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EU-RISK MANAGEMENT PLAN FOR MENQUADFI® [MENINGOCOCCAL POLYSACCHARIDE (SEROGROUPS A, C, W-135 AND Y) TETANUS TOXOID CONJUGATE VACCINE]

Data Lock Point (DLP)	19-APR-2023
RMP Version number	Version 2.0
Date of final sign-off	20-FEB-2024

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Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	The RMP is being updated to implement results from MET52 study and update the related missing information.
Summary of significant changes in this RMP	• Removal of "Co-administration with MenB vaccine in infants and toddlers" as missing information. • Update on clinical development data, studies status and postmarketing data through the DLP of the RMP. • Updated Part II, Part III, Part V, Part VI, Annex 2 and Annex 3 in context of the completed study MET 52.

DLP: Data Lock Point; EMA: European Medicines Agency; MenB: Meningococcal *S*erogroup B; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	1.2
Approved with procedure	EMEA/H/C/005084/II/0018/G
Date of approval (opinion date)	15-Dec-2022

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	[redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

ACIP:	Advisory Committee on Immunization Practices
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
ATC:	Anatomical Therapeutic Chemical
CCDS:	Company Core Data Sheet
CDI:	Carbonyldiimidazole
CFR:	Case-Fatality Rate
cGMP:	Current Good Manufacturing Practice
CI:	Confidence Interval
DART:	Developmental And Reproductive Toxicity
DIBD:	Development International Birth Date
DLP:	Data Lock Point
DTaP-IPV-HB-Hib:	Diphtheria, Tetanus, Acellular Pertussis, Poliomyelitis, Hepatitis B, And Haemophilus Influenzae Type-B
ECDC:	European Center for Disease Prevention and Control
e-CTD:	Electronic Common Technical Document
EDC:	Estimated Date of Conception
EEA:	European Economic Area
EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
EU:	European Union
GBR:	Geographical Bovine Spongiform Encephalopathy Risk
GBS:	Guillain-Barre Syndrome
GVP:	Good Pharmacovigilance Practices
HCP:	Healthcare Professional
HPV:	Human Papillomavirus
IM:	Intramuscular
IMD:	Invasive Meningococcal Disease
INN:	International Nonproprietary Name
IOM:	Institute of Medicine
LMP:	Last Menstrual Period
MCV4:	Quadrivalent Meningococcal Conjugate Vaccine
MD:	Meningococcal Disease
MenB:	Meningococcal Serogroup B
MenB-FHbp:	Meningococcal Serogroup B-Factor H-Binding Protein
MenC:	Meningococcal Serogroup C
MMR:	Measles Mumps Rubella
PBRER:	Periodic Benefit-Risk Evaluation Report
PCV13:	Pneumococcal 13-Valent Conjugate
PDCO:	Pediatric Committee
PIP:	Pediatric Investigation Plan
PSUR:	Periodic Safety Update Report
Q:	Quarter

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QPPV:	Qualified Person Responsible for Pharmacovigilance
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics
Tdap:	Tetanus, Diphtheria, Acellular Pertussis
Tdap-IPV:	Tetanus, Diphtheria, Acellular Pertussis and Poliomyelitis
UK:	United Kingdom
US:	United States
V:	Varicella

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RISK MANAGEMENT PLAN - PART I: PRODUCT(S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (INN or common name)	Four distinct capsular meningococcal group-specific polysaccharide antigens from *Neisseria meningitidis*: • *Neisseria meningitidis* group A polysaccharide[a] • *Neisseria meningitidis* group C polysaccharide[a] • *Neisseria meningitidis* group Y polysaccharide[a] • *Neisseria meningitidis* group W-135 polysaccharide[a] Meningococcal Polysaccharide (Serogroups A, C, W-135 and Y) Tetanus Toxoid Conjugate Vaccine, referred to as MenACYW conjugate vaccine in the RMP.
Pharmacotherapeutic group(s) (ATC Code)	Antiinfectives for systemic use - Vaccines - Bacterial vaccines - Meningococcal vaccines - Meningococcus A, C, Y, W-135, tetravalent purified polysaccharides antigen conjugated (J07AH08)
Marketing Authorization Holder	Sanofi Pasteur 14 Espace Henry Vallee 69007 Lyon, France
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	MENQUADFI
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Quadrivalent meningococcal conjugate vaccine.
	Summary of mode action: Meningococci are transmitted from person-to-person by respiratory droplets or secretions. Factors governing virulence of the meningococci strains are host and bacteria dependent. The most important host-dependent factor is the presence of serum bactericidal antibodies that neutralize the organism by complement-mediated bacteriolysis. The capsule is a major virulence factor of *N. meningitidis*. Anti-capsular meningococcal antibodies can protect against MD via complement mediated bactericidal activity. MENQUADFI induces the production of bactericidal antibodies specific to the capsular polysaccharides of *N. Meningitidis* serogroups A, C, W and Y.
	Important information about its composition: The Drug Product, Meningococcal Polysaccharide (Serogroups A, C, W-135 and Y) Tetanus Toxoid Conjugate Vaccine, is a 0.5 mL unit dose liquid presentation for IM use. The formulation contains four drug substances comprised of the serogroup-specific polysaccharide antigens purified from *N. meningitidis* serogroups A, C, W and Y, separately conjugated to tetanus toxoid prepared from cultures of *Clostridium tetani*.

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	The drug product vaccine formulation is prepared as a sterile, aqueous solution containing sodium acetate and sodium chloride buffers. No preservative. No adjuvant.
Hyperlink to the product information	Refer to e-CTD Module 1 - Section 1.3.1 SmPC, Labelling and Package Leaflet
Indication(s) in the EEA	Current: Active immunization of individuals from the age of 12 months and older, against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W and Y.
	Proposed: Not applicable
Dosage in the EEA	Current: Individuals 12 months of age and older receive a single 0.5 mL dose Method of administration: MENQUADFI should be administered by IM route only.
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: Solution for injection in single 0.5 mL dose vial: 10 micrograms of each meningococcal polysaccharide serogroup A, C, W and Y conjugated to approximately 55 μg of Tetanus Toxoid carrier protein/0.5 mL.
	Proposed: Not applicable
Is/will the product (be) subject to additional monitoring in the EU?	Yes

a Conjugated to tetanus toxoid carrier protein

ATC: Anatomical Therapeutic Chemical; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; IM: Intramuscular; INN: International Nonproprietary Name; MD: Meningococcal Disease; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

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RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Meningococcal Polysaccharide (Serogroups A, C, W-135 and Y) Tetanus Toxoid Conjugate Vaccine, hereafter referred to as MenACYW conjugate vaccine, is targeted for the active immunization of individuals from the age of 12 months and older, against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W and Y. The current EU registration submission covers the immunization of individuals 12 months of age and above. The epidemiology of the disease is briefly summarized in the following paragraphs and table.

General considerations

The epidemiology of *N. meningitidis* can be described as complex, unpredictable, geographically variable and changing over time. Meningococcal disease occurs worldwide in both endemic and epidemic forms with seasonal variation. *N. meningitidis* only infects humans; there is no animal reservoir. The bacteria are transmitted from person-to-person through droplets of respiratory or throat secretions from carriers. nasopharyngeal colonization with *N. meningitidis* is observed in 5 to 10% of persons and up to 25% in certain populations (highest in adolescents and closed groups). Only a small proportion (<1 to 5%) progress to invasive meningococcal disease (IMD) (1) The prevalence of carriage varies widely and does not directly predict invasive disease. Any impact on meningococcal carriage will also have an impact on the incidence of IMD. (2)

Genetic analysis of carriage strains has revealed a diverse range of organisms, with only a few of these found to be linked to IMD. Twelve serogroups of *N. meningitidis* have been identified, with 6 serogroups - A, B, C, W, X and Y, being responsible for virtually all invasive disease. The epidemiology of IMD is dynamic, with continuing changes in incidences of *N. meningitidis* serogroups and the emergence of new strain variants. (2)

A systematic review and meta-analysis including studies published from 2000 to 2017 in different geographic regions showed that globally, the highest and the lowest proportion of *N. meningitidis* serogroups in IMD was seen in serogroup B with 48.5% (95% confidence interval [CI]: 45-52) and serogroup X with 0.7% (95% CI: 0.3-1.7), respectively. (3) Among the World Health Organization regional offices, serogroup W with 57.5% (95% CI: 35-77.5) in Eastern Mediterranean, and serogroup Z with 0.1% (95% CI: 0-0.9) in America had the highest and the lowest proportion of *N. meningitidis* serogroups in IMD, respectively.

Serogroup distribution varies geographically and temporally. Currently, meningococcal serogroup B is a major cause of IMD in North America, South America, Australia, North Africa, and Europe, although a decreasing incidence trend is being observed. The incidence and prevalence of serogroup B naturally fluctuates over time and is currently at an all-time low. Meningococcal serogroup C is one of the most prevalent serogroups in Brazil, China, Russia, India, and Niger/Nigeria. In India, serogroup A is the most prevalent whereas in Japan is serogroup Y and in Southern Africa (Mozambique), meningococcal serogroup W. (4)

In Europe, serogroup B is the most frequent (51%) serogroup followed by W (17%) and C (16%). Serogroup B is dominant in all age groups under 65 years of age and account for 70% of IMD in children <5 years of age. Serogroup C is the most prominent in 25-49 year of age, accounting for

27% of cases in this age group. Serogroups W and Y are the most prominent in those ≥65 years of age, causing 30% and 26% of IMD cases respectively in this age group. (1)

In the past few years, there has been an increase of serogroup W in several geographical regions, mostly related to clonal shift in the serogroup W strain from sequence type 22 clonal complex to sequence type 11 clonal complex, a hypervirulent clonal complex that was primarily documented as a serogroup B. (3) In the United Kingdom (UK), a pronounced increase in serogroup W has been observed since 2010, with the number of reported cases due to this serogroup increasing more than tenfold from 2009-2010 (22 cases) to 2016-2017 (225 cases). Genetic analysis showed that the majority of the serogroup W isolates responsible for this rapid increase were from clonal complex 11. Whereas in France the increase in serogroup W was also associated with clonal complex 11, in Italy, this clonal complex was rather associated with an outbreak due to serogroup C. (5) Similar linkage between increase of serogroup W and clonal complex 11 have been observed in countries like Australia, Canada, Argentina and Chile.

Since the introduction of stringent coronavirus disease 2019 infection control and lockdown measures globally in 2020, there has been an impact on IMD epidemiology, and the average number of IMD cases has decreased relative to previous years. Despite this decline, outbreaks still occur in sub-Saharan meningitis belt. Furthermore, outbreaks have also more recently been reported in the EU, UK, Asia-Pacific areas, and United States (US). Surveillance must be maintained at the highest level to track a potential rebound.

Table 6 - Epidemiology of the (untreated) target disease

Indication	**Active immunization of individuals from the age of 12 months and older, against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W and Y.**
Incidence	Invasive meningococcal disease occurs worldwide, with the highest incidence of disease found in the “meningitis belt”, of sub-Saharan Africa. In this region, major epidemics occur every 5 to 12 years with attack rates reaching 1000 cases per 100 000 population. Other regions of the world experience lower overall rates of disease and occasional outbreaks. Annual attack rates in these regions averages around 0.3 to 3 per 100 000 population. (6) Due to diverse standards of IMD surveillance systems globally and country/regional differences in IMD epidemiology and data reporting period, incidence estimates vary significantly. Invasive meningococcal disease reporting rate ranges from 0.01 to 0.02 cases per 100 000 persons per year in Mexico (2014-2017) to 2 to 3.6 cases per 100 000 persons per year in Morocco (2012-2016). The incidence of IMD cases per 100 000 population is 0.70, 0.12, and 0.30 in Europe, US and Canada in 2015, respectively. (4) In Europe, 4 countries - France, Germany, Spain and the UK accounted for 58% of all confirmed cases in 2017. (7) In 2017, the notification rate of IMD was 0.6 cases per 100 000 population, the same as in 2016 and 2015. Four countries - France, Germany, Spain, and the UK accounted for 58% of all confirmed cases in 2017. The highest notification rates were observed in Lithuania (2.4 per 100 000 population), Ireland (1.5), the Netherlands (1.2), and the UK (1.2) while the mean in EU was 0.62. Of the 3221 IMD cases reported in 2017 in 30 EU/EEA countries, 92% had a known serogrouping result. The majority belonged to serogroup B (51%), followed by W (17%) and C (16%). Serogroup B caused the highest proportion of cases in all age groups below 65 years and accounted for 70% of IMD in children under the age

Indication	**Active immunization of individuals from the age of 12 months and older, against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W and Y.**
	of 5 years. Serogroup C was most prominent in 25-49-year-olds, accounting for 27% of cases in this age group. Serogroups W and Y were most prominent in those aged 65 years and above, causing 30% and 26% of IMD cases respectively in this age group. (7)
Prevalence	There are no reliable estimates of MD prevalence.
Demographics of the population in the in the authorized or proposed indication(s), as applicable	Data from the ECDC for 2017, show a notification rate of 8.2 confirmed cases per 100 000 population in children under one year of age followed by a second peak in 15 to 24 year olds, with a rate of 1.0 per 100 000. (7) Data showed higher rates of the disease among males in children <5 years of age, and higher rate of the disease among women in those ≥65 years of age. The overall male-to-female ratio was 1:1. Since 2013, notification rates decreased in all age groups below 15 years of age, remained stable in the age group 15 to 64 years and increased in those ≥65 years old. The rates of IMD are influenced by factors that enhance exposure and transmission, carriage rates of strains with different virulence potential, and host factors. Risk factors for the development of IMD include (8): • Host factors - deficiencies in the terminal common complement pathway - functional or anatomic asplenia - certain genetic factors • Environmental factors - antecedent viral infection - household crowding - active and passive smoking - occupational (microbiologists)
Main existing treatment options	• Treatment The clinical presentation of meningococcal meningitis is similar to other forms of bacterial meningitis. Consequently, empiric therapy with broad-spectrum antibiotics should be started promptly after appropriate cultures have been obtained. (8) A range of antibiotics can treat the infection, including penicillin, ampicillin and ceftriaxone. (9) • Chemoprophylaxis Chemoprophylaxis (antibiotics) is indicated for close contacts of patients with MD. • Vaccines Three quadrivalent meningococcal conjugate vaccine (MENACTRA®, MENVEO®, and NIMENRIX®), which protect against serogroups A, C, Y, and W, two serogroup B vaccines (BEXSERO® and TRUMENBA®), four monovalent vaccines against serogroup C (NEISVAC-C®, MENJUGATE®, and MENITORIX® [MENITORIX also contains Haemophilus influenzae type B]), and one monovalent vaccine against serogroup A (MENAFRIVAC®) are currently available for use for active immunization against MD in various age groups.
Natural history of the indicated condition in the untreated population including mortality and morbidity	Meningitis (30 to 60%) and sepsis (20 to 30%) are the major clinical features of IMD. (1) Less common presentations of IMD include pneumonia (5 to 15% of cases), arthritis (2%), otitis media (1%), and epiglottitis (less than 1%). (8) Invasive meningococcal disease is fatal in as many as 50 to 80% of untreated cases, (2) and the CFR of MD is 10 to 15%, even with appropriate antibiotic therapy. The CFR of meningococcemia can be as high as 40%. (8)

Indication	**Active immunization of individuals from the age of 12 months and older, against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W and Y.**
	In a recent meta-analysis including 40 studies (163 758 MD patients), 29 studies were used to estimate the overall CFR with 21 studies used to derive pooled estimates of CFRs by serogroup, and 28 studies used to examine the age effect on CFR. (10) The overall CFR from IMD ranged from 4.1 to 20.0% with the pooled overall CFR of 8.3% (95% CI: 7.5-9.1%). The highest pooled CFR was observed for serogroup W (12.8%) followed by serogroups C (12.0%), Y (10.8%) and B (6.9%). Predicted CFRs for laboratory confirmed cases by age were non-linear; decreased from 9.0% in infants to 7.0% in 7 year olds, gradually increased to 10.4% in adolescents aged 16 years, reached a peak of 15.0% in young adults aged 28 years, remained steady in adults aged between 28 and 45 years, rose rapidly in older adulthood, and reached 32.8% in 80 year olds. Case-fatality ratio doubled with age from 15% in young adults to 30% in those aged around 75 years. In Europe for 2017, the CFR was 10% among cases with known outcome. Of the four most common serogroups, CFR was highest among cases of serogroup W (14%) and C (15%), followed by Y (8%) and B (7%). Case-fatality ratio was highest in cases aged 65 years and over (18%), followed by the age group of 50 to 64 year olds (10%). (7)As many as 20% of survivors have permanent sequelae, such as include hearing loss, neurologic disability, cognitive deficits, seizure disorders, skin scarring, or limb loss. (8)
Important co-morbidities	No specificity of the target population is identified according to the demographic information provided above; therefore it is expected that co-morbidities in the treated population are broadly similar to those in the general population.

CFR: Case-Fatality Rate; CI: Confidence Interval; ECDC: European Center for Disease Prevention and Control; EEA: European Economic Area; EU: European Union; IMD: Invasive Meningococcal Disease; MD: Meningococcal Disease; UK: United Kingdom; US: United States.

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RISK MANAGEMENT PLAN - PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The preclinical development of MenACYW conjugate vaccine was conducted as following:

For the non-clinical safety evaluation of MenACYW conjugate vaccine, a repeat-dose toxicity study in the rat (Study AES/0126) was conducted to evaluate its systemic and local toxicity and to support its use in human clinical trials. A developmental and reproductive toxicity (DART) study (Study SP0047 DV1701) was conducted in the rabbit to evaluate the risk of vaccination in women of childbearing potential. (11)

The rat and the rabbit were selected for the repeat-dose toxicity study and the DART study, respectively, as they are established models for these toxicity assessments of vaccines and they elicit an immune response to group A, C, W and Y meningococcal polysaccharides following IM injections of MenACYW conjugate vaccine.

One human dose of MenACYW conjugate vaccine given to rats on four occasions by the IM route was well tolerated with no systemic or local signs of toxicity observed.

The DART study showed no adverse effects on mating performance or fertility. There was no indication of maternal systemic toxicity induced during the gestation and lactation periods, no effect on pre- and post-natal development and no indication of a teratogenic potential.

The key non-clinical findings are presented in the following table.

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • Reproductive/developmental toxicity studies: Vaccination of rabbits with repeated IM administrations at one human dose before and during gestation showed no adverse effect.	Developmental and reproductive effects are unlikely to occur in humans.
Other toxicity-related information or data • Systemic and local toxicity: Vaccination of rats with repeated IM administrations at one human dose showed no safety concern.	Systemic or local toxicity are unlikely to occur in humans.

IM: Intramuscular.

No specific juvenile toxicity study was conducted to support the administration of MenACYW conjugate vaccine in the pediatric population as the study conducted in young adult rats was considered supportive of the pediatric population and no specific risk was identified from the clinical trials in the pediatric population.

No genotoxicity evaluation was performed as the vaccine was not considered to have any genotoxicity potential.

[redacted]

[redacted]

No carcinogenicity evaluation was performed as the vaccine was not considered to have any carcinogenicity potential.

No safety pharmacology study was conducted as no specific risk was identified.

No toxicological evaluation of vaccine-drug interactions was conducted during the development program.

There were no safety concerns identified on the basis of non-clinical safety data and no further non-clinical studies were considered necessary.

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RISK MANAGEMENT PLAN - PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

Since the development international birth date (DIBD) to 19 April 2023, a total of 23 915 subjects were exposed to MenACYW conjugate vaccine/or control/comparator vaccines, of which approximately 10 207 subjects have received MenACYW conjugate vaccine (different formulations), as well as a still unknown number of subjects in the ongoing blinded clinical trials MET41, MET42, MET55, MET58 (except Group 3/Group 4) and MET61 (total number of subjects who received at least one injection in these blinded trials: 9022 subjects). Subjects received single or multiple doses of MenACYW conjugate vaccine, given alone or with at least one concomitant vaccine. Estimates of overall cumulative subject exposure are provided in Table 8, based on actual data from completed studies, and/or the enrollment/randomization schemes from ongoing studies.

The cumulative exposure of MenACYW conjugate vaccine by demographic characteristics is listed in Table 9.

Table 8 - Cumulative exposure data based on actual exposure and enrollment estimates

Trial Identifier	Treatment Group	Number of Subjects
MET28	Low Dose 2 μg[a]	132
	High Dose 10μg	78
	Control: MENJUGATE	44
MET32	Low Dose 4 μg[b]	123
	Intermediate Dose 4-10 ug	61
	High Dose 10 μg[b]	122
	Control: NEISVAC-C	62
MET35	MenACYW Conjugate Vaccine	498
	Control: MENVEO	494
MET39	High Dose 10 μg	468
	Other comparator: Routine Pediatric Vaccines	108
MET43	MenACYW Conjugate Vaccine	2681
	Control: MENACTRA	636
MET44	High Dose 10 μg	201
	Control: MENOMUNE®	100
MET49	MenACYW Conjugate Vaccine	448
	Control: MENOMUNE	453
MET50	MenACYW Conjugate Vaccine	503
	MenACYW Conjugate Vaccine + Tdap + HPV	392
	Control: MENVEO	501
	Other comparator: Tdap + HPV	296
MET51	Group 1: MenACYW Conjugate Vaccine - Naive	303

Trial Identifier	Treatment Group	Number of Subjects
	Control: Group 2 NIMENRIX - Naive	306
	Group 3: MenACYW Conjugate Vaccine - MenC primed	203
	Control: Group 4 NIMENRIX - MenC primed	102
MET54	MenACYW Conjugate Vaccine	94
	Control: NIMENRIX	94
MET56	MenACYW Conjugate Vaccine	402
	Control: MENACTRA	407
MET57	Group 1: MenACYW Conjugate Vaccine + MMR + V	103
	Group 2: MenACYW Conjugate Vaccine	52
	Group 3: MMR + V	53
	Group 4: MenACYW Conjugate Vaccine + DTaP-IPV-HB-Hib	200
	Group 5: MenACYW Conjugate Vaccine	100
	Group 6: DTaP-IPV-HB-Hib	100
	Group 7: MenACYW Conjugate Vaccine + PCV13	200
	Group 8: MenACYW Conjugate Vaccine	100
	Group 9: PCV13	99
	Group 10: MenACYW Conjugate Vaccine + MMR + V	86
	Group 11: MenACYW Conjugate Vaccine	42
	Group 12: MMR + V	42
MET59	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine	189
	MENVEO primed + MenACYW Conjugate Vaccine	188
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine + TRUMENBA	93
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine + BEXSERO	92
	Other	8
MET62	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine	42
	NIMENRIX primed + MenACYW Conjugate Vaccine	49
MEQ00065	MenACYW Conjugate Vaccine	230
	Control: NEISVAC-C	239
	Control: NIMENRIX	232
MEQ00068	MenACYW Conjugate Vaccine	179
	Control: MENACTRA	180
MET33	Group 1: MenACYW Conjugate Vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)	201
	Control: Group 2: MENVEO at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)	99

Trial Identifier	Treatment Group	Number of Subjects
	Group 3: MenACYW Conjugate Vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)	150
	Other comparator: Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)	75
MET52	Group 1: MenACYW Conjugate Vaccine at 3 months and at 12 to 13 months of age; BEXSERO at 2, 4, and 12 to 13 months of age	313
	Group 2: MenACYW Conjugate Vaccine at 3 months and at 12 to 13 months of age; BEXSERO at 2 and 4 months of age	315
	Other comparator: Group 3: BEXSERO at 2, 4, and 12 to 13 months of age	157
	Other	1
MEQ00063	MenACYW Conjugate Vaccine	288
MEQ00064	Group 3: MenACYW Conjugate Vaccine at 7 and between 12 to 16 months of age + co-administered routine pediatric vaccines (Republic of South Africa)	10
	Control: Group 4: MENACTRA vaccine at 9 and between 12 to 16 months of age + co-administered routine pediatric vaccines (Republic of South Africa)	12
MEQ00066	MENOMUNE primed + MenACYW Conjugate Vaccine at stage I	151
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine at stage I	162
	MENOMUNE primed + MenACYW Conjugate Vaccine at stage II	27
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine at stage II	25
MEQ00073	MenACYW Conjugate Vaccine at enrollment primed with MenACYW Conjugate Vaccine	91
	Other	1
MET41	MenACYW Conjugate Vaccine/MENVEO and routine pediatric vaccines (blinded)	2777
MET42	MenACYW Conjugate Vaccine/MENVEO (blinded)	2594
MET55	MenACYW Conjugate Vaccine/MENACTRA/QUADRI MENINGO® (blinded)	1318
MET58	Group 1/Group 2: MenACYW Conjugate Vaccine (2+1 regimen)/NIMENRIX (2+1 regimen) and routine vaccines (DTAP-IPV-HB-HIB + SYNFLORIX® + M-M-RVAXPRO®) (blinded)	1403
	Group 3/Group 4: MenACYW Conjugate Vaccine (2+1 regimen/3+1 regimen) and routine vaccines (DTAP-IPV-HB-HIB + PREVNAR 13® + M-M-RVAXPRO)	220
MET61	MenACYW Conjugate Vaccine/MENVEO (blinded)	731
	MenACYW Conjugate Vaccine/MENACTRA (blinded)	199
MEQ00071	MenACYW Conjugate Vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31	171
	Control: NIMENRIX on D01 and 9vHPV + Tdap-IPV vaccines on D31	171

[redacted]

Trial Identifier	Treatment Group	Number of Subjects
	MenACYW Conjugate Vaccine + 9vHPV + Tdap-IPV on D01	116
	Subtotal: All MenACYW Conjugate Vaccine Treatments	**10 207**
	Subtotal: All Control Treatments	**4132**
	Subtotal: All Other Comparator Treatments	**932**
	Subtotal: All Blinded Treatments	**9022**
	Total Number of Subjects	**23 915**

Included in this table are subjects who had at least one injection between 16-Jun-2006 through 19-Apr-2023.

a Contains both adjuvant and non-adjuvant groups.

b Contains formulation 1 and formulation 2.

Note for subtotal:

Note 1: All subjects who received their first dose of MenACYW Conjugate Vaccine, counted only once at the age when they actually received the first dose of MenACYW Conjugate Vaccine.

Note 2: For subjects who received a control or comparator as priming dose and received a booster dose of MenACYW Conjugate Vaccine, they will be counted as exposed to MenACYW Conjugate Vaccine at the age when they received their first dose of MenACYW Conjugate Vaccine.

Note 3: 1 subject in MET28 received both Low Dose and High Dose of MenACYW Conjugate Vaccine.

Note 4: 5 subjects from MET28 group 8 (controls) received a booster dose of Low Dose 2 µg + Adjuvant AlPO4 six months later.

Note 5: 42 subjects who were primed with MenACYW Conjugate Vaccine in MET54, received a booster dose 3 years after in MET62 study.

Note 6: 374 subjects who were primed with MenACYW Conjugate Vaccine in MET50 or MET43, received a booster dose 3-6 years after in MET59 study.

Note 7: 135 subjects who were primed with MENVEO in MET50 received a MenACYW Conjugate Vaccine in MET59 study, among them, five subjects who were primed with MENVEO in MET50 when they were adolescent, and then received MenACYW Conjugate Vaccine in MET59 when they were adult.

Note 8: 7 subjects received Tdap + HPV in MET50 and received MenACYW Conjugate Vaccine in MET59 study.

Note 9: 4 subjects who were primed with MENACTRA in MET43, received MenACYW Conjugate Vaccine in MET59 study.

Note 10: 187 subjects who were primed with MenACYW Conjugate Vaccine in MET49, received a booster dose 3-6 years after in MEQ00066 study.

Note 11: 178 subjects received MENOMUNE in MET49 and received MenACYW Conjugate Vaccine in MEQ00066 study.

Note 12: 49 subjects who received NIMENRIX in MET54 when they were toddlers, and then received MenACYW Conjugate Vaccine in MET62 when they were children.

Note 13: 91 subjects who were primed with MenACYW Conjugate Vaccine in MET51, received a booster dose 5 years after in MEQ00073 study.

Note 14: Treatment assignment of MET41, MET42, MET55, MET58 (except Group 3/Group 4) and MET61 are blinded.

DTaP-IPV-HB-Hib: Diphtheria, Tetanus, Acellular Pertussis, Hepatitis B, Poliomyelitis and Haemophilus Influenzae Type-B; HPV: Human Papillomavirus; MenB: Meningococcal serogroup B; MenB-FHbp: Meningococcal serogroup B-factor H-binding protein; MenC: Meningococcal Serogroup C; MMR: Measles, Mumps and Rubella; PCV13: Pneumococcal 13-Valent Conjugate; Tdap: Tetanus, Diphtheria and Acellular Pertussis; Tdap-IPV: Tetanus, Diphtheria, Acellular Pertussis and Poliomyelitis; V: Varicella.

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Table 9 - Cumulative subject exposure to investigational drug from completed and ongoing studies by age and sex

		Number of Subject			
Age Range	**Treatment Group**	**Female**	**Male**	**Unknown**	**Total**
Unknown	Group 4: MENACTRA vaccine at 9 and between 12 to 16 months of age + co-administered routine pediatric vaccines (RSA) (MEQ00064)	0	1	0	1
	MenACYW Conjugate Vaccine/MENVEO (blinded) (MET61)	1	1	0	2
	Unknown subtotal	1	2	0	3
Infant (1m to 11m)	Low Dose 2 μg and routine pediatric vaccines (MET28)[a]	44	52	0	96
	High Dose 10 μg and routine pediatric vaccines (MET28)	18	26	0	44
	MENJUGATE (MET28)	25	19	0	44
	High Dose 10 μg and routine pediatric vaccines (MET39)	201	195	0	396
	Routine Pediatric Vaccines (MET39)	44	64	0	108
	Group 1: MenACYW Conjugate Vaccine and routine pediatric vaccines in Mexico (MET33)	100	101	0	201
	Group 2: MENVEO and routine pediatric vaccines in Mexico (MET33)	54	45	0	99
	Group 3: MenACYW Conjugate Vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation) (MET33)	69	81	0	150
	Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation) (MET33)	48	27	0	75
	Group 1: MenACYW Conjugate Vaccine at 3 months and at 12 to 13 months of age; BEXSERO at 2, 4, and 12 to 13 months of age (MET52)	147	166	0	313
	Group 2: MenACYW Conjugate Vaccine at 3 months and at 12 to 13 months of age; BEXSERO at 2 and 4 months of age (MET52)	154	161	0	315
	Group 3: BEXSERO at 2, 4, and 12 to 13 months of age (MET52)	81	76	0	157
	Other (MET52)	0	1	0	1
	Group 3: MenACYW Conjugate Vaccine at 6 and between 12 to 16 months of age + co-administered routine pediatric vaccines (RSA) (MEQ00064)	3	6	0	9

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		Number of Subject			
Age Range	**Treatment Group**	**Female**	**Male**	**Unknown**	**Total**
	Group 4: MENACTRA vaccine at 9 and between 12 to 16 months of age + co-administered routine pediatric vaccines (RSA) (MEQ00064)	6	4	0	10
	MenACYW Conjugate Vaccine/MENVEO and routine pediatric vaccines (blinded) (MET41)	1329	1448	0	2777
	MenACYW Conjugate Vaccine/MENVEO (blinded) (MET42)	1226	1368	0	2594
	Group 1/Group 2: MenACYW Conjugate Vaccine (2+1 regimen)/NIMENRIX (2+1 regimen) and routine vaccines (DTaP-IPV-HB-HIB + SYNFLORIX + M-M-RVAXPRO) (blinded) (MET58)	713	690	0	1403
	Group 3/Group 4: MenACYW Conjugate Vaccine (2+1 regimen/3+1 regimen) and routine vaccines (DTaP-IPV-HB-HIB + PREVNAR 13 + M-M-RVAXPRO) (MET58)	103	117	0	220
	MenACYW Conjugate Vaccine/MENVEO (blinded) (MET61)	341	388	0	729
	Infant subtotal	4704	5031	0	9735
Toddler (>11m to 23m)	Low Dose 2 μg (MET28)	7	14	0	21
	High Dose 10 μg (MET28)	7	12	0	19
	Low Dose 4 μg (MET32)[b]	56	67	0	123
	Intermediate Dose 4-10 μg (MET32)	37	24	0	61
	High Dose 10 μg (MET32)[b]	56	66	0	122
	NEISVAC-C (MET32)	30	32	0	62
	High Dose 10 μg and routine pediatric vaccines (MET39)	28	44	0	72
	Group 1 MenACYW Conjugate Vaccine - Naive (MET51)	137	166	0	303
	Group 2 NIMENRIX - Naive (MET51)	145	161	0	306
	Group 3 MenACYW Conjugate Vaccine - MenC primed (MET51)	97	106	0	203
	Group 4 NIMENRIX- MenC primed (MET51)	53	49	0	102
	MenACYW Conjugate Vaccine (MET54)	37	57	0	94
	NIMENRIX (MET54)	53	41	0	94
	Group 1: MenACYW Conjugate Vaccine + MMR + V (MET57)	45	58	0	103
	Group 2: MenACYW Conjugate Vaccine (MET57)	17	35	0	52

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		Number of Subject			
Age Range	**Treatment Group**	**Female**	**Male**	**Unknown**	**Total**
	Group 3: MMR + V (MET57)	29	24	0	53
	Group 4: MenACYW Conjugate Vaccine + DTaP-IPV-HB-Hib (MET57)	93	107	0	200
	Group 5: MenACYW Conjugate Vaccine (MET57)	46	54	0	100
	Group 6: DTaP-IPV-HB-Hib (MET57)	48	52	0	100
	Group 7: MenACYW Conjugate Vaccine + PCV13 (MET57)	78	122	0	200
	Group 8: MenACYW Conjugate Vaccine (MET57)	51	49	0	100
	Group 9: PCV13 (MET57)	45	54	0	99
	Group 10: MenACYW Conjugate Vaccine + MMR + V (MET57)	47	39	0	86
	Group 11: MenACYW Conjugate Vaccine (MET57)	23	19	0	42
	Group 12: MMR + V (MET57)	23	19	0	42
	MenACYW Conjugate Vaccine (MEQ00065)	115	115	0	230
	NEISVAC-C (MEQ00065)	108	131	0	239
	NIMENRIX (MEQ00065)	106	126	0	232
	Group 3: MenACYW Conjugate Vaccine at 6 and between 12 to 16 months of age + co-administered routine pediatric vaccines (RSA) (MEQ00064)	1	0	0	1
	Group 4: MENACTRA vaccine at 9 and between 12 to 16 months of age + co-administered routine pediatric vaccines (RSA) (MEQ00064)	0	1	0	1
	MenACYW Conjugate Vaccine/MENACTRA (blinded) (MET61)	100	99	0	199
	Toddler subtotal	1688	1924	0	3612
Children (2y to 9y)	Group 1: MenACYW Conjugate Vaccine (MET35)	244	254	0	498
	Group 2: MENVEO (MET35)	232	262	0	494
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine (MET62)	16	26	0	42
	NIMENRIX® primed + MenACYW Conjugate Vaccine (MET62)	30	19	0	49
	MenACYW Conjugate Vaccine (MEQ00068)	2	2	0	4

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		Number of Subject			
Age Range	**Treatment Group**	**Female**	**Male**	**Unknown**	**Total**
	MENACTRA (MEQ00068)	2	2	0	4
	MenACYW Conjugate Vaccine at enrollment primed with MenACYW Conjugate Vaccine (MEQ00073)	35	56	0	91
	Other (MEQ00073)	0	1	0	1
	MenACYW Conjugate Vaccine/MENACTRA/QUADRI MENINGO (blinded) (MET55)	229	230	0	459
	Children subtotal	739	770	0	1509
Adolescent (10y to 17y)	Group 1: MenACYW Conjugate Vaccine (Lot 1) (MET43)	189	209	0	398
	Group 2: MenACYW Conjugate Vaccine (Lot 2) (MET43)	212	181	0	393
	Group 3: MenACYW Conjugate Vaccine (Lot 3) (MET43)	175	219	0	394
	Group 4: MENACTRA (MET43)	139	185	0	324
	MenACYW Conjugate Vaccine (MET50)	260	243	0	503
	MenACYW Conjugate Vaccine + Tdap + HPV (MET50)	191	201	0	392
	MENVEO (MET50)	229	272	0	501
	Tdap + HPV (MET50)	141	155	0	296
	MenACYW Conjugate Vaccine (MET56)	89	124	0	213
	MENACTRA (MET56)	96	117	0	213
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine (MET59)	90	90	0	180
	MENVEO primed + MenACYW Conjugate Vaccine (MET59)	80	97	0	177
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine + TRUMENBA (MET59)	41	51	0	92
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine + BEXSERO (MET59)	41	48	0	89
	Other (MET59)	3	5	0	8
	MenACYW Conjugate Vaccine (MEQ00068)	28	25	0	53
	MENACTRA (MEQ00068)	30	25	0	55
	MenACYW Conjugate Vaccine/MENACTRA/QUADRI MENINGO (blinded) (MET55)	222	239	0	461

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		Number of Subject			
Age Range	**Treatment Group**	**Female**	**Male**	**Unknown**	**Total**
	MenACYW Conjugate Vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31 (MEQ00071)	48	123	0	171
	NIMENRIX on D01 and 9vHPV + Tdap-IPV vaccines on D31 (MEQ00071)	56	115	0	171
	MenACYW Conjugate Vaccine + 9vHPV + Tdap-IPV on D01 (MEQ00071)	45	71	0	116
	Adolescent subtotal	2169	2524	0	4693
Adult (18y to 55y)	Low Dose 2 μg (MET28)	10	5	0	15
	High Dose 10 μg (MET28)	12	3	0	15
	Group 1: MenACYW Conjugate Vaccine (Lot 1) (MET43)	342	155	0	497
	Group 2: MenACYW Conjugate Vaccine (Lot 2) (MET43)	316	177	0	493
	Group 3: MenACYW Conjugate Vaccine (Lot 3) (MET43)	317	189	0	506
	Group 4: MENACTRA (MET43)	216	96	0	312
	MenACYW Conjugate Vaccine (MET56)	118	71	0	189
	MENACTRA (MET56)	104	89	0	193
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine (MET59)	7	2	0	9
	MENVEO primed + MenACYW Conjugate Vaccine (MET59)	5	6	0	11
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine + TRUMENBA (MET59)	0	1	0	1
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine + BEXSERO (MET59)	3	0	0	3
	MenACYW Conjugate Vaccine (MEQ00068)	54	68	0	122
	MENACTRA (MEQ00068)	63	58	0	121
	MenACYW Conjugate Vaccine/MENACTRA/QUADRI MENINGO (blinded) (MET55)	61	137	0	198
	Adult subtotal	1618	1054	0	2672
	High Dose 10 μg (MET44)	121	80	0	201

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		Number of Subject			
Age Range	**Treatment Group**	**Female**	**Male**	**Unknown**	**Total**
Older Adults (56y and older)	MENOMUNE (MET44)	55	45	0	100
	MenACYW Conjugate Vaccine (MET49)	258	190	0	448
	MENOMUNE (MET49)	259	194	0	453
	MENACTRA (MET56)	0	1	0	1
	MenACYW Conjugate Vaccine (MEQ00063)	101	187	0	288
	MENOMUNE primed + MenACYW Conjugate Vaccine at stage I (MEQ00066)	94	57	0	151
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine at stage I (MEQ00066)	102	60	0	162
	MENOMUNE® primed + MenACYW Conjugate Vaccine at stage II (MEQ00066))	14	13	0	27
	MenACYW Conjugate Vaccine primed + MenACYW Conjugate Vaccine at stage II (MEQ00066)	17	8	0	25
	MenACYW Conjugate Vaccine/MENACTRA/QUADRI MENINGO (blinded) (MET55)	55	145	0	200
	Older adults subtotal	849	842	0	1691
Subtotal: Unknown		1	2	0	3
Subtotal: All Control Treatments		0	1	0	1
Subtotal: All Blinded Treatments		1	1	0	2
Subtotal: Pediatric population (from 6 weeks old to <18 years old)		9300	10 249	0	19 549
Subtotal: All MenACYW		3412	3832	0	7244

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		Number of Subject			
Age Range	**Treatment Group**	**Female**	**Male**	**Unknown**	**Total**
Conjugate Vaccine Treatments					
Subtotal: All Control Treatments		1364	1587	0	2951
Subtotal: All Other Comparator Treatments		460	472	0	932
Subtotal: All Blinded Treatments		4160	4462	0	8622
Subtotal: Adult population (from 18 years and above)		2467	1896	0	4363
Subtotal: All MenACYW Conjugate Vaccine Treatments		1762	1201	0	2963
Subtotal: All Control Treatments		697	483	0	1180
Subtotal: All Blinded Treatments		116	282	0	398
Total Number of Subjects		11 768	12 147	0	23 915

Included in this table are subjects who had at least one injection between 16-Jun-2006 through 19-Apr-2023.

a Contains both adjuvant and non-adjuvant groups.

b Contains formulation 1 and formulation 2.

Note for subtotal:

Note 1: All subjects who received their first dose of MenACYW Conjugate Vaccine, counted only once at the age when they actually received the first dose of MenACYW Conjugate Vaccine.

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		Number of Subject			
Age Range	**Treatment Group**	**Female**	**Male**	**Unknown**	**Total**

Note 2: For subjects who received a control or comparator as priming dose and received a booster dose of MenACYW Conjugate Vaccine, they will be counted as exposed to MenACYW Conjugate Vaccine at the age when they received their first dose of MenACYW Conjugate Vaccine.
Note 3: 1 subject in MET28 received both Low Dose and High Dose of MenACYW Conjugate Vaccine.
Note 4: 5 subjects from MET28 group 8 (controls) received a booster dose of Low Dose 2 µg + Adjuvant AlPO4 six months later.
Note 5: 42 subjects who were primed with MenACYW Conjugate Vaccine in MET54, received a booster dose 3 years after in MET62 study.
Note 6: 374 subjects who were primed with MenACYW Conjugate Vaccine in MET50 or MET43, received a booster dose 3-6 years after in MET59 study.
Note 7: 135 subjects who were primed with MENVEO in MET50 received a MenACYW Conjugate Vaccine in MET59 study, among them, five subjects who were primed with MENVEO in MET50 when they were adolescent, and then received MenACYW Conjugate Vaccine in MET59 when they were adult.
Note 8: 7 subjects received Tdap + HPV in MET50 and received MenACYW Conjugate Vaccine in MET59 study.
Note 9: 4 subjects who were primed with MENACTRA in MET43, received MenACYW Conjugate Vaccine in MET59 study.
Note 10: 187 subjects who were primed with MenACYW Conjugate Vaccine in MET49, received a booster dose 3-6 years after in MEQ00066 study.
Note 11: 178 subjects received MENOMUNE in MET49 and received MenACYW Conjugate Vaccine in MEQ00066 study.
Note 12: 49 subjects who received NIMENRIX in MET54 when they were toddler, and then received MenACYW Conjugate Vaccine in MET62 when they were children.
Note 13: 91 subjects who were primed with MenACYW Conjugate Vaccine in MET51, received a booster dose 5 years after in MEQ00073 study.
Note 14: Treatment assignment of MET41, MET42, MET55, MET58 (except Group 3/Group 4) and MET61 are blinded.
DTaP-IPV-HB-Hib: Diphtheria, Tetanus, Acellular Pertussis, Hepatitis B, Poliomyelitis and Haemophilus Influenzae Type-B; HPV: Human Papillomavirus; MenC: Meningococcal Serogroup C; MMR: Measles, Mumps and Rubella; PCV13: Pneumococcal 13-Valent Conjugate; Tdap: Tetanus, Diphtheria and Acellular Pertussis; Tdap-IPV: Tetanus, Diphtheria, Acellular Pertussis and Poliomyelitis; V: Varicella.

Table 10 - Exposure by age group and gender MenACYW conjugate vaccine given alone

		MenACYW conjugate vaccine[a]								
			Gender			Age (years/month)[b]				
Age Group	**Study**	**N**	**M**	**Female n(%)**	**Male n(%)**	**M**	**Mean (SD)**	**Min; Max**	**Median**	**Q1:Q3**
All	**All**	5620	5620	3047 (54.2)	2573 (45.8)	5620	23.9 (21.60)	1.0; 89.8	13.1	10.0; 39.4
	MET35	498	498	244 (49.0)	254 (51.0)	498	6.0 (2.32)	2.0; 10.0	6.0	4.0; 8.0
	MET43	2676	2676	1549 (57.9)	1127 (42.1)	2676	27.4 (15.58)	10.0; 56.0	25.8	11.7; 41.1
	MET44	199	199	121 (60.8)	78 (39.2)	199	66.1 (7.13)	56.0; 86.8	65.0	60.1; 70.4
	MET49	448	448	258 (57.6)	190 (42.4)	448	67.0 (7.52)	56.0; 89.8	65.9	60.5; 71.2

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		MenACYW conjugate vaccine[a]								
			Gender			Age (years/month)[b]				
Age Group	Study	N	M	Female n(%)	Male n(%)	M	Mean (SD)	Min; Max	Median	Q1:Q3
	MET50	503	503	260 (51.7)	243 (48.3)	503	11.4 (1.39)	10.0; 18.0	11.1	10.5; 11.8
	MET51	506	506	234 (46.2)	272 (53.8)	506	15.6 (3.44)	12.0; 24.0	14.0	13.0; 17.8
	MET54	94	94	37 (39.4)	57 (60.6)	94	17.3 (3.63)	12.0; 24.0	16.8	14.0; 20.5
	MET56	402	402	207 (51.5)	195 (48.5)	402	20.0 (5.97)	15.1; 55.5	17.8	16.5; 22.0
	MET57	294	294	137 (46.6)	157 (53.4)	294	15.7 (3.19)	12.0; 24.0	14.4	12.9; 18.0
All Toddlers (12 through 23 months old)	Pooled MET51 and MET54	600	600	271 (45.2)	329 (54.8)	600	15.8 (3.52)	12.0; 24.0	14.5	13.0; 18.6
	Pooled MET51, MET54 and MET57	894	894	408 (45.6)	486 (54.4)	894	15.8 (3.42)	12.0; 24.0	14.4	13.0; 18.1
All Children (2 through 9 years old)	MET35	498	498	244 (49.0)	254 (51.0)	498	6.0 (2.32)	2.0; 10.0	6.0	4.0; 8.0
All Adolescents (10 through 17 years old)	Pooled MET43, MET50 and MET56	1897	1897	924 (48.7)	973 (51.3)	1897	12.4 (2.29)	10.0; 18.0	11.5	10.8; 13.1
All Adults (18 years old and above)	Pooled MET43, MET44, MET49 and MET56	2331	2331	1471 (63.1)	860 (36.9)	2331	45.7 (16.48)	18.0; 89.8	45.1	32.0; 57.9
Adults (18 through 55 years old)	Pooled MET43 and MET56	1684	1684	1092 (64.8)	592 (35.2)	1684	37.7 (10.99)	18.0; 56.0	37.6	28.5; 47.5
Older Adults and Elderly (56 years old and above)	Pooled MET44, MET49 and MET56	647	647	379 (58.6)	268 (41.4)	647	66.7 (7.41)	56.0; 89.8	65.8	60.4; 71.0
Older Adults (56 through 64 years old)	Pooled MET44, MET49 and MET56	298	298	173 (58.1)	125 (41.9)	298	60.3 (2.62)	56.0; 65.0	60.1	58.2; 62.7
Elderly (65 years old and above)	Pooled MET44 and MET49	349	349	206 (59.0)	143 (41.0)	349	72.1 (5.62)	65.0; 89.8	70.7	68.0; 75.2
65 through 74 years old	Pooled MET44 and MET49	258	258	155 (60.1)	103 (39.9)	258	69.3 (2.66)	65.0; 74.9	69.2	67.0; 71.2

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		MenACYW conjugate vaccine[a]								
			Gender			Age (years/month)[b]				
Age Group	Study	N	M	Female n(%)	Male n(%)	M	Mean (SD)	Min; Max	Median	Q1:Q3
75 years old and above	Pooled MET44 and MET49	91	91	51 (56.0)	40 (44.0)	91	80.0 (4.04)	75.0; 89.8	78.5	76.7; 83.5

Abbreviations: n, number of subjects fulfilling the characteristic listed; M, number of subjects with available data for the relevant endpoint; N, number of subjects in the Safety Analysis Set;
The values SD in parentheses represent standard deviations Q1, first quartile; Q3, third quartile; SD, standard deviation; Percentages are based on M.

a MenACYW conjugate vaccine group only includes the subjects who received MenACYW conjugate vaccine alone at Visit 01, and excludes the subjects who received MenACYW+Concomitant vaccines at Visit 01.

b Age is presented in months for toddlers and in years for other subjects. For the quantitative descriptive statistics: Age in months = (Date of first vaccination - Date of birth + 1) / (365.25 / 12), Age in years = (Date of first vaccination - Date of birth + 1) / 365.25. If date of birth was not collected, the calendar age collected in CRF was used to derive the quantitative descriptive statistics. For "All", age is presented in years.

Contributing studies: MET35, MET43, MET44, MET49, MET50, MET51, MET54, MET56 and MET57.

Table 11 - Exposure by age group, race and ethnic origin - MenACYW conjugate vaccine given alone

		MenACYW conjugate vaccine[a]										
		Race						Ethnicity				
Age Group	Study	M	White n(%)	Black or African American n(%)	Asian n(%)	Other n(%)	Not collected[b] n(%)	M	Hispanic or Latino n(%)	Not Hispanic or Latino n(%)	Missing n(%)	Not collected[b] n(%)
All	All	5620	4258 (75.8)	717 (12.8)	113 (2.0)	253 (4.5)	279 (5.0)	5620	1089 (19.4)	4190 (74.6)	62 (1.1)	279 (5.0)
	MET35	498	401 (80.5)	66 (13.3)	2 (0.4)	29 (5.8)	-	498	114 (22.9)	383 (76.9)	1 (0.2)	-
	MET43	2676	1989 (74.3)	523 (19.5)	47 (1.8)	117 (4.4)	-	2676	572 (21.4)	2100 (78.5)	4 (0.1)	-
	MET44	199	188 (94.5)	7 (3.5)	0 (0.0)	4 (2.0)	-	199	11 (5.5)	188 (94.5)	0 (0.0)	-
	MET49	448	388 (86.6)	52 (11.6)	5 (1.1)	3 (0.7)	-	448	35 (7.8)	412 (92.0)	1 (0.2)	-
	MET50	503	439 (87.3)	30 (6.0)	4 (0.8)	30 (6.0)	-	503	88 (17.5)	412 (81.9)	3 (0.6)	-

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		MenACYW conjugate vaccine[a]										
		Race						Ethnicity				
Age Group	Study	M	White n(%)	Black or African American n(%)	Asian n(%)	Other n(%)	Not collected[b] n(%)	M	Hispanic or Latino n(%)	Not Hispanic or Latino n(%)	Missing n(%)	Not collected[b] n(%)
	MET51	506	312 (61.7)	0 (0.0)	1 (0.2)	8 (1.6)	185 (36.6)	506	106 (20.9)	215 (42.5)	0 (0.0)	185 (36.6)
	MET54	94	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	94 (100.0)	94	0 (0.0)	0 (0.0)	0 (0.0)	94 (100.0)
	MET56	402	342 (85.1)	39 (9.7)	11 (2.7)	10 (2.5)	-	402	63 (15.7)	338 (84.1)	1 (0.2)	-
	MET57	294	199 (67.7)	0 (0.0)	43 (14.6)	0 (0.0)	52 (17.7)	294	100 (34.0)	142 (48.3)	0 (0.0)	52 (17.7)
All Toddlers (12 through 23 months old)	Pooled MET51 and MET54	600	312 (52.0)	0 (0.0)	8 (1.3)	279 (46.5)	279 (70.3)	600	106 (17.7)	215 (35.8)	0 (0.0)	279 (46.5)
	Pooled MET51, MET54 and MET57	894	511 (57.2)	0 (0.0)	44 (4.9)	60 (6.7)	279 (31.2)	894	206 (23.0)	357 (39.9)	52 (5.8)	279 (31.2)
All Children (2 through 9 years old)	MET35	498	401 (80.5)	66 (13.3)	2 (0.4)	29 (5.8)	-	498	114 (22.9)	383 (76.9)	1 (0.2)	-
All Adolescents (10 through 17 years old)	Pooled MET43, MET50 and MET56	1897	1515 (79.9)	259 (13.7)	23 (1.2)	100 (5.3)	-	1897	394 (20.8)	1498 (79.0)	5 (0.3)	-
All Adults (18 years old and above)	Pooled MET43, MET44, MET49 and MET56	2331	1831 (78.5)	392 (16.8)	44 (1.9)	64 (2.7)	-	2331	375 (16.1)	1952 (83.7)	4 (0.2)	-

[redacted]

[redacted]

		MenACYW conjugate vaccine[a]										
		Race						Ethnicity				
Age Group	Study	M	White n(%)	Black or African American n(%)	Asian n(%)	Other n(%)	Not collected[b] n(%)	M	Hispanic or Latino n(%)	Not Hispanic or Latino n(%)	Missing n(%)	Not collected[b] n(%)
Adults (18 through 55 years old)	Pooled MET43 and MET56	1684	1255 (74.5)	333 (19.8)	39 (2.3)	57 (3.4)	-	1684	329 (19.5)	1352 (80.3)	3 (0.2)	-
Older Adults and Elderly (56 years old and above)	Pooled MET44, MET49 and MET56	647	576 (89.0)	59 (9.1)	5 (0.8)	7 (1.1)	-	647	46 (7.1)	600 (92.7)	1 (0.2)	-
Older Adults (56 through 64 years old)	Pooled MET44, MET49 and MET56	298	250 (83.9)	41 (13.8)	4 (1.3)	3 (1.0)	-	298	26 (8.7)	272 (91.3)	0 (0.0)	-
Elderly (65 years old and above)	Pooled MET44 and MET49	349	326 (93.4)	18 (5.2)	1 (0.3)	4 (1.1)	-	349	20 (5.7)	328 (94.0)	1 (0.3)	-
65 through 74 years old	Pooled MET44 and MET49	258	238 (92.2)	17 (6.6)	0 (0.0)	3 (1.2)	-	258	16 (6.2)	242 (93.8)	0 (0.0)	-
75 years old and above	Pooled MET44 and MET49	91	88 (96.7)	1 (1.1)	1 (1.1)	1 (1.1)	-	91	4 (4.4)	86 (94.5)	1 (1.1)	-

Abbreviations: n, number of subjects fulfilling the characteristic listed; M, number of subjects with available data for the relevant endpoint; N, number of subjects in the Safety Analysis Set; Percentages are based on M.

a MenACYW conjugate vaccine group only includes the subjects who received MenACYW conjugate vaccine alone at Visit 01, and excludes the subjects who received MenACYW + Concomitant vaccines at Visit 01.

b Not collected: Race and ethnicity were not collected for subjects in Finland (MET51 and MET54) and South Korea (MET57) due to local regulations.

[redacted]

[redacted]

		MenACYW conjugate vaccine[a]										
		Race						Ethnicity				
Age Group	Study	M	White n(%)	Black or African American n(%)	Asian n(%)	Other n(%)	Not collected[b] n(%)	M	Hispanic or Latino n(%)	Not Hispanic or Latino n(%)	Missing n(%)	Not collected[b] n(%)

Contributing studies: MET35, MET43, MET44, MET49, MET50, MET51, MET54, MET56 and MET57

Table 12 - Exposure by age group and gender - MenACYW conjugate vaccine given with at least one concomitant vaccine

		MenACYW+Tdap+HPV								
			Gender			Age (years)				
Age Group	Study	N	M	Female n (%)	Male n (%)	M	Mean (SD)	Min; Max	Median	Q1; Q3
All	All	392	392	191 (48.7)	201 (51.3)	392	11.3 (1.10)	10.0; 17.5	11.1	10.5; 11.9
All Adolescents (10 through 17 years old)	MET50	392	392	191 (48.7)	201 (51.3)	392	11.3 (1.10)	10.0; 17.5	11.1	10.5; 11.9

		MenACYW+MMR+V								
			Gender			Age (years/months)[a]				
Age Group	Study	N	M	Female n(%)	Male n(%)	M	Mean (SD)	Min; Max	Median	Q1; Q3
All	All	189	189	92 (48.7)	97 (51.3)	189	1.1 (0.12)	1.0; 1.7	1.0	1.0; 1.1
All Toddlers (12 through 23 months old)	MET57	189	189	92 (48.7)	97 (51.3)	189	13.0 (1.40)	12.0; 20.0	12.6	12.2; 13.0

[redacted]

[redacted]

Age Group	Study	MenACYW+DtaP-IPV-HB-Hib								
		N	Gender			Age (years/months)[a]				
			M	Female n (%)	Male n (%)	M	Mean (SD)	Min; Max	Median	Q1; Q3
All	**All**	200	200	93 (46.5)	107 (53.5)	200	1.4 (0.23)	1.0; 2.0	1.4	1.2; 1.6
All Toddlers (12 through 23 months old)	**MET57**	200	200	93 (46.5)	107 (53.5)	200	16.9 (2.79)	12.0; 23.7	17.0	14.5; 18.6

Age Group	Study	MenACYW+ PCV13								
		N	Gender			Age (years/months)[a]				
			M	Female n (%)	Male n (%)	M	Mean (SD)	Min; Max	Median	Q1; Q3
All	**All**	200	200	78 (39.0)	122 (61.0)	200	1.4 (0.20)	1.3; 2.0	1.3	1.3; 1.5
All Toddlers (12 through 23 months old)	**MET57**	200	200	78 (39.0)	122 (61.0)	200	17.0 (2.36)	15.0; 23.7	15.9	15.4; 18.1

Abbreviations: n, number of subjects fulfilling the characteristic listed; M, number of subjects with available data for the relevant endpoint; N, number of subjects in the Safety Analysis Set; Q1, first quartile; Q3, third quartile; SD, standard deviation; Percentages are based on M.

a Age is presented in months for toddlers and in years for other subjects. For the quantitative descriptive statistics: Age in months = (Date of first vaccination - Date of birth + 1) / (365.25 / 12), Age in years = (Date of first vaccination - Date of birth + 1) / 365.25. If date of birth was not collected, the calendar age collected in CRF was used to derive the quantitative descriptive statistics. For "All", age is presented in years.

Contributing studies: MET50 and MET57

[redacted]

[redacted]

Table 13 - Exposure by age group, race and ethnic origin - MenACYW conjugate vaccine given with at least one concomitant vaccine

Age Group	Study	MenACYW+Tdap+HPV								
		Race					Ethnicity			
		M	White n(%)	Black or African American n(%)	Asian n(%)	Other n(%)	M	Hispanic or Latino n(%)	Not Hispanic or Latino n(%)	Missing n(%)
All	All	392	350 (89.3)	15 (3.8)	1 (0.3)	26 (6.6)	392	83 (21.2)	309 (78.8)	0 (0.0)
All Adolescents (10 through 17 years old)	MET50	392	350 (89.3)	15 (3.8)	1 (0.3)	26 (6.6)	392	83 (21.2)	309 (78.8)	0 (0.0)

Age Group	Study	MenACYW+MMR+V										
		Race						Ethnicity				
		M	White n (%)	Black or African American n(%)	Asian n(%)	Other n(%)	Not Collected[a] n(%)	M	Hispanic or Latino n(%)	Not Hispanic or Latino n(%)	Missing n(%)	Not Collected[a] n(%)
All	All	189	0 (0.0)	0 (0.0)	86 (45.5)	0 (0.0)	103 (54.5)	189	0 (0.0)	86 (45.5)	0 (0.0)	103 (54.5)
All Toddlers (12 through 23 months old)	MET57	189	0 (0.0)	0 (0.0)	86 (45.5)	0 (0.0)	103 (54.5)	189	0 (0.0)	86 (45.5)	0 (0.0)	103 (54.5)

Age Group	Study	MenACYW+DTaP-IPV-HB-Hib								
		Race					Ethnicity			
		M	White n(%)	Black or African American n(%)	Asian n(%)	Other n(%)	M	Hispanic or Latino n(%)	Not Hispanic or Latino n(%)	Missing n(%)
All	All	200	200 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	200	200 (100.0)	0 (0.0)	0 (0.0)

[redacted]

[redacted]

Age Group	Study	MenACYW+DTaP-IPV-HB-Hib								
		Race					Ethnicity			
		M	White n(%)	Black or African American n(%)	Asian n(%)	Other n(%)	M	Hispanic or Latino n(%)	Not Hispanic or Latino n(%)	Missing n(%)
All Toddlers (12 through 23 months old)	**MET57**	200	200 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	200	200 (100.0)	0 (0.0)	0 (0.0)

Age Group	Study	MenACYW+PCV13								
		Race					Ethnicity			
		M	White n(%)	Black or African American n(%)	Asian n(%)	Other n(%)	M	Hispanic or Latino n(%)	Not Hispanic or Latino n(%)	Missing n(%)
All	**All**	200	198 (99.0)	0 (0.0)	2 (1.0)	0 (0.0)	200	4 (2.0)	196 (98.0)	0 (0.0)
All Toddlers (12 through 23 months old)	**MET57**	200	198 (99.0)	0 (0.0)	2 (1.0)	0 (0.0)	200	4 (2.0)	196 (98.0)	0 (0.0)

Abbreviations: n, number of subjects fulfilling the characteristic listed; M, number of subjects with available data for the relevant endpoint; N, number of subjects in the Safety Analysis Set; Percentages are based on M.

a Not Collected: Race and ethnicity were not collected for subjects in South Korea (MET57) due to local regulation.

Contributing studies: MET50 and MET57

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 14 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances	MenACYW conjugate vaccine should not be administered to persons with known allergy to any of the component of the vaccine to prevent severe allergic reaction.	No	SmPC sections 4.3 and 4.4 include contraindication and warning messages. Known risk with a low frequency (very rare) based on what would be common for any vaccine, that do not impact the benefit-risk profile, require no further characterization and is followed up via routine pharmacovigilance activities. The risk minimization messages in the product information are adhered by prescribers; the corresponding actions part of standard clinical practice. No cases to date with MenACYW Conjugate Vaccine.
History of GBS	Based on postmarketing experience, GBS has been reported with marketed MCV4s. (12) A review by the IOM published in 1994 found evidence for a causal relation between tetanus toxoid vaccines and GBS. (13)	No	Potential risk based on postmarketing experience for other MCV4s occurring with a low frequency (very rare) with no definite evidence of excess risk identified in population based study (14)(15) and considered to be acceptable in relation to the severity of the indication prevented, do not impact the benefit-risk profile, require no further characterization, and is followed up via routine pharmacovigilance activities. An updated IOM review in 2011 stated that the evidence is inadequate to accept or reject a causal relationship between tetanus toxoid- containing vaccines and GBS. (16) No cases to date with MenACYW Conjugate Vaccine.
Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine.	Exaggerated local reactions can occur following administration of a tetanus-containing	No	Individuals experiencing this reaction should not be given further doses of Tetanus toxoid containing vaccine more frequently than every 10 years.

[redacted]

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	vaccine in individuals who have received frequent doses of tetanus toxoid. Persons experiencing these severe reactions should not be given further routine or emergency booster doses of tetanus more frequently than every 10 years.		Low risk considered to be acceptable in relation to the severity of the indication prevented.
Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination, or planned receipt of any vaccine prior to visit 2 except for influenza vaccination, which may be received at least 2 weeks before or after the study investigational vaccines, receipt of an investigational product as part of another clinical trial in the 4 weeks preceding the trial vaccination or planned participation, or receipt of blood products or immunoglobulin within the previous 3 months.	To exclude any possible confounder for study results.	No	In real life vaccines could be administered concomitantly.
History of meningococcal infection, confirmed either clinically, serologically, or microbiologically.	Immunogenicity study results could have been modified by previous exposure.	No	No safety risk is anticipated when a subject with history of meningococcal infection receives MenACYW conjugate vaccine.
Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥100.4°F).	Immunization shall be postponed in patients with moderate or severe acute illness, with or without fever. Temporary exclusion criterion to collect the most accurate safety data and to ensure	No	Vaccination should be postponed until recovery.

[redacted]

[redacted]

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	adequate immune response.		
Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)	Immunocompromised individual may not obtain an adequate immune response. The immunogenicity of the vaccine may be reduced by immunosuppressive treatment or immunodeficiency.	No	SmPC section 4.4 includes warning messages and preventive measures regarding the use of the vaccine in immunocompromised persons. No additional pharmacovigilance activities are required to collect more and specific data on those populations.
Verbal report of thrombocytopenia, Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion	Administration of an IM injection to these patients could increase the risk of a hematoma. Risk associated with any IM injections: bleeding may occur following an IM administration in such subjects.	No	Risk of hematoma/bleeding considered to be acceptable in relation to the severity of the indication prevented, do not impact the benefit-risk profile. No additional pharmacovigilance activities are required to collect more and specific data on those populations.
Pregnant women, or of childbearing potential and not using an effective method of contraception	Standard criterion for investigational clinical trials of new vaccines and drugs.	Yes	No evidence that the safety profile will be different from that in the general target population. Animal studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development. Although pregnancy was an exclusion criterion and pregnancy testing was performed before vaccination, a total of 12 pregnancies were reported in subjects who had received MenACYW conjugate vaccine (1 exposed and pregnant[a], 4 exposed but not yet pregnant[b], and 7 unexposed[c]). No cases of congenital abnormalities were reported in either category of exposed pregnancies. Ten subjects gave birth to healthy babies, including the subject classified as exposed and pregnant at the time of

[redacted]

[redacted]

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			vaccination. Two of the subjects who were classified as unexposed reported spontaneous abortions; neither was considered as related to the vaccine by the investigator. The review of cases of pregnant women who had received a US Licensed MCV4 (MENACTRA) from Jan-2005 through 31-Dec-2011 that were reported to the vaccine AE reporting system in the US (17), as well as cumulative experience from the Pregnancy registries for MENACTRA (12) and MENVEO (18), did not identify any safety concerns for maternal or infant health. (17) Data from a study conducted in Mali in pregnant women during the third trimester (n = 2085) also did not indicate any adverse fetal, newborn, infant, or maternal outcomes attributable to MENACTRA. (19) Considering the ACIP recommendations in the US, women in their childbearing years represent a notable proportion of the population that will receive MenACYW conjugate vaccine. The Applicant has initiated a passive pregnancy surveillance registry (MEQ00070) in the US to assess the safety of MenACYW conjugate vaccine among exposed pregnant women and their offspring. Voluntary postmarketing reports collected from outside the US will be included and described separately in the registry report.
Breast-feeding women	Standard criterion for investigational clinical trials of new vaccines and drugs.	No	There is no anticipated risk with vaccination of breast-feeding women.
Chronic illness at a stage that could interfere with trial conduct or completion	In the opinion of the investigator, subjects were excluded only if the chronic condition(s) at a stage that could interfere with trial conduct or completion.	No	Criterion which should be considered and assessed on a case-by-case basis, per country-specific recommendations for medical practice.

[redacted]

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Current alcohol abuse or drug addiction that might interfere with the ability to comply with trial procedures	In the opinion of the investigator, subjects were excluded only if alcohol abuse or drug addiction might interfere with trial conduct or completion.	No	Criterion which should be considered and assessed on a case-by-case basis, per country-specific recommendations for medical practice.

a The pregnancy was considered as "exposed to the study vaccine when the subject was pregnant" if the subject received the injection 7 days after her LMP or 7 days before the EDC (conservative risk window) or later during pregnancy.

b The pregnancy was considered as "exposed to the study vaccine but not yet pregnant" if the subject received the injection during the interval between 30 days before her LMP and 7 days after her LMP (which also corresponds to the period between 44 days and 7 days before EDC).

c All other pregnancies were considered as "unexposed".

ACIP: Advisory Committee on Immunization Practices; AE: Adverse Event; EDC: Estimated Date of Conception; GBS: Guillain-Barre Syndrome; IM: Intramuscular; IOM: Institute of Medicine; LMP: Last Menstrual Period; MCV4: Quadrivalent Meningococcal Conjugate Vaccine; SmPC: Summary of Product Characteristics; US: United States.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

A total of 7116 subjects were exposed to MenACYW conjugate vaccine during clinical development studies in the claimed indication, including 6601 MenACYW conjugate vaccine recipients in the nine pivotal/supportive studies, thus very rare adverse reactions detection might not have been possible. The size of integrated safety database allowed for the detection of very common, common and uncommon AEs that occur with a frequency over 0.1% (rate of 1/1000) with at least 95% probability.

Table 15 - Limitations common to clinical trials

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are very rare (<1/10 000) or rare (≥1/10 000 to <1/1000)	Not evaluable during the clinical program as 7116 subjects were exposed to MenACYW conjugate vaccine during clinical development.	The overall exposed group (N = 7116) will provide a probability of approximately 95% of observing any AE with a true incidence of 1 in 2372 or 0.042%.
Due to prolonged exposure	Not applicable	Not applicable
Due to cumulative effects	Not applicable	Not applicable
Which have a long latency	Not applicable	Not applicable

AE: Adverse Event.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 16 - Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	The use of the MenACYW conjugate vaccine has not been studied in pregnant or lactating women. Although pregnancy was an exclusion criterion in all clinical studies with the MenACYW conjugate vaccine and pregnancy testing was performed on female subjects of childbearing potential before each vaccination, the vaccine was administered to female subjects who became pregnant after vaccination or who were not aware of their pregnancy whereas urine pregnancy test was negative on vaccination day. A total of 12 pregnancies were reported from clinical trial participants in MenACYW conjugate vaccine group (1 exposed and pregnant[a], 4 exposed but not yet pregnant[b], and 7 unexposed[c]).
Breast-feeding women	
Patients with relevant comorbidities	
• Patients with hepatic impairment	MenACYW conjugate vaccine has not been evaluated in subjects with hepatic impairment
• Patients with renal impairment	MenACYW conjugate vaccine has not been evaluated in subjects with renal impairment
• Patients with cardiovascular impairment	MenACYW conjugate vaccine has not been evaluated in subjects with cardiovascular impairment
• Immunocompromised patients	MenACYW conjugate vaccine has not been evaluated in immunocompromised patients
• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable as every vaccine trial for a preventative vaccine is done on healthy subjects.
Populations with relevant different ethnic origin	No clinically significant differences were observed between various ethnicities.
Subpopulations carrying known and relevant genetic polymorphisms	MenACYW conjugate vaccine has not been evaluated in subjects carrying known and relevant polymorphisms.

a The pregnancy was considered as "exposed to the study vaccine when the subject was pregnant" if the subject received the injection 7 days after her last menstrual period LMP or 7 days before the EDC (conservative risk window) or later during pregnancy.

b The pregnancy was considered as "exposed to the study vaccine but not yet pregnant" if the subject received the injection during the interval between 30 days before her LMP and 7 days after her LMP (which also corresponds to the period between 44 days and 7 days before EDC).

c All other pregnancies were considered as "unexposed".

EDC: Estimated Date of Conception; LMP: Last Menstrual Period.

Limited data are available concerning the use of MenACYW conjugate vaccine in pregnant women. However, women in their childbearing years represent a notable proportion of the population that will receive MenACYW conjugate vaccine. Therefore, the use of MenACYW conjugate vaccine in pregnant women is considered as missing information. Refer to Table 14, [Module SVII] and [Part III] for more details.

The use of MenACYW conjugate vaccine in the other subpopulations included in Table 16 was not considered a safety concern.

[redacted]

Breast-feeding women

There is no anticipated risk with vaccination of breast-feeding women. Given the severity of MD, breast-feeding should not preclude vaccination when the benefit-risk ratio of administering MenACYW conjugate vaccine is considered favorable. MenACYW conjugate vaccine should be given to a breast-feeding woman only if clearly needed, such as during an outbreak or prior to travel to an endemic area, and only following an assessment of the risks and benefits.

Patients with relevant comorbidities

There is no anticipated risk with vaccination of patients with relevant comorbidities, including cardiac disorders, renal and hepatic impairment.

While efficacy may be compromised in patients with known or suspected immunodeficiency, including organ transplant patients, no specific safety issue is expected.

Patients of different racial and/or ethnic origins

No clinically significant differences were observed between various ethnicities.

Subpopulations carrying known and relevant genetic polymorphisms

To date, there is no information suggesting the existence of polymorphism relevant to the efficacy or safety of MenACYW conjugate vaccine in the currently proposed indication.

[redacted]

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1. Method used to calculate exposure

Internal sales have been used as the source for sales data retrieval. This data was calculated based on information provided by the internal Business Warehouse, a module of the Systems Applications and Products system. This data represents product sold by the marketing authorization holder to third party wholesalers and distributors, rather than vaccines actually administered to patients.

Exposure from the cumulative experience is available from 01 March 2021 through 30 April 2023. No sales data is available prior to 01 March 2021. Detailed usage data are not available therefore presentation of patient exposure by age, sex, and indication is not possible. The usage data is only presented by region and countries.

SV.1.2. Exposure

During the reference period from01 March 2021 to 30 April 2023, 6 874 713 doses of MENQUADFI have been sold, including 719 392 doses in EU. Assuming that subjects received one dose, in accordance with the recommended schedule (single dose), the estimated number of patients who received MENQUADFI is 6 874 713.

Assuming that subjects received one dose (0.5 mL), in accordance with the recommended schedule in the company core data sheet (CCDS), the estimated number of subjects who received MENQUADFI is 6 874 713 doses, including 719 392 doses in EU, for the reference period from 01 March 2021 to 30 April 2023.

Table 17 - Exposure by region

Area	Countries	Number of doses distributed
Latin America	[redacted]	
	TOTAL	32 688
[redacted]		
FODT	[redacted]	

[redacted]

[redacted]

Area	Countries	Number of doses distributed
	[redacted]	
	TOTAL	66
EEA	[redacted]	
	TOTAL	719 392
Asia Pacific	[redacted]	
	TOTAL	22 496
Africa	[redacted]	
	TOTAL	350 230
[redacted]		
Middle East	[redacted]	
	TOTAL	1020
Cumulative Overall Total Doses	6 874 713	
Patients exposure (1 dose)	6 874 713	

EEA: European Economic Area; FODT: French Overseas Departments and Territories; US: United States.

[redacted]

[redacted]

RISK MANAGEMENT PLAN – PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

Potential for misuse of MenACYW conjugate vaccine for illegal purposes is considered low given the nature of this product. The vaccine is used by healthcare professionals (HCPs) only; this limits the risk of illegal use.

[redacted]

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The following safety topics will be discussed in this section and will be presented in Section SVII.1.1 (if the risks are not considered important for inclusion in the list of safety concerns in the RMP) or in Section SVII.1.2 (it the risks are considered important for inclusion in the list of safety concerns in the RMP):

- Potential harm from overdose
- Potential for risks resulting from medication errors
- Potential for transmission of infectious agents
- Potential for off-label use
- Risks related to the administration procedure
- Pediatric safety issues
- Important risks associated with the use of any marketed vaccines in general: Anaphylaxis
- Important risks associated with the use of marketed MCV4s: Guillain-Barre syndrome, Bell's palsy
- Important risks associated with the use of marketed tetanus toxoid-containing vaccines: Guillain-Barre syndrome
- Risk in pregnant and lactating women
- Risk in immunocompromised and immunodeficient individuals
- Co-administration with Meningococcal B vaccine in adolescents

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

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

The definitions of important identified and potential risks and missing information in good pharmacovigilance practices (GVP) Module V Rev. 2 apply in the context of RMP. However, the list of safety concerns in RMP and periodic benefit-risk evaluation reports (PBRERs) might differ.[1]

The risks not considered as safety concerns in the RMP are those that showed a minimal impact on patients or a low frequency in relation to the severity of the indication. These risks require no

[1] EMA Explanatory Note to GVP Module VI, EMA/670256/2017, 31 October 2017 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp- module-vii-periodic-safety-update-report-explanatory_en.pdf

[redacted]

[redacted]

further characterization and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. Additionally, they have no impact on the benefit-risk profile of MenACYW conjugate vaccine.

Table 18 provides a summary of the risks and missing information in the claimed indication not considered important for inclusion in the list of safety concerns in the initial RMP submission, and the reasons for non-inclusion. The Applicant will specifically monitor these risks and missing information through routine pharmacovigilance activities, and there will be regular review of those events in the PBRER.

Table 18 - Risk or missing information not considered as important for inclusion in the list of safety concerns

Risk or missing information not considered as important for inclusion in the list of safety concerns	**Justification** **Risk minimization activities**
Risk: Potential harm from overdose	As MenACYW conjugate vaccine is a single 0.5 mL dose vial presentation (no multidose vial presentation available at the time of the current application) and is injected by qualified medical personnel, this situation should be exceptional.
	No risk minimization measures
Risk: Potential for medication errors	Cases of vaccine misuse or vaccination errors occur extremely rarely in the course of clinical trials. By definition, wrong dosing events are recorded as they do correspond to subjects who did not complete the trials per protocol. As such these subjects are considered in the intent-to-treat analysis, and their data are reported and available in the different clinical study reports. During the clinical development of MenACYW conjugate vaccine, no cases of medication errors have been reported. The risk of wrong MCV4 administered is considered very low as MenACYW conjugate vaccine is a fully liquid presentation while the other MCV4s currently licensed in EU are supplied as a sterile lyophilized powder or cake.
	Routine risk communication: SmPC sections 4.2 and 4.4 to minimize the risk of wrong route and site of administration. Intramuscular route is also indicated on the outer packaging (ie, box, carton) and the primary label (ie, label stuck on the vial).
Risk: Potential for transmission of infectious agents	The risk for transmission of infectious agents with MenACYW conjugate vaccine is considered as negligible. Sanofi Pasteur has worked closely with its suppliers of raw materials to provide extensive documentation on animal origin information. Whenever possible, animal origin raw materials have been replaced with non-animal origin raw materials. Where non-animal origin raw materials could not be obtained, Sanofi Pasteur Inc. has applied stringent safety and traceability requirements requiring that animal origin raw materials be sourced only from countries classified as GBR level I or II, in compliance with EMEA/410/01.

[redacted]

Risk or missing information not considered as important for inclusion in the list of safety concerns	Justification
	Risk minimization activities
	Information related to the materials of biological origin, criteria applied for selection of materials of biological origin, seed bank history testing and characterization data, raw material sources, purification/inactivation procedures applied during the manufacture of drug substance intermediates, drug substance and drug product provide reasonable confidence that there is negligible risk of any possible viral contamination in the drug product. In addition, the manufacturing process includes several steps that are capable of the inactivation of viral particles, including treatments with phenol, ethanol, CDI, EDAC and cyanoborohydride. No materials of animal origin were used during the manufacture of: • Tetanus toxoid filtered concentrate • *N. meningitidis* polysaccharide purified bulk powder, groups A, C, W-135 and Y • Drug Substance: *N. meningitidis* polysaccharide tetanus toxoid *conjugate* concentrate, serogroups A, C, W-135 and Y, drug product meningococcal polysaccharide (Serogroups A, C, W-135 and Y) • Drug Product: *meningococcal* polysaccharide (Serogroups A, C, W-135 and Y) tetanus toxoid conjugate vaccine The manufacturing processes are performed under controlled conditions in a cGMP manufacturing environment in qualified facilities. The in-process control and quality control release tests were applied throughout the manufacturing processes. In case of suspicion of transmission of an infectious agent in the postmarketing setting, Sanofi Pasteur Global pharmacovigilance initiates a manufacturing investigation of the concerned batch in collaboration with industrial operation quality department.
	No risk minimization measures
Risk: Potential for off-label use	The only anticipated off-label use refers to the use of MenACYW conjugate vaccine in the pediatric population below 12 months of age. The Applicant has initiated clinical studies in infants down to 6 weeks of age.
	No risk minimization measures
Risk: Specific Pediatric issues	Pediatric Investigation Plan: No safety/efficacy issues in relation to pediatric use were considered as particular causes of concern for consideration in the RMP/Pharmacovigilance activities by the PDCO in the EMA decision on the PIP (PIP procedure number EMEA-001930-PIP01-16) dated 01-Dec-2017, as well as in the PDCO opinion and EMA decision on modification of an agreed PIP (PIP procedure number EMEA-001930-PIP01-16-M01) dated 06-May-2019. Following feedback from EMA Scientific Advice and PDCO, the ongoing clinical trial program includes safety assessment with collection of AESIs (Generalized seizures [febrile and non-febrile], Kawasaki disease, GBS, and idiopathic thrombocytopenic purpura) in the phase 3 program that needed to be monitored, documented and

Risk or missing information not considered as important for inclusion in the list of safety concerns	Justification Risk minimization activities
	managed in a pre-specified manner. No safety concerns relating to these AESIs were identified. Potential for pediatric off-label use: The vaccine is currently intended for use in individuals 12 months of age and older. The Applicant has initiated clinical studies in infants down to 6 weeks of age.
	No risk minimization measures.
Risks related to the administration procedure	Routine administration procedure for a vaccine: MenACYW conjugate vaccine should be administered as a single 0.5 mL injection by the IM route, preferably in the anterolateral thigh or deltoid region or the anterolateral thigh depending on the recipient's age and muscle mass.
	SmPC sections 4.2 and 4.4 to minimize the risk of wrong route and site of administration. IM route is also indicated on the outer packaging (ie, box, carton) and the primary label (ie, label stuck on the vial).
Risk: Anaphylaxis	Known risk occurring at a low frequency (very rare) based on what would be common for any vaccine. It does not impact the benefit-risk profile and requires no further characterization. The risk minimization messages in the product information are adhered by prescribers; the corresponding actions part of standard clinical practice. No cases to date with MenACYW conjugate vaccine.
	Routine risk communication: SmPC sections 4.3 and 4.4.
Risk: Guillain-Barre syndrome	Potential risk based on postmarketing experience for other MCV4s occurring at a low frequency (very rare) (12) with no definite evidence of excess risk identified in population based studies. (14)(15) It is considered to be acceptable in relation to the severity of the indication prevented, does not impact the benefit-risk profile, and requires no further characterization. A review by the IOM published in 1994 found evidence for a causal relation between tetanus toxoid vaccines and GBS. (13) Because the conclusion was not based on controlled studies, no estimate of incidence or relative risk was available. An updated IOM review in 2011 stated that the evidence is inadequate to accept or reject a causal relationship between tetanus toxoid-containing vaccines and GBS. (16) No cases to date with MenACYW conjugate vaccine.
	No risk minimization measures.
Risk: Bell's palsy	Potential risk based on post-marketing experience for other MCV4s occurring at a low frequency (very rare). (12) It is considered to be acceptable in relation to the severity of the indication prevented, does not impact the benefit-risk profile, and requires no further characterization.

Risk or missing information not considered as important for inclusion in the list of safety concerns	Justification
	Risk minimization activities
	In a postmarketing observational safety study conducted in a US health maintenance organization, data from electronic health records of 48 899 persons 11 through 21 years of age were used to evaluate pre-specified events of interest following vaccination with MCV4-CRM (MENVEO). (20) Using a self-controlled case series method, this study found a statistically significant increased risk of Bell's palsy in the period 1 to 84 days post vaccination compared with the control period, with an overall adjusted relative incidence of 2.9 (95% CI: 1.1-7.5). However, stratified analysis demonstrated a statistically significant association with Bell's palsy only when MCV4-CRM was administered concomitantly with other vaccines (Tdap, HPV, and/or influenza vaccine), while no association was found when the vaccine was administered alone. In addition, this study used a longer risk interval than used in previous studies, beyond the biologically plausible, and widely accepted risk interval of 42 days. No cases to date with MenACYW conjugate vaccine within 42 days of vaccination.
	No risk minimization measures
Missing Information: Use during lactation	No evidence that the safety profile will be different from that in the general target population.
	Routine risk communication: SmPC section 4.6.
Missing Information: Use in immunocompromised and immunodeficient individuals (including persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation)	No evidence that the safety profile will be different from that in the general target population The expected immune response may not be obtained with the associated risk of clinical vaccine failure. Known risk based on what would be common for any vaccine given in this population not studied, that requires no further characterization.
	Routine risk communication: SmPC section 4.4.

AESI: Adverse Event of Special Interest; CDI: Carbonyldiimidazole; cGMP: Current Good Manufacturing Practice; CI: Confidence Interval; EMA: European Medicines Agency; EU: European Union; GBR: Geographical Bovine Spongiform Encephalopathy Risk; GBS: Guillain-Barre Syndrome; HPV: Human Papillomavirus; IM: Intramuscular; IOM: Institute of Medicine; MCV4: Quadrivalent Meningococcal Conjugate Vaccine; PDCO: Pediatric Committee; PIP: Pediatric Investigation Plan; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics; Tdap: Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis; US: United States.

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

No identified or potential risks are considered important for inclusion in the list of safety concerns of the initial submission of the RMP of MenACYW conjugate vaccine.

Missing information on long-term persistence of the vaccine immune response after priming vaccination with MenACYW conjugate vaccine, safety and immunogenicity of a booster dose of MenACYW conjugate vaccine in individuals primed with MenACYW conjugate vaccine,

co-administration with MenB vaccine, and use during pregnancy have been selected for inclusion in the list of safety concerns of the initial submission of the RMP of MenACYW conjugate vaccine.

Table 19 - Missing information considered for inclusion in the list of safety concerns: Long-term persistence of the vaccine response, and safety and immunogenicity of booster in individuals primed with MenACYW conjugate vaccine

Long-term persistence of the vaccine response, and safety and immunogenicity of booster in individuals primed with MenACYW conjugate vaccine	
Scientific rationale for anticipating a different safety profile in the particular subpopulation	Waning protection over time can be expected for any vaccine. Data on the need and timing of revaccination with MenACYW conjugate vaccine, as well as the immunogenicity and safety of a booster dose in individuals primed with MenACYW conjugate vaccine has not been determined.
Risk-benefit impact	There is a risk of lack of efficacy due to waning immunity. Overall rates of solicited injection site reactions and solicited systemic reactions of MenACYW conjugate vaccine in previously vaccinated participants 15 years of age and older who have been previously vaccinated with either MCV4-DT (MENACTRA) or MCV4-CRM (Menveo) were comparable to those observed in unvaccinated participants after a single MenACYW conjugate vaccine dose (Study MET56). A single dose of MCV4-TT (NIMENRIX) induced immunological memory and robust booster responses against all vaccine capsular groups in individuals aged ≥12 months. The risk of a marked increase in reactogenicity between primary and booster vaccination is considered small.

MCV4: Quadrivalent Meningococcal Conjugate Vaccine.

Table 20 - Missing information considered for inclusion in the list of safety concerns: Co-administration with MenB vaccine

Co-administration with MenB vaccine	
Scientific rationale for anticipating a different safety profile in the particular subpopulation	Potential for interference in case of co-administration of MenACYW conjugate vaccine with MenB vaccine.
Risk-benefit impact	No evidence that the safety profile will be different from that in the population receiving MenB vaccine without MenACYW conjugate vaccine, or MenACYW conjugate vaccine without MenB vaccine.

MenB: Meningococcal Serogroup B.

Table 21 - Missing information considered for inclusion in the list of safety concerns: Use during pregnancy

Use during pregnancy	
Scientific rationale for anticipating a different safety profile in the particular subpopulation	Pregnancy was an exclusion criterion. There is a limited amount of data from the use of MenACYW conjugate vaccine in pregnant women.
Risk-benefit impact	The risks of MenACYW conjugate vaccine to a pregnant woman and an unborn baby are unknown at this time.

Use during pregnancy	
	No evidence that the safety profile will be different from that in the general target population. The review of cases of pregnant women who had received a US licensed MCV4 (MENACTRA) from Jan-2005 through 31-Dec-2011 that were reported to the vaccine AE reporting system in the US, as well as cumulative experience from the Sanofi Pasteur Pregnancy registry for MCV4-DT (MENACTRA) (12) and MCV4-CRM (MENVEO) (18) did not identify any safety concerns for maternal or infant health. (17) Data from a study funded by the Bill & Melinda Gates Foundation and conducted in Mali in pregnant women during the third trimester (n = 2085) also did not indicate any adverse fetal, newborn, infant, or maternal outcomes attributable to MCV4-DT. (19)

AE: Adverse Event; MCV4: Quadrivalent Meningococcal Conjugate Vaccine; US: United States.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

The EU-RMP is updated in the context of the completed MET 52[2] trial - No safety concerns identified. The missing information "Co-administration with MenB vaccine in infants and toddlers" is removed based on the new study results MET 52, MenACYW conjugate vaccine safety concerns were reassessed in this RMP version 2.0.

Co-administration with MenB vaccine in infants and toddlers data is now available (MET 52)

The missing information "Co-administration with MenB vaccine in infants and toddlers" has been removed based on the data available on safety and immunogenicity of co-administration with MenB vaccine in infants and toddlers from study MET52.

The Applicant completed a study (MET52) to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine when administered concomitantly with a MenB vaccine and other routine pediatric vaccines as part of the National Immunization Schedule in healthy infants and toddlers in the UK. Its national immunization program already includes a childhood immunization schedule with a meningococcal serogroup B vaccine (Bexsero®), at 2, 4, and between 12 and 13 months of age in infants and toddlers. The non-inferiority of the human serum bactericidal activity assay vaccine seroprotection rate (antibody titer ≥ 1:8) for the meningococcal serogroups A, C, Y, and W was successfully demonstrated following administration in the second year of life of MenACYW conjugate vaccine with Bexsero® (Group 1) as compared to MenACYW conjugate vaccine alone (Group 2) in the PPAS3. Non-inferiority was also demonstrated in the FAS3.

Vaccination with MenACYW conjugate vaccine given alone, or concomitantly with a MenB vaccine (Bexsero®) was found to be well tolerated with no safety concerns identified. MenACYW

[2] Study was considered completed after the DLP of this RMP, as the final clinical study report was finalized in August 2023. However, database locks and/or final statistical reports were completed at the time of the DLP of this RMP and review during routine pharmacovigilance activities (PBRER).

conjugate vaccine was administered concomitantly with Bexsero® (Group 1) in the second year of life compared to when MenACYW conjugate vaccine was given alone (Group 2).

Overall, the immunogenicity and safety profiles of MenACYW conjugate vaccine was comparable when administered alone or with Bexsero®.

Considering the above, the marketing authorization holder proposes to remove the missing information "Co-administration with MenB vaccine in infants and toddlers" for this submission for EU approval.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

No identified or potential risks have been considered important for inclusion in the list of safety concerns in the RMP of MenACYW conjugate vaccine.

The following risks have been identified for MenACYW conjugate vaccine:

- Important identified risk:
  - None
- Important potential risk:
  - None
- Missing information
  - Use during pregnancy

Limited data are available on the use of MenACYW conjugate vaccine in pregnant women. This missing information has been selected to be part of the list of the safety concerns in the RMP of MenACYW conjugate vaccine. A passive pregnancy surveillance registry (MEQ00070 study) to assess maternal, obstetrical, pregnancy, and neonatal and infant outcomes among women vaccinated with MenACYW conjugate vaccine during pregnancy or in the 30 days preceding their last menstrual period is ongoing and presented in Table 23.

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

Not applicable

SVII.3.2 Presentation of the missing information

Table 22 - Missing Information: Use during pregnancy

Missing Information	Use during pregnancy
Evidence source(s) and strength of evidence	Pregnancy was an exclusion criterion. There is a limited amount of data from the use of MenACYW conjugate vaccine in pregnant women.

Missing Information	Use during pregnancy
	Although pregnancy was an exclusion criterion and pregnancy testing was performed before vaccination, a total of 12 pregnancies were reported in subjects who had received MenACYW conjugate vaccine (1 exposed and pregnant[a], 4 exposed but not yet pregnant[b], and 7 unexposed[c]). No cases of congenital abnormalities were reported in either category of exposed pregnancies. Ten subjects gave birth to healthy babies, including the subject classified as exposed and pregnant at the time of vaccination. Two of the subjects who were classified as unexposed reported spontaneous abortions; neither was considered as related to the vaccine by the Investigator. Women in their childbearing years represent a notable proportion of the population that will receive MenACYW conjugate vaccine.
Anticipated risk/consequence of the missing information or Population in need for further characterization	No evidence that the safety profile will be different from that in the general target population. No known safety concern is anticipated. Considering the current ACIP recommendations in the US, women in their childbearing years represent a notable proportion of the population that will receive MenACYW conjugate vaccine. The Applicant has initiated a passive pregnancy surveillance registry (MEQ00070) in the US to assess the safety of MenACYW conjugate vaccine among exposed pregnant women and their offspring. Voluntary postmarketing reports collected from outside the US will be included and described separately in the registry report.

a The pregnancy was considered as "exposed to the study vaccine when the subject was pregnant" if the subject received the injection 7 days after her LMP or 7 days before the EDC (conservative risk window) or later during pregnancy.

b The pregnancy was considered as "exposed to the study vaccine but not yet pregnant" if the subject received the injection during the interval between 30 days before her LMP and 7 days after her LMP (which also corresponds to the period between 44 days and 7 days before EDC).

c All other pregnancies were considered as "unexposed".

ACIP: Advisory Committee on Immunization Practices; EDC: Estimated Date of Conception; LMP: Last Menstrual Period; US: United States.

[redacted]

RISK MANAGEMENT PLAN – PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risk	None
Important potential risk	None
Missing information	Use during pregnancy

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[redacted]

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The Applicant maintains systems and standard practices for routine pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepares reports for regulatory authorities (eg, individual case safety reports, PBRER, etc), and maintains continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities). The Applicant maintains a pharmacovigilance system master file which contains further details of these systems and standard practices.

The safety profile of MenACYW conjugate vaccine will continue to be further characterized in real life setting through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports, product technical complaints relating to AEs and signal detection.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Use during pregnancy

The Applicant has initiated a pregnancy surveillance registry (MEQ00070) to assess the safety of MenACYW conjugate vaccine among exposed pregnant women and their offspring in the US. Voluntary postmarketing reports collected from outside the US will be included and described separately in the registry report.

Table 23 - Additional pharmacovigilance activities (category 1 to 3) summary

MEQ00070 – Pregnancy registry (Cat. 3)
Study short name and title Pregnancy registry (MEQ00070)
Rationale and study objectives To assess maternal, obstetrical, pregnancy, and neonatal and infant outcomes among women vaccinated with MenACYW conjugate vaccine during pregnancy or in the 30 days preceding their last menstrual period or estimated date of conception.
Study design Observational, postmarketing, passive surveillance program
Study populations Pregnant women and their offspring residing in the US and its territories who are exposed to MenACYW conjugate vaccine during their pregnancy or within 30 days prior to their last menstrual period, for whom the exposure is reported to the pregnancy registry.
Milestones Planned submission of final study report: Q2 2029

MenB: Meningococcal Serogroup B; Q: Quarter; UK: United Kingdom; US: United States.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 24 - Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Pregnancy registry (MEQ00070) Ongoing	To assess maternal, obstetrical, pregnancy, and neonatal and infant outcomes among women vaccinated with MenACYW conjugate vaccine during pregnancy or in the 30 days preceding their last menstrual period or estimated date of conception.	Use during pregnancy	Planned submission of final study report	Q2 2029

Q: Quarter.

[redacted]

RISK MANAGEMENT PLAN PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for MenACYW conjugate vaccine.

[redacted]

[redacted]

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 25 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Use during pregnancy	**Routine risk communication:** SmPC section 4.6. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None

SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 26 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use during pregnancy	**Routine risk minimization measures:** SmPC section 4.6. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Pregnancy registry (MEQ00070)

SmPC: Summary of Product Characteristics.

[redacted]

[redacted]

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for MENQUADFI (Meningococcal Polysaccharide [Serogroups A, C, Y and W-135] Tetanus Toxoid Conjugate Vaccine)

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

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

This summary of the RMP for MENQUADFI 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 MENQUADFI's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

MENQUADFI is authorized for active immunization of individuals from the age of 12 months and older, against invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W and Y. The use of this vaccine should be in accordance with available official recommendations (see SmPC for the full indication). It contains 10 μg of each of the meningococcal polysaccharide serogroups A, C, W and Y as the active substance and it is given by intramuscular (IM) route, preferably in the deltoid region or anterolateral thigh depending on the recipient's age and muscle mass.

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

https://www.ema.europa.eu/en/medicines/human/EPAR/menquadfi

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of MENQUADFI, together with measures to minimize such risks and the proposed studies for learning more about MENQUADFI's risks, are outlined in the next sections.

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

[redacted]

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (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 MENQUADFI is not yet available, it is listed under "missing information" outlined in the next section.

II.A List of important risks and missing information

Important risks of MENQUADFI are risks that need special risk management activities to further investigate or minimize 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 MENQUADFI. 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 (eg, on the long-term use of the medicine);

Table 27 - List of important risks and missing information

Important identified risk	None
Important potential risk	None
Missing information	Use during pregnancy

II.B Summary of important risks

Table 28 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use during pregnancy

Use during pregnancy	
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.6.

Use during pregnancy	
	Additional risk minimization measures: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Pregnancy registry (MEQ00070). See Section II.C of this summary for an overview of the post-authorization development plan.

SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of MENQUADFI.

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

Table 29 - Other studies in post-authorization development plan

Pregnancy registry (MEQ00070) (Cat. 3)
Purpose of the study: This study assesses maternal, obstetrical, pregnancy, and neonatal and infant outcomes among women vaccinated with MenACYW conjugate vaccine during pregnancy or in the 30 days preceding their last menstrual period or estimated date of conception.

[redacted]

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RISK MANAGEMENT PLAN - PART VII: ANNEXES

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