EU RISK MANAGEMENT PLAN (RMP)

for

Dengue Tetravalent Vaccine (Live, Attenuated)

RMP Version number: 1.0

Date: 11-October-2022

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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: 1.0

Data lock point for this RMP: 1-April-2022

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Rationale for submitting an updated RMP:

The rationale of the update of RMP version 0.4 to RMP version 1.0 to remove study DEN-401 from the RMP and instead, include the study in the list of post-authorization measures. In addition, RMP was updated to reflect the DEN-303 trial protocol amendment (amendment to protocol version 4.0, 22 February 2021 to version 5.0, 22 August 2022).

Summary of significant changes in this RMP:

RMP Part/Module	Significant changes
Part I – Product overview	Revision in Brief description of the product: sentence shortened to remove information which is considered Commercially Confidential Information
Part II – Safety specifications	Revision in Module SVI - Additional EU requirements for the safety specification: - to reflect changes made in the updated PI under section 4.6 - sentence shortened to remove information which is considered Commercially Confidential Information
Module SVII – Identified and potential risks	Revision in SVII.3.1. Presentation of important identified risks and important potential risks and SVII.3.2. Presentation of the missing information to reflect changes made in the updated PI under section 4.4 and 4.6
Module SVIII – Summary of the safety concerns	No changes
Part III – Pharmacovigilance activities	III.2. Additional pharmacovigilance activities: - Trial DEN-303 changes - Study DEN-401 removed from the additional pharmacovigilance activities III.3. Summary table of additional pharmacovigilance activities revised to reflect changes made for DEN-303 and DEN-401
Part IV - Plans for post-authorisation efficacy studies	No changes

RMP Part/Module	Significant changes
Part V - Risk minimisation measures	Study DEN-401 removed
Part VI - Summary of the risk management plan	II.C.2. Other studies in post-authorisation development plan updated to remove DEN-401 II.B Summary of important risks - study DEN-401 removed
Part VII – Annexes	Annex 2 updated

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Not applicable

QPPV name: Dr. Sumit Munjal, Takeda VP EU-QPPV

QPPV signature: Refer to the electronic signature at the end of the document

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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
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
GLP	Good Laboratory Practice
GMO	Genetically modified organism
HAV	Hepatitis A virus
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary names
IR	Incidence rate
JE	Japanese encephalitis
log	Logarithm
MA	Marketing Authorization
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder

Abbreviation	Definition/Description
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
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 candidate also known as TAK-003
TFUQ	Targeted follow up questionnaires
US	United States
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)* **Produced in Vero cells by recombinant DNA technology. Genes of serotype-specific surface proteins engineered into dengue virus serotype 2 backbone.* *#Produced in Vero cells by recombinant DNA technology.*
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 candidate 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 dengue disease caused by any of 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 ≥3.3 log_{10} PFU/dose, TDV-2 ≥2.7 log_{10} PFU/dose, TDV-3 ≥4.0 log_{10} PFU/dose, TDV-4 ≥4.5 log_{10} PFU/dose).
Hyperlink to the Product Information (PI)	Refer to CTD Module 1.3.1 for proposed PI.
Indication(s) in the EEA	Current (if applicable): Not applicable.
	Proposed (if applicable): Qdenga is indicated for the prevention of dengue disease in individuals from 4 years of age.
Dosage in the EEA	Current (if applicable): Not applicable.
	Proposed (if applicable): 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.
Pharmaceutical form(s) and strengths	Current (if applicable): Not applicable.
	Proposed (if applicable): Powder and solvent for solution for injection. After reconstitution, 1 dose (0.5 ml) contains: Active ingredients: Dengue virus serotype 1 (live, attenuated)*: ≥3.3 log_{10} PFU**/dose Dengue virus serotype 2 (live, attenuated)#: ≥2.7 log_{10} PFU**/dose Dengue virus serotype 3 (live, attenuated)*: ≥4.0 log_{10} PFU**/dose Dengue virus serotype 4 (live, attenuated)*: ≥4.5 log_{10} PFU**/dose **Produced in Vero cells by recombinant DNA technology. Genes of serotype-specific surface proteins engineered into dengue virus serotype 2 backbone.* *#Produced in Vero cells by recombinant DNA technology.* ***PFU = Plaque-forming units*
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:	Dengue is caused by infection with the wild-type dengue virus serotype (DENV), a ribonucleic acid (RNA) virus that occurs as 4 recognized serotypes, DENV-1, DENV-2, DENV-3 or DENV-4. These dengue viruses are transmitted from human to human by mosquitoes (primarily Aedes aegypti) [1]. The 4 dengue viruses have spread worldwide and are now endemic in more than 120 countries throughout Asia, the Pacific Islands, the Caribbean, parts of Africa, Australia, and Central and South America, with almost 3.9 billion people thought to be at risk [2]. 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 [3]. The World Health Organization (WHO) frequently cites 50 to 100 million as the annual number of symptomatic cases of dengue [4]. Using geostatistical methods, modelling groups estimated that 294 million asymptomatic infections and 96 million symptomatic infections occurred in 2010, of which 70% were in Asia, 16% were in Africa, and 14% were in the Americas [5]. Over the past 20 years, the number of dengue cases reported to the WHO increased more than 8-fold [6], from less than 505,430 cases in 2000, to over 2.4 million in 2010, and 4.2 million in 2019. From a sub-regional perspective, Southeast Asia has the highest age-standardized incidence, estimated at 34.3 cases/1000 people annually. Within Latin America, the Caribbean has the highest age-standardized incidence, with 18.2 cases/1000 people [3]. 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 [7]. 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 [8,9]. In 2017, Indonesia reported 59,047 DHF cases and 444 DHF-associated deaths (IR = 23/100k, Case Fatality Rate (CFR) = 0.75%) [8]. 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 [5]. 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 [11].

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 [12]. All four dengue serotypes circulate in Malaysia, with shifts in dominance. Between 2014 and 2017, DENV-1 and DENV-2 were most prominent [13].

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 [14]. 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 [15]. 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 [16].

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 Aedes larvae to below 1% [17].

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 [18]. In 2020, Singapore experienced its largest dengue outbreak on record, with more than 35,300 cases reported [19]. 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 [20].

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 [21].

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 [22]. All four serotypes circulate in Sri Lanka annually, but the 2017 outbreak was predominated by DENV-2 [23]. The majority of cases reported during the 2017 outbreak were among working-age adults [24].

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 [25].

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

2009 and 2019, an average of 89,846 suspected dengue cases were reported in Thailand annually, ranging from 41,082 in 2014 to 154,000 in 2013 [26]. Dengue has been hyperendemic in Thailand since 1958 [27], and a recent study found a high incidence of DENV serotype and genotype co-circulation, particularly in urban areas [28].

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 [29]. 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 [14].

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 Aedes aegypti mosquito has spread southward to latitude 35°S, near Buenos Aires [30].

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 record dengue season, with 58,415 confirmed cases [31]. Three serotypes have cocirculated during 2020, with DENV-1 predominating [32].

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 [33].

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 [31]. By far, Brazil has the largest dengue burden in Latin America. Among all dengue cases that were recorded in the Americas in 2019, more than 70% were from Brazil [31]. Even still, dengue is under reported in Brazil, with one notification estimated for every twenty cases of dengue fever [34].

Every year for the past 10 years, Brazil has reported the cocirculation of all four dengue serotypes.[31] 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) [35].

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 [14].

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. During most years,

multiple dengue serotypes circulate in Colombia. In 2019, DENV-1, DENV-2, and DENV-3 were detected. DENV-4 was last reported in Colombia in 2016 [36].

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 [14].

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 [37]. 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 [31]. All four dengue serotypes generally circulate annually in Mexico. In 2019, all four serotypes were detected, with DENV-2 predominating [38].

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 [14].

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 [39], and accounts for an estimated 2% of all febrile illnesses in travellers returning from the tropics [16, 40].

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 [39]. 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 [41]. Travellers returning home with dengue also contribute to the spread of the disease to non-endemic areas where Aedes aegypti and Aedes albopictus mosquitoes are present [42].

Dengue in Europe

Sporadic dengue outbreaks have been recorded over the past decade in continental Europe, including in Croatia (2010), France (2010, 2013-2015, 2018, 2019), Spain (2018), and Italy (2020) [43-45]. 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 [46].

Dengue in European territories

Several European territories are endemic for dengue:

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. Aedes albopictus, the primary vector of this outbreak, are also widely established in the European Union [44].

Mayotte is a French territory between Madagascar and Mozambique with 256,000 inhabitants. A representative seroprevalence study of 1,154 inhabitants aged ≥2 years in Mayotte in 2006 found 23% IgG antibody seropositivity, indicating

	substantial prior exposure of dengue among the population of Mayotte [47]. 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 and 2020 [48]. 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 [43]. 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 [49]. In New Caledonia, a special collectivity of France with a population of 278,000, dengue occurs regularly. In 2018, 20, 30 dengue cases including two deaths were reported. DENV-2 was the predominant circulating serotype, comprising 1,149 of the 1,336 (86%) typed cases [50]. 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 [51]. 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 [52]. 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 [53]. 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 [54]. 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 [55]. 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 [56].
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 [14]. 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 [29,57].
Demographics of the target population in the indication:	Age: People of all ages are at risk of dengue infection [58]. Though the data are limited, the results of some studies suggest that elderly dengue patients have the highest dengue case-fatality rates [59-61]. In Southeast Asia, dengue has historically been a paediatric disease and clinical dengue in adults has been rare [62]. Throughout the region, the majority of children in endemic areas have already had a primary dengue infection before the age of 9 years [14]. In Asia, DHF and Dengue shock syndrome (DSS) mostly occur in children aged 2 to 15 years [63]. However, data from Singapore, Malaysia, Indonesia, Thailand, and Bangladesh point to a recent increase in dengue incidence among older age groups [29,64-67]. 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 [29,68,69]. 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 [70,71]. In Latin America, first infections have generally been among young adults and severe disease occurs in a significant number of adults [72]. 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 [73]. 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 [74,75]. Increases in multitypic immunity among adults may also explain the recent increase in severe dengue observed among children in Colombia, Venezuela, Nicaragua, and Mexico [76-78]. Gender: 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 [79-82].

	Racial and/or ethnic origin: Some association has been described for people of African genetic ancestry who are less affected by severe dengue outcomes [83,84]. 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 [85,86]. 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 [78,87-92]. 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 [76,90,93-99].
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 [100]. Dengvaxia is the only dengue vaccine to have been commercialized to date, with licensure by regulatory authorities in multiple endemic countries [101]. In December 2018, Dengvaxia received approval in the EU [102].
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 [5]. Clinically, infection with a dengue virus can result in a range of symptoms, often with unpredictable clinical progression and outcome [103]. 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) [100]. Severe dengue occurs in a small fraction of cases (<5%), and is associated with severe bleeding, severe organ dysfunction, and/or severe plasma leakage [100,104]. Illness rarely lasts beyond 10 days, though some symptoms can be persistent and debilitating [100,105]. Without appropriate treatment, fatality rates can exceed 20%, however, with proper case management, the rate can be less than 1% [46]. The WHO estimates about 500,000 people with severe dengue require hospitalization annually, and about 2.5% of those affected die [6].
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) [106-108]. Obesity and advanced age are also associated with more severe forms of dengue [106,109].

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).	
– Single-dose toxicity study (DEN-001) 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. Viremia 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.
– Repeat-dose toxicity studies 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 $\log_{10}$ PFU/dose (actual minimal dose administered 5.9 $\log_{10}$ 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	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.

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 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 $\log_{10}$ 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 $\log_{10}$ 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 $\log_{10}$ PFU/dose (1.07 x 10^7 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 10^7 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 $\log_{10}$ 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 $\log_{10}$ 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 $\log_{10}$ 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	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 10^6 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 10^5 PFU/dose) tested in clinical studies.

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 log_{10} PFU/dose (5.93 x 10^6 PFU/dose).	
– Reproductive and Developmental Toxicity 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.
– Genotoxicity 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	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.

product.	
– Carcinogenicity 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	
- Neurovirulence (DEN-014) 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 ~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 homologues recombinant dengue research strains. Therefore, TDV is considered to have an acceptable neurotoxic profile and no human safety concern has arisen from this study.
– Biodistribution and Shedding 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	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

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 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.	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.

– 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: Age group and gender*

	TDV (final formulation, safety set)		
Age (years)	**Male, n (%)**	**Female, n (%)**	**Total, n (%)**
<4	176 (2.1)	178 (2.1)	354 (2.1)
4-11	5176 (60.8)	5049 (59.2)	10225 (60.0)
12-17	2405 (28.3)	2496 (29.3)	4901 (28.8)
18-60	756 (8.9)	807 (9.5)	1563 (9.2)
Total	8513	8530	17043

Source: CTD Module 5.3.5.3, ISA Table 1.1.1.2. for age ≥4 years and Ad-hoc Table SIII.1 for age <4 years.
Note: Studies included: DEN-106, 203, 204, 205, 301, 304, 305 (Group 2), 313, 314 (Group 2), and 315.
*The table presents subjects aged 1.5 to 60 years, limited to those subjects who were eligible for the pooled safety analysis of phase 2 and phase 3 trials. All phase 1 trials – all in adults - were not included in the safety pooling because they were mainly designed to explore different doses, schedules, and vaccine formulations, as well as different methods or routes of administration; subjects who were co-administered YF or Japanese Encephalitis (JE) vaccine were excluded from the pooled safety analysis to avoid confounding of data interpretation, and their safety data are assessed separately; Trials DEN-307 and DEN-210 were not included in the pooled analysis as both were ongoing studies with only preliminary safety information available at the time of the overall safety data cut-off date.

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

	Number of Subjects							
	TDV			Any TDV[c]	Placebo		Other Vaccines	N Total[e]
	≥1 Dose	1 Dose[a]	2 Doses[b]	≥1 Dose	PBO Only	≥1 Dose	≥1 Dose[d]	
Total for Phase 1 Trials								
	0	0	0	414	41	81	0	455
Total for Phase 2 and Phase 3 Trials								
	18145	1096	17049	19566	7226	9445	1438	27118
Total Phase 1-Phase 3 Trials (1.5-60 years)								
	18145	1096	17049	19980	7267	9526	1438	27573
Total for Target Population (4-60 years)								
	17791	992	16799	19589	7203	9116	1438	27118

Source: CTD Module 2.7.4, Appendix A.
Abbreviations: CSR, clinical study report; NA, not applicable; HAV, hepatitis A virus; PBO, placebo; YF, yellow fever.
Trial DEN-303 data are not included because subjects in this trial have previously participated in the parent Trials DEN-304 or DEN-315. Therefore, they do not contribute to the overall number of subjects exposed: As of the data cut-off date for the overall safety data, all 365 subjects enrolled into Trial DEN-303 were still in the 15-month follow-up period (i.e., none has received the booster dose).
(a) This includes 1 subject of Trial Group 4 from study DEN-204 who received TDV instead of the assigned placebo dose at Month 12.
(b) 195 subjects from study DEN-204 had final TDV at both Month 0 and Month 3.
(c) Includes any subjects who received any non-final TDV formulation (1 or 2) doses.
(d) Other Vaccines include vaccines for Yellow Fever (YF) and Hepatitis A Virus (HAV).

(e) DEN-204,305,314 study design allowed administration of either one or two doses of final formulation TDV followed by one or two placebo or YF/HAV doses to the same subject. Subjects who received more than one IMP are counted under each IMP they received but are counted only once in the Total column.

Table SIII.2.B: Dose (any TDV formulation, safety set)*

	Number of subjects exposed to any TDV formulation			
Age (years)	**Received one dose, n (%)**	**Received two doses, n (%)**	**Received Month 12 injection (DEN-204)[a], n (%)**	**Total [b], n (%)**
<4	7 (0.8)	384 (2.2)	339 (22.3)	391 (2.1)
4-11	172 (19.8)	10219 (58.1)	901 (59.2)	10391 (56.3)
12-17	88 (10.1)	4829 (27.4)	283 (18.6)	4917 (26.6)
18-60	603 (69.3)	2162 (12.3)	NA	2765 (15)
Total	870	17594	1523	18464

Source: CTD Module 5.3.5.3, ISA Table 1.2.1.2. for age ≥4 years and Ad-hoc Table SIII.2.A for age <4 years.
Note: Studies included: DEN-106, 203, 204, 205, 301, 304, 305 (Group 2), 313, 314 (Group 2), and 315.
(a) In Trial DEN-204, subjects received a third injection of trial vaccine at Month 12 of either TDV (Group 3; second injection of TDV) or placebo (Group 1, 2, and 4).
(b) The Total column shows sum of subjects received one doses only and two doses, each of subject is only counted once.
*The table presents subjects aged 1.5 to 60 years, limited to those subjects who were eligible for the pooled safety analysis of phase 2 and phase 3 trials. All phase 1 trials – all in adults - were not included in the safety pooling because they were mainly designed to explore different doses, schedules, and vaccine formulations, as well as different methods or routes of administration; subjects who were co-administered YF or Japanese Encephalitis (JE) vaccine were excluded from the pooled safety analysis to avoid confounding of data interpretation, and their safety data are assessed separately; Trials DEN-307 and DEN-210 were not included in the pooled analysis as both were ongoing studies with only preliminary safety information available at the time of the overall safety data cut-off date.

Table SIII.2.C: Dose (TDV final formulation, safety set)*

	Number of subjects exposed to TDV final formulation			
Age (years)	**Received one dose, n (%)**	**Received two doses, n (%)**	**Received Month 12 injection (DEN-204)[a], n (%)**	**Total[b], n (%)**
<4	7 (1.3)	347 (2.1)	339 (22.3)	354 (2.1)
4-11	170 (30.4)	10055 (61.0)	901 (59.2)	10225 (60.0)
12-17	88 (15.7)	4813 (29.2)	283 (18.6)	4901 (28.8)
18-60	295 (52.7)	1268 (7.7)	NA	1563 (9.2)
Total	560	16483	1523	17043

Source: CTD Module 5.3.5.3, ISA Table 1.2.1.2. for age ≥4 years and Ad-hoc Table SIII.2.B for age <4 years.

Note: Studies included: DEN-106, 203, 204, 205, 301, 304, 305 (Group 2), 313, 314 (Group 2), and 315.
(a) In Trial DEN-204, subjects received a third injection of trial vaccine at Month 12 of either TDV (Group 3; second injection of TDV) or placebo (Group 1, 2, and 4).
(b) The Total column shows sum of subjects received one doses only and two doses, each of subject is only counted once.
*The table presents subjects aged 1.5 to 60 years, limited to those subjects who were eligible for the pooled safety analysis of phase 2 and phase 3 trials. All phase 1 trials – all in adults - were not included in the safety pooling because they were mainly designed to explore different doses, schedules, and vaccine formulations, as well as different methods or routes of administration; subjects who were co-administered YF or Japanese Encephalitis (JE) vaccine were excluded from the pooled safety analysis to avoid confounding of data interpretation, and their safety data are assessed separately; Trials DEN-307 and DEN-210 were not included in the pooled analysis as both were ongoing studies with only preliminary safety information available at the time of the overall safety data cut-off date.

Table SIII.3: Ethnic origin (safety set)*

Ethnic origin	**Number (%) of TDV subjects (TDV final formulation[(b)])**
American Indian or Alaska native	6274 (36.8)
Asian	6575 (38.6)
Black or African American	2205 (12.9)
White	1425 (8.4)
Multiracial or other[(a)]	564 (3.3)
Total	17043

Source: CTD Module 5.3.5.3, ISA Table 1.1.1.2. for age ≥4 years and Ad-hoc Table SIII.3 for age <4 years.
Note: Studies included: DEN-106, 203, 204, 205, 301, 304, 305 (Group 2), 313, 314 (Group 2), and 315.
(a) Includes subjects of the categories Native Hawaiian or other Pacific Islander, Multiple, Not reported and Unknown.
(b) Include TDV final formulation subjects with age <4 years to 60 years.
*The table presents subjects aged 1.5 to 60 years, limited to those subjects who were eligible for the pooled safety analysis of phase 2 and phase 3 trials. All phase 1 trials – all in adults - were not included in the safety pooling because they were mainly designed to explore different doses, schedules, and vaccine formulations, as well as different methods or routes of administration; subjects who were co-administered YF or Japanese Encephalitis (JE) vaccine were excluded from the pooled safety analysis to avoid confounding of data interpretation, and their safety data are assessed separately; Trials DEN-307 and DEN-210 were not included in the pooled analysis as both were ongoing studies with only preliminary safety information available at the time of the overall safety data cut-off date.

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

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

Females 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 [110]. 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 [111-113]. 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. Anaphylaxis including anaphylactic shock is classified as an important potential risk. 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) and Hepatitis A virus (HAV) vaccines for which data from the development program are included in the marketing authorization 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 ≥38°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 27,573 subjects, from 18 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 36 months after the second dose of trial vaccine in Trial DEN-301. Overall, 19,980 subjects received at least 1 dose of TDV in these trials. Among all 19,980 subjects exposed to any TDV, 18,145 subjects (90.8%) received at least 1 SC 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 planned follow-up period covers up to 4.5 years after the last TDV injection. Moreover, available follow-up data are 3 years 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). As of 01-October-2020, 34 pregnancies have been identified as exposed to TDV in clinical trials. These limited data are insufficient to conclude on the presence or 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 (76%). 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; 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 proposed 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 program.

Part II: Module SV - Post-authorisation experience

Not applicable (no post-authorisation experience available thus far).

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 viremia. However, wild type dengue infections resulting from needle stick injuries during the care of febrile patients have been reported [114,115]. 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 [116].

Environmental escape of TDV by mosquito transmission could only occur if (i) a mosquito vector feeds on a vaccinee with a sufficient viremia 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 MID_{50} for both Aedes aegypti and Aedes albopictus mosquitoes [117,118]. With the very low mosquito infection, dissemination and transmission capacity of TDV in Aedes aegypti and Aedes albopictus and the low levels of TDV viremia 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 [119,120]. 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 [10,121]. 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 [121,122]. In a study, dengue virus has not been detected in the semen in five patients with acute dengue virus infection [123]. Cases of likely sexual transmission and cases of presence of dengue virus in semen or vaginal secretions have been reported but are considered anecdotal [124-126]. 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 [127].

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 [128,129] (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 [128-132]. Intrauterine transmission of dengue has been associated with high maternal serum viremia titers [132] and may be related to endothelial damage and increased vascular permeability caused by the wild type dengue virus infection [122]. 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 [133].

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 - prefilled syringe, are sterile. Therefore, no potential infectious contaminants from the manufacturing process are expected.

Reversion to virulence

Vaccine viremia 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 viremia

and potential reversions independent of the presence of replication-competent vaccine virus was determined in DEN-205. The proportion of subjects with vaccine viremia 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 viremia 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 viremia 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 viremia. Subjects with vaccine viremia may develop systemic symptoms such as headache, arthralgia, or myalgia that can also occur in the absence of viremia, 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 viremia.

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 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 viremia. 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.

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 [2].

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 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 [134]. Thus, the genome tends to be relatively fixed [135-138]. 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

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 authorization 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 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 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.

The application will include 2 presentations:

- 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.

As recommended by the WHO, errors in immunisation will be considered in the initial evaluation of all adverse event following immunisation (AEFI) [139]. Correct usage will be monitored within routine pharmacovigilance activities and any changes in the safety profile of TDV related to immunisation errors will be 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 30-Oct-2020), 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
Anaphylaxis including anaphylactic shock	There were no TDV-related anaphylactic reactions or anaphylactic shock events reported during the clinical development program. However, anaphylaxis is a severe and potentially fatal systemic reaction which has been reported for most vaccines [140].
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 seronegatives 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 and YF	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

Not applicable (initial marketing authorisation application).

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: Anaphylaxis including anaphylactic shock	
Potential mechanisms:	Anaphylaxis is a Type 1 immediate hypersensitivity reaction (Geland Coombs classification) mediated by the interaction of IgE antibodies against a particular vaccine component. Therefore, previous exposure and sensitization to the triggering substance or a cross reactive allergen is necessary. When a vaccine component (allergen) binds to the IgE receptors on the surface of mast cells and basophils this results in cellular activation and release of preformed mediators such as histamine and tryptase that elicit the signs and symptoms of anaphylaxis [141].
Evidence source(s) and strength of evidence:	Case descriptions of anaphylaxis for other vaccines exist in the literature [140]. TDV contains human serum albumin which has been associated with urticarial hypersensitivity reactions to rabies vaccine [142, 143]. Persons with prior allergic reactions to albumin containing products may be at higher risk of an allergic reaction to TDV. No published evidence for a potential hypersensitivity potential of other constituents of TDV was identified.
Characterisation of the risk:	Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement (≥2) that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to the different components of the vaccine. Anaphylactic shock is the most severe manifestation of anaphylaxis [141]. Anaphylaxis after vaccination in general occurs very rarely but is a potentially life-threatening medical emergency [144-148]. It has been estimated to occur at a rate of approximately one to ten per 1,000,000 doses for most commonly administered vaccines [149-151]. The true rate of allergic reactions is unknown because most reactions are not reported [152]. No cases of anaphylaxis have been observed in the TDV pre-clinical development program. There were no TDV-related anaphylactic reactions or anaphylactic shock events reported during the clinical development program. TDV was not associated with an increased risk for serious anaphylactic shock or severe hypersensitivity events.
Risk factors and risk groups:	Clinical risk factors that have been identified for anaphylaxis are [153-155]: – History of allergies to the active substances or any of the other components of the TDV vaccine. – History of an allergic reaction after a previous immunisation with TDV. – Coexisting atopic disease, particularly asthma. However, allergic reactions may occur in patients without known risk factors [156].

Preventability:	Predictability/prevention for new onset anaphylaxis is not possible due to it being idiosyncratic. The best practice to prevent anaphylactic reactions is to identify at-risk individuals by obtaining the history of severe allergic reactions to any component of the vaccine or to previous vaccinations that might indicate an underlying hypersensitivity and avoid their vaccination.[157] The SmPC Section 4.3 contains the following contraindication: "Hypersensitivity to the active substances or to any of the excipients listed in Section 6.1. or hypersensitivity to a previous dose of Qdenga". As per general recommendations on immunisation, individuals should be observed after vaccination and appropriate medical treatment of anaphylaxis should always be readily available. Early recognition of symptoms and intervention can minimise the reaction sequalae/severity. The SmPC Section 4.4 contains the following Special warnings and precautions for use: "As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in the event of a rare anaphylactic reaction following administration of the vaccine."
Impact on the risk-benefit balance of the product:	A severe anaphylactic reaction can be life threatening. When promptly treated, the prognosis is good.
Public health impact:	Currently, 18,273 doses of TDV were administered with no anaphylactic reactions to TDV reported. This potential risk is not expected to have a serious impact on public health.

Important Potential Risk: Dengue disease due to waning protection against dengue over time	
Potential mechanisms:	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.
Evidence source(s) and strength of evidence:	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.
Characterisation of the risk:	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 *versus* 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.
Risk factors and risk groups:	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) [159]. 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.
Impact on the risk-benefit balance of the product:	The impact of waning protection against dengue over time on the risk-benefit balance is expected to be minimal.
Public health impact:	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 [100]. The most severe forms of dengue infection, dengue haemorrhagic fever (DHF) and dengue sock syndrome (DSS) [58], 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) [160]. 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 [161]. The mechanism for more severe disease associated with a second infection is not well understood although ADE [162], cytokine storm [163,164] or cross-reactive T cells are hypothesized [165]. 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 [166]. 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 [167].
Evidence source(s) and strength of evidence:	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 [6]. 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: Virologically Confirmed Dengue 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 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 [148]. Patients with severe dengue require immediate emergency treatment to avert death and those with warning signs should be assessed and treated without delay. 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 (ie, 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).
Risk factors and risk groups:	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 [168]. 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 [169]. 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.

Preventability:	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.
Impact on the risk-benefit balance of the product:	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 od 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.
Public health impact:	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	
Evidence source:	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 [111-113]. 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. As of 01 October 2020, 34 pregnancies were identified as exposed to TDV: 27 had normal outcomes, 4 spontaneous abortion and 3 elective termination. There were no clinically important differences regarding the frequencies of spontaneous abortions or elective terminations between women exposed to TDV and women exposed to placebo only. In addition, one neonatal death occurred after an exposed pregnancy. However, the death was considered not causally related to TDV. 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 [127]. 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 [170,171].

Safety and immunogenicity in immunocompromised individuals	
Evidence source:	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 [172]. Published data on dengue virus infection and immunocompromised patients come from case reports or small case series [173-178] 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 viremia 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. [179] 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 viruria 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 [180] and animal models [165,181,182]. 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 [183,184]. 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 [185]. 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)

Safety and immunogenicity of concomitant administration with other vaccines other than HAV and YF	
Evidence source:	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 [186]. 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). 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 [187-190]. 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). TDV may be administered concomitantly with an HAV vaccine. Coadministration has only been studied in adults. 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). Co-administration data with other vaccines, other than YF and HAV, are missing.

Safety and reactogenicity of a booster dose	
Evidence source:	Population in need of further characterisation: Although a generally consistent overall efficacy and continued protection against hospitalised dengue is observed after a 2-dose vaccination regimen with TDV (two single doses 3 months apart), data also indicate a trend of declining efficacy over time, as reflected in lower vaccine efficacy estimates in Years 2 and 3 compared with the preceding period. This observation suggests a waning in vaccine efficacy and therefore the effect of a booster dose is being investigated in 2 ongoing clinical trials (DEN-301 and DEN-303). Currently, the need for a booster dose has not been established (SmPC Section 4.2).

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	Anaphylaxis including anaphylactic shock 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 and YF Safety and reactogenicity 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: Anaphylaxis including anaphylactic shock, vaccination failure, 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 6 months.

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 will be provided in PBRERs/PSURs.

III.2. Additional pharmacovigilance activities

Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (Part 4 and 5)
Study short name and title: 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).
Rationale and study objectives: 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 last 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. Secondary safety objectives include: • To describe the safety of TDV Exploratory objectives include: 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.
Study population: 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.
Milestones: Interim Reports: End of Part 4 CSR: Q4 2024 (planned) Final Report (Final CSR Parts 1, 2, 3, 4 and 5): Q1 2026 (planned)

Long-term safety and antibody persistence of TDV and the impact of a booster dose in Trial DEN-303
Study short name and title: DEN-303 - A Phase 3, Follow-up Trial to Evaluate Long-term Safety and Antibody Persistence, and the Impact of a Booster Dose of TDV in Healthy Adolescents and Adults in Areas Non-Endemic for Dengue.
Rationale and study objectives: This Phase 3 trial will evaluate long-term antibody persistence and safety data in healthy subjects in areas non-endemic for dengue who have previously received a primary TDV vaccination in either DEN-304 and DEN-315 trials (termed here as "parent trials"). The immunogenicity and safety of a TDV booster dose in this population will then be assessed. The primary objectives are: • To describe antibody persistence for each of the 4 dengue serotypes for up to 63 months after the first vaccination in the primary vaccination series for subjects from parent Trial DEN-315 (Mexico) and for up to 36 months after the first vaccination in the primary vaccination series for subjects from parent Trial DEN-304 (United States). • To describe the impact of a TDV booster dose vs placebo on antibody response for each of the 4 dengue serotypes at 1 month and 6 months post administration of the TDV booster or placebo. The secondary objectives are: *Immunogenicity* Antibody Persistence • To describe the overall trend in antibody decay for all 4 dengue serotypes from values obtained after the primary vaccination series in the parent trials through 63 months after the first vaccination in the primary vaccination series for subjects from parent Trial DEN-315 (Mexico) and through 36 months after the first vaccination in the primary vaccination series for subjects from parent Trial DEN-304 (United States). Impact of a TDV Booster Dose

- To describe the impact of a TDV booster on antibody response for each of the 4 dengue serotypes for up to 69 months following the first vaccination in the primary vaccination series for subjects from the parent Trial DEN-315 (Mexico) and for up to 42 months following the first vaccination in the primary vaccination series for subjects from parent Trial DEN-304 (United States).

Safety

- To describe the long-term safety of TDV for up to 63 months in previously vaccinated subjects from parent Trial DEN-315 (Mexico) and for up to 36 months in previously vaccinated subjects from parent Trial DEN-304 (United States).
- To assess safety for 6 months following administration of the TDV booster or placebo in Group 1 and 2, respectively*.

*Group 1 = TDV, Group 2 = Placebo

Exploratory Objectives:

Applicable to subjects from parent trial DEN-315 (Mexico only):

- To evaluate aspects of the long-term humoral immune response to Takeda's TDV in all subjects at 63 months after the first vaccination in the primary vaccination series in the parent trials; this is inclusive of, but not restricted to, an assessment of the anti-dengue Non-Structural Protein 1 (NS1) antibody response.

Applicable to subjects from parent Trial DEN-304 (United States only):

- To evaluate aspects of the long-term humoral immune response to Takeda's TDV in all subjects at 36 months after the first vaccination in the primary vaccination series in the parent trial (DEN-304), and in the CMI subset at 1 month and 6 months post booster in the current trial; this is inclusive of, but not restricted to, an assessment of the antidengue NS1 antibody response.
- To evaluate aspects of the long-term cell-mediated immune response to Takeda's TDV up to 36 months after the first vaccination in the primary vaccination series in the parent trial (DEN-304) and at 1 month and 6 months post booster in the current trial; this is inclusive of, but not restricted to, the magnitude (Interferon-gamma Enzyme-Linked Immunospot [IFN-γ ELISpot]) of the long-term T cell-mediated immune response to TDV (CMI subset only).

Study design:

This is a Phase 3 follow-up trial that will evaluate the long-term antibody persistence and safety of Takeda's TDV in healthy adolescents and adults in areas non-endemic for dengue in addition to assessing the impact of a booster dose in this population. . Subjects who previously received TDV in two parent trials, DEN-304 and DEN-315, are invited to participate in this follow-up trial. DEN-303 will include up to 600 healthy subjects aged ≥13 to ≤63 years at trial entry. To enable the assessment of a booster dose, the trial will be double-blinded, randomized, and placebo-controlled from Visit 3 onwards.

Study population:

Healthy subjects aged ≥13 and ≤63 years at trial entry in areas non-endemic for dengue who received at least one dose of Takeda's TDV in the parent trial.

Milestones:

Final CSR: Q1 2025

Immunogenicity and safety of TDV and 9vHPV in subjects aged ≥9 to <15 years in Trial DEN-308

Study short name and title:

DEN-308 – A phase 3 open-label, randomised trial to investigate the immunogenicity and safety of the co-administration of a subcutaneous dengue tetravalent vaccine (live, attenuated) and intramuscular recombinant 9-valent human papillomavirus (9vHPV) vaccine in subjects aged ≥9 to <15 years in endemic country for dengue.

Rationale and study objectives:

The WHO recommends that new vaccines should be introduced according to existing national immunisation programs. Recombinant 9-valent human papillomavirus (HPV) vaccine is recommended either in a 2-dose or 3-dose schedule 6 to 12 months apart in subjects 9 through 14 years of age. Further, if the second dose is administered earlier than 5 months after the first dose, then a third dose should be administered at least 4 months after the second dose. Many similarities exist between the proposed vaccination schedule for TDV and the approved schedule for 9-valent HPV (9vHPV) vaccine, including the overlapping target age group and the potential delivery through school immunisation programs.

In order to avoid barriers to the inclusion of TDV in routine national vaccination programs, the effect of adding TDV to such programs needs to be examined. This is particularly relevant for low-income countries where the cost of a standalone vaccination could be too high, and potentially undermine TDV uptake, if inclusion in routine vaccine schedules were not possible.

Study design:

This is a phase 3, open-label, randomised, multicentre trial in 614 healthy subjects aged ≥9 to <15 years in endemic areas for dengue to investigate the immunogenicity and safety of the co-administration of TDV and 9vHPV vaccine versus 9vHPV vaccine alone. Subjects will be randomized equally to 1 of 2 groups (307 subjects per trial group):

Group 1: first doses of 9vHPV vaccine + TDV co-administered on Day 1 (Month 0 [M0]), second dose of TDV administered on Day 90 (M3), second dose of 9vHPV vaccine administered on Day 180 (M6).

Group 2: first dose of 9vHPV vaccine administered on Day 1 (M0), second dose of 9vHPV vaccine administered on Day 180 (M6).

The primary objective is:

- To demonstrate the non-inferiority (NI) of the immune response (in terms of geometric mean titers [GMTs]) to 2 doses of 9vHPV vaccine, 1 co-administered with TDV, compared with 2 doses of 9vHPV vaccine administered alone.

The secondary objectives are:

Immunogenicity

- To describe the immune response to HPV (in terms of seroresponse) in subjects administered 2 doses of 9vHPV vaccine, 1 co-administered with TDV, compared with subjects administered 2 doses of 9vHPV vaccine alone.
- To describe the immune response to TDV at 1 month following a second dose of TDV given 3 months after the first dose of TDV administered concomitantly with 9vHPV vaccine.

Safety

- To describe the safety profile after administration of TDV concomitantly with 9vHPV vaccine.

Study population: Healthy subjects (male or female) aged ≥9 and <15 years in endemic areas for dengue.
Milestones: Final CSR: Q4 2023

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 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	Interim report: End Part 4 CSR	Q4 2024 (planned)
			Final Report (Final CSR Parts 1, 2, 3, 4 and 5)	Q1 2026 (planned)
Long-term safety and antibody persistence of TDV and the impact of a booster dose (Trial DEN-303) Study status: ongoing	To assess the immunogenicity and safety of a TDV booster dose in Healthy Adolescents and Adults.	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 Safety and reactoge-nicity of a booster dose	Final CSR	Q1 2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Immunogenicity and safety of TDV and 9vHPV in subjects aged ≥9 to <15 years (Trial DEN-308) Study status: ongoing	To investigate the immunogenicity and safety of the co-administration of a subcutaneous dengue tetravalent vaccine and intramuscular recombinant 9-valent human papillomavirus (9vHPV) vaccine in subjects aged ≥9 to <15 years in endemic country for dengue	Safety and immunogenicity of concomitant administration with other vaccines other than HAV and YF	Final CSR	Q4 2023

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
Anaphylaxis including anaphylactic shock	**Routine risk communication:** SmPC Section 4.3 Contraindications and 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
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 and YF	**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 and reactogenicity 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
Anaphylaxis including anaphylactic shock	**Routine risk minimisation measures:** SmPC Section 4.3 and Section 4.4 PL Section 2 **No additional risk minimisation measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Cumulative review **No additional 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) DEN-303 – Long-term immunogenicity trial (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) DEN-303 – Long-term immunogenicity trial (includes administration of a booster dose)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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 than HAV and YF	**Routine risk minimisation measures:** SmPC Section 4.5 PL Section 2 **No additional risk minimisation measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Cumulative review **Additional pharmacovigilance activities:** Coadministration with 9vHPV vaccine Trial (DEN-308)
Safety and reactogenicity 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) DEN-303 – Long-term immunogenicity trial (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	Anaphylaxis including anaphylactic shock 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 and YF Safety and reactogenicity of a booster dose

II.B Summary of important risks

Important potential risk: Anaphylaxis including anaphylactic shock	
Evidence for linking the risk to the medicine	There were no TDV-related anaphylactic reactions or anaphylactic shock events reported during the clinical development program. Anaphylaxis is a rare, severe allergic reaction and can occur with vaccines.

Risk factors and risk groups	Clinical risk factors that have been identified for anaphylaxis are: – history of allergies to the active substances or any of the other components of the Dengue Tetravalent Vaccine (Live, Attenuated) Takeda referred to as TDV vaccine, – history of an allergic reaction after a previous immunisation with TDV, – coexisting atopic disease, particularly asthma. However, allergic reactions may occur in patients without known risk factors.
Risk minimisation measures	Routine risk minimisation measures: – Summary of product characteristics (SmPC) Section 4.3 and Section 4.4 – Package Leaflet (PL) Section 2 No additional risk minimisation measures

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) DEN-303 – Long-term immunogenicity trial (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 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 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). DEN-303 – Long-term immunogenicity trial (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 and YF	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.5 PL Section 2 No additional risk minimisation measures
Additional pharmacovigilance activities	Coadministration with 9vHPV vaccine Trial (DEN-308) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Safety and reactogenicity 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) DEN-303 – Long-term immunogenicity trial (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.

Long-term safety and antibody persistence of TDV and the impact of a booster dose (Trial DEN-303)

Purpose of the study:

This Phase 3 trial will evaluate long-term antibody persistence and safety data in healthy subjects in areas non-endemic for dengue who have previously received a primary TDV vaccination in either DEN-304 and DEN-315 trials (termed here as "parent trials"). It will then go on to assess the immunogenicity and safety of a TDV booster dose in this population.

Immunogenicity and safety of TDV and 9vHPV in subjects aged ≥9 to <15 years (Trial DEN-308)

Purpose of the study:

The WHO recommends that new vaccines should be introduced according to existing national immunisation programs. Recombinant 9-valent human papillomavirus (HPV) vaccine is recommended either in a 2-dose or 3-dose schedule 6 to 12 months apart in subjects 9 through 14 years of age. Further, if the second dose is administered earlier than 5 months after the first dose, then a third dose should be administered at least 4 months after the second dose. Many similarities exist between the proposed vaccination schedule for TDV and the approved schedule for 9-valent HPV (9vHPV) vaccine, including the overlapping target age group and the potential delivery through school immunisation programs.

In order to avoid barriers to the inclusion of TDV in routine national vaccination programs, the effect of adding TDV to such programs needs to be examined. This is particularly relevant for low-income countries where the cost of a standalone vaccination could be too high, and potentially undermine TDV uptake, if inclusion in routine vaccine schedules were not possible.

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	Anaphylaxis including anaphylactic shock. 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 and YF. Safety and reactogenicity of a booster dose.

II.B Summary of important risks

Important potential risk: Anaphylaxis including anaphylactic shock	
Evidence for linking the risk to the medicine	There were no TDV-related anaphylactic reactions or anaphylactic shock events reported during the clinical development program. Anaphylaxis is rare, severe allergic reaction and can occur with vaccines.
Risk factors and risk groups	Clinical risk factors that have been identified for anaphylaxis are: – History of allergies to the active substances or any of the other components of Dengue Tetravalent Vaccine (live, Attenuated) referred to as TDV. – History of an allergic reaction after a previous immunisation with TDV. – Coexisting atopic disease, particularly asthma. However, allergic reactions may occur in patients without known risk factors.

Risk minimisation measures	Routine risk minimisation measures: – Summary of Product Characteristics (SmPC) Section 4.3 and Section 4.4 – Package Leaflet (PL) Section 2 No additional risk minimisation measures

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) DEN-303 – Long-term immunogenicity trial (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) DEN-303 – Long-term immunogenicity trial (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 and YF	
Risk minimisation measures	Routine risk minimisation measures: – SmPC Section 4.5 – PL Section 2 No additional risk minimisation measures
Additional pharmacovigilance activities	Coadministration with 9vHPV vaccine Trial (DEN-308) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Safety and reactogenicity 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) DEN-303 – Long-term immunogenicity trial (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 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.

Long-term safety and antibody persistence of TDV and the impact of a booster dose (study DEN-303)

Purpose of the study:

This Phase 3 trial will evaluate long-term antibody persistence and safety data in healthy subjects in areas non-endemic for dengue who have previously received a primary TDV vaccination in either DEN-304 and DEN-315 trials (termed here as "parent trials"). It will then go on to assess the immunogenicity and safety of a TDV booster dose in this population.

Immunogenicity and safety of TDV and 9vHPV in subjects aged ≥9 to <15 years (study DEN-308)

Purpose of the study:

The WHO recommends that new vaccines should be introduced according to existing national immunisation programs. Recombinant 9-valent human papillomavirus (HPV) vaccine is recommended either in a 2-dose or 3-dose schedule 6 to 12 months apart in subjects 9 through 14 years of age. Further, if the second dose is administered earlier than 5 months after the first dose, then a third dose should be administered at least 4 months after the second dose. Many similarities exist between the proposed vaccination schedule for TDV and the approved schedule for 9-valent HPV (9vHPV) vaccine, including the overlapping target age group and the potential delivery through school immunisation programs.

In order to avoid barriers to the inclusion of TDV in routine national vaccination programs, the effect of adding TDV to such programs needs to be examined. This is particularly relevant for low-income countries where the cost of a standalone vaccination could be too high, and potentially undermine TDV uptake, if inclusion in routine vaccine schedules were not possible.

Part VII: Annexes

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6: Details of proposed additional risk minimisation activities

Not applicable.