considered rare [152].

The mechanism for more severe disease associated with a second infection is not well understood although ADE [153], cytokine storm [154, 155] or cross-reactive T cells are hypothesized [156].

The mechanism for a higher risk of severe and hospitalized dengue in seronegative subjects after Dengvaxia vaccination is currently not understood but has been compared to the phenomenon of secondary dengue infection in the wild type situation [157]. Younger children may be more susceptible to this phenomenon as this group includes a high proportion of subjects who are dengue seronegative.

The recombinant construct of TDV is different from the licensed dengue vaccine Dengvaxia in that the four vaccine viruses use the replicative genetic backbone of a dengue virus (DENV-2; PDK 53) instead of the YF vaccine virus 17D. These differences result in an immunogenicity profile that is unique to TDV. TDV is expected to elicit CD8⁺ T-Cell response directed at the structural and non-structural proteins of dengue virus rather than the structural proteins of the dengue virus and non-structural proteins of the YF virus. Generally, virus specific cytotoxic T-Cell responses are thought to be important for the rapid clearance of viral infections and cytotoxic T-Cell responses directed against dengue antigens have been associated with sub-clinical second dengue infections in children [158].

<u>Evidence source(s) and strength of evidence:</u>	Today, severe dengue in the absence of dengue vaccination affects most Asian and Latin American countries and has become a leading cause of hospitalization and death among children and adults in these regions [2]. Efficacy results by baseline dengue serostatus (determined for all subjects), demonstrated overall VE against VCD and VCD leading to hospitalization regardless of prior exposure to dengue. Efficacy against individual dengue serotypes varied. The totality of data on VCD, hospitalized VCD, and severe forms of dengue, along with the clinical characteristics of these cases, as assessed in Trials DEN-301, DEN-313, and DEN-204, did not reveal an identified risk of increased disease severity or disease enhancement attributable to vaccination in the post-vaccination period. Trial DEN-301: VCD and hospitalised VCD from baseline up to 54 months after the Second Vaccine Dose (Safety Set), irrespective of baseline serostatus and for all serotypes combined: • Relative risk of VCD (95% CI): 0.40 (0.36, 0.46) • Relative risk of hospitalised VCD (95% CI): 0.16 (0.12, 0.23) Trial DEN-301: Severe forms of dengue (Dengue Case Adjudication Committee [DCAC]-defined severe dengue and DHF) from baseline up to 54 months after the last vaccine dose (safety set), irrespective of baseline serostatus and for all serotypes combined: • Relative risk of DCAC-defined severe dengue (95% CI): 0.30 (0.07, 1.25) • Relative risk of DHF (95% CI): 0.30 (0.13, 0.68) Exploratory efficacy analyses at 54 months after the second vaccine dose did not suggest efficacy for VCD caused by serotype DENV-3 in baseline seronegative subjects (RR: 1.11 [95% CI: 0.62, 1.99]). An imbalance in hospitalized VCD caused by DENV-3 was noted in baseline seronegative subjects, with 11 cases in the TDV group (0.3%) compared with 3 cases in placebo group (0.2%), with a relative risk of 1.81 (95% CI: 0.51, 6.48). In the baseline seronegative subgroup, a total of 2 subjects with VCD were assessed as DCAC defined severe dengue (both in the TDV group; 0.05% of 3714 subjects). Both cases occurred early in the trial during Parts 1 and 2 (i.e., before 18 months post second dose). Five subjects experienced DHF as per programmed algorithm, WHO 1997 DHF criteria), 4 of 3714 subjects (0.11%) in the TDV group and 1 of 1832 subjects (0.05%) in the placebo group. Of note, 1 of these 4 DHF cases in the TDV group was also classified as DCAC-defined severe dengue. All of these cases in baseline seronegative subjects were caused by DENV-3. The assessment of whether TDV may be associated with an increased risk of severe forms of dengue in baseline seronegative subjects who experience VCD caused by serotype DENV-3 remained inconclusive; the data are limited by the small number of cases. In baseline seronegative subjects, an increased risk of hospitalization and/or severe forms of dengue caused by serotype DENV-3 following vaccination in baseline seronegative subjects is considered an important potential safety risk. The evaluation of VE against VCD caused by DENV-4 in baseline seronegative subjects up to 54 months after the second dose was limited by the overall small number cases (n = 15) reflective of the generally lowest prevalence for this dengue serotype worldwide. Additionally, most
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	of the DENV-4 cases occurred in the later part of the trial when data indicated waning efficacy against other serotypes, which also precluded a robust conclusion. For instance, the VE in Year 1 post second dose could not be ascertained for DENV-4 in baseline seronegative subjects because no cases were reported in that period. Importantly, none of the DENV-4 cases in the TDV group in baseline seronegative subjects required hospitalization or were a severe form of dengue, which suggested no change in the severity of presentation. Conservatively, risk of hospitalization and/or clinically severe forms of dengue caused by serotype DENV-4 is considered an important potential safety risk in individuals not previously infected by dengue virus.
<u>Characterisation of the risk:</u>	WHO estimated that in the absence of vaccination about 3.9 billion people, in more than 128 countries, are at risk of dengue infection, with approximately 390 million dengue infections occurring annually of which 96 million manifests clinically (with any severity of disease). About 500,000 persons require hospitalization due to warning signs or severe dengue, and about 20,000 deaths are estimated to occur due to severe dengue every year [159]. Patients with severe dengue require immediate emergency treatment to avert death and those with warning signs should be assessed and treated without delay. Clinical trials data: In Trial DEN-301, the incidence and relative risk of VCD overall and hospitalized VCD up to 54 months after the second vaccine dose (all 4 serotypes combined) were lower in the TDV group than in the placebo group. Overall, 442 VCD cases (0.7 cases per 100 person-years) were identified in the TDV group compared with 547 cases (1.9 cases per 100 person-years) in the placebo group. The incidence of severe forms of dengue (DCAC-defined severe dengue and DHF) in the TDV group was <0.1 cases per 100 person-years. Up to 54 months after the second dose, the incidences of hospitalised VCD caused by DENV-3 were low (3 cases in the placebo group and 12 cases in the TDV group; 2:1 randomization ratio to be considered) and fluctuated over time depending on local epidemiology and hospitalisation practices. There was no worsening over time in terms of potentially increased severity of cases caused by DENV-3 in the baseline seronegative subpopulation: two cases in TDV recipients that were assessed as severe by the independent adjudication committee occurred early in the trial during Parts 1 and 2 (i.e., before 18 months post second dose). No hospitalized or severe forms of dengue caused by DENV-4 occurred in the TDV group. The relative risk of VCD caused by DENV-3 in baseline seronegative subjects declined over time, with a relative risk point estimate of <1 during Year 3 (relative risk 0.91 [95% CI: 0.34, 2.45]) and Year 4 (relative risk 0 [95% CI: not estimable]); no VCD caused by DENV-3 occurred after Year 4 up to the end of Part 3. This is reflected in the declining trend of cumulative relative risks assessed at 12, 24, 36 months after second dose (refer to CTD Module 2.7.4); the data obtained in the last 18 months of follow-up up to Month 54 is consistent with this trend (refer to CTD Module 5.3.5.1: DEN-301 M54 Data Tables and Graphs). In Part 4 of Trial DEN-301, the incidence and relative risk of VCD overall and hospitalised VCD up to 13 months after the booster vaccine dose (all 4 serotypes combined) were lower in the TDV group than in the placebo group. Overall, 42 VCD cases (0.7 cases per 100 person-years) were identified in the TDV group compared with 100 cases (3.2 cases per

	100 person-years) in the placebo group. Following booster vaccination, severe cases of dengue (DCAC-defined severe dengue and DHF) only occurred in the placebo group: 1 case of severe VCD according to the DCAC criteria and 3 cases of DHF according to the WHO 1997 criteria (VE of 100.0% [95% CI not estimable] each) (CTD Module 2.5 Addendum for DEN-301 Part 4 and DEN-303). Up to 13 months after the booster dose, no cases of hospitalised VCD caused by DENV-3 in baseline seronegative were reported. Only 1 case of hospitalised VCD caused by DENV-4 was reported in baseline seronegative (in the TDV group). This case, however, did not meet DHF or DCAC-defined severe dengue criteria (CTD Module 2.7.4 Addendum for DEN-301 Part 4 and DEN-303). Up to 13 months after the booster dose, the relative risk (95% CI) of VCD was 0.21 (0.15, 0.30) and for hospitalized VCD was 0.06 (0.02, 0.21). The relative risk (95% CI) of VCD caused by DENV-3 in baseline seronegative subjects up to 13 months after the booster vaccine dose was 0.51 (0.07, 3.62). The relative risk (95% CI) of VCD caused by DENV-4 in baseline seronegative subjects was 0.41 (0.11, 1.52) (CTD Module 2.5 Addendum for DEN-301 Part 4 and DEN-303). In Trial DEN-303, febrile illness data was not collected as the trial was conducted in non-endemic areas. However, no SAEs of dengue fever were reported during the trial (i.e., no study participants acquired dengue fever during the trial). Post-marketing data: A review of post-marketing cases received up to 18 February 2025, did not reveal evidence of increased severity in dengue seronegative vaccine recipients. However, for most cases received from spontaneous sources neither the baseline serostatus nor the infecting serotype could be confirmed, limiting a meaningful assessment.
<u>Risk factors and risk groups:</u>	Risk factors for severe dengue in unvaccinated subjects are described in section Epidemiology of the indication(s) and target population(s) (see Part II Module SI) and include persons with a secondary dengue infection of a heterologous DENV serotype, co-morbidities, nutritional status, the two extremes of age, genetic composition, pregnancy, and the time interval since primary infection. The main risk factor found for severe dengue following vaccination with Dengvaxia was a seronegative baseline status [160]. The risk of severe dengue following vaccination of seronegative subjects seemed to be related to the speed of the waning immunity in combination with the local dengue epidemiology [161]. In the Trial DEN-301 for TDV, efficacy results by baseline dengue serostatus, which was determined for all subjects, demonstrate overall VE against VCD. The trial also showed high overall efficacy against DHF.
<u>Preventability:</u>	In Trial DEN-301, TDV was shown to be efficacious in prevention of symptomatic dengue manifesting as outpatient fever, febrile illness requiring hospitalisation or DHF in subjects 4 to 16 years of age. The SmPC includes in Section 4.4 the following Special warning and Precaution for use: "A protective immune response with Qdenga may not be elicited in all vaccinees against all serotypes of dengue virus and may decline over time (see SmPC Section 5.1). It is currently unknown whether a lack of protection could result in an increased severity of dengue. It is recommended to continue personal protection measures against mosquito

	bites after vaccination. Individuals should seek medical care if they develop dengue symptoms or dengue warning signs". Information is also provided in PL Section 2 .
<u>Impact on the risk-benefit balance of the product:</u>	In Trial DEN-301 , TDV was shown to be efficacious in prevention of symptomatic dengue manifestations as outpatient fever, febrile illness requiring hospitalisation or DHF in subjects 4 to 16 years of age. There was rapid onset of efficacy after the first dose, and efficacy was seen in varied epidemiological settings of Asia and Latin America in both dengue seropositive and seronegative subjects, while no additional risk of severe forms of dengue was identified. TDV has a positive benefit-risk balance in the indication proposed and TDV could play an important role as a component of a multimodal approach to reducing the global burden of dengue.
<u>Public health impact:</u>	This potential risk is not expected to have a serious impact on public health. The overall public health impact of severe dengue is provided in Part II Module SI .

SVII.3.2. Presentation of the missing information

Safety profile of inadvertent use in pregnant or lactating women	
<u>Evidence source:</u>	Population in need of further characterisation: A study in rabbits did not indicate direct or indirect harmful effects insufficient of TDV with respect to reproductive toxicity (Module 4.2.3.5.1, Study Report 20129939). TDV has not been studied in pregnant women because pregnancy was an exclusion criterion in all clinical trials. There are limited data on pregnancy outcomes following vaccine dose administration; these are based on TDV or placebo inadvertently administered to women who were pregnant or who became pregnant shortly after vaccination ("exposed pregnancies"). These data, however, are not sufficient to conclude on the absence of potential effects of TDV on pregnancy, embryo-fetal development, parturition, and postnatal development. There are conflicting data in the literature regarding the association between wild type dengue infection during pregnancy and increased risks of both a more severe course of disease and adverse pregnancy outcomes [120-122]. As with other live attenuated vaccines, women of childbearing potential should avoid pregnancy for at least 1 month following vaccination. Women who intend to become pregnant should be advised to delay vaccination. Clinical trials data (refer to CTD M5.3.5.3. Pregnancy analysis Table 3): Cumulatively, as of 18 February 2025, 34 pregnancies exposed to TDV were retrieved from clinical trials: 26 had normal outcomes (live birth), 4 spontaneous abortions, 3 elective terminations and 1 unknown/pending outcome. The majority of exposed pregnancies resulted in live birth. Among pregnancies exposed to TDV, 11.8% resulted in spontaneous abortions. These rates were well within background rates for spontaneous abortions as reported in the wider literature, ranging between 10.9% and 24% [162, 163].

	Post-marketing data: Cumulatively, as of 18 February 2025, 82 cases of exposure during breast-feeding and 57 cases of exposure during pregnancy have been recorded. There is limited amount of data from the use of TDV in pregnant women. These data are not sufficient to conclude on the absence of potential effects of TDV on pregnancy, embryo-fetal development, parturition and post-natal development. The review of the cases related to inadvertent use in pregnant or lactating women did not identify any new safety concerns. It is unknown whether TDV is excreted in human milk. There are limited data on the excretion of wild-type dengue via breast milk. In a small study, dengue virus was detected in breast milk samples from 9 (75%) of 12 infected breastfeeding mothers [136]. Qdenga is contraindicated in pregnant and breast-feeding women (see SmPC Section 4.3 Contraindications and PL Section 2). The SmPC Section 4.4 contains also Special warnings and precautions for use: "As with other live attenuated vaccines, women of childbearing potential should avoid pregnancy for at least one month following vaccination." Information is also provided in SmPC Section 4.6 and PL Section 2. In addition to the impact of maternal dengue infection, concerns have been raised on the effect of maternal infection on subsequent infections in the infant. Declining levels of maternal antibodies have been shown to sensitize infants born to dengue-immune mothers to severe disease during primary infection, through the process of antibody-dependent enhancement of infection [164, 165].
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Safety and immunogenicity in immunocompromised individuals	
<u>Evidence source:</u>	Population in need of further characterisation: Generally, live-attenuated virus vaccines are contraindicated or not recommended for use in severely immunocompromised individuals due to a potential risk of impaired immune response, uncontrolled replication of the attenuated vaccine virus or vaccine reversion to natural virulence resulting in uncontrolled wild type disease [166]. Published data on dengue virus infection and immunocompromised patients come from case reports or small case series [167-172] often with mixed patient populations (for example variability in underlying conditions or interventions, differing degrees of immunocompromised, different ethnic and geographical backgrounds). From the limited data available, overall clinical outcomes for dengue virus infection in immunocompromised patients appear to be similar to those for dengue virus infection in immunocompetent patients. For wild type DENV, there is a theoretical risk of prolonged dengue viraemia in profoundly immunocompromised patients, and it is not clear whether dengue virus could persist in certain organs after becoming undetectable in serum or plasma. Ng et al. [173] reported a case of persistent DENV infection in a lymphopenic renal transplant recipient who was therapeutically immunosuppressed to prevent organ rejection. Authors showed that low

	CD8+ T cell count contributes to the persistence of DENV – longer in podocytes and coincidence of rising CD8+ T cell count with viraemia clearance suggests that cytotoxic T cells are needed for sterilizing DENV infection. Their role in the clearance of acute human DENV infection has remained unclear although CD8+ T cell epitopes have been characterized in DENV patients [174] and animal models [156, 175, 176]. Delayed DENV clearance has been observed previously in a renal and bone marrow transplant patients, although the duration of viral persistence lasted only 19 and 80 days, respectively [177, 178]. The patient remained RNAemic and viruric despite consistently detectable levels of DENV-3 neutralizing antibodies. Moreover, the IgG subclass composition would also not prevent IgG antibodies from being secreted into the urine. These observations suggest that an effective DENV vaccine needs to stimulate both humoral and cellular response. There are no reliable data available from any immunocompromised patient group to assess duration of viral RNA detection in blood, semen or other compartments. It is possible that severe immunosuppression could be associated with more severe illness following flavivirus infections, but conclusive data are lacking. Immunocompromised international travellers are potentially at risk because the vaccine may not elicit a protective immune response and the risk of disease acquisition would be high [179]. Vaccination with TDV was not studied in subjects with primary or secondary immune deficiencies and is contraindicated in individuals with congenital or acquired immune deficiency, including immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids within 4 weeks prior to vaccination and in individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function (SmPC Section 4.3). Clinical trials data: Cumulatively, as of 18 February 2025, one serious adverse event in one individual immunosuppressed due to HIV infection (which was unreported at study entry) was reported. No safety concerns were identified. Post-marketing data: A review of cases identified up to 18 February 2025, involving use in immunocompromised individuals did not identify any new safety concerns.
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Safety and immunogenicity of concomitant administration with other vaccines, other than HAV, YF and HPV vaccines

<u>Evidence source:</u>	Population in need of further characterisation: Simultaneous or concomitant administration of vaccines is defined as administering more than one vaccine on the same clinic day, at different anatomic sites, and not combined in the same syringe [180]. Potential interactions between concomitantly administered vaccines may compromise the immunogenicity/effectiveness (e.g., vaccination failure from interference) and/or safety (e.g., increased rates or severity of adverse events).
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	Recent reviews on the simultaneous administration of the most widely used live and inactivated vaccines has produced seroconversion rates and rates for adverse reactions similar to those observed when the vaccines are administered separately [181-184]. TDV may be administered concomitantly with an HAV vaccine. Coadministration has only been studied in adults (SmPC Section 4.5). TDV may be administered concomitantly with a YF vaccine. In a clinical study involving approximately 300 adult subjects who received TDV concomitantly with YF 17D vaccine, there was no effect on YF seroprotection rates. Dengue antibody responses were decreased following concomitant administration of TDV and YF 17D vaccine. The clinical significance of this finding is unknown (SmPC Section 4.5). TDV may be administered concomitantly with an HPV vaccine. Coadministration has been studied in subjects aged 9 to 14 years (SmPC Section 4.5). Clinical trials data: Co-administration of TDV with YF and HAV vaccines was evaluated in two phase 3 trials conducted in non-endemic areas (DEN-305 and DEN-314 respectively), and co-administration of TDV with recombinant 9-valent human papillomavirus (9vHPV) vaccine was evaluated in a phase 3 trial conducted in dengue-endemic country (DEN-308). Post-marketing data: A review of cases identified up to 18 February 2025, involving co-administration with other vaccines or administration of co-suspect vaccines did not identify any new safety concerns. Co-administration data with other vaccines, other than YF, HAV and HPV, are missing.
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Safety of a booster dose	
<u>Evidence source:</u>	Population in need of further characterisation: In general, VE estimates varied over time, with trends of declining efficacy observed in Years 2 and 3, but later increasing in Year 4, reflecting variability in the VE estimate as evident from the associated 95% CIs. Currently, the need for a booster dose has not been established (SmPC Section 4.2). The reactogenicity of a booster dose was investigated in Part 4 of Trial DEN-301, with participants aged 6 to 17 years at the time of booster vaccination in dengue-endemic countries (Brazil, Colombia, Dominican Republic, Nicaragua, Panama, Philippines, Thailand and Sri Lanka). Trial DEN-303 was conducted with participants aged 13 to 63 years at the time of receiving a booster dose in non-endemic dengue regions (Mexico City and USA). Trial DEN-301 Part 4 Reactogenicity: In Part 4 of Trial DEN-301, 600 subjects received a placebo booster dose and were assessed for solicited AEs and 1200 subjects received a TDV booster dose and were assessed for solicited AEs. The overall incidence of subjects with solicited local AEs within 7 days after the booster vaccination

	was 16.6% in the placebo group and 26.3% in the TDV group. The most common solicited local AE within 7 days after the booster vaccination in each group was pain at the injection site (16.6% for placebo and 25.9% for TDV) (CTD Module 2.5 Addendum for DEN-301 Part 4 and DEN-303). The overall incidence of subjects with solicited local AEs was similar following the TDV booster vaccination (26.3%) compared to first (27.8%) and second (23.5%) TDV vaccination. The overall incidence of subjects with solicited systemic AEs within 14 days after the booster vaccination was 20.7% in the placebo group and 24.9% in the TDV group. Headache was the most frequently reported solicited systemic AE within 14 days after the booster vaccination (13.8% for placebo and 17.1% for TDV) (CTD Module 2.7.4 Addendum for DEN-301 Part 4 and DEN-303). The overall incidence of subjects with solicited systemic AEs was similar following the booster vaccination (25.7%) compared to first (33.1%) and second (23.7%) TDV vaccination. The majority of solicited local and systemic AEs were of mild to moderate intensity. No clinically important differences were observed based on baseline serostatus in the profile of solicited local or solicited systemic AEs after booster vaccination. Safety: The incidence of unsolicited AEs in the 28 days after the booster vaccination was 1.8% (placebo) and 1.9% (TDV). The most reported SOC was infections and infestations (1.3% [placebo] and 1.3% [TDV]) and no PTs were reported by >1% of subjects for either group. Most unsolicited AEs were mild in severity (CTD Module 2.7.4 Addendum for DEN-301 Part 4 and DEN-303). The incidence of SAEs was 4.2% for placebo and 2.7% for TDV (CTD Module 2.7.4 Addendum for DEN-301 Part 4 and DEN-303). None of the SAEs were considered related to the booster vaccination. No new important safety risks were identified in terms of solicited AEs, unsolicited AEs, or SAEs. Trial DEN-303 Reactogenicity: In Trial DEN-303, 118 subjects received a placebo booster dose and were assessed for solicited AEs and 115 subjects received a TDV booster dose and were assessed for solicited AEs (CTD Module 2.7.4 Addendum for DEN-301 Part 4 and DEN-303). The overall incidence of subjects with solicited local AEs within 7 days after the booster vaccination was 22.6% in the placebo group and 66.1% in the TDV group. Most of solicited AEs were of mild to moderate intensity and pain at the injection site (61.6% in the TDV group) was by far the most frequent solicited local AE (CTD Module 2.7.4 Addendum for DEN-301 Part 4 and DEN-303). More participants had solicited local AEs following the booster vaccination (66.1%) than after the first (DEN-304: 48.4%-51.0%, DEN-315: 56.2%) or second (DEN-304: 37.1%-42.1%, DEN-315: 52.2%) TDV vaccination in the parent trials. The overall incidence of subjects with solicited systemic AEs within 14 days after the booster vaccination was 45.2% (placebo) and 52.7% (TDV). Most of solicited AEs were of mild to moderate intensity and headache was the most frequently reported solicited systemic AE within 14 days after
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	the booster vaccination (33.0% [placebo] and 37.5% [TDV]) (CTD Module 2.7.4 Addendum for DEN-301 Part 4 and DEN-303). The overall incidence of subjects with solicited systemic AEs was higher following the TDV booster vaccination (52.7%) than after the first or second vaccinations in the parent trials: • DEN-304: booster vaccination (43.7%), first vaccination (up to 43.4%) and second vaccination (up to 29.2%) (CTD Module 2.7.4 Addendum for DEN-301 Part 4 and DEN-303). Of note, Trial DEN-304 investigated lot-to-lot consistency of 3 lots of TDV. • DEN-315: booster vaccination (68.3%), first vaccination (66.6%), and second vaccination (49.3%) (CTD Module 2.7.4 Addendum for DEN-301 Part 4 and DEN-303) Safety: Unsolicited AEs in the 28 days after the booster vaccination were reported by 6.8% (placebo) and 6.1% (TDV) of subjects and MAAEs were reported by 16.9% and 11.3% of subjects, respectively (CTD Module 2.7.4 Addendum for DEN-301 Part 4 and DEN-303). There were no SAEs following the TDV booster, and no deaths in the booster phase of the trial. No new important safety risks were identified in the long-term follow-up of Trial DEN-303. The booster period of Trial DEN-301 Part 5 is currently ongoing. Long-term safety data from DEN-301 Part 4 will be analysed with data from DEN-301 Part 5 to comprehensively assess the safety profile of a booster dose. With the results of Trials DEN-301 Part 4 and DEN-303, the reactogenicity of a booster dose is characterized and the missing information "Safety and reactogenicity of a booster dose" is reclassified to "Safety of a booster dose". No new safety concerns have been identified in these trials.
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Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Dengue disease due to waning protection against dengue over time. Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus.
Missing information	Safety profile of inadvertent use in pregnant or lactating women. Safety and immunogenicity in immunocompromised individuals. Safety and immunogenicity of concomitant administration with other vaccines, other than HAV, YF and HPV vaccines. Safety of a booster dose.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are in place for several safety concerns as described below.

Other forms of routine pharmacovigilance activities for the following safety concerns:

Cumulative reviews will be conducted for the following safety concerns: Hospitalized including severe forms of dengue, Safety in pregnant and lactating women, Safety and efficacy in immunocompromised individuals and, Safety and immunogenicity of concomitant administration with other vaccines.

The objectives of these activities are to closely monitor the safety concerns mentioned above. These analyses will be done every year.

Any spontaneous reports in the post-marketing setting of inadvertent exposure during pregnancy or lactation will be followed as required to ensure adequate and timely collection of case information, collation, follow-up, assessment and reporting in accordance with regulations. In addition, information on inadvertent exposure during pregnancy or lactation are provided in PBRERs/PSURs.

III.2. Additional pharmacovigilance activities

Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (Part 4 and 5)
<u>Study short name and title:</u> DEN-301 - Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial to Investigate the Efficacy, Safety and Immunogenicity of TDV Administered Subcutaneously in Healthy Children Aged 4 - 16 Years Old. Part 4 and 5 assess VE of a booster dose of TDV against symptomatic dengue illness due to any serotype and will provide data on the effect of a booster dose on VE after a 2-dose vaccination regimen with TDV (2 single doses 3 months apart).
<u>Rationale and study objectives:</u> The WHO recommends a long-term follow-up to evaluate safety of dengue vaccines for 3 to 5 years. The total follow-up period including Parts 1, 2 and 3 of this study lasted 4 to 4.5 years after the second dose. Part 3 fulfils the WHO recommendation of long-term follow-up to evaluate safety. The booster phase of this phase III trial is comprised of 2 parts (Parts 4 and 5). Part 4 includes modified active surveillance post-booster vaccination and lasts a minimum of 13 months for each subject. Part 5 includes modified active surveillance following the completion of Part 4 and lasts 1 year for each subject. <u>Secondary safety objectives include:</u> • To describe the safety of TDV. <u>Exploratory objectives include:</u> Parts 1, 2, and 3

Efficacy:

- To describe the efficacy of TDV in preventing virologically confirmed dengue fever between first and second vaccinations.
- To describe the efficacy of TDV in preventing virologically confirmed dengue fever from first vaccination until end of Part 2.
- To describe virologically confirmed and hospitalized dengue fever identified during Part 3.
- To describe virologically confirmed dengue fever identified during Part 3.
- For the correlate of protection, a threshold antibody titer value may be evaluated to predict VE using descriptive methodology.
- To describe the profiles of IgG, IgM, and NS1 antigen during episodes of febrile illness.

Booster phase (Parts 4 and 5)

Efficacy:

- To assess the efficacy of a TDV booster dose in preventing symptomatic dengue fever of any severity induced by any dengue serotype.
- To assess the efficacy of a TDV booster dose in preventing symptomatic dengue fever of any severity by dengue exposure status at baseline.
- To assess the efficacy of a TDV booster dose in preventing hospitalization due to virologically confirmed dengue fever induced by any dengue serotype.
- To assess the efficacy of a TDV booster dose in preventing severe dengue induced by any dengue serotype.

Safety:

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

Booster immunogenicity:

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

Study design:

This is a phase 3, double-blind, randomized, placebo-controlled trial with 2 parallel groups. 20,099 participants were enrolled and randomly assigned 2:1 to receive two doses of TAK-003 or two doses of placebo. The trial includes 3 time periods (Parts 1, 2 and 3) for surveillance of febrile illness with potential dengue aetiology. The trial includes 2 additional time periods (Parts 4 and 5) for surveillance of febrile illness with potential dengue aetiology for subjects participating in the booster phase of the trial.

Part 1 constitutes the primary analysis period, including primary efficacy analysis.

Part 2 constitutes a period of additional active surveillance for secondary efficacy analyses.

Part 3 constitutes modified active surveillance for the assessment of long-term safety. Part 3 is a modified active surveillance for the assessment of safety in all subjects following the completion of Part 2 and lasting 2.5 to 3 years for each subject. The modified surveillance during Part 3 will maintain at least weekly contacts through Part 3 of the trial, but the intensity of investigation will be modified based on the need for hospitalization. Surveillance will identify febrile illness of any severity that could potentially be due to dengue. All virologically confirmed hospitalized dengue cases are adjudicated to identify cases of severe dengue.

Part 4 and 5 constitute a period of modified active surveillance for exploratory efficacy, immunogenicity, and safety analyses post-booster vaccination.

Part 4 is a modified active surveillance post-booster vaccination and lasting minimum 13 months for each subject. Part 5 is a modified active surveillance following the completion of Part 4 and lasting 1 year for each subject.
<u>Study population:</u> Healthy subjects aged 4 to 16 years inclusive (Part 1 to 3) and aged 4 to 11 (Part 4 to 5) years, at the time of randomization, living in dengue-endemic countries.
<u>Milestones:</u> Interim Reports: End of Part 4 CSR (completed): Submission June 2025 Final Report: Final CSR Parts 1, 2, 3, 4 and 5: Q3 2026

III.3. Summary table of additional pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (Part 4 and 5) Study status: ongoing	To evaluate the efficacy, immunogenicity and safety of a TDV booster dose	Dengue disease due to waning protection against dengue over time	Interim report: End Part 4 CSR	June 2025 (completed)
		Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus Safety and reactogenicity of a booster dose	Final Report (Final CSR Parts 1, 2, 3, 4 and 5)	Q3 2026

Part IV: Plans for post-authorisation efficacy studies

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None	Not applicable	Not applicable	Not applicable	Not applicable
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None	Not applicable	Not applicable	Not applicable	Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Dengue disease due to waning protection against dengue over time	Routine risk communication: SmPC Section 4.4 Special Warnings and Precautions for Use PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Not applicable
Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus	Routine risk communication: SmPC Section 4.4 Special Warnings and Precautions for Use PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Not applicable
Safety profile of inadvertent use in pregnant or lactating women	Routine risk communication: SmPC Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use and Section 4.6 Fertility, pregnancy and lactation PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Not applicable

Safety and immunogenicity in immunocompromised individuals	Routine risk communication: SmPC Section 4.3 Contraindications, Section 4.5 Interactions with Medicinal Products and other forms of interactions PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Not applicable
Safety and immunogenicity of concomitant administration with other vaccines, other than HAV, YF and HPV vaccines	Routine risk communication: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Not applicable
Safety of a booster dose	Routine risk communication: SmPC Section 4.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Not applicable

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in [Part V.1.](#) are sufficient to manage the safety concerns of the vaccine.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Dengue disease due to waning protection against dengue over time	Routine risk minimisation measures: SmPC Section 4.4 PL Section 2 No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Cumulative review Additional pharmacovigilance activities: Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose)
Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus	Routine risk minimisation measures: SmPC Section 4.4 PL Section 2 No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Cumulative review Additional pharmacovigilance activities: Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose)
Safety profile of inadvertent use in pregnant or lactating women	Routine risk minimisation measures: SmPC Section 4.3 , Section 4.4 and Section 4.6 PL Section 2 No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Cumulative review No additional pharmacovigilance activities
Safety and immunogenicity in immunocompromised individuals	Routine risk minimisation measures: SmPC Section 4.3 and Section 4.5 PL Section 2 No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Cumulative review No additional pharmacovigilance activities
Safety and immunogenicity of concomitant administration with other vaccines, other	Routine risk minimisation measures: SmPC Section 4.5 PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Cumulative review

Safety concern	Risk minimisation measures	Pharmacovigilance activities
than HAV, YF and HPV vaccines	No additional risk minimisation measures	No additional pharmacovigilance activities
Safety of a booster dose	Routine risk minimisation measures: SmPC Section 4.2 No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose)

Part VI: Summary of the risk management plan - Article 58 Application

Summary of risk management plan for Dengue Tetravalent Vaccine (Live, Attenuated) Takeda (Dengue tetravalent vaccine (live, attenuated)) – Article 58 Application

This is a summary of the risk management plan (RMP) for Dengue Tetravalent Vaccine (Live, Attenuated) Takeda. The RMP details important risks of Dengue Tetravalent Vaccine (Live, Attenuated) Takeda, how these risks can be minimised, and how more information will be obtained about Dengue Tetravalent Vaccine (Live, Attenuated) Takeda risks and uncertainties (missing information).

Dengue Tetravalent Vaccine (Live, Attenuated) Takeda summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Dengue Tetravalent Vaccine (Live, Attenuated) Takeda should be used.

This summary of the RMP for Dengue Tetravalent Vaccine (Live, Attenuated) Takeda should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Dengue Tetravalent Vaccine (Live, Attenuated) Takeda RMP.

I. The medicine and what it is used for

Dengue tetravalent vaccine (Live, Attenuated) is authorised for the prevention of dengue disease caused in individuals from 4 years of age (see SmPC for the full indication). It contains Dengue virus serotype 1 (live, attenuated), Dengue virus serotype 2 (live, attenuated), Dengue virus serotype 3 (live, attenuated) and Dengue virus serotype 4 (live, attenuated) as the active substances and it is given by subcutaneous injection.

Further information about the evaluation of Dengue Tetravalent Vaccine (Live, Attenuated) Takeda benefits can be found in Dengue Tetravalent Vaccine (Live, Attenuated) EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

[\[ENTER LINK TO THE EPAR SUMMARY LANDING PAGE\]](#).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Dengue Tetravalent Vaccine (Live, Attenuated) Takeda, together with measures to minimise such risks and the proposed studies for learning more about Dengue Tetravalent Vaccine (Live, Attenuated) Takeda risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Dengue Tetravalent Vaccine (Live, Attenuated) Takeda is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Dengue Tetravalent Vaccine (Live, Attenuated) Takeda are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Dengue Tetravalent Vaccine (Live, Attenuated) Takeda. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Dengue disease due to waning protection against dengue over time. Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus.
Missing information	Safety profile of inadvertent use in pregnant or lactating women. Safety and immunogenicity in immunocompromised individuals. Safety and immunogenicity of concomitant administration with other vaccines, other than HAV, YF and HPV vaccines. Safety of a booster dose.

II.B Summary of important risks

Important potential risk: Dengue disease due to waning protection against dengue over time	
Evidence for linking the risk to the medicine	In a year-by-year analysis until 4.5 years after the second dose in Trial DEN-301, VE in preventing VCD was shown for all four serotypes in baseline dengue seropositive subjects. In baseline seronegative subjects, VE was shown for DENV-1 and DENV-2, but not suggested for DENV-3 and could not be shown robustly for DENV-4 due to lower incidence of cases. During the third year of Trial DEN-301, although some decline in efficacy compared with Year 2 was observed, largely driven by non-hospitalized VCD cases, efficacy against VCD was demonstrated overall, as well as in both baseline seronegative and seropositive subjects. Efficacy against VCD leading to hospitalization remained robust with little change compared with Year 2. The data obtained in the last 18 months of follow-up up to Month 54 showed continued long-term protection against overall VCD and a sustained high level of protection against hospitalized VCD regardless of baseline serostatus. Waning immunity resulting in a loss of protection over time is applicable to all vaccines. The maximum duration of protection with TDV is not known currently.

Risk factors and risk groups	In general, lack of response to vaccination can occur due to immunodeficiency, elderly age, interference due to wild type infectious agents, acute or chronic disease and suboptimal health, as well as nutritional status, immunological interference. In addition, there may be failure to respond due to the normal expected variation in immune response across healthy individuals (i.e., a "low responder" or "non-responder"). Additionally, vaccine effectiveness may wane with increasing time since vaccination. Depending on the vaccine, rates of decline of vaccine effectiveness may vary across antigens. A number of variables influence duration of vaccine protection, including age, serostatus at vaccination, presence or absence of exposures to circulating wild type virus (natural boosting), possible evolution of the wild type virus, as well as unknown factors. No risk factors have been identified for TDV vaccination failure.
Risk minimisation measures	Routine risk minimisation measures: - SmPC Section 4.4 - PL Section 2 No additional risk minimisation measures
Additional pharmacovigilance activities	Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus	
Evidence for linking the risk to the medicine	Efficacy results by baseline dengue serostatus (determined for all subjects), demonstrated overall VE against VCD and VCD leading to hospitalization regardless of prior exposure to dengue. Efficacy against individual dengue serotypes varied. The totality of data on VCD, hospitalized VCD, and severe forms of dengue, along with the clinical characteristics of these cases, as assessed in Trials DEN-301, DEN-313, and DEN-204, did not reveal an identified risk of increased disease severity or disease enhancement attributable to vaccination in the post-vaccination period. Exploratory efficacy analyses at 54 months after the second vaccine dose did not suggest efficacy for VCD caused by serotype DENV-3 in baseline seronegative subjects (RR: 1.11 [95% CI: 0.62, 1.99]). For hospitalized VCD caused by DENV-3 there were 11 cases in the TDV group (0.3%) compared with 3 cases in placebo group (0.2%), with a relative risk of 1.81 (95% CI: 0.51, 6.48). In the baseline seronegative subgroup, a total of 2 subjects with VCD were assessed as severe dengue as defined by the Adjudication Committee (both in the TDV group; 0.05% of 3714 subjects). Both cases occurred early in the trial during Parts 1 and 2 (i.e., before 18 months post second dose). Five subjects experienced DHF as per programmed algorithm, WHO 1997 DHF criteria), 4 of 3714 subjects (0.11%) in the TDV group and 1 of 1832 subjects (0.05%) in the placebo group. Of note, 1 of these 4 DHF cases in the TDV group was

	also classified as DCAC-defined severe dengue. All of these cases in baseline seronegative subjects were caused by DENV-3. The assessment of whether TDV may be associated with an increased risk of severe forms of dengue in baseline seronegative subjects who experience VCD caused by serotype DENV-3 remained inconclusive; the data are limited by the small number of cases. In baseline seronegative subjects, an increased risk of hospitalization and/or clinically severe forms of dengue caused by serotype DENV-3 following vaccination in subjects not previously infected by dengue virus is considered an important potential safety risk. Conservatively, due to limited data for DENV-4, risk of hospitalization due to dengue and/or clinically severe forms of dengue caused by serotype DENV-4 in baseline seronegative subjects is considered an important potential safety risk, although up to the 54 months after the second vaccine dose no hospitalisations caused by DENV-4 occurred in TDV recipients.
Risk factors and risk groups	No risk factors for severe dengue with TDV have been identified.
Risk minimisation measures	Routine risk minimisation measures: – SmPC Section 4.4 – PL Section 2 No additional risk minimisation measures
Additional pharmacovigilance activities	Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose). See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Safety profile of inadvertent use in pregnant or lactating women	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3, Section 4.4 and Section 4.6 PL Section 2 No additional risk minimisation measures

Missing Information: Safety and immunogenicity in immunocompromised individuals	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 and Section 4.5 PL Section 2 No additional risk minimisation measures

Missing Information: Safety and immunogenicity of concomitant administration with other vaccines, other than HAV, YF and HPV vaccines	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.5 PL Section 2 No additional risk minimisation measures

Missing Information: Safety of a booster dose	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 No additional risk minimisation measures
Additional pharmacovigilance activities	Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose) See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the Scientific Opinion or specific obligation of Dengue Tetravalent Vaccine (Live, Attenuated) Takeda.

II.C.2. Other studies in post-authorisation development plan

Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (Part 4 and 5)

Purpose of the study:

WHO recommends long-term follow-up to evaluate the safety of dengue vaccines for 3 to 5 years. The total follow-up period including Parts 1, 2 and 3 of this study last 4 to 4.5 years after the second dose. For those participants in the booster phase, Parts 4 and 5, there is approximately 2 years of additional follow-up.

Part VI: Summary of the risk management plan – EU MAA

Summary of risk management plan for Qdenga (Dengue tetravalent vaccine (live, attenuated)) – EU MAA

This is a summary of the risk management plan (RMP) for Qdenga. The RMP details important risks of Qdenga, how these risks can be minimised, and how more information will be obtained about Qdenga's risks and uncertainties (missing information).

Qdenga's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Qdenga should be used.

This summary of the RMP for Qdenga should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Qdenga's RMP.

I. The medicine and what it is used for

Qdenga is authorised for the prevention of dengue disease in individuals from 4 years of age (see SmPC for the full indication). It contains Dengue virus serotype 1 (live, attenuated), Dengue virus serotype 2 (live, attenuated), Dengue virus serotype 3 (live, attenuated) and Dengue virus serotype 4 (live, attenuated) as the active substances and it is given by subcutaneous injection.

Further information about the evaluation of Qdenga's benefits can be found in Qdenga's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

[\[ENTER LINK TO THE EPAR SUMMARY LANDING PAGE\]](#).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Qdenga, together with measures to minimise such risks and the proposed studies for learning more about Qdenga's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Qdenga is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Qdenga are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a

link with the use of Qdenga. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Dengue disease due to waning protection against dengue over time. Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus.
Missing information	Safety profile of inadvertent use in pregnant or lactating women. Safety and immunogenicity in immunocompromised individuals. Safety and immunogenicity of concomitant administration with other vaccines, other than HAV, YF and HPV vaccines. Safety of a booster dose.

II.B Summary of important risks

Important potential risk: Dengue disease due to waning protection against dengue over time	
Evidence for linking the risk to the medicine	In a year-by-year analysis until 4.5 years after the second dose in Trial DEN-301, VE in preventing VCD was shown for all four serotypes in baseline dengue seropositive subjects. In baseline seronegative subjects, VE was shown for DENV-1 and DENV-2, but not suggested for DENV-3 and could not be shown robustly for DENV-4 due to lower incidence of cases. During the third year of Trial DEN-301, although some decline in efficacy compared with Year 2 was observed, largely driven by non-hospitalized VCD cases, efficacy against VCD was demonstrated overall, as well as in both baseline seronegative and seropositive subjects. Efficacy against VCD leading to hospitalization remained robust with little change compared with Year 2. The data obtained in the last 18 months of follow-up up to Month 54 showed continued long-term protection against overall VCD and a sustained high level of protection against hospitalized VCD regardless of baseline serostatus. Waning immunity resulting in a loss of protection over time is applicable to all vaccines. The maximum duration of protection with TDV is not known currently.
Risk factors and risk groups	In general, lack of response to vaccination can occur due to immunodeficiency, elderly age, interference due to wild type infectious agents, acute or chronic disease and suboptimal health, as well as nutritional status, immunological interference. In addition, there may be failure to respond due to the normal expected variation in immune response across healthy individuals (i.e., a “low responder” or “non-responder”). Additionally, vaccine effectiveness may wane with increasing time since vaccination. Depending on the vaccine, rates of decline of vaccine effectiveness may vary across antigens. A number of variables influence duration of vaccine protection, including age, serostatus at

	vaccination, presence or absence of exposures to circulating wild type virus (natural boosting), possible evolution of the wild type virus, as well as unknown factors. No risk factors have been identified for TDV vaccination failure.
Risk minimisation measures	Routine risk minimisation measures: - SmPC Section 4.4 - PL Section 2 No additional risk minimisation measures.
Additional pharmacovigilance activities	Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus	
Evidence for linking the risk to the medicine	Efficacy results by baseline dengue serostatus (determined for all subjects), demonstrated overall VE against VCD and VCD leading to hospitalization regardless of prior exposure to dengue. Efficacy against individual dengue serotypes varied. The totality of data on VCD, hospitalized VCD, and severe forms of dengue, along with the clinical characteristics of these cases, as assessed in Trials DEN-301, DEN-313, and DEN-204, did not reveal an identified risk of increased disease severity or disease enhancement attributable to vaccination in the post-vaccination period. Exploratory efficacy analyses at 54 months after the second vaccine dose did not suggest efficacy for VCD caused by serotype DENV-3 in baseline seronegative subjects (RR: 1.11 [95% CI: 0.62, 1.99]). For hospitalized VCD caused by DENV-3 there were with 11 cases in the TDV group (0.3%) compared with 3 cases in placebo group (0.2%), with a relative risk of 1.81 (95% CI: 0.51, 6.48). In the baseline seronegative subgroup, a total of 2 subjects with VCD were assessed as severe dengue as defined by the Adjudication Committee (both in the TDV group; 0.05% of 3714 subjects). Both cases occurred early in the trial during Parts 1 and 2 (i.e., before 18 months post second dose). Five subjects experienced DHF as per programmed algorithm, WHO 1997 DHF criteria), 4 of 3714 subjects (0.11%) in the TDV group and 1 of 1832 subjects (0.05%) in the placebo group. Of note, 1 of these 4 DHF cases in the TDV group was also classified as DCAC-defined severe dengue. All of these cases in baseline seronegative subjects were caused by DENV-3. The assessment of whether TDV may be associated with an increased risk of severe forms of dengue in baseline seronegative subjects who experience VCD caused by serotype DENV-3 remained inconclusive; the data are limited by the small number of cases. In baseline seronegative subjects, an increased risk of hospitalization due to dengue and/or clinically severe forms of dengue caused by serotype DENV-3 is considered an important potential safety risk. Conservatively, due to limited data for DENV-4, risk of hospitalization due to dengue and/or clinically severe forms of dengue caused by serotype DENV-4 in baseline seronegative subjects is considered an

	important potential safety risk, although up the 54 months after the second vaccine dose no hospitalisations caused by DENV-4 occurred in TDV recipients.
Risk factors and risk groups	No risk factors for severe dengue with TDV have been identified.
Risk minimisation measures	Routine risk minimisation measures: - SmPC Section 4.4 - PL Section 2 No additional risk minimisation measures
Additional pharmacovigilance activities	Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Safety profile of inadvertent use in pregnant or lactating women

Risk minimisation measures	Routine risk minimisation measures: - SmPC Section 4.3, Section 4.4 and Section 4.6 - PL Section 2 No additional risk minimisation measures
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Missing Information: Safety and immunogenicity in immunocompromised individuals

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 and Section 4.5 PL Section 2 No additional risk minimisation measures
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Missing Information: Safety and immunogenicity of concomitant administration with other vaccines, other than HAV, YF, and HPV vaccines

Risk minimisation measures	Routine risk minimisation measures: - SmPC Section 4.5 - PL Section 2 No additional risk minimisation measures
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Missing Information: Safety of a booster dose

Risk minimisation measures	Routine risk minimisation measures: - SmPC Section 4.2 No additional risk minimisation measures
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Additional pharmacovigilance activities	Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose) See Section II.C of this summary for an overview of the post-authorisation development plan.
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II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Qdenga.

II.C.2. Other studies in post-authorisation development plan

Efficacy, Safety and Immunogenicity of TDV in Trial [DEN-301](#) (Part 4 and 5)

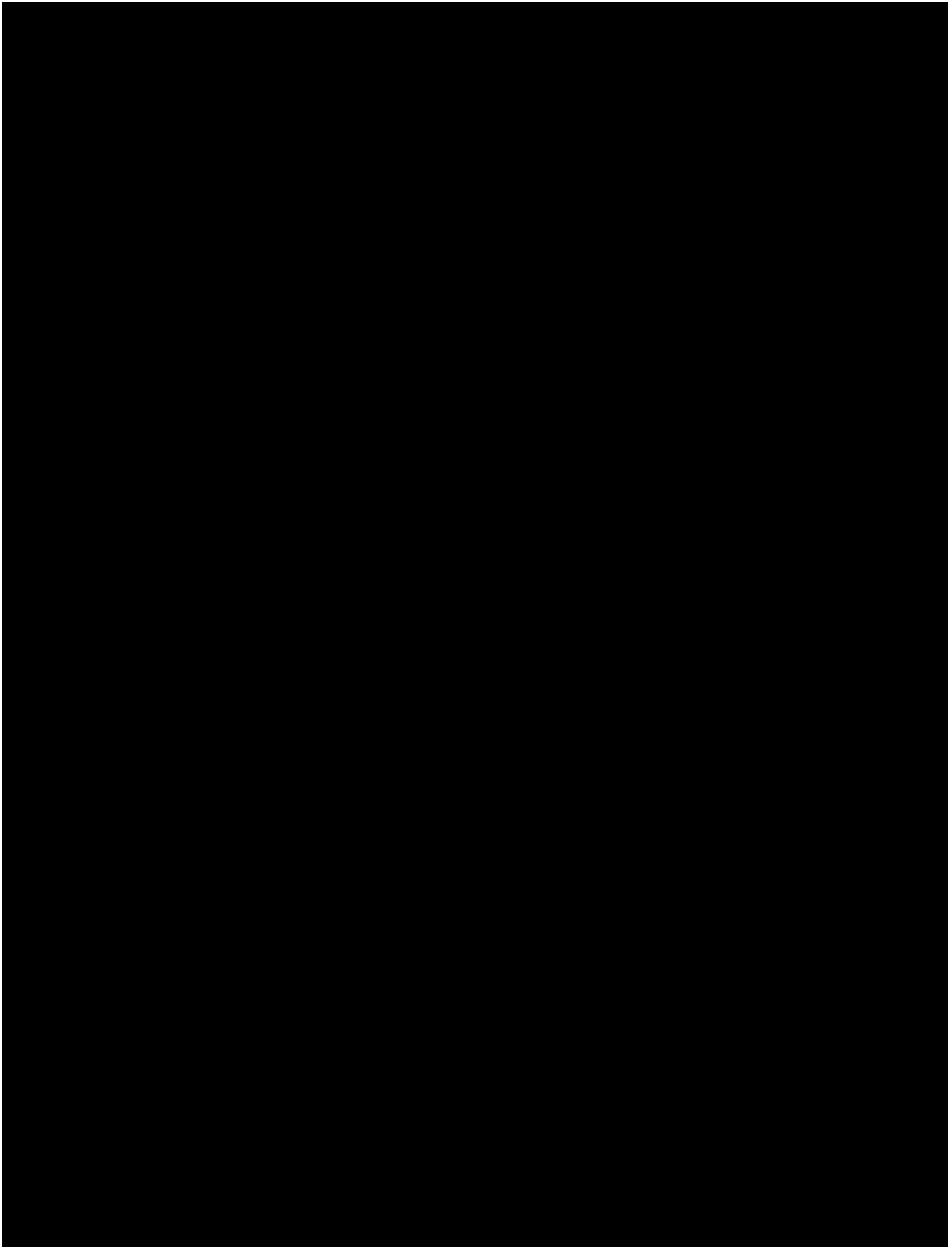
Purpose of the study:

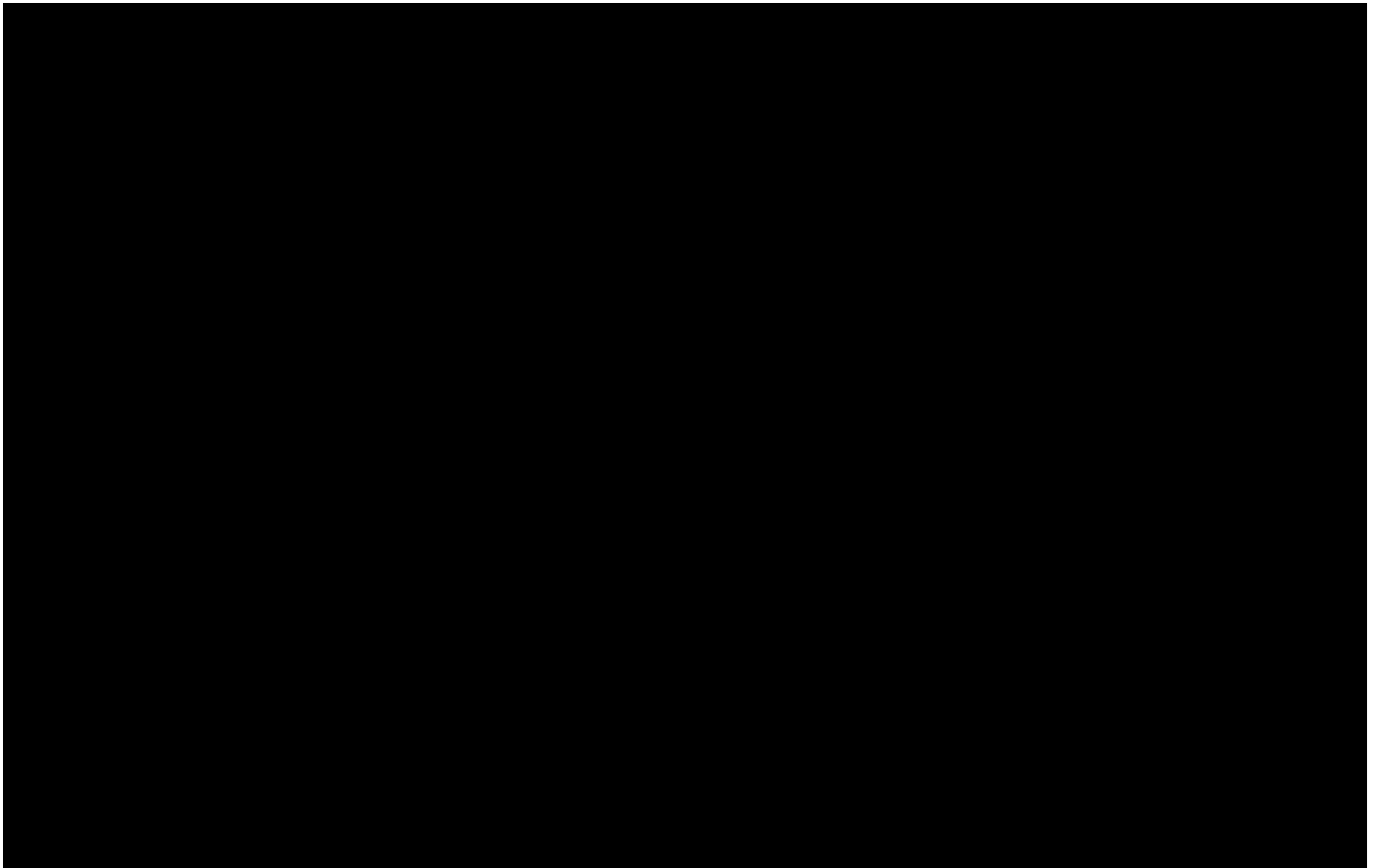
WHO recommends long-term follow-up to evaluate the safety of dengue vaccines for 3 to 5 years. The total follow-up period including Parts 1, 2 and 3 of this study last 4 to 4.5 years after the second dose. For those participants in the booster phase, Parts 4 and 5, there is approximately 2 years of additional follow-up.

Part VII: Annexes

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Annex 4: Specific adverse drug reaction follow-up forms

Not applicable.



Annex 6: Details of proposed additional risk minimisation activities

Not applicable.

