17 September 2020
EMA/522942/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

MenQuadfi

International non-proprietary name: meningococcal group A, C, W135 and Y conjugate vaccine

Procedure No. EMEA/H/C/005084/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

1/dil	1/dilution
Ab	antibody
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
AESI	Adverse event of special interest
ALT	alanine aminotransferase
ANOVA	Analysis of variance
aP	acellular pertussis
AQL	Acceptance quality limit
AR	Adverse reaction
AS	active substance
AST	aspartate aminotransferase
BL	blood sample
C&MQO	Clinical and Medical Quality Assessment
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CDM	Clinical Data Management
CFR	case fatality rate
CI	Confidence interval
CLC	Clinical Logistics Coordinator
cLIA	competitive Luminex immunoassay
CPM	counts per minute
CPP	Critical process parameter
CQA	Clinical Quality Assessment
CQA	critical quality attributes
CRA	Clinical Research Associate
CRB	Case Report Book
CRF	(electronic) case report form
CRM or CRM197	A non-toxic variant of diphtheria toxin (used as carrier protein)
CRO	Contract Research Organization
CSR	clinical study report
CTA	clinical trial agreement
CTD	common technical document
CTL	Clinical Team Leader
CTP	Concentrated tetanus protein
D	Day
DART	Development and reproductive toxicity
DC	Diary card
DM	Data management
DNA	deoxyribonucleic acid
DOD	delta optical density
DTaP-IPV-HB-Hib	diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis and Haemophilus influenzae type b
DTP	Diphtheria, Tetanus, and Pertussis
ECL	electrochemiluminescent
EDC	Electronic data capture
EEG	electroencephalogram
EIA	enzyme immunoassay
EMA	European Medicines Agency
EPA	United States enviromental protection agency
eSAE	Electronic Serious Adverse Event (Form)
EU	European Union
FAS	Full analysis set
FDA	US Food and Drug Administration
FHA	filamentous hemagglutinin
FIM / FIM2,3	fimbriae types 2 and 3
Fimea	Finnish Medicines Agency

FP	finished product
FVFS	First visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GM	geometric mean
GMC	geometric mean concentration
GMP	Good Manufacturing Practice
GMT(s)	geometric mean titer(s)
GMTR(s)	geometric mean titer ratio(s)
gp	glycoprotein
GPV	Global PharmacoVigilance
GSO	Global Safety Officer
HBsAg	anti-hepatitis B surface antigen
HCP	health care provider
HepBs	anti-hepatitis Bs
Hib	Haemophilus influenzae type b
HIV	human immunodeficiency virus
HPV	human papilloma virus (vaccine)
hSBA	Serum bactericidal assay using human complement
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IM	Intramuscular
IMD	Invasive meningococcal disease
IND	Investigational New Drug Application
IOM	Institute of Medicine
IPA	Isopropyl alcohol
IPV	inactivated polio vaccine
IRB	Institutional Review Board
ITP	idiopathic thrombocytopenic purpura
IU	international unit(s)
IVRS	interactive voice response system
IWRS	Interactive Web Response System
JL135	Jeryl Lynn 135
L	litre
LAR	Legally acceptable representative
LCLS	last contact, last subject
LDH	lactate dehydrogenase
LLOQ	Lower limit of quantitation
LLT	lowest level term
LOQ	limit of quantitation
LVLS	last visit, last subject
MA	memory aid
MAAE	medically attended adverse event
MAAESI	medically-attended adverse event of special interest
mAb	monoclonal antibody
MCV4	quadrivalent meningococcal conjugate vaccine
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
Min; Max	minimum, maximum
MIT	micrometabolic inhibition test
mIU	milli-international unit
mL	milliliter(s)
mm	Millimeter

MMR	measles-mumps-rubella
mMU/mL	milli-Merck units per milliliter
MRC-5	Medical Research Council cell strain 5
MRI	magnetic resonance imaging
MSB	master seed bank
MSD	MesoScale Discovery
MSL	master seed lot
NCI	National Coordinating Investigator
NIP	National Immunization Program
NLT	Not less than
NM	non-measurable
NMT	Not more than
NR	not reportable
NSAID	Non-steroidal anti-inflammatory drug
OD	optical density
OPV	oral polio vaccine
PCV	pneumococcal conjugate vaccine
PETG	polyethylene terephthalate glycol
PFU	plaque-forming unit
Ph. Eur./EP	European Pharmacopoeia
PI	Principal Investigator
PnPS	pneumococcal capsular polysaccharide
PPAS	Per-protocol analysis set
ppm	part per million
PRN	pertactin
PRP	polyribosyl-ribitol phosphate
PS	polysaccharide(s)
PSO	Product Safety Officer
PT	pertussis toxoid or preferred term
PTP	Purified tetanus protein
Q	quartile
QA	quality assurance
QP	Qualified person
RCDC	Reverse cumulative distribution curve
rDNA	recombinant deoxyribonucleic acid
RIA	radioimmunoassay
RLU	relative light units
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using rabbit complement
SAE	Serious adverse event
SafAS	Safety analysis set
SAP	Statistical analysis plan
SBA	serum bactericidal assay
SC	subcutaneous
SCD	Soybean casein digest
SCT	Safety concern threshhold
SD	standard deviation
SIL	sample inventory list
SMT	Safety management team
SOC	System Organ Class
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TCID50	tissue culture infectious dose
Tdap	tetanus, diphtheria, acellular pertussis (vaccine)
TetraMen-T (Demo)	Phase I demo lot
TetraMen-T clinical formulation	Phase II GMP lot
TMF	trial master file
TSE	transmissible spongiform encephalopathy
TT	Tetanus Toxoid (used as carrier protein)

TUKIJA	National Committee on Medical Research Ethics (Finland)
UAR	unexpected adverse reaction
ULOQ	upper limit of quantification
US	United States
USP	Unites States pharmacopoeia
UTN	Universal Trial Number
V	varicella
VLP	virus-like particle
VZV	varicella zoster virus
WFI	Water for injection
WHO	World Health Organization
WSB	working seed banks
WSL	working seed lot
WT	wild-type
µg	microgram(s)
µg/µL	Microgram/Microliter
µL	microliter(s)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi Pasteur submitted on 4 October 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for MenQuadfi, through the centralised procedure under Article 28 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 31 May 2018.

The agreed indication is the following:

MenQuadfi is indicated for active immunisation 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 legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0164/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0164/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active substance status

The applicant indicated the active substance meningococcal group A, C, W135 and Y conjugate vaccine contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant received the following Scientific advices on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 July 2015	EMEA/H/SA/3131/1/2015/III	Dr Jan Mueller-Berghaus, Dr Hans Ovelgönne
18 May 2017	EMEA/H/SA/3131/1/FU/2017/II	Dr Mair Powell, Dr Jan Mueller-Berghaus

The scientific advises pertained to the following aspects:

- Quality: release and stability programs, comparability of the clinical material produced at different scales

- Clinical: choice of comparators, development plan and design of clinical phase III studies, definitions of endpoints, methods, safety database, generation of co-administration data, schedule and strategy for immunogenicity for the infant.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Andrea Laslop Co-Rapporteur: Ingrid Wang

The application was received by the EMA on	4 October 2019
The procedure started on	31 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 January 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 January 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	3 February 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 February 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 May 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to	09 July 2020

CHMP during the meeting on	
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	23 July 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	03 September 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to MenQuadfi on	17 September 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The assessed product is an intended vaccine to prevent meningococcal disease by triggering the production of serum bactericidal antibodies against the capsular polysaccharides of *Neisseria meningitidis* serogroups A, C, Y, and W. The proposed therapeutic indication is as follows:

"MenQuadfi is indicated for active immunisation 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."

2.1.2. Epidemiology and prevention

Meningococci (*Neisseria meningitidis*) are transmittable bacteria with a high incidence to induce meningococcal disease in humans. Their virulence is mostly based on the biochemical structure of capsular polysaccharides. So far 12 distinct meningococcal serogroups have been classified, with serogroups A, B, C, W, X and Y being responsible for most cases of meningococcal disease. Dynamics of meningococcal transmission, acquisition, and carriage in humans are a major influence on the incidence and likelihood of meningococcal disease. However, the worldwide incidences of meningococcal disease vary greatly among regions. The European population is mostly affected by serogroup B, but also C and Y are responsible for some of the reported cases (Peterson et al. 2019). The presently best-known prevention against meningococcal disease is the up-front immunization with vaccines targeting the relevant serogroups.

2.1.3. Biologic features Aetiology

The natural habitat and reservoir of meningococci are the upper respiratory nasopharyngeal mucosal membranes. *N. meningitidis* is a common commensal, carried by approximately 8% to 20% of the normal population, but the prevalence of carriage varies widely and does not directly predict meningococcal disease. However, any impact on meningococcal carriage will also have an impact on the incidence of meningococcal disease. The rates of meningococcal disease are influenced by factors that enhance exposure and transmission, carriage rates of strains with different virulence potential, and host factors. Transmission is by direct contact with or inhalation of meningococcus in large droplet nuclei that are acquired through close contact with respiratory secretions and saliva. However, acquisition can be transient, induce meningococcal disease or lead to colonialization and carriage.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

During the course of meningococcal infection, a meningitis and sepsis can develop, both being potentially lethal. Thus, the untreated mortality rate of meningococcal disease is high and the pathogenesis is not completely understood. Additionally, survivors of the disease often suffer from severe neurological, visual or

hearing impairments (Peterson et al. 2019). The best-known method for prevention of the disease is the immunization against disease-causing serogroups.

2.1.5. Management

The most important host-dependent factor is the presence of serum bactericidal antibodies that neutralize the organism by complement-mediated bacteriolysis. Anti-capsular meningococcal antibodies protect against meningococcal disease via complement mediated bactericidal activity.

Meningococcal vaccines induce the production of bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups. MenACYW conjugate vaccine is intended to induce antibody production specific for the capsular polysaccharides of *N. meningitidis* serogroups A, C, Y, and W. In multiple European countries meningococcal C (MenC) vaccination is recommended for toddlers, even though the favoured timing of vaccination differs among countries. Additionally, two quadrivalent MenACWY vaccinations are available in Europe: Nimenrix, licensed in the EU since 20/04/2012 and indicated for the immunization from the age of 6 weeks, as well as Menveo, licensed in the EU since 15/03/2010 and indicated for the immunization of children from 2 years of age, adolescents and adults.

Menveo is also available in the US but not Nimenrix. In addition, other MenACWY vaccinations are available in the US: Menactra is approved from infants as young as 9 months of age to adults 55 years of age, and Menomune-A/C/Y/W-135, a polysaccharide vaccine, which was licensed for persons 2 years of age and older at the time of the clinical trials. The production was discontinued in 2017 by the applicant (MAH of Menomune). According to the applicant, the decision was strategic and not based on any quality, safety, or efficacy issues.

About the product

Mode of Action

Anti-capsular meningococcal antibodies protect against meningococcal diseases via complement mediated bactericidal activity.

MenQuadfi induces the production of bactericidal antibodies specific to the capsular polysaccharides of Neisseria meningitidis serogroups A, C, W, and Y.

Pharmacological Class

Pharmacotherapeutic group: meningococcal vaccines

ATC code: J07AH08

Claimed Indication and Proposed Clinical Use

MenQuadfi is indicated for active immunisation 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.

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) is presented as a 0.5 mL solution for injection containing as active substance (AS) 10 µg each of serogroups A, C, W (also referred to as W135) and Y meningococcal polysaccharide (PS), individually conjugated to 55 µg tetanus toxoid carrier.

Other ingredients are: sodium chloride, sodium acetate and water for injection.

The conjugate vaccine FP is available in a 2 mL Type I borosilicate clear glass vial with a 13 mm chlorobutyl stopper and a flip off seal.

2.2.2. Active Substance

General information

The *N. meningitidis* Polysaccharide (Groups A, C, Y and W135) Conjugate Vaccine contains four active substances comprised of serogroup-specific polysaccharide antigens purified from *Neisseria meningitidis* Serogroups A, C, Y, and W135, separately conjugated to tetanus toxoid.

The meningococcal polysaccharide components were originally EU-authorised as the active substances Menomune A, Men – C, Men A/C and Menomune A/C/Y/W135 and are the same as those used in the manufacture of the meningococcal (serogroups A, C, Y, and W135) polysaccharide diphtheria toxoid conjugate vaccine (Menactra). The tetanus toxoid protein component used to prepare the polysaccharide-protein monovalent conjugates is the same as that used as a carrier in the EU authorised *Haemophilus* influenzae type b tetanus protein conjugate vaccine (ActHIB).

Manufacture, characterisation and process controls

Sanofi Pasteur, 1541 Avenue Marcel Mérieux, 69280 Marcy l'Etoile, France is responsible for manufacture of the tetanus toxoid carrier protein (concentrated tetanus protein intermediate).

Sanofi Pasteur, Inc. Discovery Drive Swiftwater, PA 18370-0187 USA is responsible for manufacture of the AS intermediate (*N. meningitidis* polysaccharide purified bulk powder) and AS (*N. meningitidis* polysaccharide tetanus toxoid conjugate concentrate, serogroup A, C, Y, and W). Approved contract testing facilities are also specified. Appropriate GMP certificates/ authorisations are available for all sites.

Description of manufacturing process and process controls

Manufacture of polysaccharide bulk powder

Neisseria meningitidis working seed banks (WSBs) of the respective serogroups (Groups A, C, Y and W135) are individually propagated and fermentation is upscaled in fermenters. The fermentation broth is harvested and inactivated using phenol. The inactivated broth is concentrated. After precipitation the diluted filtrate is concentrated and treated with enzymes to remove nucleic acids and proteins, extracted with phenol, precipitated and dried to yield the AS intermediates, *N. meningitidis* Polysaccharide Purified Bulk Powders (Groups A, C, Y and W135). In process controls during fermentation are considered appropriate. There are no

reprocessing steps for *N. meningitidis* polysaccharide purified bulk powder, serogroup production process. The AS intermediate, *N. meningitidis* polysaccharide purified bulk powder is filled into bottles and stored.

Manufacture of tetanus toxoid (TT)

Inoculated working seed lot (WSL) is cultivated, fermented and upscaled. After cell lysis and harvest, the toxin is diafiltered and concentrated. Precipitation is followed by dialysis and filtration. The purified tetanus toxin is then inactivated. The purified tetanus toxoid, referred to as purified tetanus protein (PTP), is further concentrated and purified, yielding the concentrated tetanus protein (CTP). CTP is filtered, Sanofi Pasteur Inc., Swiftwater, PA, USA for storage. Once it is received at Sanofi Pasteur Inc., Swiftwater, PA, USA, it is referred to as tetanus toxoid, purified.

For serogroups C, Y and W135, a concentration step is additionally performed on the tetanus toxoid, purified prior to filtration until used for conjugation. For serogroup A, the tetanus toxoid protein is filtered into bags.

In process controls during the PTP and CTP, purified manufacturing process are suitably documented. There are no established reprocessing procedures for concentrated tetanus protein or tetanus toxoid, filtered concentrate. Hold times proposed throughout the AS manufacturing process are considered acceptable based on the information provided.

Manufacture of conjugate

Serogroup A purified bulk powder is activated and derivatised using a linker. Serogroup C, Y and W purified bulk powder is depolymerised and activated. Depolymerised and activated bulk powder is purified and may be stored under defined conditions before conjugation. After diafiltration and purification, the active substance is 0.2 µm filtered into bioprocess bags stored. Shelf life and storage conditions have been proposed for the AS and found acceptable. In-process controls are suitably defined. In the event a breach or integrity failure is observed from the beginning of the conjugate filtration process until the completion of dispense process, one refiltration of the conjugate is permitted. Details of the refiltration process are suitably defined.

Control of materials

The bacterial seed bank system consists of a *N. meningitidis* pre-master seed, animal component free master seed and animal component free working seed for each serogroup. Preparation of the seed banks and associated in-process controls are defined. All the seed banks are stored at ≤ 60°C.

The seed lot system for *Clostridium tetani* consists of a master seed bank and an intermediate seed bank. From the intermediate seed bank, new working cell banks are established. The same seed bank system was assessed for the company's *Haemophilus* type B conjugated polysaccharide vaccine licensed in several EU member states (Act-HIB). The approach adopted to monitor the stability of WSL for *C. tetani* and WSBs for *N. meningitidis* Serogroups A, C, Y and W135 is considered acceptable. A protocol for establishment of future WSLs/WSBs has been provided.

The applicant provides a detailed list of the control of raw materials, of prepared solvents, reagents, media and buffer material, water for manufacturing and gases used in the manufacturing process of the ASs. Raw materials are divided into pharmacopoeial grade components (Ph. Eur. or USP) and non-pharmacopoeial grade components. The specifications for the non-pharmacopoeial grade materials are provided in sufficient detail. The internal specifications are well defined and are acceptable for the intended use of the material. Materials of ruminant origin used in the production of concentrated purified tetanus protein bulk comply with

Ph. Eur. 1483 and 5.2.8 with respect to transmissible spongiform encephalopathy (TSE) safety (see adventitious agents' section).

Control of critical steps and intermediates

During the manufacture of the active substances, critical process parameters (CPPs), in-process controls and release tests have been implemented to ensure that the manufacturing process steps remain under control and meet their established operating range and specifications. Ranges of critical process parameters during the manufacturing process of the active substances and its intermediates have been verified by small scale studies and are considered adequate. The control strategy has been adequately explained.

Purified bulk powder

Specifications and batch analysis data have been provided for the purified bulk powder and the activated/derivatised (serogroup A) and depolymerised/activated (serogroup C, Y, W135) polysaccharide intermediates. Critical steps for the manufacturing of the purified bulk powder are accurately defined and controlled.

A stability study was conducted using three batches of purified bulk polysaccharide powder of each serogroup. The outcome of the study justifies the established hold time of this intermediate. The dried powder was tested for molecular size, phosphorous content, O-acetyl content, identity, bacterial endotoxin, nucleic acids content, protein content and moisture.

Batch analysis data shows that the activated/derivatised and depolymerised/activated polysaccharide intermediates are manufactured consistently. Phase III batches, manufactured in building 46 of Swiftwater, PA, USA site, used in clinical studies have been compared to batches manufactured in building 56 of Swiftwater, PA, USA site showing consistency of critical quality attributes (CQAs) throughout clinical development.

A hold study was performed to support the storage conditions and hold time of activated polysaccharides. Tested parameters were total and free linker, reducing activity and bioburden.

Tetanus toxoid

The intermediates involved in the manufacture of the tetanus component of the AS are the: purified tetanus protein (PTP); concentrated tetanus protein (CTP) and tetanus toxoid, filtered concentrate. Each intermediate can be stored. Each intermediate, except the tetanus toxoid, filtered concentrate, is analysed by quality control release tests and must be in compliance with its specification. Batch analyses data are provided.

Release tests for the PTP include protein/total nitrogen content and ratio, OD280/OD260 ratio, flocculating titre, antigenic purity, molecular size distribution and sterility. Release tests performed on the CTP are protein nitrogen content, OD280/OD260 ratio, phosphorous limit test, residual free formaldehyde, flocculation titre, antigenic purity, molecular size distribution, sterility, endotoxin and absence of toxin/irreversibility of toxoid.

CPPs and their ranges for PTP and for the CTP have been evaluated and accurately defined. Batch analyses have been performed on the three intermediate levels (PTP, CTP, TT filtered concentrate), showing the consistency of the manufacturing process. Stability data provided justify claimed hold time.

Process validation

Purified Tetanus Protein (PTP): The validation of the PTP production was divided into the validation of the *Clostridium tetani* fermentation process and harvest/purification /detoxification steps of the concentrated tetanus toxin to obtain the PTP. All CPPs, in-process control testing and quality control acceptance criteria

were met. In conclusion, the manufacturing process for the purified tetanus protein is validated, from the inoculum preparation to the detoxification stage.

Concentrated Tetanus Protein (CTP): The CPP and the quality control testing for concentrated tetanus protein batches were met. The manufacturing process for the concentration steps of the PTP to obtain the CTP is validated. Shipping validation of the CTP is provided.

Tetanus Toxoid, Filtered Concentrate: By evaluating the CQAs, the study validated the consistency of the AS intermediate, tetanus toxoid, filtered concentrate manufacturing process. In addition, a study was performed to establish the hold time for the tetanus toxoid filtered, concentrate stored at 1 °C to 5 °C in bags prior to conjugation. All validation data showed conformity to the acceptance criteria. The tetanus toxoid, filtered concentrate process consistently produced an AS intermediate that meets the critical quality attributes thus demonstrating suitability for use in the conjugation process.

N. meningitidis polysaccharide purified bulk powders (serogroups A, C, Y, W135): During process validation, the critical process parameters and critical quality attributes were evaluated. Results for all three validation/consistency lots met pre-defined acceptance criteria. These results demonstrated that the manufacturing process for the AS intermediates, *N. meningitidis* polysaccharide purified bulk powders (serogroups A, C, Y, W135), consistently produced a product that meets all the specifications and quality characteristics.

N. meningitidis polysaccharide tetanus toxoid conjugate concentrates serogroups (A, C, Y and W135): The manufacturing processes for the ASs are comprised of both common unit operations and serogroup-related specificities. The validation studies supporting unit operations and performed with batches produced in Building 46 (B46) are presented. The unit operation validation studies include: mixing studies, column chromatography studies, filtration (& re-filtration under specified conditions) validation, hold-time studies and column re-use studies.

The manufacturing process for the ASs, *N. meningitidis* polysaccharide tetanus toxoid conjugate concentrates (serogroups A, C, Y, W135), was initially developed and validated in the B46 production facility. After the production of process validation/clinical consistency batches, the AS manufacturing was transferred to the production facility in Building 56 (B56) for commercial manufacturing. Three comparability batches were manufactured in B56 and the data collected was assessed against the same validation criteria as batches manufactured in B46.

The process consistency and comparability validation studies performed using six batches of the AS of each serogroup are provided: 3 consecutive, full-scale validation and consistency batches manufactured in B46, and 3 consecutive, full-scale comparability batches manufactured in B56.

Manufacturing process development

Changes during the manufacturing process from Phase I have been described extensively and the impact of changes have been assessed by comparing consistency lots of every different serogroup to historical data. All acceptance criteria were met for all batches.

The major changes in the manufacturing process between production of AS (conjugate concentrates) clinical Phase I lots and Phase III comparability lots include increase in batch size of PTP and change in the seed lot system. The comparability exercise is considered acceptable. There were no changes in the manufacturing process of *N. meningitidis* polysaccharide tetanus toxoid conjugate concentrate, serogroup A, C, Y and W135, between Phase III clinical consistency/process validation and comparability lots produced at manufacturing scale.

Characterisation

For the characterization of the purified polysaccharide bulk powder, 1D proton nuclear magnetic resonance (NMR) spectroscopy and high-performance size exclusion chromatography with multi angle laser light scattering (HPSEC-MALS) testing have been performed. For characterization of TT carrier protein intermediates, differential scanning colorimetry (DSC) for PTT, PTP and CTP intermediates was performed. Characterization studies confirm chemical and structural attributes of intermediates.

The concentration of process residuals was measured in the active substance and the concentration in the finished product was calculated. Process residuals have been assessed in the AS and FP. All parameters were below the acceptance criteria. The extent and results of the study justifies the absence of routine testing of the identified process residuals. Batches tested for impurities are representative of clinical material.

Regarding product-related impurities, degradation impurities confirm the efficiency of the conjugation process over time. The concentration of free polysaccharide and free protein are considered as stability indicating and provide information about degradation of the active substance. Free polysaccharide and free protein assays are performed on each batch of the AS during stability.

Specification

The AS release specifications for each serogroup conjugate include appropriate physicochemical tests and tests for identity, protein content, polysaccharide content, polysaccharide to protein ratio, molecular size distribution, free polysaccharide content, free protein content, O-acetyl, endotoxin and bioburden test.

The release specifications for free protein will be reassessed once an adequate number of batches are tested and the results are analysed (see recommendation 1). The specifications have been justified in accordance with ICH Q6B.

The release specifications of the active substances were requested to include specifications for appearance. The applicant will evaluate the need for the test for routine operation after a minimum of 30 active substance batches from each serogroup (see recommendation 3). This is considered acceptable.

Analytical methods

The extent of validation of the analytical methods, with some exceptions, corresponds to ICH Q2 (R1) and the respective chapters of Ph. Eur. The analytical procedures are considered appropriate for the intended purpose.

Batch analysis

Active substance phase III clinical consistency/process validation batches and comparability batches of every serogroup were tested. Analytical procedures and specifications were the same as for release testing.

The results of all batches are within the acceptance criteria. No apparent trend or shift in analytical results between validation lots and comparability lots has been identified. Batch to batch consistency has been demonstrated for the validation lots, and comparability lots. It is concluded that the batches were manufactured consistently and according to pre- defined quality standards, and that the production process has been successfully transferred to the site intended for commercial production.

Reference materials

The applicant stated that no reference standard is used for the ASs. For the purified tetanus protein and concentrated tetanus protein, the reference material is an in-house flocculating standard for tetanus (antitoxin) calibrated against the international flocculation standard for tetanus (NIBSC) and stored at 2 °C to 8 °C. Polysaccharide concentrates are used to demonstrate the serogroup identity and specificity, and also that purified polysaccharide powders do not contain other serogroups.

During the procedure, the applicant was requested to provide information on all internal reference materials used in the control testing at any stage of product manufacture, including information on the type of reference, preparation instructions, storage conditions and shelf life of the different reference standards and materials. The applicant has now satisfactorily provided the requested information on the in-house reference materials used and the process for qualification of new reference lots is described.

Container Closure System

The container closure system for the ASs, *N. meningitidis* polysaccharide tetanus toxoid conjugate concentrate, Group A, C, Y and W135 is a bioprocess bag. Compliance with the Ph.Eur. requirements for the container closure system has been demonstrated. Comprehensive extractable and leachable studies have been performed, the results of which are acceptable.

Stability

The stability testing program presented by the applicant is considered to be appropriate and in accordance with ICH. Stability studies have been performed on the same phase III clinical consistency/process validation batches and comparability batches used for batch analysis. An accelerated study has been completed. A real time study is ongoing and the applicant commits to complete the stability testing for all ongoing studies according to the presented stability protocol.

The analytical procedures chosen for the program are suitably stability-indicating for the active substance. The containers used for the study conforms to the ones used in the manufacturing process. Tests are scheduled at appropriate time points.

The data presented shows that all results generated so far met the pre- set specifications and no apparent trend could be observed in the real time stability study. Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA. Shelf-life and storage conditions for the active substance have been proposed by the applicant and found acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product (FP) is presented as a 0.5 mL solution for injection for intramuscular use containing 10 µg each serogroups A, C, W and Y polysaccharide, individually conjugated to 55 µg tetanus toxoid carrier as active substance. Other ingredients are sodium chloride, sodium acetate and water for injections. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The composition of the FP is presented in **Table 1** below.

Table 1 Composition of Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine

Ingredient	Reference	Amount	Function
Meningococcal (Serogroup A) Polysaccharide (Monovalent Conjugate)	In-house	10 µg	Active Ingredient
Meningococcal (Serogroup C) Polysaccharide (Monovalent Conjugate)	In-house	10 µg	Active Ingredient
Meningococcal (Serogroup Y) Polysaccharide (Monovalent Conjugate)	In-house	10 µg	Active Ingredient
Meningococcal (Serogroup W135) Polysaccharide (Monovalent Conjugate)	In-house	10 µg	Active Ingredient
Tetanus Toxoid, Filtered Concentrate	In-house	55 µg*	Carrier Protein
Sodium Chloride (within 1.675% Sodium Chloride Solution)	USP/EP	3.35 mg (0.67%)	Excipient used to adjust tonicity
Sodium Acetate (within 50 mM Sodium Acetate, pH 6.0 Solution)	USP/EP	1.23 mg (30mM)	Excipient used to maintain pH
Water for injection	q.s. to volume		Ph.Eur.

* Tetanus toxoid quantity is approximate and dependent on the polysaccharide to protein ratio for the conjugates used in each formulation.

Different polysaccharide contents were used during Phase I studies: 2 µg, 4 µg and 10 µg per polysaccharide per dose, as well as 10 µg of polysaccharide for serogroups A and W135 and 4 µg of polysaccharide for serogroups C and Y. The Phase II clinical batches were manufactured with the final formulation of 10 µg polysaccharide per serogroup per dose. The Phase IIb and Phase III clinical batches utilised a manufacturing process that was scaled up. There are no differences in the formulation between the Phase IIb / Phase III clinical batches and the final formulation. Manufacturing was transferred to the site of commercial production during phase III. Phase III and commercial batches of the finished product are formulated/filled at Sanofi Pasteur site in Swiftwater, PA, USA. Comparability between the batches throughout Phase I to Phase III manufacturing process has been shown.

Comparability was demonstrated showing that the final container vaccine manufactured using the Phase I through Phase III processes are comparable based on the critical quality attributes.

In accordance with the Ph.Eur. monograph for meningococcal conjugated vaccines (07/2019:3066), the production method is required to be validated in order to demonstrate that the product, if tested, would

comply with the test for pyrogens (Ph.Eur. 2.6.8). Sufficient justification regarding the pyrogenicity of the product was provided by the applicant during the procedure.

The vaccine is filled in 2 ml glass vials, closed with an appropriate stopper and a flip-off seal. For phase I and phase II, 3 ml glass vials were used. The suitability of the container closure system has been demonstrated by extractables, leachables, cytotoxicity and stability studies. The container-closure system complies with Ph. Eur. requirements.

Manufacture of the product and process controls

Meningococcal polysaccharide (serogroups A, C, Y, and W135) tetanus toxoid conjugate vaccine, is manufactured by Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370, USA. The site for EU batch release is Sanofi Pasteur, Industrial Park Incarville, 27100 Val de Reuil, France. Appropriate GMP certification for these sites has been provided.

Each monovalent conjugate is thawed. Sodium acetate buffer, conjugates and sodium chloride buffer are mixed. Following 0.22 µm filtration, the mixture is transferred to portable tanks. Sodium chloride buffer is added to the final volume through the 0.22 µm filter. The portable tank is stored at 1 ºC to 5 ºC for up to 6 months.

Prior to filling, the contents of the portable container are mixed and then 0.22 µm filtered. 2 ml vials are rinsed with WFI and depyrogenated before filling.

The 0.22 µm filtration of the bulk from the portable tanks prior to filling is considered a critical process step. Therefore, bioburden is measured before filtration. Pre-filtration bioburden is also measured before filling in the 2 ml vials. Weight check is performed in order to control the filling volume. Final containers are 100% visually examined according to USP. There is no pooling of AS batches in the preparation of one FP lot.

Comprehensive studies have been performed for the validation of the formulation and filling process, at two different scales. All CPPs and CQAs have been defined and assessed, on a total of seven lots for the small-scale process and four lots for the large scale process.

Studies were conducted on the formulation tank and portable tanks to validate mixing. The measurements of all time points of all tanks met the pre-set criteria.

The lots were assessed against validation acceptance criteria which consisted of the established process parameters, in-process controls and CQAs for the filling validation. Routine testing for the FP was conducted. Additional non-routine samples were taken across the fill to evaluate the total and % free polysaccharide, total protein and pH.

A summary of the non-critical controlled and/or monitored process parameters for the FP manufacturing process including a clarification of the classification exercise was requested in the list of questions. The requested information on non-critical and/or monitored process parameters for finished product has been provided and is considered acceptable. Critical process parameters and quality attributes are therefore considered well defined and controlled. Appropriate media fill studies and filter validation studies were conducted.

The packaged finished product is shipped from the production facility to the Sanofi distribution centre. A summary of the shipping validation study has been provided upon request and is acceptable.

Overall, a detailed description of the manufacturing process for the AS has been presented by the applicant. The deviations filed during the process validation studies are extensively explained and considered to have no impact on the quality of the studies and still permit a conclusion that the process is under suitable control. The production process for the FP is considered to be acceptably validated.

Product specification

The FP specifications include appropriate physicochemical tests and tests for identity, purity and potency. The panel of product specifications for release of the final lot vaccine comprises tests for identity, total and free polysaccharide, total protein, molar mass, appearance, volume, pH, endotoxin, container closure integrity and sterility.

Release specifications for the bulk and final container product have been justified according to ICH Q6B and are considered acceptable. The applicant was asked to evaluate the risk of the presence of nitrosamine impurities in the MenQuadfi finished product in accordance with the published Art. 5(3) Referral on Nitrosamines (https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf). A respective risk assessment has now been provided, showing no risk of nitrosamine impurities in the FP.

In conclusion, the program for control of finished product is considered adequate and conforms to the Ph. Eur. monographs 3066 Meningococcal group A, C, W135 and Y Conjugate Vaccine as well as 0153 Vaccines for Human Use.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. The panel of release tests for final lot vaccine comprises tests for identity, total and free polysaccharide, total protein, molar mass, appearance, volume, pH, endotoxin, container closure integrity and sterility

Batch analysis

The final container FP was tested according to the release specifications. All tests passed the acceptance criteria. No visible shift or trend could be identified between the phase III clinical batches and the commercial batches. Therefore, it is concluded that the manufacturing process of the FP is consistent.

Reference materials

The dossier describes relevant reference materials utilized within the test methods and procedures for use.

Stability of the product

Stability studies have been performed on the bulk formulated and on the filled FP. The extent of the stability study program presented by the applicant is seen as adequate and in accordance with ICH guidelines. The chosen analytical procedures are stability-indicating and validated accordingly. The studies have been performed in the same containers that will be used for commercial batches.

Stability studies performed at actual storage conditions (2 °C to 8 °C) demonstrate the ability of the container closure system to maintain product sterility over the proposed holding period of the formulated bulk. Studies for the filled FP included a real time stability study, an accelerated stability study, photostability study and a forced degradation study.

The applicant commits to re-evaluate the end of shelf life specification, as soon as 8 more lots reach the end of shelf life at the stability program. The photostability study, conducted according to ICH guideline Q1B, shows that exposure to light has no influence on the packaged product.

A FP shelf life of 42 months at 2-8 °C is agreed.

Adventitious agents

The applicant provides a list of materials of animal origin used for establishment of the meningococcal seed lot system. For the master seed, no material of biological origin was used. Materials used for the establishment of the pre-master seed comply with the requirements of EMEA/410/01. Raw materials of ruminant origin are used in the production of *Clostridium tetani* seed lots (skimmed milk, meat extract, casein peptone, L-cysteine) and concentrated purified tetanus protein bulk (casein peptone, tryptone V, beef heart infusion, l-tyrosine, peptide N3) and comply with Ph. Eur. 1483 and 5.2.8 with respect to TSE safety.

The seed lots are tested for purity and the manufacturing process is performed aseptically and includes bacterial inactivation during the purification of the bacterial antigens. The finished product is tested for sterility. Viral clearance studies for the bacterial vaccine are not required as there is no host available for the propagation of virus. Some steps have the potential for the inactivation of viral particles. Therefore, there is a low risk for contamination with adventitious agents, which is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The information provided in section 3 of the CTD is considered acceptable. The applicant gives a detailed description of the manufacturing process and process development of all ASs and FP. The production processes have been validated satisfactorily, CPPs and CQAs have been identified and implemented accordingly. The control strategies for all ASs and FP are considered to be acceptable. Analytical methods are considered to be scientifically sound and adequately validated. Consistency of the manufacturing process has been demonstrated.

Three recommendations are proposed see Table in 2.2.6 section.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the

CHMP recommends the following points for investigation:

Area	Number	Description	Classification*
Quality	001	A re-evaluation of the active substance release specification limits for free protein should be provided after testing of 30 AS batches of each serogroup.	REC
Quality	002	It is recommended that a re-evaluation of the finished product specification limits for free polysaccharide for each serogroup at the end of shelf life should be provided, after completion.	REC
Quality	003	An evaluation of the need for a release test for appearance should be performed and the information provided, after a minimum of 30 active substance batches from each serogroup. This test, if required, would need to be introduced to the MA by variation.	REC

*REC- recommendation

2.3. Non-clinical aspects

2.3.1. Introduction

To support MenACYW Conjugate Vaccine clinical development, nonclinical pharmacology studies were performed to demonstrate the ability of the vaccine to induce a specific and bactericidal antibody response to meningococcal polysaccharide antigens (Serogroups A, C, Y and W). The toxicology programme comprises a repeated dose toxicity study in CD rats and a preliminary immunogenicity and DART study in NZW rabbits. These studies were conducted to understand the toxicological profile of MenQuadfi, including the potential systemic and local effects and the potential risk to women of childbearing potential and their offspring. Additionally, immunogenicity examinations were included in all toxicology studies to demonstrate that the vaccine induces a specific immune response to the meningococcal polysaccharide antigens contained in MenQuadfi.

2.3.2. Pharmacology

It is considered acceptable that nonclinical pharmacology studies are limited to demonstration of immunogenic response via SBA assay and IgG response. No nonclinical data on protection against meningococcal infection by vaccine candidates (challenge studies) were generated. This is also in line with current guidance.

Mice, rat and rabbit strains were tested for their immunological responses after immunization with tetravalent meningococcal polysaccharide (serogroups A, C, Y, and W) conjugate vaccine formulations. The highest and most reproducible results were obtained in mice. Thus, different mouse strains were further evaluated to select the best fitted mouse model. Highest IgG and SBA titers against all four polysaccharides (serogroup A, C, Y and W) were measured in selected strain of mice. Thus, selected strain of mice were determined to represent the best model for the planned immunogenicity studies. The selected immunization dose of each meningococcal polysaccharide was found suitable for evaluating the immunogenicity of formulations of

tetravalent meningococcal polysaccharide conjugated to tetanus toxoid since it induced an immune response against all 4 polysaccharides with titers in the middle of the dose response curve.

For the selection of the appropriate immunization schedule and dose for polysaccharide specific total IgG and polysaccharide specific bactericidal response, additional dose-range finding studies were conducted in the selected strain of mice.

Selected strain of mice were immunized two or three times with the optimized level of polysaccharide/dose or with a decreasing dose regimen (0.5 µg, 0.25 µg and 0.13 µg of each serogroup/dose). Except for serogroup C (SBA Titer), PS specific total IgG and bactericidal antibody titers were similar or higher three weeks after the final boost injection. Although three injections of the optimized level of PS resulted in higher SBA titer and IgG levels, the responses after two injections were also significantly increased in a short period of time compared to the physiological saline control, and thus the applicant regarded the three-dose schedule to not offer any advantage over the two-dose schedule. Variable data was observed for the decreasing dose regimen with no significant benefit observed over the unique dose regimen.

The two-immunization schedule with optimized level of PS/dose associated with serum sampling three weeks post final boost were thus selected for PS specific total IgG and PS specific bactericidal response evaluation in the selected strain of mice. According to the submitted data immunological responses after three vaccinations were strongly increased compared to the two-dose regimen. Thus, the applicant's conclusion that the three-dose schedule does not offer ANY advantage over the two-dose schedule is not completely conclusive to the assessor. However, further studies using the two-dose schedule were subsequently performed and showed positive results when using the proposed dosing regimen.

Subcutaneous injection was performed in mice to allow a higher volume to be administered as compared to the clinically used intramuscular route. Additional studies injecting higher volumes via the intramuscular route would be feasible, e.g. in NZW rabbit, but have not been conducted. Intramuscular injection was investigated in toxicological studies in rats.

For immunogenicity evaluation of the final clinical formulation, groups of selected strain of mice were immunized with the GMP batch according to the dosing schedule determined in the previous studies, i.e. two subcutaneous injections (prime and booster) containing optimal concentration of each serogroup per dose. Three weeks after the second immunization the animals were bled and serum samples were tested using ELISA for PS specific total IgG determination and serum bactericidal assay (SBA) to determine PS specific bactericidal antibody titers.

For serogroup A, total IgG response was higher for the TetraMen-T (Demo) batch than with the clinical formulation. Both meningococcal vaccine batches showed significantly higher total IgG responses than the physiological saline control.

For serogroup C, vaccination responses for both, TetraMen-T (Demo) and clinical batch, were observed to be significantly higher than when using saline control. No significant differences were observed between serogroup C specific IgG responses induced by either TetraMen-T or TetraMen-Dt. However, in general, anti-C IgG responses induced by two of the meningococcal vaccines available commercially were higher than the antibody responses induced by the TetraMen-T (Demo) and TetraMen-Dt vaccines and in some cases the results were significant.

For serogroup Y and serogroup W135 similar results were obtained. All treatment groups showed significantly higher total IgG responses than the saline control, with TetraMen-T (Demo) formulation again showing

somewhat but insignificant higher total IgG response than the clinical batch. For serogroup C, the response after vaccination with TetraMen-T was higher than with TetraMen-Dt.

When testing for bactericidal antibody response, all serogroups were found significantly higher after meningococcal vaccination compared to the physiological saline control. For serogroup A and C, the TetraMen-T (Demo) formulation again showed significantly higher responses than the clinical formulation, for serogroup W135, the both TetraMen-T formulations showed significantly higher results than the saline, but the TetraMen-Dt formulation did not.

There was a strong correlation between the level of PS specific IgG and bactericidal antibodies induced in mice injected with TetraMen-T formulations for serogroups A, Y, W135 whereas the correlation between IgG and bactericidal responses elicited by the TetraMen-Dt vaccine was not always evident.

Summarized, MenACYW Conjugate Vaccine induced serogroup specific total IgG and bactericidal antibody responses in all serogroups (A, C, Y, W). Responses were significantly higher than the antibody responses observed in the saline control groups. There was a strong correlation between the level of PS specific IgG and bactericidal antibodies induced in mice injected with MenACYW Conjugate Vaccine formulations for serogroups A, Y, W, but not for serogroup C.

Dedicated studies on secondary pharmacodynamics and safety pharmacology were not performed. This is in accordance with relevant guidance. Pharmacodynamic drug interaction studies have not been conducted. However, interactions between MenQuadfi and other vaccines frequently administered to the same population have been investigated in clinical studies.

2.3.3. Pharmacokinetics

No non-clinical pharmacokinetics studies were submitted, which is in accordance with recent guidelines.

2.3.4. Toxicology

To support vaccine development and registration, a non-clinical toxicology programme was designed to assess the toxicological profile of MenQuadfi. This programme comprises a repeated dose toxicity study in CD rats (Study AES/0126) and a preliminary immunogenicity study (Study RED_00091026) and DART study (Study SP00047 DV1701) in NZW rabbits. The design of these studies is considered to be in line with recent guidelines.

Repeat dose toxicity

The toxicology studies were performed in compliance with GLP, except for the immunogenicity study phase in the repeat-dose toxicity study (Study AES/0126) in rats which was conducted in a non-GLP compliant facility. The lack of GLP compliance has neither been explained by the applicant in sufficient detail nor justified. Therefore, it was decided that the results of this study should be considered as not relevant for the clinical use of MenQuadfi. Nevertheless, in the rat repeated dose toxicity study (Study AES/0126), no critical findings were reported, indicating that the administration of MenQuadfi was well tolerated in rats.

However, several rats receiving the vaccine formulation did not show detectable antibody responses specific to an individual polysaccharide serogroup. Therefore, as the reliability of the results of study AES/0126 could not be sufficiently established, the applicant's original statement in the SmPC section 5.3 ("*Non-clinical safety*

data revealed no special risks for humans based on a repeat-dose toxicity and local tolerance study in rats …") was not supported. The applicant therefore conducted a change in the SmPC wording and deleted all references to the rat repeated dose toxicity study AES/0126. This amendment was considered acceptable

On Day 2 of the study, dark faeces were noted in the bedding of all cages housing treated animals. The applicant remarked to this observation that with no evidence of histopathological changes this finding was not considered toxicologically significant. However, the lack of a histopathological correlate could of course also be related to a transient adverse effect at the beginning of the study that resolved during the further course of the study until the animals were killed and their organs histologically examined. Hence, the lack of a histopathological correlate cannot be used as rationale to consider that this finding is not of toxicological relevance. The fact that dark faeces were found in all cages of treated animals strongly suggests that this observation is treatment related. However, considering that the relevance of the rat repeated dose study for humans was doubted, it was unclear whether this finding also beared relevance for the clinical use of MenQuadfi.

Genotoxicity and carcinogenicity

The absence of genotoxicity and carcinogenicity studies is considered acceptable based on the type of product and in line with current guidelines on non-clinical evaluation of vaccines.

Reproduction Toxicity

A developmental and reproductive toxicity (DART) study was conducted to evaluate the potential effects of MenACYW conjugate vaccine on female fertility, embryo-foetal development (including an evaluation of teratogenicity) and early post-natal development of female NZW rabbits.

The study indicates that MenQuadfi does not pose relevant risks on the investigated endpoints of mating, fertility, ovarian and uterine parameters and natural delivery. Furthermore, MenQuadfi was demonstrated to be non-teratogenic, and no adverse effects were observed regarding pup survival, growth and development. In fact, the endpoints evaluated in the treatment group of this DART study were almost never statistically different to the ones of the vehicle group. In addition, the fact that antibodies against serogroup C capsular polysaccharides were detected in all treated dams and also in foetuses and pups indicates that the NZW rabbit was a suitable non-clinical model for the conduct of a DART study with MenQuadfi.

Toxicokinetic data

Studies assessing toxicokinetics of MenQuadfi have not been conducted. This is in line with applicable guidelines.

Local Tolerance

As part of the DART study in rabbits, the local tolerance to repeat IM doses of MenQuadfi vaccine was assessed in New Zealand White rabbits and no additional local tolerance studies were performed which is acceptable.

2.3.5. Ecotoxicity/environmental risk assessment

According to the EMA ERA guideline (EMEA/CHMP/SWP/4447/00 corr 21*), an ERA should be provided for vaccine products that may consist of a justification for not submitting ERA studies, e.g. due to their nature they are unlikely to result in a significant risk to the environment.

The applicant submitted a justification. In addition, as MenQuadfi does not contain adjuvants, the applicant's position that MenQuadfi vaccine is unlikely to result in a significant risk to the environment was accepted by the Committee.

2.3.6. Discussion on non-clinical aspects

The applicant refers to pharmacology studies in different animal species (mouse, rat, rabbit) where the species' ability to produce an immune response to MenACYW conjugate vaccine has been compared. According to the Pharmacology written summary, the mouse model was chosen due to highest and most reproducible immune response. In humans, MenACYW conjugate vaccine is administered by intramuscular (IM) injection, while in the nonclinical studies, the vaccine is dosed subcutaneously (SC) to mice, and IM to rats and rabbits.

Overall, results from the nonclinical experiments in selected strain of mice form a reasonable basis to justify selection of MenACYW Conjugate Vaccine formulation for further evaluation in the clinic. Due to factors such as difference in size, MHC/HLA dissimilarities, and differences with regard to route of administration and dosing regimen, animal models may have limited predictive value for immunogenicity in humans and results from animal studies should thus be considered with caution. The use of the tetanus toxoid (TT) conjugate protein, which is already in use in other vaccines, appears acceptable. The safety of the vaccine must be taken into account in this regard.

The toxicology programme of this submission comprises a repeated dose toxicity study in CD rats (Study AES/0126), a preliminary immunogenicity study (Study RED_00091026) and a DART study (Study SP00047 DV1701) in NZW rabbits. These studies demonstrate that MenQuadfi was well tolerated in the rat and the rabbit. Overall, the non-clinical safety data demonstrate that MenQuadfi has an acceptable safety profile.

2.3.7. Conclusion on the non-clinical aspects

From a nonclinical point of view, marketing authorisation can be supported.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2: Tabular overview of clinical studies

Study ID – Phase Objectives	Study design Comparator, concomitant vaccinations	Main efficacy objectives	Population
Main studies			
MET35 - Phase III Immunogenicity and Safety	modified double-blind, randomized, parallel-group, active-controlled, multi-center trial Control: Menveo	To demonstrate the non-inferiority of the vaccine seroresponse	1000 healthy, meningococcalvaccine naïve children aged 2 through 9 years in the US and Puerto Rico
MET43 - Phase III Immune Lot Consistency, Immunogenicity, and Safety	modified double-blind, randomized, parallel-group, active-controlled, multi-center study Control: Menactra (MCV4-DT)	- To demonstrate the immune lot consistency - To demonstrate the non- inferiority of the antibody responses	3300 healthy, meningococcalvaccine naïve adolescents and adults aged 10 through 55 years in the US
M**ET49 -** Phase III Immunogenicity and Safety	modified double-blind, randomized, parallel-group, active-controlled, multi-center trial Control: Menomune - A/C/Y/W-135	To demonstrate the non-inferiority of the vaccine seroresponse	900 healthy, meningococcal-vaccine naïve adults ≥ 56 years of age in the US and Puerto Rico
MET50 - Phase II Immunogenicity and Safety	open-label, randomized, parallelgroup, controlled, multi-center study Control: Menveo (MCV4-CRM) Concomitants: Adacel / Covaxis (Tdap) and Gardasil (HPV) vaccines	- To evaluate the antibody responses compared with Menveo - To evaluate the antibody responses concomitantly with Tdap and HPV vaccines	1700 healthy, meningococcal vaccine-naïve adolescents 10 through 17 years of age in the US
MET51 - Phase III Immunogenicity and Safety	modified double-blind, randomized, parallel-group, active-controlled, multi-center trial Control: Nimenrix	To demonstrate the non-inferiority of the antibody response	918 healthy toddlers aged 12 to 23 months in the European Union (Spain, Hungary, Finland, and Germany) who were either meningococcal vaccine-naïve or had received monovalent MenC vaccination during infancy
MET56 - Phase III Immunogenicity and Safety	modified double-blind, randomized, parallel-group, active-controlled, multi-center trial Control: Menactra	To demonstrate the non-inferiority of the vaccine seroresponse following the administration of a booster dose	800 healthy adolescents (15 through 17 years old) and adults (≥ 18years old) in the US and Puerto Rico who had received 1 dose of a quadrivalent meningococcal conjugate vaccine 4 to 10 years previously

MET57 - Phase III Immunogenicity and Safety	open-label, randomized, parallelgroup, controlled, multi-center study No meningococcal control vaccine Concomitants: M-M-RII + VARIVAX (MMR+V) or Hexaxim/Hexyon/Hexacima (DTaP-IPV-HB-Hib),or (Prevenar 13/Prevnar 13 (PCV13)	- To describe the immunogenicity profile of MenACYW conjugate vaccine administered alone or concomitantly with licensed pediatric vaccine(s) - To describe the immunogenicity profile of licensed pediatric vaccine(s) administered alone or concomitantly.	1200 healthy meningococcal vaccine-naïve toddlers aged 12 to 23 months in South Korea, Mexico, the Russian Federation, and Thailand
Supportive studies			
MET28 - Phase I Safety and Immunogenicity	randomized, modified single-blind, active-controlled (infants only), four-stage, step-down, comparative, multi-center study. Menjugate (Monovalent C vaccine)	To describe the immunogenicity ans safety profile following a booster dose with different formulations	270 healthy, meningococcal vaccine-naïve subjects: 30 Adults ≥ 18 through < 40 years old 40 Toddlers ≥ 12 through < 19 months 200 Infants 2 months (+28 days old) in Canada
MET32 - Phase I/II Safety and Immunogenicity	exploratory, randomized, observerblinded, active-controlled, parallel, multicentre study. Control: NeisVac-C (Monovalent C vaccine)	To describe the immunogenicity profile	360 healthy, meningococcal vaccine-naïve toddlers 12 months ± 21 days in Australia
MET44 - Phase II Immunogenicity and Safety	randomized, open-label, multi-center study. Control: Menomune - A/C/Y/W-135 (MPSV-4)	To describe the antibody responses	300 healthy, meningococcal vaccine-naïve adults aged 56 through 64 and ≥ 65 years on the day of enrollment in the US
MET54 - Phase II Immunogenicity and Safety	open-label, randomized, parallel, active-controlled, multi-center study Control: Nimenrix (MCV4-TT)	- To evaluate the antibody responses - To evaluate the antibody responses against tetanus	200 healthy, meningococcal vaccine-naïve toddlers aged 12 to 23 months in Finland
MET39 - Phase II Immunogenicity and safety	Randomized, open-label, multi-center study Concomitants: Pneumococcal 7-valent or 13-valent Conjugate Vaccine [Prevnar or Prevnar 13 vaccinesa], rotavirus vaccine [RotaTeq or ROTARIX], Varicella vaccine [VARIVAX], Measles, mumps, rubella vaccine [M-M-R II], DTaP-IPV/Hib vaccine [Pentacel]).	- To describe the safety and immunogenicity profile of MenQuadfi administered at 5 different schedules and concomitantly with routine pediatric vaccinations - To describe the immunogenicity profiles of selected licensed pediatric vaccines when administered either concomitantly or alone	Not part of the applied indication 580 infants after a 1-, 2-, or 3-dose schedule in the first year of life with an additional dose of MenACYW conjugate vaccine in the 2nd year of life in the US

Ongoing and planned studies

The applicant has listed 'Long-term persistence of the vaccine response, and safety and immunogenicity of booster in individuals primed with MenACYW conjugate vaccine' as missing information in the RMP. Further, according to the applicant the following clinical studies to assess the long-term immunogenicity of the MenACYW conjugate vaccine are currently ongoing or are planned:

MET62: Phase IIIb follow-up of MET54. Immunogenicity and Safety of MenACYW conjugate vaccine given as a booster injection in children vaccinated 3 years earlier with MenACYW conjugate vaccine as toddlers

MET59: Phase IIIb follow-up of MET50. Immunogenicity and Safety of MenACYW conjugate vaccine given as a Booster Injection in Adolescents and Adults vaccinated 3 to 6 years earlier with MenACYW conjugate vaccine. Additionally, this follow-up study aims to assess the effect of a booster vaccination with the MenACYW conjugate vaccine in recipients of either the MenACYW conjugate vaccine or the licensed vaccine Menveo, as well as the effect of concomitant administration of a Meningococcal group B vaccine with the booster dose of MenACYW conjugate vaccine.

MEQ00066: Immunogenicity and Safety of MenACYW conjugate vaccine given as a booster injection in older adults and elderly individuals vaccinated at least 3 years earlier with MenACYW conjugate vaccine

2.4.2. Pharmacokinetics

No pharmacokinetic studies were conducted, which is in accordance with the EMA Guideline on "the Clinical Evaluation of New Vaccines".

2.4.3. Pharmacodynamics

Pharmacodynamics of MenACWY vaccines represents the immune response to the vaccine. Since the efficacy of MenACWY vaccines is also assessed by immunological criteria, all clinical studies will be discussed under Clinical Efficacy.

2.4.4. Discussion on clinical pharmacology

All clinical studies carried out are immunogenicity studies, which are discussed under Clinical Efficacy section.

2.4.5. Conclusions on clinical pharmacology

Please refer to section 2.5.3 Conclusions on clinical efficacy.

2.5. Clinical efficacy

Of note, no efficacy studies have been submitted. All studies described in this section are immunogenicity studies

2.5.1. Dose response studies and main clinical studies

Study MET28

Study MET28 was a phase I, randomized, modified single-blind, active-controlled (infants only), four-stage, step-down (by age), comparative (comparator Menjugate [monovalent C vaccine]), multi-center study to the evaluate safety and immunogenicity of 3 formulations of MenACYW conjugate vaccine (previously referred to as TetraMen-T) in healthy adults (aged ≥ 18 through < 40 years), toddlers (aged ≥ 12 through < 19 months), and infants (aged 2 months +28 days [60 through 88 days]) in Canada between July 25th 2006 and August 27th 2008.

Study description

The study included four stages:

Stage I:

Two groups of adults aged ≥ 18 to < 40 years received one injection of TetraMen-T: either a low-dose adjuvanted formulation (2 µg polysaccharide per serogroup with $AlPO_4$) or a high-dose formulation (10 µg polysaccharide per serogroup) without adjuvant.

Stage II:

Two groups of toddlers aged ≥ 12 to < 19 months received one injection of TetraMen-T: either a low-dose adjuvanted formulation (2 µg polysaccharide per serogroup with $AlPO_4$) or a high-dose formulation (10 µg polysaccharide per serogroup) without adjuvant.

Stage III:

Four groups of infants aged 2 months +28 days (60–88 days) at enrolment were to receive three doses of meningococcal vaccine at 2, 4, and 6 months of age, concomitantly with the routine vaccines Pentacel, Prevnar, and Engerix-B. The meningococcal vaccine was either to be the low-dose formulation of TetraMen-T (2 µg polysaccharide per serogroup without adjuvant), the low-dose adjuvanted formulation of TetraMen-T (2 µg polysaccharide per serogroup with $AlPO_4$), the high-dose formulation of TetraMen-T (10 µg polysaccharide per serogroup without adjuvant), or the licensed meningococcal vaccine Menjugate. Menjugate (Novartis) is a monovalent (serogroup C) meningococcal vaccine conjugated to diphtheria CRM197 protein.

Stage IV:

A subset of subjects from all 4 infant groups were to receive a booster dose of TetraMen-T at 13 months of age (±28 days). Subjects who had received one of the 3 formulations of TetraMen-T in Stage III were to be given the same formulation for their booster dose. Those subjects who had received Menjugate in Stage III were to be given the low-dose adjuvanted formulation of TetraMen-T for their booster dose.

Blood for serological testing was collected before vaccination at Visit 1 (Day 0) from all subjects; at 28 to 42 days after vaccination from adults and toddlers; and at 28 to 42 days after the 3rd vaccination from infants. Infants who received a 4th dose in the 2nd year of life also provided a blood sample just prior to vaccination and at 28 to 42 days after the 4th dose.

Functional antibodies to meningococcal serogroups A, C, Y, and W-135 were measured by serum bactericidal assay using human complement (SBA-HC) and/or baby rabbit complement (SBA-BR). No efficacy data were collected in this trial.

Results

Adults (Stage I):

All adult subjects (100.0%) achieved rSBA titers ≥ 1:8 for the 4 serogroups after vaccination. For both formulations, geometric means of rSBA titers were significantly higher for all 4 serogroups after vaccination as compared to pre-vaccination levels. The magnitude of the antibody response was higher in Group 2 (10 µg vaccine) versus Group 1 (2 µg vaccine + $AlPO_4$).

Toddlers (Stage II):

The percentages of toddlers with an hSBA titer ≥ 1:8 were lowest for serogroup A in both groups: 52.6% in Group 3 (2 µg vaccine + $AlPO_4$) and 63.2% in Group 4 (10 µg vaccine) relative to the other serogroups in both groups: 100.0%, 78.9%, and 68.4% for serogroups C, Y, and W, respectively in Group 3 and 89.5% for each of the serogroups C, Y, and W in Group 4. There was no increase in geometric mean titers (GMTs) post-vaccination for serogroup A in Group 3 subjects, and just a marginal increase in Group 4 subjects. The highest increase was seen for serogroup C in both groups.

Infants (Stage III):

The percentage of infants, who received MenACYW conjugate vaccine, achieving an hSBA titer ≥ 1:8 after 3 doses ranged from 22.5% (Group 5, 2 µg vaccine) to 61.5% (Group 6, 2 µg vaccine + $AlPO_4$) for serogroup A; from 94.9% (Group 6) to 97.6% (Group 5) for serogroup C; from 90.2% (Group 5) to 100.0% (Group 6) for serogroup Y; and from 83.3% (Group 7, 10 µg vaccine) to 87.2% (Group 6) for serogroup W. In the control group, 100.0% of subjects achieved a post-Dose 3 titer ≥ 1:8 for serogroup C.

Infants (Stage IV, booster):

After the 4th dose, an hSBA titer ≥ 1:8 was achieved by 100.0% of subjects in Groups 5, 6, and 7 for serogroups Y and W; and by 83.3% to 100% for serogroup C. Similar to the other stages, the percentages of subjects achieving hSBA titers ≥ 1:8 for serogroup A was lower relative to the other serogroups in all groups, ranging from 22.2% in Group 7 to 58.3% in Group 6. The percentages were lower for Group 8 (Menjugate) subjects, who were receiving MenACYW conjugate vaccine for the first time. Post-Dose 4 GMTs confirmed the same low immune responses to serogroup A and robust immune responses for the other 3 serogroups in Groups 5, 6, and 7.

Study MET32

Study MET32 was a phase I/II, exploratory, randomized, observer-blinded, active-controlled (comparator NeisVac-C vaccine), parallel, multi-center study to the evaluate safety and immunogenicity of 2 formulations and different dose levels of TetraMen-T Quadrivalent Meningococcal (A, C, Y and W-135) Polysaccharide Tetanus Protein Conjugate Vaccine in healthy, meningococcal vaccine-naïve toddlers (12 months ±21 days aged) in Australia between April 21st 2008 and October 28th 2008.

Study description

The vaccine formulation underwent optimization to address the lower immune response to serogroup A observed in MET28, and study MET32 was conducted to evaluate 2 new formulations. Each of these 2 formulations of MenACYW conjugate vaccine was evaluated at different dose levels (described below), in order to look for a dose-response effect. The doses selected were based on the results from study MET28.

A single dose of one of the formulations or control vaccine was evaluated in a total of 368 toddlers aged 12 months (± 21 days) randomized to one of the following 6 groups:

- Group 1: Formulation 1, low dose (4 µg polysaccharide per serogroup; and a total of 22.1 µg tetanus toxoid protein)
- Group 2: Formulation 1, intermediate dose (4 µg polysaccharide per serogroups C and Y; 10 µg polysaccharide per serogroups A and W; and a total of 36.6 µg tetanus toxoid protein)
- Group 3: Formulation 1, high dose (10 µg polysaccharide per serogroup; and a total of 54.8 µg tetanus toxoid protein)
- Group 4: Formulation 2, low dose (4 µg polysaccharide per serogroup; and a total of 33.9 µg tetanus toxoid protein)
- Group 6: Formulation 2, high dose (10 µg polysaccharide per serogroup; and a total of 84.8 µg tetanus toxoid protein)
- Group 7: NeisVac-C (10 µg *N. meningitidis* group C polysaccharide, 10 to 20 µg tetanus toxoid, 0.5 mg Al^{3+} from aluminum hydroxide)

Blood for serological testing was collected from all subjects at Visit 1 (Day 0) before vaccination, and at Visit 2, 30 days (+7 days) after vaccination. Immunogenicity was assessed using hSBA and rSBA.

No efficacy data were collected in this trial.

Results

Table 3: Number and Proportion of Subjects with a Titer ≥1:8 at Baseline and 30 Days Post-vaccination, SBA-HC Assay (Per-Protocol Population)

Antigen strain	Time point	Group 1 (N=54)	Group 2 (N=51)	Group 3 (N=51)	Group 4 (N=48)	Group 6 (N=51)	Group 7 (N=51)
		n/M % 95% CI	n/M % 95% CI	n/M % 95% CI	n/M % 95% CI	n/M % 95% CI	n/M % 95% CI
A	Pre-Vaccination	19/ 54 35.2 (22.7; 49.4)	11/ 51 21.6 (11.3; 35.3)	15/ 50 30.0 (17.9; 44.6)	9/ 48 18.8 (8.9; 32.6)	16/ 51 31.4 (19.1; 45.9)	13/ 51 25.5 (14.3; 39.6)
	Post-Vaccination	47/ 54 87.0 (75.1; 94.6)	50/ 50 100.0 (92.9; 100.0)	45/ 51 88.2 (76.1; 95.6)	36/ 48 75.0 (60.4; 86.4)	47/ 51 92.2 (81.1; 97.8)	23/ 50 46.0 (31.8; 60.7)
C	Pre-Vaccination	0/ 54 0.0 (0.0; 6.6)	0/ 51 0.0 (0.0; 7.0)	0/ 51 0.0 (0.0; 7.0)	1/ 48 2.1 (0.1; 11.1)	0/ 51 0.0 (0.0; 7.0)	0/ 51 0.0 (0.0; 7.0)
	Post-Vaccination	49/ 54 90.7 (79.7; 96.9)	44/ 51 86.3 (73.7; 94.3)	43/ 51 84.3 (71.4; 93.0)	45/ 48 93.8 (82.8; 98.7)	49/ 51 96.1 (86.5; 99.5)	51/ 51 100.0 (93.0; 100.0)
Y	Pre-Vaccination	1/ 54 1.9 (0.0; 9.9)	2/ 51 3.9 (0.5; 13.5)	1/ 51 2.0 (0.0; 10.4)	0/ 48 0.0 (0.0; 7.4)	0/ 51 0.0 (0.0; 7.0)	3/ 51 5.9 (1.2; 16.2)
	Post-Vaccination	36/ 54 66.7 (52.5; 78.9)	40/ 51 78.4 (64.7; 88.7)	40/ 51 78.4 (64.7; 88.7)	44/ 48 91.7 (80.0; 97.7)	42/ 51 82.4 (69.1; 91.6)	4/ 51 7.8 (2.2; 18.9)
W-135	Pre-Vaccination	0/ 54 0.0 (0.0; 6.6)	0/ 51 0.0 (0.0; 7.0)	0/ 51 0.0 (0.0; 7.0)	0/ 48 0.0 (0.0; 7.4)	0/ 51 0.0 (0.0; 7.0)	0/ 51 0.0 (0.0; 7.0)
	Post-Vaccination	35/ 54 64.8 (50.6; 77.3)	35/ 50 70.0 (55.4; 82.1)	33/ 51 64.7 (50.1; 77.6)	30/ 48 62.5 (47.4; 76.0)	36/ 51 70.6 (56.2; 82.5)	1/ 50 2.0 (0.1; 10.6)

Source: Section 9, Table 9.71 and Table 9.72

N is the total number of subjects per group from the per-protocol analysis set

n is the number of subjects experiencing the endpoint listed in the first column

M: for fold-rise, number of subjects with both pre- and post-vaccination valid serology results for the particular antigen, including results reported as <LLOQ and >ULOQ

M: for titers, number of subjects with valid serology results for the particular antigen, including results reported as <LLOQ and >ULOQ

Table 4: Geometric Mean Titers (GMTs) at Baseline and 30 Days Post-Vaccination, SBA-HC Assay (Per-Protocol Population)

Antigen	Bleed	Group 1 (N=54)	Group 2 (N=51)	Group 3 (N=51)	Group 4 (N=48)	Group 6 (N=51)	Group 7 (N=51)
		GMT (95% CI)	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
A	Pre	4.79 (3.75; 6.11)	3.84 (3.12; 4.73)	4.17 (3.35; 5.19)	3.83 (3.07; 4.78)	4.77 (3.59; 6.35)	3.84 (3.11; 4.74)
	Post	21.22 (14.85; 30.33)	41.64 (30.30; 57.24)	29.10 (20.18; 41.95)	14.89 (10.54; 21.03)	29.10 (21.30; 39.75)	6.87 (5.10; 9.26)
C	Pre	2.00 (2.00; 2.00)	2.03 (1.97; 2.08)	2.03 (1.97; 2.08)	2.06 (1.94; 2.18)	2.00 (2.00; 2.00)	2.08 (1.99; 2.18)
	Post	60.80 (37.71; 98.01)	46.19 (29.29; 72.82)	73.32 (42.18; 127.43)	131.75 (80.90; 214.56)	252.54 (170.84; 373.32)	471.91 (373.90; 595.60)
Y	Pre	2.08 (1.96; 2.20)	2.14 (1.94; 2.36)	2.20 (1.86; 2.60)	2.00 (2.00; 2.00)	2.00 (2.00; 2.00)	2.32 (1.96; 2.76)
	Post	13.89 (9.19; 21.00)	17.36 (11.50; 26.21)	23.73 (14.86; 37.90)	26.52 (18.61; 37.79)	26.46 (17.29; 40.49)	2.42 (2.09; 2.80)
W-135	Pre	2.03 (1.97; 2.08)	2.00 (2.00; 2.00)	2.03 (1.97; 2.08)	2.03 (1.97; 2.09)	2.03 (1.97; 2.08)	2.00 (2.00; 2.00)
	Post	10.21 (7.32; 14.25)	13.00 (8.59; 19.66)	16.00 (9.74; 26.28)	10.53 (7.10; 15.60)	15.57 (10.56; 22.95)	2.17 (2.01; 2.34)

N is the total number of subjects per group from the per-protocol analysis set

n is the number of subjects experiencing the endpoint listed in the first column

M is the number of subjects with valid serology results for the particular antigen, including results reported as <LLOQ and >ULOQ

Formulation Differences

Data from this study have been used to support the final decision on the formulation to be carried forward in subsequent clinical studies.

The addition of the ADH linker improved antibody responses for serogroup A as demonstrated in the results using either human (Table 3.2) or baby rabbit complement sources in the SBA assay. Supported by the clinical results from Study MET32 (formulation 1 and formulation 2), the formulation evaluated in subsequent Phase II studies was a combination of serogroups A and C from formulation 1 and serogroups Y and W from formulation 2.

The conjugation chemistry for serogroup A was the same chemistry that was used in formulation 1 (ADH linker using CDI). The results of the Phase I/II clinical trial indicated that the high pH conjugation formulation 2 resulted in slightly more immunogenic conjugates; however, the higher polysaccharide:protein loading ratio was also lower likely due to base catalyzed hydrolysis of the polysaccharide and/or reactive aldehyde groups. Therefore, for the subsequent Phase II clinical trial the conjugation reaction was maintained at pH 8.0 ± 0.2 in order to maintain a higher polysaccharide: protein loading ratio, but a base treatment (partial de-O-acetylation) step was added to the polysaccharide activation/depolymerization process. The resulting serogroup C conjugate was the most immunogenic conjugate tested. The conjugation chemistry for serogroup C was the same chemistry that was used in Phase I formulation 1 with the exception of a base treatment of the polysaccharide prior to activation by sodium metaperiodate. For serogroups Y and W, the results of Study MET32 indicated that the higher pH conjugation (formulation 2) resulted in slightly more

immunogenic conjugates, and therefore, the conjugation reaction was maintained at pH 9.5 ± 0.5 for the Phase II batches. The conjugation chemistry for serogroups Y and W was the same chemistry that was used in Phase I formulation 2.

Main studies

Studies MET51, MET35, MET 57, MET43, MET49, MET50 and MET56 are considered main evidence for this MAA and are presented if not indicated otherwise in this order in each section.

MET 51

Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and describe the safety of a single dose of MenACYW conjugate vaccine to a single dose of a licensed quadrivalent meningococcal polysaccharide groups A, C, W-135, and Y conjugate vaccine (MenACWY-TT, Nimenrix) in toddlers (12 to 23 months of age) in the European Union (Spain, Hungary, Finland and Germany) who were either meningococcal vaccine-naïve or had received monovalent MenC vaccination during infancy.

Healthy toddlers aged 12 to 23 months were randomized as follows depending on their meningococcal vaccine background:

Meningococcal vaccine-naïve subjects:

Subjects were randomized in a 1:1 ratio to the following 2 groups:

Group 1: MenACYW conjugate vaccine

Group 2: Nimenrix

MenC-primed subjects:

Subjects were randomized in a 2:1 ratio to the following 2 groups:

Group 3: MenACYW conjugate vaccine

Group 4: Nimenrix

Enrollment of MenC-primed subjects was stratified by the type of primed vaccine, MenC-TT (NeisVac-C) or MenC-CRM (Menjugate, Meningitec), considering that at least 25% and a maximum of 50% of subjects were to have been primed with MenC-CRM.

MET 35

Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine compared to Menveo in healthy children 2 through 9 years of age in the USA and Puerto Rico.

Subjects received a single dose of MenACYW conjugate vaccine or Menveo on D0:

- Group 1: MenACYW conjugate vaccine
- Group 2: Menveo

Enrollment was stratified by age: 250 children 2 through 5 years of age and 250 children 6 through 9 years of age, respectively, were planned to be enrolled in each group. Subjects provided a pre-vaccination blood sample at D0 and a post-vaccination sample at Visit 2 (30 to 44 days after the vaccination).

MET 57

Phase III, open-label (immunology laboratory technicians were blinded to group assignment), randomized, parallel-group, controlled, multi-center study to describe the immunogenicity and safety of a single dose of MenACYW conjugate vaccine in healthy meningococcal vaccine- naïve toddlers when administered alone compared to when administered concomitantly with other paediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13). Subjects were randomized in South Korea, Mexico, the Russian Federation, and Thailand as described below:

Table 5: Randomization of subjects in study MET 57

Country	Group	Age of subjects	Vaccine(s) received on D0
South Korea	Group 1	12 to 23 months	MenACYW conjugate vaccine + MMR + V
	Group 2		MenACYW conjugate vaccine
	Group 3		MMR + V
Mexico	Group 4	12 to 23 months	MenACYW conjugate vaccine + DTaP-IPV-HB-Hib
	Group 5		MenACYW conjugate vaccine
	Group 6		DTaP-IPV-HB-Hib vaccine
The Russian Federation	Group 7	15 to 23 months	MenACYW conjugate vaccine + PCV13
	Group 8	12 to 14 months or 16 to 23 months	MenACYW conjugate vaccine
	Group 9	15 to 23 months	PCV13
Thailand	Group 10	12 to 23 months	MenACYW conjugate vaccine + MMR + V
	Group 11		MenACYW conjugate vaccine
	Group 12		MMR + V

All subjects provided a pre-vaccination blood sample at D0 and a post-vaccination sample at D30 (+14 days).

MET 43

Phase III, modified double-blind, randomized, parallel-group, active-controlled, multicenter study to evaluate immune lot consistency of MenACYW conjugate vaccine, evaluate the immune noninferiority versus Menactra, and describe the safety and additional immunogenicity of study vaccines in adolescents and adults aged 10 through 55 years in the USA

Subjects received a single dose of MenACYW conjugate vaccine from 1 of 3 lots or Menactra on D0:

- Group 1: MenACYW conjugate vaccine (Lot 1)
    - Group 1a (subjects 10 through 17 years of age)
    - Group 1b (subjects 18 through 55 years of age)
- Group 2: MenACYW conjugate vaccine (Lot 2)
    - Group 2a (subjects 10 through 17 years of age)
    - Group 2b (subjects 18 through 55 years of age)

- Group 3: MenACYW conjugate vaccine (Lot 3)
    - Group 3a (subjects 10 through 17 years of age)
    - Group 3b (subjects 18 through 55 years of age)
- Group 4: Menactra
    - Group 4a (subjects 10 through 17 years of age)
    - Group 4b (subjects 18 through 55 years of age)

Subjects provided a pre-vaccination blood sample at D0 and a post-vaccination sample at Visit 2 (30 through 44 days after the vaccination at Visit 1).

MET49

Phase III modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and safety of MenACYW conjugate vaccine to Menomune - A/C/Y/W-135 in adults ≥ 56 years of age in the USA and Puerto Rico.

Subjects received a single dose of MenACYW conjugate vaccine or Menomune - A/C/Y/W-135 on D0.

- Group 1: MenACYW conjugate vaccine
- Group 2: Menomune - A/C/Y/W-135

Enrollment was stratified by age: subjects 56 through 64 years of age and subjects 65 years of age and older. These older subjects were further stratified into 2 age groups: subjects 65 through 74 years of age and subjects 75 years of age and older. Subjects provided a pre-vaccination blood sample at D0 and a post-vaccination sample at Visit 2 (30 to 44 days after the vaccination at Visit 1).

MET 50

Phase II, open-label (the laboratory technicians were blinded to group assignment), randomized, parallel-group, controlled, multi-center study to evaluate the immunogenicity and safety profile of a single dose of MenACYW conjugate vaccine compared to that of the licensed vaccine Menveo, and when MenACYW conjugate vaccine was given with TdaP (tetanus, diphtheria, and acellular pertussis) and HPV (human papillomavirus) vaccines, in healthy adolescents 10 through 17 years of age in the USA.

Subjects received vaccine(s) according to the following schedule in Table 6. Subjects in all groups provided a pre-vaccination blood sample at Visit 1 (D0) and a post-vaccination sample at Visit 2 (23 to 37 days after the vaccination at Visit 1). Subjects in Group 3 and Group 4 provided an additional blood sample at D210 (Visit 5, 23 to 37 days after HPV vaccination at Visit 4).

Table 6: MET50 study groups and vaccination schedule

Group	D0, Visit 1	D60, Visit 3	D180, Visit 4
1	MenACYW conjugate vaccine	NA	NA
2	Menveo	NA	NA
3	MenACYW conjugate vaccine TdaP, HPV	HPV	HPV
4	TdaP, HPV	HPV	HPV

Abbreviations: D, day; NA, not applicable

MET 56

Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and describe the safety of a booster dose of MenACYW conjugate vaccine to a licensed vaccine in MCV4-primed adolescents (≥ 15 through < 18 years) and adults (≥ 18 years) in the USA and Puerto Rico.

Subjects who had received 1 dose of a quadrivalent meningococcal conjugate vaccine 4 to 10 years previously were enrolled in the study. Subjects received a single dose of MenACYW conjugate vaccine or Menactra on D0.

- Group 1: MenACYW conjugate vaccine
- Group 2: Menactra

Subjects provided a pre-vaccination blood sample at D0 and a post-vaccination sample 30 to 44 days after the vaccination at Visit 1. A subset of subjects from both groups provided an additional blood sample 5 to 7 days after vaccination at Visit 1.

Methods

Study Participants

In the presented studies, healthy subjects were included from different age groups:

- MET51: Toddlers 12-23 months
- MET35: Children 2-9 years
- MET57: Toddlers 12-23 months
- MET43: Adolescents and Adults 10-55 years
- MET49: Adults 56 years and older
- MET50: Adolescents 10 - 17 years
- MET56: Adolescents, Adults ≥ 15 years

The majority of studies included meningococcal-vaccine naïve subjects (MET51, MET35, MET57, MET43, MET49, MET50). Study MET51 included in addition toddlers who received a monovalent meningococcal C conjugate (MenC) vaccination during infancy. Study MET56 included adolescent and adult subjects (15-55 years) previously vaccinated with a meningococcal quadrivalent conjugate vaccine.

Treatments

Comparators and concomitant vaccines used in the main clinical studies

Table 7: Comparators and concomitant vaccines used in the main clinical studies

Study Code	Age Group	Comparator	Concomitant Vaccines
MET51	Toddlers 12-23 months	Nimenrix (MCV4-TT)	N/A
MET35	Children 2-9 years	Menveo (MCV4-CRM)	N/A
MET57	Toddlers	N/A	MMR+V, DTaP-IPV-HB-Hib, PCV13
MET43	Adolescents, Adults 10-55 years	Menactra (MCV4-DT)	N/A
MET49	Adults 56 years and older	Menomune – A/C/Y/W-135 (MPSV-4)	N/A
MET50	Adolescents	Menveo (MCV4-CRM)	TdaP, HPV
MET56	Adolescents, Adults	Menactra (MCV4-DT)	N/A

Dose Selection and Timing

In all studies subjects received one dose of MenACWY at Visit 1/Day 0.

The comparators Nimenrix/Menveo/Menactra/Menomune were administered as single dose on Visit 1/Day 1 in the respective studies

Concomitant Vaccines:

MET57: All subjects in Groups 1, 3, 10, and 12 were to receive 1 dose of M-M-R II on D0. All subjects in Groups 1, 3, 10, and 12 were to receive 1 dose of VARIVAX on D0. All subjects in Groups 4 and 6 were to receive 1 dose of Hexaxim on D0 All subjects in Groups 7 and 9 were to receive 1 dose of Prevenar 13 on D0.

MET50: All subjects in Group 3 and 4 were to receive 1 dose of TdaP vaccine on D0. All subjects in Group 3 and 4 were to receive 1 dose of HPV vaccine on D0, D60 (Visit 3), and D180 (Visit 4).

Objectives

MET51 (Meningococcal Vaccine-Naïve or MenC-primed Toddlers 12 to 23 months)

Primary Objectives

- **Non-inferiority** of hSBA seroprotection rate for all 4 serogroups at D30 in meningococcal vaccine-naïve or MenC-primed toddlers: MenACYW conjugate vaccine vs Nimenrix
- **Non-inferiority** of hSBA seroprotection rate for all 4 serogroups at D30 in meningococcal vaccine-naïve toddlers: MenACYW conjugate vaccine vs Nimenrix

Secondary Objectives

- **Comparison** of hSBA GMTs at D30 in all subjects irrespective of their meningococcal vaccine background: MenACYW conjugate vaccine vs Nimenrix
- **Comparison** of hSBA GMTs at D30 in meningococcal vaccine naïve subjects: MenACYW conjugate vaccine vs Nimenrix
- **Comparison** of hSBA GMTs at D30 in MenC-primed subjects: MenACYW conjugate vaccine vs Nimenrix

Observational Objectives

- To **describe the antibody response** to meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after a dose of MenACYW conjugate vaccine or Nimenrix in terms of rSBA titers ≥ 1:8 and ≥ 1:128 in toddlers in a subset of subjects per group: Group 1 and Group 2: 100 subjects each; Group 3: 50 subjects in each subgroup (MenC-Tetanus Toxoid [TT] or MenC-CRM primed subjects); Group 4: 25 subjects in each subgroup (MenC-TT or MenC-CRM primed subjects)
- **To describe the antibody response** to meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine in toddlers
- **To describe the antibody responses** to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with Nimenrix in toddlers
- **To describe the antibody responses** to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix in toddlers who received monovalent MenC vaccine conjugated to the tetanus toxoid carrier protein during infancy
- **To describe the antibody responses** to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix in toddlers who received monovalent MenC vaccine conjugated to the CRM197 protein carrier during infancy

MET35 (Meningococcal Vaccine-Naïve Children 2 - 9 years of age)

Primary Objective

- **Non-inferiority** of hSBA vaccine seroresponse for all 4 serogroups at D30: MenACYW conjugate vaccine vs Menveo

Secondary Objectives

- **Comparison** of hSBA GMTs at D30: MenACYW conjugate vaccine vs Menveo
- **Comparison** of hSBA GMTs at D30 by age group: MenACYW conjugate vaccine vs Menveo for subjects aged 2 through 5 years and for subjects aged 6 through 9 years
- **Comparison** of hSBA vaccine seroresponse at D30 by age group: MenACYW conjugate vaccine vs Menveo for subjects aged 2 through 5 years and for subjects aged 6 through 9 years

Observational Objectives

- **To describe the antibody titers** against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Menveo

- **To describe the antibody titers** against meningococcal serogroups A, C, Y, and W measured by rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Menveo in a subset of subjects

MET57 (Meningococcal Vaccine- Naïve Toddlers 12 to 23 months)

Primary Objective

- **To describe the immunogenicity profile** of MenACYW conjugate vaccine administered alone or concomitantly with licensed paediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13).

Secondary Objective

- **To describe the immunogenicity profile** of licensed paediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13) when administered alone or concomitantly with MenACYW conjugate vaccine.

Observational Objective

- **To describe the antibody (Ab) responses** to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugated vaccine measured by serum bactericidal antibody assay using rSBA in all subjects in Group 1 and Group 2 and in a subset of subjects in Group 4, Group 5, Group 7, and Group 8 (100 subjects per group in Groups 1, 4, and 7; 50 subjects per group in Groups 2, 5, and 8) (South Korea, Mexico, and the Russian Federation only).

MET43 (Meningococcal Vaccine-Naïve Adolescents and Adults 10 - 55 years of age)

Primary Objectives

- **Equivalence** of 3 MenACYW Conjugate **Vaccine lots** in terms of hSBA GMTs at D30
- **Non-inferiority of hSBA vaccine seroresponse** for all 4 serogroups at D30: MenACYW conjugate vaccine (3 lots pooled) vs Menactra

Secondary Objectives

- **Non-inferiority** of hSBA vaccine seroresponse for all 4 serogroups at D30 in adults 18 through 55 years old: MenACYW conjugate vaccine (3 lots pooled) vs Menactra
- **Non-inferiority** of hSBA vaccine seroresponse for all 4 serogroups at D30 in adolescents 10 through 17 years old: MenACYW conjugate vaccine (3 lots pooled) vs Menactra
- **Comparison** of 3 MenACYW conjugate vaccine lots in terms of hSBA vaccine seroresponse
- **Comparison** of MenACYW conjugate vaccine (3 lots pooled) to Menactra in terms of hSBA GMTs

Observational Objective

- **To describe the antibody responses** to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra.

MET49 (Meningococcal Vaccine-Naïve Adults ≥ 56 years of age)

Primary Objective

- **Non-inferiority** of hSBA vaccine seroresponse for all 4 serogroups at D30: MenACYW conjugate vaccine vs Menomune – A/C/Y/W-13

Secondary Objective

- **Comparison** of the hSBA GMTs at D30: MenACYW conjugate vaccine vs Menomune – A/C/Y/W-13

Observational Objectives

- **To describe antibody titers** against meningococcal serogroups A, C, Y, and W measured by hSBA at baseline (before vaccination) and 30 days after vaccination with MenACYW conjugate vaccine or Menomune – A/C/Y/W-135
- **To describe antibody titers** against meningococcal serogroups A, C, Y, and W measured by rSBA at baseline (before vaccination) and 30 days after vaccination with MenACYW conjugate vaccine or Menomune – A/C/Y/W-135 in a subset of 100 subjects per treatment group

MET50 (Meningococcal Vaccine-Naïve Adolescents 10 - 17 years of age)

Primary Objective

- **Non-inferiority** of hSBA vaccine seroresponse for all 4 serogroups at D30: MenACYW conjugate vaccine vs Menveo

Secondary Objectives

- **Non-inferiority** of hSBA vaccine seroresponse for all 4 serogroups at D30: MenACYW conjugate vaccine vs Menveo
- **Non-inferiority** of pertussis antigens in terms of GMCs when TdaP vaccine was administered concomitantly with MenACYW conjugate vaccine and HPV vaccine compared to TdaP vaccine administered with HPV vaccine alone
- **Non-inferiority** of tetanus and diphtheria antigens when TdaP vaccine was administered concomitantly with MenACYW conjugate vaccine and HPV vaccine compared to TdaP vaccine administered with HPV vaccine alone
- **Non-inferiority** of the immune response to HPV vaccine in terms of GMTs after the 3-dose series when the first dose was administered concomitantly with MenACYW conjugate vaccine and TdaP vaccine compared to when the first dose of HPV vaccine was administered with TdaP vaccine alone
- **Non-inferiority** of the immune response to HPV vaccine in terms of seroconversion after the 3-dose series when the first dose was administered concomitantly with MenACYW conjugate vaccine and TdaP vaccine compared to when the first dose of HPV vaccine was administered with TdaP vaccine alone

Observational Objectives

- **To describe the antibody titers** against meningococcal serogroups (A, C, Y, and W) after MenACYW conjugate vaccine is administered alone or concomitantly with licensed vaccines (TdaP and HPV)
- **To describe the antibody titers** against meningococcal serogroups (A, C, Y, and W) after administration of Menveo vaccine
- **To describe the antibody concentrations** against tetanus and diphtheria in subjects who received MenACYW conjugate vaccine or Menveo vaccine
- **To describe the antibody concentrations** against antigens of a licensed vaccine (TdaP) when it is administered concomitantly with MenACYW conjugate vaccine and HPV vaccine and when it is administered with HPV vaccine only
- **To describe the antibody titers** against antigens of a licensed vaccine (HPV) after the 3-dose series, when the first dose is administered concomitantly with MenACYW conjugate vaccine and TdaP vaccine and when the first dose is administered with TdaP vaccine only

MET56 (MCV4 Primed Adolescents and Adults ≥ 15 years of age)

Primary Objective

- **Non-inferiority** of hSBA vaccine seroresponse for all 4 serogroups at D30: MenACYW conjugate vaccine vs Menactra

Secondary Objectives

- **Comparison** of hSBA vaccine seroresponse at D06: MenACYW conjugate vaccine vs Menactra
- **Comparison** of antibody responses (GMTs) at D30 MenACYW conjugate vaccine vs Menactra

Observational Objectives

- **To describe the antibody titers** against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at D0, D06, and D30 days after vaccination
- **To describe the antibody responses** to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra measured by rSBA in a subset of subjects

Outcomes/endpoints

The following endpoints were used to describe the immune responses:

Table 8: endpoints used to describe the immune responses

Endpoints	hSBA assay	rSBA assay
Seroprotection	Titer ≥ 1:8	Titer ≥ 1:128
Vaccine seroresponse	X	X
Other threshold	Titer ≥ 1:4	Titer ≥ 1:8
GMTs	X	X
Titer distribution and RCDC	X	X
Titer ≥ 4-fold rise from pre- to postvaccination	X	X

RCDC: reverse cumulative distribution curve X meaning assessed

hSBA Vaccine Seroresponse Definitions

Two different hSBA vaccine seroresponse definitions have been used in the individual CSRs and are summarized in Table 9.

The first definition was used in the 3 earliest studies (MET44, MET50, and MET54). The second is the latest definition accepted by the Center for Biologics Evaluation and Research / US Food and Drug Administration (CBER/FDA). This definition was used in the individual Studies MET35, MET43, MET49, MET51, MET56, and MET57 and is the definition used in the integrated/pooled analysis in this Summary of Clinical Efficacy.

Table 9: hSBA vaccine seroresponse definition

Study Code	hSBA Vaccine seroresponse definition
MET44, MET50, and MET54	- The response of subjects with an hSBA titer < 1:8 at baseline who then achieved an hSBA titer ≥ 1:8 - The response of subjects with an hSBA titer ≥ 1:8 at baseline who thenachieved a ≥ 4-fold increase in hSBA titer
MET35, MET43, MET49, MET51, MET56, and MET57 and integrated/pooled analysis	- The response of subjects with an hSBA titer < 1:8 at baseline who then achieved an hSBA titer ≥ 1:16 - The response of subjects with an hSBA titer ≥ 1:8 at baseline who then achieved a ≥ 4-fold increase in hSBA titer.

rSBA Vaccine Seroresponse Definition

For the purpose of integrated/pooled analysis, the seroresponse definition used for serogroups A, C, Y, and W was computed as follows.

Table 10: rSBA vaccine seroresponse definition

Study Code	hSBA Vaccine seroresponse definition
MET35, MET43, MET49, MET50, MET51, MET54*, MET56, and MET57	- The response of subjects with an rSBA titer < 1:8 at baseline who then achieved an rSBA titer ≥ 1:32 - The response of subjects with an rSBA titer ≥ 1:8 at baseline who then achieved a ≥ 4-fold increase in rSBA titer
MET54, MET44	- The response of subjects with an rSBA titer < 1:8 at baseline who then achieved an rSBA titer ≥ 1:8 - The response of subjects with an rSBA titer ≥ 1:8 at baseline who then achieved a ≥ 4-fold increase in rSBA titer.

*In Study MET54, both definitions were used in the CSR, but only the first one was used for the integrated analysis

Immunological assays

Functional meningococcal antibody activity against serogroups A, C, Y, and W-135 is measured using serum bactericidal antibody (SBA) assay. The SBA is an in vitro method using a complement source from either baby rabbit (BR) or human (HC), that measures the antibody-mediated, complement-dependent killing of target bacteria for the purpose of measuring the immunological response to the capsular polysaccharides of Neisseria meningitides serogroups A, C, Y, or W-135. Bacteria, complement, and serially diluted serum are incubated together in microtiter plates. An agar overlay is added to the serum/complement/bacteria mixture and the plates are incubated again. The number of resulting bacterial colonies present in the wells is inversely proportional to the level of functional antibody present in the serum, which correlates with the immunological response of the subject. The endpoint titer is determined by the reciprocal serum dilution yielding ≥ 50% killing compared to the mean of the complement control wells containing no serum.

Immunity acquired through either natural exposure or vaccination to meningococcal antigens has been shown to correlate well with the level of complement-dependent bactericidal antibody detected by the SBA. The SBA-determined level of these functional antibodies is considered a widely acceptable surrogate of protective immunity and acceptable evidence for efficacy of vaccines prepared from the capsular polysaccharides of N. meningitidis serogroups A, C, Y, and W-135. The surrogate was established from the assay utilizing human complement. To facilitate inter-laboratory comparisons of the bactericidal activity induced by meningococcal vaccines, an SBA-BR assay was established through a multi-laboratory study conducted by the Centers for Disease Control and Prevention (CDC), in which Sanofi Pasteur participated. In 1999, under the auspices of the WHO, a meeting was held to further assess laboratory assays for the analysis of human serum for meningococcal serogroup A- and C-specific antibodies. From that meeting, several recommendations were made regarding the SBAs; including adoption of the CDC standardized SBA-BR as the optimal methodology to measure meningococcal antibodies. However, recent developments in the field have led CBER to require a human complement– based assay for the assessment and licensure of meningococcal vaccines. Overall, the comparison indicates that both assays demonstrate serogroup specificity.

Table 11 lists the key serological assays implemented in the studies included in this CTD. For details of each assay please refer to the clinical assessment report.

Table 11: Serological assays used to assess immune response to antigens in the study vaccines

Antigens	Assay	LLOQ	Vaccine	Studies	Section of 5.3.5.4
Polysaccharides of Serogroups A, C, Y, W	hSBA and rSBA	4 (1/dil)	MenACYW conjugate vaccine	All	[Section 2.1] (hSBA) [Section 3.1] (rSBA)
			Nimenrix®	MET51, MET54	
			Menveo®	MET35, MET50	
			Menactra®	MET43, MET56	
			Menomune® - A/C/ Y/W-135	MET44, MET49	
Diphtheria Toxin	Diphtheria Toxin Neutralization Assay	0.005 IU/mL	Tdap	MET50	[Section 3.2]
	IgG ECL	0.005 IU/mL	DTaP-IPV-HB-Hib	MET57	[Section 3.6]
Pertussis Antigens: pertussis toxoid, FHA, PRN, and FIM	Component Pertussis IgG ELISAs	4 EU/mL for PT, PRN and FIM 3 EU/mL for FHA	Tdap	MET50	[Section 3.4]
	IgG ECL	2.00 EU/mL	DTaP-IPV-HB-Hib	MET57	[Section 3.6]
Tetanus Toxoid	Tetanus IgG ELISA	0.01 IU/mL	Tdap	MET50	[Section 3.3]
	IgG ECL	0.01 IU/mL	DTaP-IPV-HB-Hib	MET57	[Section 3.6]
HPV antigens: HPV 6, 11, 16, 18	HPV cLIA	20 mMU/mL for HPV-6 and HPV-16 20 mMU/mL for HPV-11 24 mMU/mL for HPV-18	HPV	MET50	[Section 3.5
Poliovirus types 1, 2, and 3	Neutralization Assay	4 (1/dil)	DTaP-IPV-HB-Hib	MET57	[Section 3.9]
Hepatitis B surface antigen (HBsAg)	VITROS ECi Immunodiagnostic system	5 mIU/mL	DTaP-IPV-HB-Hib	MET57	[Section 3.10]
Haemophilus influenzae type b (Hib) Capsular Polysaccharide (PRP)	Farr-type RIA	0.06 µg/mL	DTaP-IPV-HB-Hib	MET57	[Section 3.7]
Streptococcus pneumoniae PS (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F)	IgG ECL	0.15 µg/mL	PCV13	MET57	[Section 3.8]
Measles virus	IgG EIA	60 mIU/mL	MMR	MET57	[Section 3.11]
Mumps virus	IgG ELISA	10 Mumps Ab units/mL	MMR	MET57	[Section 3.12]
Rubella virus	IgG EIA	5 IU/mL	MMR	MET57	[Section 3.13]
Varicella zoster virus (VZV)	gpELISA	0.625 gpELISA Ab units/mL	V	MET57	[Section 3.14]

Abbreviations: cLIA, competitive Luminex immunoassay; ECL, Electrochemiluminescent assay; EIA, Enzyme immunoassay; ELISA, enyme-linked immunosorbent assay; FHA, filamentous hemagglutinin; FIM, fimbriae types 2 and 3; gp, glycoprotein; Hib, *Haemophilus influenzae* type b; hSBA, serum bactericidal antibody assay using human complement; IgG, Immunoglobulin G; LLOQ, lower limit of quantitation; mMU, milli-Merck Units; PRN, pertactin; PRP, polyribosyl ribitol phosphate; PT, pertussis toxin; RIA, radioimmunoassay; rSBA, serum bactericidal antibody assay using baby rabbit complement

Randomisation and blinding (masking)

Throughout comparative immunogenicity studies, subjects were randomly assigned to respective vaccination groups. Depending on the study population and objective, randomisation was stratified by demographic parameters (e.g. MET51: priming status, MET35, MET57, MET49: age). In several studies, stratification was not accounted for in the statistical analysis. Importantly, the statistical analysis of lot to lot consistency (MET43) did not take into account the stratified randomization by age-group.

Since the primary objectives of the studies had serological endpoints and the vaccines for the study groups had different appearances, the studies had a modified double-blind design. This means it contained an unblinded vaccine administrator while the subject/the subject's parent/LAR, the Investigator, the Sponsor and the rest of the study team, including laboratory technicians in charge of executing the serological testing, remained blinded to the subjects' group allocations throughout the entire study up to the database lock to avoid any bias. The unblinded site personnel prepared all vaccines, and then administered the vaccines to the subjects and did not participate in any safety evaluation of the subjects during study conduct.

Study 50 and 57, both evaluating MenQuadfi with concomitant vaccinations were open-label studies where only the laboratory technicians were blinded to group assignment.

Statistical methods

MET51: Meningococcal Vaccine-Naïve or MenC-primed Toddlers 12 to 23 months

Missing data will not be imputed. No test or search for outliers will be performed.

Analysis sets:

The FAS is defined as the subset of subjects who received at least 1 dose of the study vaccine and had a valid post-vaccination serology result. All subjects will be analysed according to the treatment group to which they were randomized.

Safety Analysis Set: The SafAS is defined as those subjects who have received at least 1 dose of the study vaccine and have any safety data available. All subjects will have their safety analysed according to the vaccine they actually received. If the vaccine received by a subject does not correspond to any study group, the subject will be excluded from the SafAS. The corresponding safety data will be presented in separate listings.

Per-Protocol Analysis Set: The PPAS is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS: Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria: […]

Co-primary 1 (naïve and primed):

Each of the serogroups A, C, Y, and W were tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 percentages was > -10%, the inferiority assumption was rejected. For the 4 non-inferiority hypotheses using the response rates (percentages of subjects who achieved an hSBA titer ≥ 1:8), the 95% CI was stratified on the priming status (meningococcal vaccine naïve or primed with monovalent MenC vaccination during infancy) and calculated using the Wald method (normal approximation). Weighted average of the difference over strata was calculated using the Minimal Risk weights with the null variance method (10).

Co-primary 2 (naïve only):

Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%, the inferiority assumption was rejected.

For the 4 non-inferiority hypotheses using the response rates (percentages of subjects who achieved an hSBA titer ≥ 1:8), the CI of the difference in proportions was computed using the Wilson Score method without continuity correction (11).

MET35: Meningococcal Vaccine-Naïve Children 2 - 9 years of age

Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%, the inferiority assumption was rejected. For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in percentages (p1 - p2) was computed using the Wilson Score method without continuity correction (20).

Missing data will not be imputed. No test or search for outliers will be performed Analysis sets:

The FAS is defined as the subset of subjects who received at least one dose of the study vaccine and had a valid post-vaccination serology result. All subjects will be analysed according to the treatment group to which they were randomized.

The Per-Protocol Analysis Set (PPAS) is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS: Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria […]

Primary Analysis:

Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%, the inferiority assumption was rejected. For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in percentages (p1 - p2) was computed using the Wilson Score method without continuity correction (20).

MET57: Meningococcal Vaccine- Naïve Toddlers 12 to 23 months

No hypotheses were tested. Descriptive statistics were presented by group and by pooled group for subjects included in South Korea and Thailand (Groups 1 and 10 pooled, Groups 2 and 11 pooled, and Groups 3 and 12 pooled)

MET43: Meningococcal Vaccine-Naïve Adolescents and Adults 10 - 55 years of age

Missing data was not imputed. No test or search for outliers was performed.

Analysis sets:

The FAS was defined as the subset of subjects who had received 1 dose of the study vaccine and had a valid post-vaccination blood sample result, ie a result different from not reportable (NR) or missing for at least 1 serogroup. All subjects were analyzed according to the treatment group to which they were randomized.

The SafAS was defined as those subjects who had received at least 1 dose of the study vaccine and had any safety data available. All subjects had their safety analyzed according to the vaccine they actually received.

The PPAS was a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations were excluded from the PPAS: […]

Primary objective 1:

Each of the antigens of A, C, Y, and W serogroups was tested separately. If the 2-sided 95% CI of the ratio of the GMTs was > 1/2 and < 2 for each pair of lots and each antigen, the non-equivalence assumption was rejected (i.e. if the equivalence was demonstrated for each pair of lots).

For each of the equivalence hypotheses using the GMT ratios, the statistical methodology was based on the use of the 2-sided 95% CI of difference in means of postvaccination Log10 transformed titers between pairs of lots with normal approximation.

Primary objective 2:

For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in proportions were computed for each of the serogroups A, C, Y, and W using the Wilson Score method without continuity correction (3).

MET49: Meningococcal Vaccine-Naïve Adults ≥ 56 years of age

Missing data:

No replacement was done. In all subject listings, partial and missing data were clearly indicated as missing.

Analysis sets:

The FAS is defined as the subset of subjects who received at least one dose of the study vaccine and had a valid post-vaccination serology result. All subjects were analyzed according to the treatment group to which they were randomized.

Per-Protocol Analysis Set: The PPAS is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations were excluded from the PPAS: Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria.

Primary analysis:
Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions was > -10%, the inferiority assumption was rejected. For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in proportions (p1 – p2) was computed using the Wilson Score method without continuity correction

MET50: Meningococcal Vaccine-Naïve Adolescents 10 - 17 years of age

Thirty days after the administration of MenACYW conjugate vaccine or MENVEO, the percentages of subjects who achieve an hSBA seroresponse for meningococcal serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2.

Null hypothesis (H0): p(men, G1) - p(men, G2) ≤ -10%

Alternative hypothesis (H1): p(men, G1) - p(men, G2) > -10%

where p(men, G1) and p(men, G2) are the percentages of subjects who achieve an hSBA seroresponse in Group 1 and Group 2, respectively.

Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions is > -10%, the inferiority assumption was rejected. For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in proportions (p1 - p2) was computed using the Wilson Score method without continuity correction (5).

MET56: MCV4 Primed Adolescents and Adults ≥ 15 years of age

Thirty days after the administration of MenACYW conjugate vaccine or Menactra, the percentages of subjects who achieve an hSBA seroresponse for meningococcal serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2.

Null hypothesis (H0): p(G1) - p(G2) ≤ -10%

Alternative hypothesis (H1): p(G1) - p(G2) > -10%

where p(G1) and p(G2) are the percentages of subjects who achieve an hSBA seroresponse in Group 1 and Group 2, respectively. Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%, the inferiority assumption was rejected. For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in proportions (p1 – p2) was computed using the Wilson Score method without continuity correction (3).

Results

Participant flow

Details of the participant flow are discussed in the clinical assessment report.

Baseline data

Subjects who received MenACYW Conjugate Vaccine

Overall, there were more females (53.5%) than males (46.5%) who received MenACYW conjugate vaccine. The mean age (± SD) at enrolment of all subjects was 21.5 ± 21.28 years. The age of subjects ranged from a minimum of 1 year through a maximum of 89.8 years. The majority (75.9%) of all subjects who received MenACYW conjugate vaccine was White, followed by Black or African American (10.9%); 3.2% of subjects were Asian. The majority (73.5%) of all subjects who received MenACYW conjugate vaccine was not Hispanic or Latino; 19.7% of subjects were Hispanic or Latino.

Subjects who received a Comparator Vaccine

Menactra

Overall, 53.2% of subjects who received Menactra were females; 46.8% were males. The mean age (± SD) at enrollment for all subjects was 23.5 ± 12.86 years and ranged from a minimum of 10.0 through a maximum of 58.7 years. The majority (77.9%) of all subjects who received Menactra were White, followed by Black or African American (16.3%); 1.6% of subjects were Asian. The majority (80.3%) of all subjects who received Menactra were not Hispanic or Latino.

Menveo

Overall, 46.2% of subjects who received Menveo were females and 53.8% were males. The mean age (± SD) at enrollment for all subjects was 8.8 ± 3.30 years and ranged from a minimum of 2.0 through a maximum of 18.0 years. The majority (86.9%) of all subjects who received Menveo were White, followed by Black or African American (7.9%); 0.4% of subjects were Asian. The majority (79.1%) of all subjects who received Menveo were not Hispanic or Latino.

Menomune – A/C/Y/W-135

Overall, there were more females (56.4%) than males (43.6%). The mean age (± SD) at enrollment was 67.0 ± 7.39 years and ranged from a minimum of 56.0 through a maximum of 97.2 years. The majority (91.2%) of all subjects who received Menomune – A/C/Y/W-135 were White, followed by Black or African American (8.0%); 0.2% of subjects were Asian. The majority (93.3 %) of all subjects who received Menomune – A/C/Y/W-135 were not Hispanic or Latino.

Nimenrix

Overall, 49.7% of subjects who received Nimenrix were females and 50.3% were males. The mean age (± SD) at enrollment for all subjects was 16.2 ± 3.48 months and ranged from a minimum of 12.0 months through a maximum of 24.0 months. The race was not collected for 51.6% of the subjects (toddlers) who received Nimenrix; for the other toddlers, 46.4% were White, 0.6% Black or African American and 0.4% Asian. Ethnicity was not collected for 33.7% of toddlers, and for the others 38.5% of all subjects who received Nimenrix were not Hispanic or Latino.

Numbers analysed

Table 12: Number of subjects in the SafAS and in the PPAS who received MenACYW conjugate vaccine, meningococcal control vaccines, or concomitant vaccines in clinical trials conducted with MenACYW conjugate vaccine as part of the clinical database included in the Application – by study

Study Identifier/ Phase	Age of Study Population	Population Analyzed	Number of Subjects*						
			MenACYW Conjugate Vaccine	MenACYW Conjugate + Concomitant Vaccines	Controls				Concomitant Vaccines
					Menactra®	Menveo®	Menomune®	Nimenrix®	
MET44 / Phase II Supportive	Adults ≥ 56 years old	PPAS	195	-	-	-	94	-	-
		SafAS	199	-	-	-	100	-	-
MET50 / Phase II Pivotal	Adolescents 10 through 17 years old	PPAS	823†	-†	-	464	-	-	-†
		SafAS	503	392	-	501	-	-	296
MET54 / Phase II Supportive	Toddlers 12 to 23 months	PPAS	91	-	-	-	-	86	-
		SafAS	94	-	-	-	-	94	-
MET35 /Phase III Pivotal	Children 2 through 9 years old	PPAS	458	-	-	460	-	-	-
		SafAS	498	-	-	494	-	-	-
MET43 / Phase III Pivotal	Adolescents 10 through 17 years old; Adults 18 through 55 years old	PPAS	2508	-	593	-	-	-	-
		SafAS	2676	-	635	-	-	-	-
MET49 / Phase III Pivotal	Adults ≥ 56 years old	PPAS	433	-	-	-	431	-	-
		SafAS	448	-	-	-	453	-	-
MET51 / Phase III Pivotal	Toddlers 12 to 23 months	PPAS	491	-	-	-	-	395	-
		SafAS	303‡	-	-	-	-	306‡	-
MET56 / Phase III Pivotal	Adolescents 15 through 17 years old; Adults ≥ 18 years old	PPAS	384	-	389	-	-	-	-
		SafAS	402	-	407	-	-	-	-
MET57 /Phase III Pivotal	Toddlers 12 to 23 months	PPAS	790	-†	-	-	-	-	-†
		SafAS	294	589	-	-	-	-	294
	TOTAL:	PPAS	6173	-	982	924	525	481	-
		SafAS	5417	981	1042	995	553	400	590

Studies are presented in numerical order by Phase

Abbreviations: MCV4-CRM, quadrivalent meningococcal diphtheria CRM conjugate vaccine; MCV4-DT, quadrivalent meningococcal diphtheria toxoid conjugate vaccine; MCV4-TT, quadrivalent meningococcal tetanus toxoid conjugate vaccine; MPSV-4, quadrivalent meningococcal polysaccharide vaccine; PPAS, per-protocol analysis set; SafAS, safety analysis set;

*Number of subjects in the pooled / integrated analysis performed for this Application

†For immunogenicity analyses, subjects who received MenACYW conjugate vaccine with concomitant vaccines were pooled with the subjects who received MenACYW conjugate vaccine alone in study MET50, and in Study MET57. Subjects who received only the concomitant vaccines were not included in the pooled / integrated immunogenicity analyses.

‡ MenC primed toddlers of MET51 study are not part of the integrated safety analysis

Modified from 5.3.5.3 Efficacy Integrated Analysis Report Table 1.1.1 and 5.3.5.3 Safety Integrated Analysis Report Table 2.1.1.

Table 13: Number of subjects in the SafAS and in the PPAS who received MenACYW conjugate vaccine or meningococcal control vaccine in clinical trials conducted with MenACYW conjugate vaccine as part of the clinical database included in the Application – by baseline

Age Group	Studies	Number of Subjects in the PPAS*				
		MenACYW Conjugate Vaccine	Controls			
			Menactra®	Menveo®	Menomune®	Nimenrix®
Subjects with a Meningococcal Vaccine-Naïve Background						
All	All	5591†	593	924	525	382
Toddlers 12-23 months old	MET51, MET54 and MET57	1174†	-	-	-	382
Children 2 through 9 years old	MET35	458	-	460	-	-
Adolescents 10 through 17 years old	MET43, MET50	1921†	300	464	-	-
Adults ≥ 18 years old	MET43, MET44, MET49	2038	293	-	525	-
Adults 18 through 55 years old	MET43	1410	293	-	-	-
Older Adults and Elderly ≥ 56 years old	MET44 and MET49	628	-	-	525	-
Older Adults 56 through 64 years old	MET44 and MET49	290	-	-	235	-
Elderly Adults ≥ 65 years old	MET44 and MET49	338	-	-	290	-
Elderly Adults 65 through 74 years old	MET44 and MET49	252	-	-	215	-
Elderly Adults ≥ 75 years old	MET44 and MET49	86	-	-	75	-
Subjects with a Meningococcal Vaccine-Primed Background						
All	MET56, MET51	582	389	-	-	99
Toddlers 12-23 months old	MET51	198	-	-	-	99
Adolescents 15 through 17 years old	MET56	201	201	-	-	-
Adults ≥ 18 years old	MET56	183	188	-	-	-
All Subjects						
All	All	6173	982	924	525	481

Abbreviation: MCV4-CRM, quadrivalent meningococcal diphtheria CRM conjugate vaccine; MCV4-DT, quadrivalent meningococcal diphtheria toxoid conjugate vaccine; MCV4-TT, quadrivalent meningococcal tetanus toxoid conjugate vaccine; MPSV-4, quadrivalent meningococcal polysaccharide vaccine; PPAS, Per-Protocol Analysis Set

*Number of subjects in the pooled / integrated analysis performed for this Application

†Subjects who received MenACYW conjugate vaccine with concomitant vaccines were pooled with the subjects who received MenACYW conjugate vaccine alone (Study MET50, and Study MET57). Subjects who received only the concomitant vaccines were not included in the pooled / integrated immunogenicity analyses.

Modified from 5.3.5.3 Efficacy Integrated Analysis Report Table 1.1.1

Table 14: Number of subjects in the SafAS who received study vaccine, meningococcal control vaccines, or concomitant vaccines in clinical trials with MenACYW conjugate vaccine as part of the clinical database included in this Application – by age group

Age Group	Studies	Number of Subjects in the SafAS*						
		MenACYW Conjugate Vaccine	MenACYW Conjugate + Concomitant Vaccines	Controls				Concomitant Vaccines
				Menactra® (MCV4-DT)	Menveo® (MCV4-CRM)	Menomune® (MPSV-4)	Nimenrix® (MCV4-TT)	
All	All	5417	981	1042	995	553	400	590
Toddlers 12-23 months old	MET51, MET54, and MET57	691	589	-	-	-	400	294
	MET51 and MET54	397	-	-	-	-	400	-
Children 2 through 9 years old	MET35	498	-	-	494	-	-	-
Adolescents 10 through 17 years old	MET43, MET50, MET56	1897	392	536	501	-	-	296
Adults ≥ 18 years old	MET43, MET44, MET49, MET56	2331	-	506	-	553	-	-
Adults 18 through 55 years old	MET43, MET56	1684	-	505	-	-	-	-
Older Adults and Elderly ≥ 56 years old	MET44, MET49, MET56	647	-	1	-	553	-	-
Older Adults 56 through 64 years old	MET44, MET49, MET56	298	-	1	-	249	-	-
Elderly Adults ≥ 65 years old	MET44, MET49	349	-	-	-	304	-	-
Elderly Adults 65 through 74 years old	MET44, MET49	258	-	-	-	224	-	-
Elderly Adults ≥ 75 years old	MET44, MET49	91	-	-	-	80	-	-

Abbreviations: MCV4-CRM, quadrivalent meningococcal diphtheria CRM conjugate vaccine; MCV4-DT, quadrivalent meningococcal diphtheria toxoid conjugate vaccine; MCV4-TT, quadrivalent meningococcal tetanus toxoid conjugate vaccine; MPSV-4, quadrivalent meningococcal polysaccharide vaccine; SafAS, safety analysis set;

*Number of subjects in the pooled / integrated analysis performed for this Application

Modified from 5.3.5.3 Safety Integrated Analysis Report Table 2.1.1.

Outcomes and estimation

Table 15: summary table with the results of non-inferiority studies

Study Comparator	**Age group**	**Seroresponse rates MenQuadfi (95% CI)** **Difference to comparator: MenQuadfi – comparator (95% CIs)**							
		Serogroup A		***Serogroup C***		***Serogroup Y***		***Serogroup W***	
MET51 [1)] Nimenrix	Naïve toddlers 12-23 months	76.8 %	(71.5; 81.5)	98.3 %	(96.1; 99.4)	81.9 %	(77.0; 86.1)	67.6 %	(61.9; 72.9)
	MenC-primed toddlers	76.1 %	(69.6; 81.9)	95.4 %	(91.5; 97.9)	89.2 %	(84.0; 93.2)	75.5 %	(68.9; 81.4)
Stratified difference [2)]		-2.20	(-7.70; 3.30)	17.9	(13.4; 22.5)	5.43	(0.289; 10.6)	1.11	(-4.95; 7.17)
MET35 Menveo	Children 2-9 years	55.4 % 7.6	(50.7; 60.0) (1.1, 14.0)	95.2 % 47.4	(92.8; 97.0) (42.2, 52.2)	91.5 % 12.2	(88.5; 93.9) (7.7, 16.7)	78.8 % 14.8	(74.8; 82.5) (8.9, 20.5)
MET50 Menveo	Adolescents 10-18 years	75.6 9.2	(71.4; 79.4) (3.4; 15.0)	97.2 24.6	(95.2; 98.5) (20.3; 29.0)	97.0 16.2	(95.0; 98.3) (12.3; 20.2)	86.2 19.6	(82.7; 89.2) (14.2; 24.8)
MET43 Menactra	Adolescents, Adults 10-55 years	73.8 % 19.1	(72.0; 75.5) (14.8; 23.5)	88.8 % 40.9	(87.5; 90.0) (36.7; 45.0)	91.4 % 18.1	(90.3; 92.5) (14.5; 21.9)	80.3 % 19.1	(78.7; 81.8) (14.9; 23.3)
MET49 Menomune	adults >56 years	58.2 % 15.7	(53.4; 62.9) (9.08; 22.2)	77.1 % 27.5	(72.9; 81.0) (21.2; 33.5)	74.4 % 31.0	(70.0; 78.4) (24.6; 37.0)	62.6 % 17.8	(57.8; 67.2) (11.2; 24.2)
MET56 Menactra	Men4-primed Adolescents and Adults ≥ 15 years	92.2 % 5.0	(89.0; 94.7) (0.74; 9.38)	97.1 % 5.4	(94.9; 98.6) (2.16; 8.76)	97.4 % 1.8	(95.3; 98.7) (-0.91; 4.55)	98.2 % 7.4	(96.3; 99.3) (4.30; 10.9)

Study Comparator	**Age group**	**Seroprotection rates MenQuadfi (95% CI)** **Difference to comparator: MenQuadfi – comparator (95% CIs)**							
		Serogroup A		***Serogroup C***		***Serogroup Y***		***Serogroup W***	
MET51 Nimenrix	Naïve toddlers	90.8 % 1.3	(86.9; 93.8) (-3.60; 6.20)	99.3 % 18.0 %	(97.6; 99.9) (13.6; 22.8)	93.2 % 1.6	(89.7; 95.8) (-2.76; 6.03)	83.6 % 0.2	(78.9; 87.7) (-5.85; 6.18)
	MenC-primed toddlers	89.8 %	(84.8; 93.7)	99.0 %	(96.4; 99.9)	95.9 %	(92.2; 98.2)	86.7 %	(81.2; 91.1)
Stratified difference [2)]		-2.03	(-5.84; 1.78)	12.1	(8.16; 16.1)	2.42	(-1.34; 6.19)	0.458	(-4.37; 5.28)

[1)] seroresponse was initially only included as observational objective; NI analysis was provided as requested

[2)] NI was tested for toddlers who either were meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy (MenC-primed)

Ancillary analyses

Post-hoc Evaluation of the Superiority of MenACYW Conjugate Vaccine

Superiority of immune response of MenACYW conjugate vaccine, in terms of hSBA seroprotection rate (≥1:8), as compared to the respective comparator vaccine was tested as a posthoc analysis in meningococcal vaccine-naïve subjects of MET35, MET43, MET49, MET50, and MET51 Studies per Scientific Advice (EMA/CHMP/SAWP/467602/2015) as all these five studies demonstrated non-inferiority of immune response between MenACYW conjugate vaccine and comparator vaccines. The serogroups were sequentially tested in the order of C, Y, W, and A to follow the epidemiological prevalence as observed globally across various age groups and were performed until a test did not succeed.

Superiority was achieved if the lower limit of the 2-sided 95% CI of the difference was greater than 0%.

Superiority of the immune response induced by MenACYW conjugate vaccine in terms of hSBA seroprotection rate (≥1:8) was demonstrated for all 4 serogroups versus the different comparators in subjects aged 2 years and above:

- in meningococcal vaccine-naïve children as compared to Menveo in MET35
- in meningococcal vaccine-naïve adolescents and adults (10-55 years) as compared to Menactra in MET43
- in meningococcal vaccine-naïve adults aged 56 years and above as compared to Menomune in MET49
- in meningococcal vaccine-naïve adolescents as compared to Menveo in MET50

Superiority of the immune response induced by MenACYW conjugate vaccine in terms of hSBA seroprotection rate (≥1:8) was also demonstrated in meningococcal vaccine-naïve toddlers for serogroup C as compared to Nimenrix in MET51.

Analysis performed across trials (pooled analyses and meta-analysis)

Integrated Analysis

Data obtained from the 9 Phase II and Phase III studies assessing the final formulation of MenACYW conjugate vaccine given as a single dose (Phase II studies MET44, MET50, and MET54, and Phase III studies MET35, MET43, MET49, MET51, MET56, and MET57) were presented in a pooled / integrated analysis report (5.3.5.3 Efficacy Integrated Analysis Report).

All Phase II and Phase III studies included in the pooled / integrated analysis report (see Table 1.3) were consistent in terms of general study design, the assessment of outcome measures, vaccine formulation, and in terms of the use of the hSBA assay for the assessment of bactericidal antibody titers against *N meningitidis* serogroups A, C, W, and Y. The immunogenicity pooled / integrated analysis was performed by meningococcal vaccine background (whether meningococcal vaccine-naïve or vaccine-primed).

The analysis for the meningococcal vaccine-naïve subjects was performed by the following age groups:

- Toddlers 12 to 23 months (pooled MET51, MET54, and MET57) (N=1174)
- Children 2 through 9 years of age (MET35) (Na=458)
- Adolescents 10 through 17 years of age (pooled MET43 and MET50) (N=1921)
- Adults 18 through 55 years of age (MET43) (N=1410)
- Older adults and elderly ≥ 56 years of age (pooled MET44 and MET49) (N=628)
- Older adults 56 through 64 years of age (N=290)
- Elderly adults ≥ 65 years of age (N=338)
- Elderly adults 65 through 74 years of age (N=252)
- Elderly adults ≥ 75 years of age (N=86)

The analysis for the meningococcal vaccine-primed subjects was performed in the following age groups:

- Toddlers 12 to 23 months (MET51) (N=198)
- Adolescents and adults ≥15 years (MET56) (N=384)

Table 16: Comparison of the hSBA seroprotection rate (percentage of subjects >= 1:8) at D30 for MenACYW conjugate vaccine versus meningococcal control vaccine - meningococcal vaccine-naïve subjects - pivotal active-controlled studies (MET35, MET43, MET49, MET50, and MET51 studies) - PPAS

MET51 (naïve subjects)		MenACYW (N=293)			Nimenrix (N=296)			MenACYW - Nimenrix	
Age	Serogroup	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	95% CI
12 to 23 months	A	266/293	90.8	(86.9 ; 93.8)	264/295	89.5	(85.4 ; 92.7)	1.3	(-3.6, 6.2)
	C	291/293	99.3	(97.6 ; 99.9)	240/295	81.4	(76.4 ; 85.6)	18.0	(13.6, 22.8)
	Y	273/293	93.2	(89.7 ; 95.8)	271/296	91.6	(87.8 ; 94.5)	1.6	(-2.8, 6.0)
	W	245/293	83.6	(78.9 ; 87.7)	247/296	83.4	(78.7 ; 87.5)	0.2	(-5.8, 6.2)
MET35		MenACYW (N=458)			MENVEO (N=460)			MenACYW - MENVEO	
Age	Serogroup	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	95% CI
2-9 years	A	394/456	86.4	(82.9; 89.4)	363/458	79.3	(75.3; 82.9)	7.1	(2.3, 12.0)
	C	448/458	97.8	(96.0; 98.9)	308/459	67.1	(62.6; 71.4)	30.7	(26.2, 35.2)
	Y	451/458	98.5	(96.9; 99.4)	417/459	90.8	(87.8; 93.3)	7.6	(4.8, 10.7)
	W	434/458	94.8	(92.3; 96.6)	396/459	86.3	(82.8; 89.3)	8.5	(4.7, 12.3)
2-5 years	A	193/228	84.6	(79.3; 89.1)	169/221	76.5	(70.3; 81.9)	8.2	(0.9, 15.5)
	C	223/229	97.4	(94.4; 99.0)	144/223	64.6	(57.9; 70.8)	32.8	(26.1, 39.4)
	Y	224/229	97.8	(95.0; 99.3)	193/222	86.9	(81.8; 91.1)	10.9	(6.1, 16.1)
	W	208/229	90.8	(86.3; 94.2)	179/222	80.6	(74.8; 85.6)	10.2	(3.8, 16.7)
6-9 years	A	201/228	88.2	(83.2; 92.0)	194/237	81.9	(76.3; 86.5)	6.3	(-0.2, 12.8)
	C	225/229	98.3	(95.6; 99.5)	164/236	69.5	(63.2; 75.3)	28.8	(22.6, 35.0)
	Y	227/229	99.1	(96.9; 99.9)	224/237	94.5	(90.8; 97.0)	4.6	(1.4, 8.3)
	W	226/229	98.7	(96.2; 99.7)	217/237	91.6	(87.3; 94.8)	7.1	(3.3, 11.5)
MET50		MenACYW (N=463)			MENVEO (N=464)			MenACYW - MENVEO	
Age	Serogroup	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	95% CI
10-17 years	A	433/463	93.5	(90.9 ; 95.6)	384/464	82.8	(79.0 ; 86.1)	10.8	(6.7, 14.9)
	C	455/462	98.5	(96.9 ; 99.4)	352/463	76.0	(71.9 ; 79.8)	22.5	(18.5, 26.6)
	Y	450/463	97.2	(95.2 ; 98.5)	386/464	83.2	(79.5 ; 86.5)	14.0	(10.3, 17.9)
	W	459/463	99.1	(97.8 ; 99.8)	421/464	90.7	(87.7 ; 93.2)	8.4	(5.7, 11.4)
MET43		MenACYW (N=2508)			Menactra (N=593)			MenACYW - Menactra	
Age	Serogroup	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	95% CI
10-17 years	A	1055/1097	96.2	(94.9; 97.2)	267/300	89.0	(84.9; 92.3)	7.2	(3.8, 11.3)
	C	1081/1098	98.5	(97.5; 99.1)	224/300	74.7	(69.3; 79.5)	23.8	(19.1, 29.0)
	Y	1087/1097	99.1	(98.3; 99.6)	283/300	94.3	(91.1; 96.7)	4.8	(2.5, 8.0)
	W	1078/1097	98.3	(97.3; 99.0)	281/300	93.7	(90.3; 96.1)	4.6	(2.2, 8.0)
18-55 years	A	1317/1408	93.5	(92.1; 94.8)	258/293	88.1	(83.8; 91.5)	5.5	(2.0, 9.9)
	C	1316/1408	93.5	(92.0; 94.7)	228/293	77.8	(72.6; 82.4)	15.7	(11.0, 20.9)
	Y	1390/1410	98.6	(97.8; 99.1)	238/293	81.2	(76.3; 85.5)	17.4	(13.2, 22.2)
	W	1333/1410	94.5	(93.2; 95.7)	235/293	80.2	(75.2; 84.6)	14.3	(10.0, 19.4)

MET49		MenACYW (N=433)			Menomune (N=431)			MenACYW - Menomune	
Age	Serogroup	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	95% CI
≥56 years	A	387/433	89.4	(86.1; 92.1)	363/431	84.2	(80.4; 87.5)	5.2	(0.6, 9.7)
	C	390/433	90.1	(86.9; 92.7)	306/431	71.0	(66.5; 75.2)	19.1	(13.9, 24.2)
	Y	397/433	91.7	(88.7; 94.1)	292/431	67.7	(63.1; 72.1)	23.9	(18.8, 29.0)
	W	335/433	77.4	(73.1; 81.2)	272/431	63.1	(58.4; 67.7)	14.3	(8.2, 20.2)
56-64 years	A	171/192	89.1	(83.8; 93.1)	156/189	82.5	(76.4; 87.7)	6.5	(-0.5, 13.6)
	C	179/192	93.2	(88.7; 96.3)	140/189	74.1	(67.2; 80.2)	19.2	(11.9, 26.4)
	Y	180/192	93.8	(89.3; 96.7)	129/189	68.3	(61.1; 74.8)	25.5	(17.9, 32.9)
	W	158/192	82.3	(76.1; 87.4)	126/189	66.7	(59.5; 73.3)	15.6	(6.9, 24.1)
≥ 65 years	A	216/241	89.6	(85.1; 93.2)	207/242	85.5	(80.5; 89.7)	4.1	(-1.8, 10.0)
	C	211/241	87.6	(82.7; 91.4)	166/242	68.6	(62.3; 74.4)	19.0	(11.7, 26.0)
	Y	217/241	90.0	(85.5; 93.5)	163/242	67.4	(61.1; 73.2)	22.7	(15.5, 29.6)
	W	177/241	73.4	(67.4; 78.9)	146/242	60.3	(53.9; 66.5)	13.1	(4.7, 21.3)
65-74 years	A	153/172	89.0	(83.3; 93.2)	152/175	86.9	(80.9; 91.5)	2.1	(-4.9, 9.1)
	C	150/172	87.2	(81.3; 91.8)	124/175	70.9	(63.5; 77.5)	16.4	(7.8, 24.6)
	Y	158/172	91.9	(86.7; 95.5)	121/175	69.1	(61.7; 75.9)	22.7	(14.6, 30.6)
	W	132/172	76.7	(69.7; 82.8)	107/175	61.1	(53.5; 68.4)	15.6	(5.9, 24.9)
≥ 75 years	A	63/69	91.3	(82.0; 96.7)	55/67	82.1	(70.8; 90.4)	9.2	(-2.4, 21.0)
	C	61/69	88.4	(78.4; 94.9)	42/67	62.7	(50.0; 74.2)	25.7	(11.4, 38.9)
	Y	59/69	85.5	(75.0; 92.8)	42/67	62.7	(50.0; 74.2)	22.8	(8.1, 36.4)
	W	45/69	65.2	(52.8; 76.3)	39/67	58.2	(45.5; 70.2)	7.0	(-9.1, 22.7)

N: number of subjects in the Per-Protocol Analysis Set

M: number of subjects with available data for the endpoint

n: number of subjects who achieve an hSBA titers >= 1:8 at D30

Modified from 5.3.5.3 Efficacy Integrated Analysis Report Table 9.1.2, Table 9.2.2, Table 9.3.2, Table 9.4.2, and Table 9.5.2, and 1.3.1 SmPC complementary outputs, Table 7.19.

Table 17: Summary of hSBA Vaccine Seroresponse - Meningococcal Vaccine Naïve Subjects - by Age Groups – PPAS

	Serogroup A			Serogroup C			Serogroup Y			Serogroup W		
Age Group (N)	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
MenACYW Conjugate Vaccine												
Toddlers 12 - 23 months old (N=1174)	842/1173	71.8	(69.1; 74.3)	1137/1174	96.8	(95.7; 97.8)	1053/1174	89.7	(87.8; 91.4)	953/1174	81.2	(78.8; 83.4)
Children 2 - 9 years old (N=458)	252/455	55.4	(50.7; 60.0)	436/458	95.2	(92.8; 97.0)	419/458	91.5	(88.5; 93.9)	361/458	78.8	(74.8; 82.5)
Adolescents 10 - 17 years old (N=1921)	1402/1920	73.0	(71.0; 75.0)	1840/1919	95.9	(94.9; 96.7)	1796/1919	93.6	(92.4; 94.6)	1613/1920	84.0	(82.3; 85.6)
Adults 18 - 55 years old (N=1410)	1034/1406	73.5	(71.2; 75.8)	1173/1406	83.4	(81.4; 85.3)	1241/1408	88.1	(86.3; 89.8)	1084/1408	77.0	(74.7; 79.2)
Older Adults & Elderly ≥ 56 years old (N=628)	369/628	58.8	(54.8; 62.6)	461/628	73.4	(69.8; 76.8)	459/628	73.1	(69.4; 76.5)	395/628	62.9	(59.0; 66.7)
Older Adults 56 -64 years old	178/290	61.4	(55.5; 67.0)	215/290	74.1	(68.7; 79.1)	221/290	76.2	(70.9; 81.0)	188/290	64.8	(59.0; 70.3)
Elderly ≥ 65 years old	191/338	56.5	(51.0; 61.9)	246/338	72.8	(67.7; 77.5)	238/338	70.4	(65.2; 75.2)	207/338	61.2	(55.8; 66.5)
Elderly 65 - 74 years old	141/252	56.0	(49.6; 62.2)	182/252	72.2	(66.3; 77.7)	183/252	72.6	(66.7; 78.0)	161/252	63.9	(57.6; 69.8)
Elderly ≥ 75 years old	50/86	58.1	(47.0; 68.7)	64/86	74.4	(63.9; 83.2)	55/86	64.0	(52.9; 74.0)	46/86	53.5	(42.4; 64.3)
Nimenrix®												
Toddlers 12 - 23 months old (N=382)	289/381	75.9	(71.2; 80.1)	275/381	72.2	(67.4; 76.6)	317/382	83.0	(78.8; 86.6)	278/382	72.8	(68.0; 77.2)
Menveo®												
Children (N=460) 2 - 9 years old	219/458	47.8	(43.2; 52.5)	219/458	47.8	(43.2; 52.5)	364/459	79.3	(75.3; 82.9)	294/459	64.1	(59.5; 68.4)
Adolescents (N=464) 10 - 17 years old	280/464	60.3	(55.7; 64.8)	285/463	61.6	(57.0; 66.0)	310/464	66.8	(62.3; 71.1)	260/464	56.0	(51.4; 60.6)

	Serogroup A			Serogroup C			Serogroup Y			Serogroup W		
Age Group (N)	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
Menactra®												
Adolescents (N=300) 10 - 17 years old	166/300	55.3	(49.5; 61.0)	160/300	53.3	(47.5; 59.1)	257/300	85.7	(81.2; 89.4)	216/300	72.0	(66.6; 77.0)
Adults (N=293) 18 - 55 years old	158/293	53.9	(48.0; 59.7)	124/293	42.3	(36.6; 48.2)	178/293	60.8	(54.9; 66.4)	147/293	50.2	(44.3; 56.0)
Menomune® – A/C/Y/W-135												
Older Adults & Elderly ≥ 56 years old (N=525)	223/525	42.5	(38.2; 46.8)	256/525	48.8	(44.4; 53.1)	227/525	43.2	(39.0; 47.6)	236/525	45.0	(40.6; 49.3)
Older Adults 56 -64 years old	103/235	43.8	(37.4; 50.4)	120/235	51.1	(44.5; 57.6)	110/235	46.8	(40.3; 53.4)	108/235	46.0	(39.5; 52.6)
Elderly ≥ 65 years old	120/290	41.4	(35.7; 47.3)	136/290	46.9	(41.0; 52.8)	117/290	40.3	(34.7; 46.2)	128/290	44.1	(38.3; 50.1)
Elderly 65 - 74 years old	92/215	42.8	(36.1; 49.7)	102/215	47.4	(40.6; 54.3)	90/215	41.9	(35.2; 48.8)	97/215	45.1	(38.3; 52.0)
Elderly ≥ 75 years old	28/75	37.3	(26.4; 49.3)	34/75	45.3	(33.8; 57.3)	27/75	36.0	(25.2; 47.9)	31/75	41.3	(30.1; 53.3)

Abbreviations: M, number of subjects with available data for the endpoint; N, number of subjects in the PPAS; n: number of subjects who achieve an hSBA vaccine seroresponse;

hSBA vaccine seroresponse in the integrated analysis report is defined as: for a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16; for a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer

Selected results from the pooled / integrated analyses per age group

Meningococcal-naïve subjects

Table 18: Summary of hSBAA vaccine seroresponse rate for MenACYW conjugate vaccine versus comparator vaccines – Meningococcal Vaccine-Naïve Toddlers – PPAS (Pooled MET51, MET54, and MET 57)

		MenACYW conjugate vaccine (N=1174)			Nimenrix® (N=382)		
Serogroup	**Baseline Status**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
A	**Any**	842/1173	71.8	(69.1; 74.3)	289/381	75.9	(71.2; 80.1)
	S-	624/744	83.9	(81.0; 86.4)	247/309	79.9	(75.0; 84.3)
	S+	218/429	50.8	(46.0; 55.6)	42/72	58.3	(46.1; 69.8)
C	**Any**	1137/1174	96.8	(95.7; 97.8)	275/381	72.2	(67.4; 76.6)
	S-	1084/1103	98.3	(97.3; 99.0)	269/366	73.5	(68.7; 77.9)
	S+	53/71	74.6	(62.9; 84.2)	6/15	40.0	(16.3; 67.7)
Y	**Any**	1053/1174	89.7	(87.8; 91.4)	317/382	83.0	(78.8; 86.6)
	S-	945/1029	91.8	(90.0; 93.4)	288/344	83.7	(79.4; 87.5)
	S+	108/145	74.5	(66.6; 81.4)	29/38	76.3	(59.8; 88.6)
W	**Any**	953/1174	81.2	(78.8; 83.4)	278/382	72.8	(68.0; 77.2)
	S-	912/1102	82.8	(80.4; 84.9)	274/377	72.7	(67.9; 77.1)
	S+	41/72	56.9	(44.7; 68.6)	4/5	80.0	(28.4; 99.5)

N: number of subjects in the Per-Protocol Analysis Set; M: number of subjects with available data for the endpoint; n: number of subjects who achieve an hSBA vaccine seroresponse

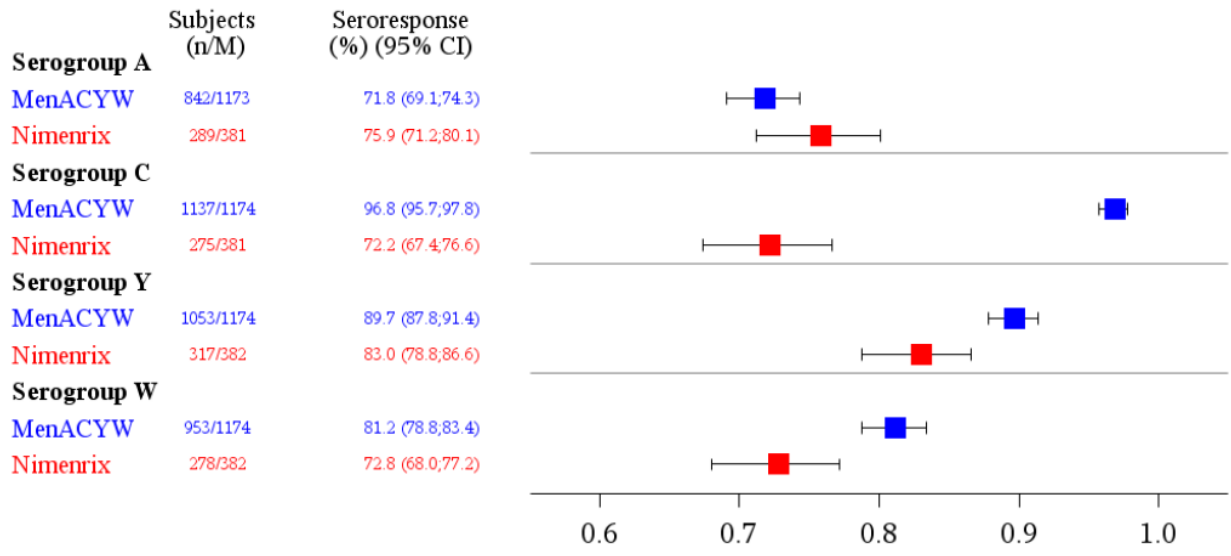
Toddlers are 12 through 23 months old.

hSBA vaccine seroresponse in the integrated analysis report is defined as: for a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16; for a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

S-: Pre-vaccination baseline titer is < 1:8

S+: Pre-vaccination baseline titer is ≥ 1:8

Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Table 2.1.1



n: number of subjects who achieved an hSBA vaccine seroresponse
M: number of subjects with valid serology results for the particular serogroup
95% CI of the single proportion calculated from the exact binomial method
Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Figure 4.1

Figure 1: Forest plots of hSBA vaccine seroresponse against meningococcal serogroup A, C, Y and W - Meningococcal Toddlers - PPAS (Poleed MET51, MET54 and MET57)

Table 19: Summary of hSBA vaccine seroresponse rate for MenACYW conjugate vaccine versus comparator vaccines – Meningococcal Vaccine-Naïve Children – PPAS (MET35)

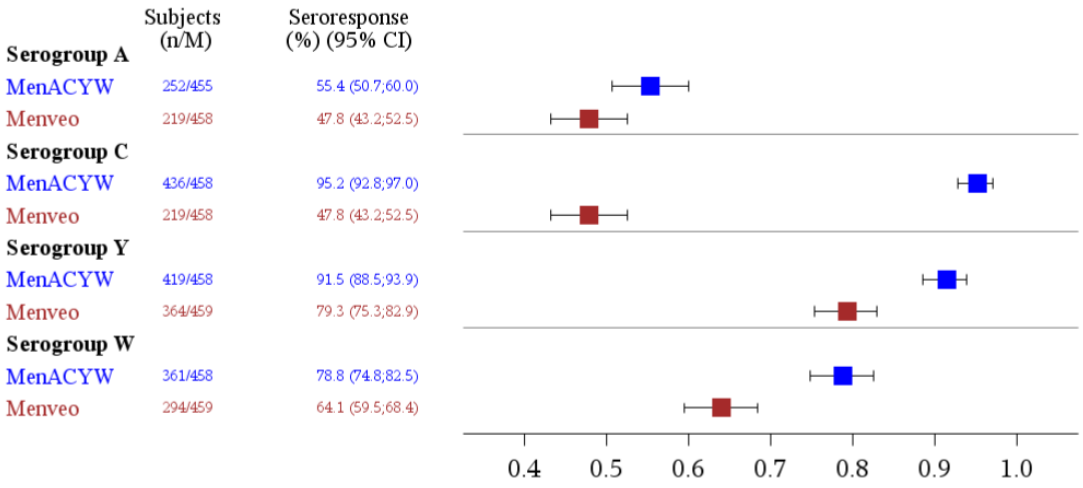
		MenACYW conjugate vaccine (N=458)			Menveo® (N=460)		
Serogroup	Baseline Status	n/M	%	(95% CI)	n/M	%	(95% CI)
A	Any	252/455	55.4	(50.7; 60.0)	219/458	47.8	(43.2; 52.5)
	S-	152/230	66.1	(59.6; 72.2)	128/234	54.7	(48.1; 61.2)
	S+	100/225	44.4	(37.8; 51.2)	91/224	40.6	(34.1; 47.4)
C	Any	436/458	95.2	(92.8; 97.0)	219/458	47.8	(43.2; 52.5)
	S-	387/402	96.3	(93.9; 97.9)	185/399	46.4	(41.4; 51.4)
	S+	49/56	87.5	(75.9; 94.8)	34/59	57.6	(44.1; 70.4)
Y	Any	419/458	91.5	(88.5; 93.9)	364/459	79.3	(75.3; 82.9)
	S-	380/404	94.1	(91.3; 96.2)	325/402	80.8	(76.7; 84.6)
	S+	39/54	72.2	(58.4; 83.5)	39/57	68.4	(54.8; 80.1)
W	Any	361/458	78.8	(74.8; 82.5)	294/459	64.1	(59.5; 68.4)
	S-	311/368	84.5	(80.4; 88.1)	256/366	69.9	(65.0; 74.6)
	S+	50/90	55.6	(44.7; 66.0)	38/93	40.9	(30.8; 51.5)

Abbreviations: M, number of subjects with available data for the endpoint; N, number of subjects in the PPAS; n: number of subjects who achieve an hSBA vaccine seroresponse; S-, Pre-vaccination baseline titer is < 1:8; S+, Pre-vaccination baseline titer is ≥ 1:8;

Children are 2 through 9 years old.

hSBA vaccine seroresponse in the integrated analysis report is defined as: for a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16; for a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Table 3.1.1



n: number of subjects who achieved an hSBA vaccine seroresponse
M: number of subjects with valid serology results for the particular serogroup
95% CI of the single proportion calculated from the exact binomial method
Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Figure 4.2

Figure 2: Forest plot of hSBA vaccine seroresponse against meningococcal serogroup A, C, Y and W – Naïve Children - PPAS (MET35)

Table 20: Summary of hSBA vaccine seroresponse rate for MenACYW conjugate vaccine versus comparator vaccines – Meningococcal Vaccine-Naïve Adolescents – OOAS (Pooled MET43 and MET50)

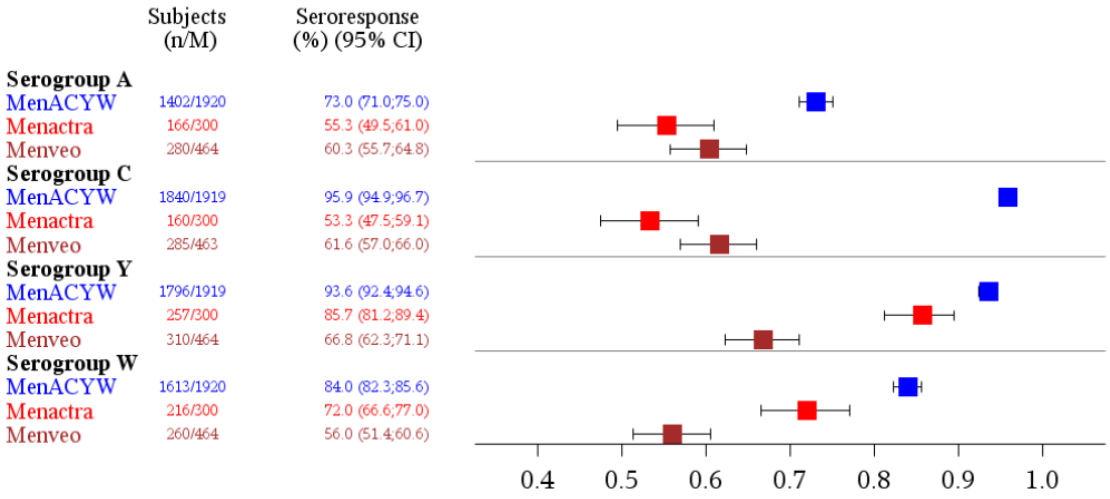
		MenACYW conjugate vaccine (N=1921)			Menactra® (N=300)			Menveo® (N=464)		
Serogroup	Baseline Status	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
A	Any	1402/1920	73.0	(71.0; 75.0)	166/300	55.3	(49.5; 61.0)	280/464	60.3	(55.7; 64.8)
	S-	650/789	82.4	(79.5; 85.0)	50/72	69.4	(57.5; 79.8)	181/275	65.8	(59.9; 71.4)
	S+	752/1131	66.5	(63.7; 69.2)	116/228	50.9	(44.2; 57.5)	99/189	52.4	(45.0; 59.7)
C	Any	1840/1919	95.9	(94.9; 96.7)	160/300	53.3	(47.5; 59.1)	285/463	61.6	(57.0; 66.0)
	S-	1373/1411	97.3	(96.3; 98.1)	112/199	56.3	(49.1; 63.3)	236/394	59.9	(54.9; 64.8)
	S+	467/508	91.9	(89.2; 94.1)	48/101	47.5	(37.5; 57.7)	49/69	71.0	(58.8; 81.3)
Y	Any	1796/1919	93.6	(92.4; 94.6)	257/300	85.7	(81.2; 89.4)	310/464	66.8	(62.3; 71.1)
	S-	1581/1667	94.8	(93.7; 95.9)	219/254	86.2	(81.4; 90.2)	294/437	67.3	(62.7; 71.7)
	S+	215/252	85.3	(80.3; 89.4)	38/46	82.6	(68.6; 92.2)	16/27	59.3	(38.8; 77.6)
W	Any	1613/1920	84.0	(82.3; 85.6)	216/300	72.0	(66.6; 77.0)	260/464	56.0	(51.4; 60.6)
	S-	1121/1185	94.6	(93.2; 95.8)	164/194	84.5	(78.7; 89.3)	195/283	68.9	(63.2; 74.3)
	S+	492/735	66.9	(63.4; 70.3)	52/106	49.1	(39.2; 59.0)	65/181	35.9	(28.9; 43.4)

Abbreviations: M, number of subjects with available data for the relevant endpoint; N, number of subjects in the PPAS; n, number of subjects who achieve an hSBA vaccine seroresponse; S-, Pre-vaccination baseline titer is < 1:8; S+, Pre-vaccination baseline titer is≥ 1:8;

Adolescents are 10 through 17 years old.

hSBA vaccine seroresponse in the integrated analysis report is defined as: for a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16; for a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Table 4.1.1



n: number of subjects who achieved an hSBA vaccine seroresponse
M: number of subjects with valid serology results for the particular serogroup
95% CI of the single proportion calculated from the exact binomial method
Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Figure 4.3

Figure 3: Forest plot of hSBA vaccine seroresponse against meningococcal serogroup A, C, Y and W – Meningococcal Vaccine Naïve Adolescents - PPAS (Pooled MET43 and MET50)

Table 21: Summary of hSBA vaccine seroresponse rate for MenACYW conjugate vaccine versus comparator vaccines - Meningococcal Vaccine-Naive Adults - PPAS (MET43)

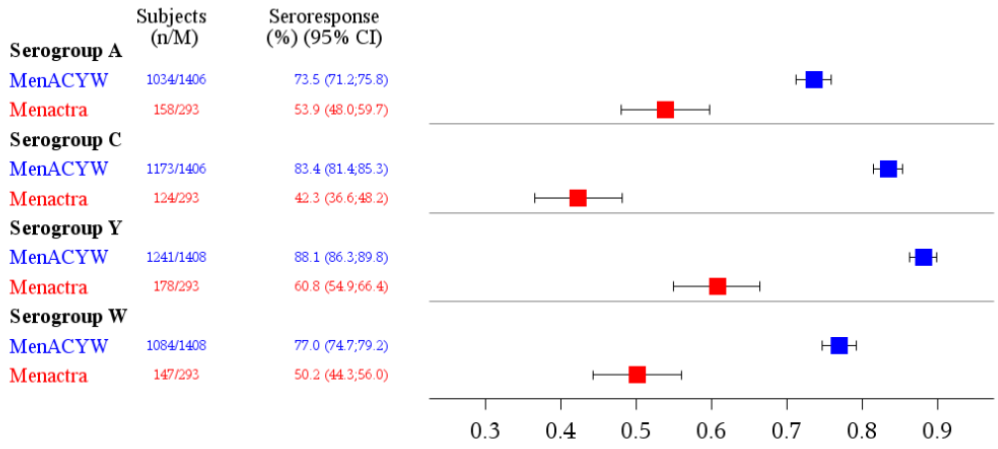
Serogroup	Baseline Status	MenACYW conjugate vaccine (N=1410)			Menactra® (N=293)		
		n/M	%	(95% CI)	n/M	%	(95% CI)
A	Any	1034/1406	73.5	(71.2; 75.8)	158/293	53.9	(48.0; 59.7)
	S-	309/354	87.3	(83.4; 90.6)	56/73	76.7	(65.4; 85.8)
	S+	725/1052	68.9	(66.0; 71.7)	102/220	46.4	(39.6; 53.2)
C	Any	1173/1406	83.4	(81.4; 85.3)	124/293	42.3	(36.6; 48.2)
	S-	641/740	86.6	(84.0; 89.0)	58/138	42.0	(33.7; 50.7)
	S+	532/666	79.9	(76.6; 82.9)	66/155	42.6	(34.7; 50.8)
Y	Any	1241/1408	88.1	(86.3; 89.8)	178/293	60.8	(54.9; 66.4)
	S-	868/917	94.7	(93.0; 96.0)	125/192	65.1	(57.9; 71.8)
	S+	373/491	76.0	(71.9; 79.7)	53/101	52.5	(42.3; 62.5)
W	Any	1084/1408	77.0	(74.7; 79.2)	147/293	50.2	(44.3; 56.0)
	S-	756/906	83.4	(80.9; 85.8)	98/183	53.6	(46.0; 60.9)
	S+	328/502	65.3	(61.0; 69.5)	49/110	44.5	(35.1; 54.3)

Abbreviations: M, number of subjects with available data for the endpoint; N, number of subjects in the PPAS; n, number of subjects who achieve an hSBA vaccine seroresponse; S-, Pre-vaccination baseline titer is < 1:8; S+, Pre-vaccination baseline titer is ≥ 1:8;

Adults are 18 through 55 years old.

hSBA vaccine seroresponse in the integrated analysis report is defined as: for a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16; for a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Table 5.1.1



n: number of subjects who achieved an hSBA vaccine seroresponse
M: number of subjects with valid serology results for the particular serogroup
95% CI of the single proportion calculated from the exact binomial method

Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Figure 4.4

Figure 4: Forest plot of hSBA vaccine seroresponse against meningococcal serogroup A, C, Y and W – Meningococcal Vaccine-Naïve Adults - PPAS (MET43)

Table 22: Summary of hSBA vaccine seroresponse rate for MenACYW conjugate vaccine versus comparator vaccines – Meningococcal Vaccine-Naïve Older Adults and Elderly PPAS (Pooled MET44 and MET49)

Age Group	Sero-group	Baseline Status	MenACYW conjugate vaccine (N=628)			Menomune® (N=525)		
			n/M	%	(95% CI)	n/M	%	(95% CI)
Overall (≥ 56 years)	A	Any	369/628	58.8	(54.8; 62.6)	223/525	42.5	(38.2; 46.8)
		S-	135/189	71.4	(64.4; 77.8)	81/159	50.9	(42.9; 58.9)
		S+	234/439	53.3	(48.5; 58.0)	142/366	38.8	(33.8; 44.0)
	C	Any	461/628	73.4	(69.8; 76.8)	256/525	48.8	(44.4; 53.1)
		S-	352/476	73.9	(69.8; 77.8)	204/397	51.4	(46.3; 56.4)
		S+	109/152	71.7	(63.8; 78.7)	52/128	40.6	(32.0; 49.7)
	Y	Any	459/628	73.1	(69.4; 76.5)	227/525	43.2	(39.0; 47.6)
		S-	388/491	79.0	(75.1; 82.5)	166/373	44.5	(39.4; 49.7)
		S+	71/137	51.8	(43.1; 60.4)	61/152	40.1	(32.3; 48.4)
	W	Any	395/628	62.9	(59.0; 66.7)	236/525	45.0	(40.6; 49.3)
		S-	338/531	63.7	(59.4; 67.8)	199/443	44.9	(40.2; 49.7)
		S+	57/97	58.8	(48.3; 68.7)	37/82	45.1	(34.1; 56.5)
Older Adults (56 through 64 years)	A	Any	178/290	61.4	(55.5; 67.0)	103/235	43.8	(37.4; 50.4)
		S-	55/71	77.5	(66.0; 86.5)	35/68	51.5	(39.0; 63.8)
		S+	123/219	56.2	(49.3; 62.8)	68/167	40.7	(33.2; 48.6)
	C	Any	215/290	74.1	(68.7; 79.1)	120/235	51.1	(44.5; 57.6)
		S-	167/224	74.6	(68.3; 80.1)	102/179	57.0	(49.4; 64.3)
		S+	48/66	72.7	(60.4; 83.0)	18/56	32.1	(20.3; 46.0)
	Y	Any	221/290	76.2	(70.9; 81.0)	110/235	46.8	(40.3; 53.4)
		S-	179/222	80.6	(74.8; 85.6)	85/176	48.3	(40.7; 55.9)
		S+	42/68	61.8	(49.2; 73.3)	25/59	42.4	(29.6; 55.9)
	W	Any	188/290	64.8	(59.0; 70.3)	108/235	46.0	(39.5; 52.6)
		S-	156/233	67.0	(60.5; 73.0)	93/197	47.2	(40.1; 54.4)
		S+	32/57	56.1	(42.4; 69.3)	15/38	39.5	(24.0; 56.6)
Elderly (≥ 65 years)	A	Any	191/338	56.5	(51.0; 61.9)	120/290	41.4	(35.7; 47.3)
		S-	80/118	67.8	(58.6; 76.1)	46/91	50.5	(39.9; 61.2)
		S+	111/220	50.5	(43.7; 57.2)	74/199	37.2	(30.5; 44.3)
	C	Any	246/338	72.8	(67.7; 77.5)	136/290	46.9	(41.0; 52.8)
		S-	185/252	73.4	(67.5; 78.8)	102/218	46.8	(40.0; 53.6)
		S+	61/86	70.9	(60.1; 80.2)	34/72	47.2	(35.3; 59.3)

Age Group	Sero-group	Baseline Status	MenACYW conjugate vaccine (N=628)			Menomune® (N=525)		
			n/M	%	(95% CI)	n/M	%	(95% CI)
Elderly (≥ 65 years)	**Y**	**Any**	238/338	70.4	(65.2; 75.2)	117/290	40.3	(34.7; 46.2)
		S-	209/269	77.7	(72.2; 82.5)	81/197	41.1	(34.2; 48.3)
		S+	29/69	42.0	(30.2; 54.5)	36/93	38.7	(28.8; 49.4)
	W	**Any**	207/338	61.2	(55.8; 66.5)	128/290	44.1	(38.3; 50.1)
		S-	182/298	61.1	(55.3; 66.6)	106/246	43.1	(36.8; 49.5)
		S+	25/40	62.5	(45.8; 77.3)	22/44	50.0	(34.6; 65.4)
65 through 74 years	**A**	**Any**	141/252	56.0	(49.6; 62.2)	92/215	42.8	(36.1; 49.7)
		S-	60/89	67.4	(56.7; 77.0)	39/68	57.4	(44.8; 69.3)
		S+	81/163	49.7	(41.8; 57.6)	53/147	36.1	(28.3; 44.4)
	C	**Any**	182/252	72.2	(66.3; 77.7)	102/215	47.4	(40.6; 54.3)
		S-	142/190	74.7	(67.9; 80.7)	77/160	48.1	(40.2; 56.2)
		S+	40/62	64.5	(51.3; 76.3)	25/55	45.5	(32.0; 59.4)
	Y	**Any**	183/252	72.6	(66.7; 78.0)	90/215	41.9	(35.2; 48.8)
		S-	159/203	78.3	(72.0; 83.8)	63/147	42.9	(34.7; 51.3)
		S+	24/49	49.0	(34.4; 63.7)	27/68	39.7	(28.0; 52.3)
	W	**Any**	161/252	63.9	(57.6; 69.8)	97/215	45.1	(38.3; 52.0)
		S-	142/221	64.3	(57.6; 70.6)	79/180	43.9	(36.5; 51.5)
		S+	19/31	61.3	(42.2; 78.2)	18/35	51.4	(34.0; 68.6)
≥ 75 years	**A**	**Any**	50/86	58.1	(47.0; 68.7)	28/75	37.3	(26.4; 49.3)
		S-	20/29	69.0	(49.2; 84.7)	7/23	30.4	(13.2; 52.9)
		S+	30/57	52.6	(39.0; 66.0)	21/52	40.4	(27.0; 54.9)
	C	**Any**	64/86	74.4	(63.9; 83.2)	34/75	45.3	(33.8; 57.3)
		S-	43/62	69.4	(56.3; 80.4)	25/58	43.1	(30.2; 56.8)
		S+	21/24	87.5	(67.6; 97.3)	9/17	52.9	(27.8; 77.0)
	Y	**Any**	55/86	64.0	(52.9; 74.0)	27/75	36.0	(25.2; 47.9)
		S-	50/66	75.8	(63.6; 85.5)	18/50	36.0	(22.9; 50.8)
		S+	5/20	25.0	(8.7; 49.1)	9/25	36.0	(18.0; 57.5)
	W	**Any**	46/86	53.5	(42.4; 64.3)	31/75	41.3	(30.1; 53.3)
		S-	40/77	51.9	(40.3; 63.5)	27/66	40.9	(29.0; 53.7)
		S+	6/9	66.7	(29.9; 92.5)	4/9	44.4	(13.7; 78.8)

Abbreviations: M, number of subjects with available data for the endpoint; N, number of subjects in the PPAS; n: number of subjects who achieve an hSBA vaccine seroresponse; S-, Pre-vaccination baseline titer is < 1:8; S+, Pre-vaccination baseline titer is ≥ 1:8;

Older adults are 56 through 64 years old, and elderly subjects are 65 years old and above.

hSBA vaccine seroresponse in the integrated analysis report is defined as: for a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16; for a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Table 6.1.1

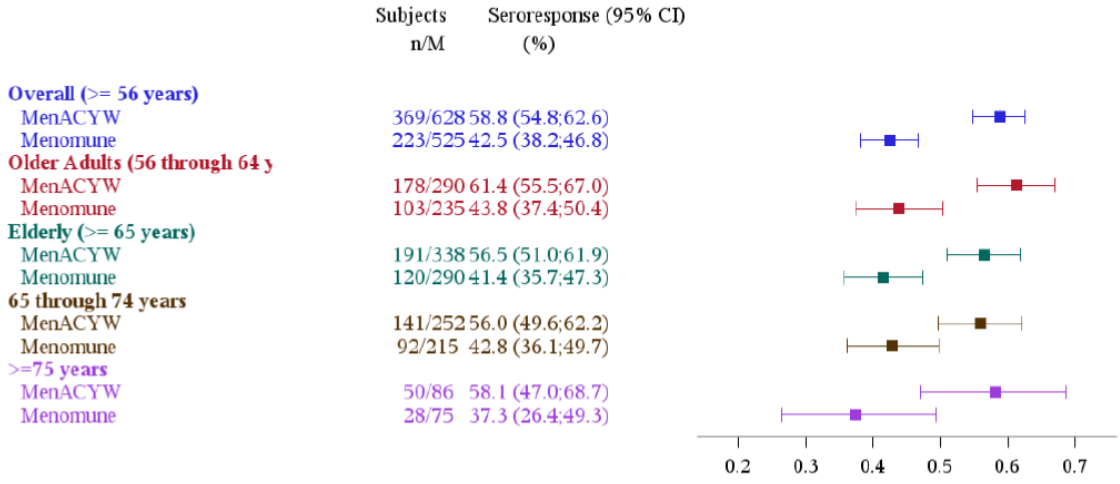


Figure 5: Forest plot of hSBA vaccine seroresponse against meningococcal serogroup A, C, Y and W – Meningococcal Vaccine Naïve Older Adults and Elderly - PPAS (Pooled MET44 and MET49)

Meningococcal-primed subjects

Table 23: Summary of hSBA vaccine seroresponse rate for MenACYW conjugate vaccine versus comparator vaccine – Primed Toddlers – PPAS (MET51)

		MenACYW conjugate vaccine (N=198)			Nimenrix® - MenC primed (N=99)		
Serogroup	**Baseline Status**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
A	**Any**	150/197	76.1	(69.6; 81.9)	89/98	90.8	(83.3; 95.7)
	S-	116/152	76.3	(68.7; 82.8)	67/71	94.4	(86.2; 98.4)
	S+	34/45	75.6	(60.5; 87.1)	22/27	81.5	(61.9; 93.7)
C	**Any**	187/196	95.4	(91.5; 97.9)	93/98	94.9	(88.5; 98.3)
	S-	57/61	93.4	(84.1; 98.2)	22/24	91.7	(73.0; 99.0)
	S+	130/135	96.3	(91.6; 98.8)	71/74	95.9	(88.6; 99.2)
Y	**Any**	174/195	89.2	(84.0; 93.2)	77/98	78.6	(69.1; 86.2)
	S-	167/186	89.8	(84.5; 93.7)	75/90	83.3	(74.0; 90.4)
	S+	7/9	77.8	(40.0; 97.2)	2/8	25.0	(3.2; 65.1)
W	**Any**	148/196	75.5	(68.9; 81.4)	72/97	74.2	(64.3; 82.6)
	S-	143/190	75.3	(68.5; 81.2)	71/95	74.7	(64.8; 83.1)
	S+	5/6	83.3	(35.9; 99.6)	1/2	50.0	(1.3; 98.7)

N: number of subjects in the Per-Protocol Analysis Set; M: number of subjects with available data for the endpoint subjects who achieve an hSBA vaccine seroresponse

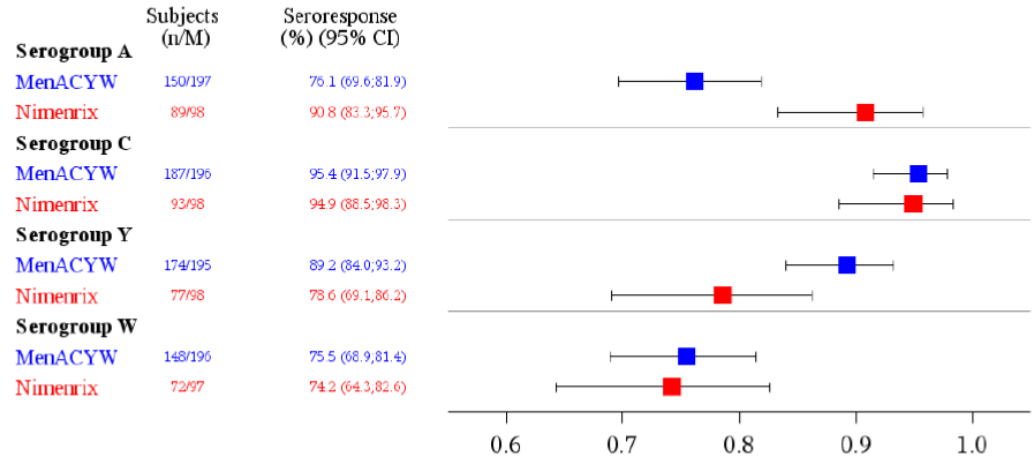
Toddlers are 12 through 23 months old.

hSBA vaccine seroresponse in the integrated analysis report is defined as: for a subject with a pre-vaccination titer vaccination titer must be ≥ 1:16; for a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be greater than the pre-vaccination titer.

S-: Pre-vaccination baseline titer is < 1:8

S+: Pre-vaccination baseline titer is ≥ 1:8

Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Table 7.1.1



n: number of subjects who achieved an hSBA vaccine seroresponse
M: number of subjects with valid serology results for the particular serogroup
95% CI of the single proportion calculated from the exact binomial method
Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Figure 4.9

Figure 6: Forest plot of hSBA vaccine seroresponse against meningococcal serogroup A, C, Y and W – Primed Toddlers - PPAS (MET51)

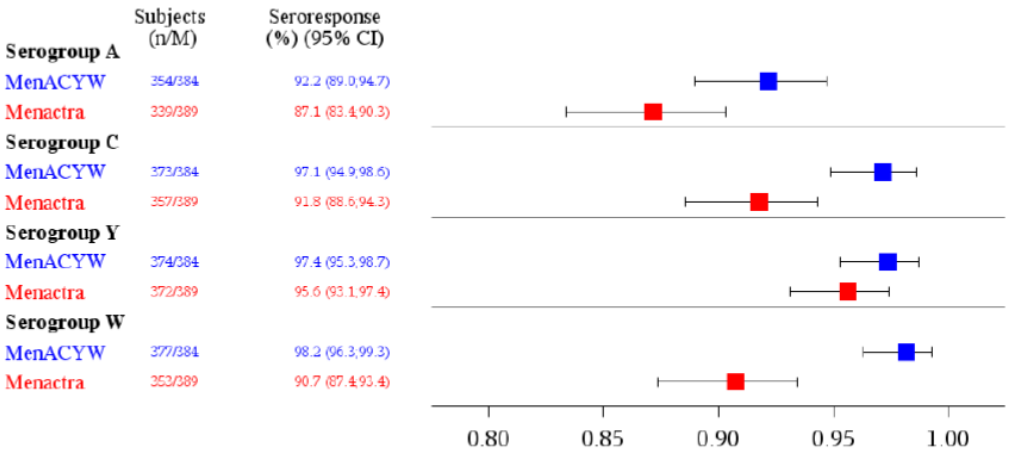
Table 24: Summary of hSBA vaccine seroresponse rate for MenACYW conjugate vaccine versus comparator vaccines – Primed Adolescentes and Adults – PPAS (MET56)

		MenACYW conjugate vaccine (N=384)			Menactra® (N=389)		
Serogroup	Baseline Status	n/M	%	(95% CI)	n/M	%	(95% CI)
A	Any	354/384	92.2	(89.0; 94.7)	339/389	87.1	(83.4; 90.3)
	S-	76/76	100.0	(95.3; 100)	64/69	92.8	(83.9; 97.6)
	S+	278/308	90.3	(86.4; 93.3)	275/320	85.9	(81.6; 89.6)
C	Any	373/384	97.1	(94.9; 98.6)	357/389	91.8	(88.6; 94.3)
	S-	172/174	98.9	(95.9; 99.9)	165/171	96.5	(92.5; 98.7)
	S+	201/210	95.7	(92.0; 98.0)	192/218	88.1	(83.0; 92.1)
Y	Any	374/384	97.4	(95.3; 98.7)	372/389	95.6	(93.1; 97.4)
	S-	216/216	100.0	(98.3; 100)	219/223	98.2	(95.5; 99.5)
	S+	158/168	94.0	(89.3; 97.1)	153/166	92.2	(87.0; 95.8)
W	Any	377/384	98.2	(96.3; 99.3)	353/389	90.7	(87.4; 93.4)
	S-	150/150	100.0	(97.6; 100)	152/155	98.1	(94.4; 99.6)
	S+	227/234	97.0	(93.9; 98.8)	201/234	85.9	(80.8; 90.1)

Abbreviations: M, number of subjects with available data for the endpoint; N, number of subjects in the PPAS; n, number of subjects who achieve an hSBA vaccine seroresponse; S-, Pre-vaccination baseline titer is < 1:8; S+, Pre-vaccination baseline titer is ≥1:8;

hSBA vaccine seroresponse in the integrated analysis report is defined as: for a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16; for a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

Reproduced from Efficacy Integrated Analysis Report Table 8.1.1



n: number of subjects who achieved an hSBA vaccine seroresponse
M: number of subjects with valid serology results for the particular serogroup
95% CI of the single proportion calculated from the exact binomial method
Reproduced from 5.3.5.3 Efficacy Integrated Analysis Report Figure 4.10

Figure 7: Forest plot of hSBA vaccine seroresponse against meningococcal serogroup A, C, Y and W – Primed Adolescents and Adults - PPAS (MET56)

Clinical studies in special populations

Since the *paediatric population* (older than 12 month of age) is part of the marketing authorization application, the presented respective studies are already presented in other parts of the report. Please refer to the respective sections above.

The same applied to the results for the *elderly population*.

Table 25: Repartition of subjects in trials according to age group - Older Adults –All Randomized Subjects

	Age 65-74 (Older subjects number /total number)		Age 75-84 (Older subjects number /total number)		Age 85+ (Older subjects number /total number)	
	(n/N)	%	(n/N)	%	(n/N)	%
Controlled Trials	483/654	73.9	147/654	22.5	24/654	3.7
Non-Controlled Trials	N/A*	N/A*	N/A*	N/A*	N/A*	N/A*

*All studies are controlled
n: number of randomized subjects in the defined category in each age group
N: total number of randomized subjects
Percentages are based on N.
Contributing studies: MET44 and MET49
Source: D120 Responses Statistical Appendix [Table 3.1]

No other special populations were included in the development programme.

Supportive studies

Study MET44

Study MET44 was a phase II, randomized, open-label (the laboratory technicians were blinded to group assignment), active-controlled, multi-center study to compare safety and immunogenicity of MenACYW conjugate vaccine to the comparator Menomune – A/C/Y/W-135 in healthy meningococcal vaccine-naïve subjects 56 years of age and older in between November 12th 2012 and January 17th 2013.

The applicant's conclusion that a difference between subjects' age of 56-64 years or ≥64 appeared to have not an impact on the immune response is supported.

There was a trend towards higher seroresponse rates in group 1 (MenQuadfi) compared to group 2 (Menomune). No concerns arise from the presented data.

Study MET54

Study MET54 was a phase II, randomized, parallel, open-label, active-controlled, multi-center study to compare safety and immunogenicity of MenACYW conjugate vaccine to the comparator Nimenrix in toddlers in Finland between 31 March 2015 and 19 August 2015.

Seroresponse rates 30 days following vaccination were in general comparable between MenQuadfi and Nimenrix.

This study was one of only two studies conducted in the EU in support of this MAA. Regarding differences compared to the toddlers study conducted outside the EU, please refer to assessment and the respective OC of study MET57.

Study MET39

Study MET39 was a phase II, randomized, open-label, multi-center study to evaluate 5 different schedules of MenACYW conjugate vaccination regarding safety and immunogenicity compared to concomitant routine paediatric vaccination (not including meningococcal vaccination) in healthy infants and toddlers in the US between December 16st 2009 and February 13th 2012.

This study is included in the AR for completeness only. The included patient population does not reflect the intended target population of this MAA. Therefore, no assessment of the immunogenicity or safety results was done.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Immunogenicity of MenQuadfi has been evaluated in seven pivotal studies. Additional evidence has been generated in five supportive studies.

Overall, the design of the presented main studies is similar and considered adequate. In all studies the subjects received one dose of MenQuadfi or a comparator vaccine. Immunogenicity was evaluated immediately before vaccination and 30 days after vaccination. No immunogenicity data beyond 30 days after vaccination are currently available which is also considered as missing information in the RMP. The applicant plans three post marketing studies to provide respective data for long-term immune persistence. The studies will also evaluate the ability of MenQuadfi to boost itself. All three studies are added in Annex II as category I post-marketing obligations.

In a scientific advice it was agreed to base the clinical development programme on immunogenicity studies and that no efficacy studies are necessary. This is based on the fact that a widely accepted immunological correlate of protection for meningococcal vaccines containing serogroups A, C, W and Y exists. This approach has also been used for licensing of previous conjugated meningococcal vaccines in Europe (Menveo, Nimenrix). This is also in line with the relevant EMA and WHO guidelines. The use of hSBA for primary immunogenicity analyses was adequately justified by the applicant and accepted in a previous SA. As supportive evidence, the applicant also provided data derived from rSBA for all patients in studies MET 50, 56 and 35 and for a subset of subjects in studies MET 43, 49, 51 and 57.

The presented serological assays are overall considered appropriate and suitable to generate sufficient data on immunogenicity of the vaccine.

The applicant presented three main endpoints for the evaluation of immunogenicity: seroprotection, seroresponse and geometric mean titers (GMTs). Seroprotection is defined as the percentage of subjects with an hSBA titer ≥1:8 while seroresponse extends this definition by taking into account prevaccination titers: For subjects with a pre-vaccination titer ≥1:8, an at least 4-fold increase of titer needs to be demonstrated. In addition, GMTs are presented for each vaccination group, allowing the assessment of differences in immune response between vaccines. In general, the chosen endpoints seroresponse, seroprotection and GMTs were considered acceptable and adequate to address the study objectives. Additionally, percentages of subjects achieving an at least 4-fold increase of titres and RCDs were presented.

Although the cut-off for definition of hSBA seroprotection was ≥1:8, as also recommended in the SA, the applicant used a cut-off of ≥1:16 for definition of seroresponse in most of the pivotal studies (reaching an hSBA titer of ≥1:16 if <1:8 pre-vaccination or achieving a 4-fold increase in hSBA titer if ≥1:8 pre-vaccination). This is based on requirements of CBER/FDA. Although a hSBA titer of ≥1:4 can be considered as widely accepted correlate of protection for meningococcal serogroups A, C, W and Y, the use of higher cut-offs does not raise concerns per se.

In 4 studies non-inferiority of seroresponse rates after MenQuadfi against a comparator vaccine (quadrivalent meningococcal vaccine) was the primary objective (MET35, MET43, MET49, MET50). In study MET51, the primary objective was non-inferiority of seroprotection rates. It was not considered acceptable to adequately assess immunogenicity by sole achievement of a protective titer regardless of prevaccination titres in light of the rather high percentage of subjects with seroprotective titres at baseline. For seropositive subjects at baseline an, at least, 4-fold increase of titer needs to be demonstrated. Upon request, the non-inferiority analysis of seroresponse for study MET57 was also provided. The evaluation of seroresponse was considered more informative for the assessment of immunogenicity.

The applicant justified the applied non-inferiority margins mainly based on precedence from other development programs, as well as feasibility concerns. A justification based on clinical considerations (e.g. relevance of a 10% lower seroresponse rate in terms of vaccine efficacy) or statistical considerations (e.g. assay sensitivity) was considered missing. However, given the reference to other development programmes

as well as the clear demonstration of NI against various comparator vaccines across studies, this issue was not further pursued.

No alternative vaccination schedule has been evaluated in the presented studies. Also, in the dose-finding studies, only one dose of MenQuadfi was investigated. Only study MET39 investigated different vaccination schedules, where the study population (healthy infants) does not reflect the currently intended target population (subjects from 12 months of age). In a previous scientific advice (EMA/CHMP/SAWP/467602/2015), it was recommended to include evaluation of one vs. two doses in one of the toddler studies. However, no such data are available. Of note, nonclinical immunogenicity data are only available from a two (or more) dose regimen. Based on non-clinical data it was therefore not considered self-evident why only a one-dose-regimen was investigated in clinical studies. Given the absence of persistence data as well as the general knowledge of rapid waning of antibodies against serogroup A from other licensed vaccines, a justification for the absence of investigation of one vs two doses in toddlers was requested. The applicant explained that no other vaccination schedules have been tested in toddlers since MenQuadfi was evaluated compared to the current standard of care in the EU (MET51: Nimenrix) with the respective vaccination schedule of a single dose. The applicant argued that further investigations of other vaccination schedules are not necessary since non-inferiority to Nimenrix has been shown. It was acknowledged that non-inferiority of seroresponse has been shown compared to Nimenrix at D30. However, no long-term data is available. Given that rapid waning has been observed for other MenACYW vaccines, and no data exists that this does not apply for MenQuadfi, a general statement on rapid waning of antibodies against serogroup A known from other vaccines was added in section 4.4. of the SmPC.

The studies evaluating MenQuadfi with a comparator vaccine all had a modified double-blind design. Only the vaccine administrator (preparation and administration of vaccines, no involvement in safety evaluation) was unblinded in these studies. This was considered necessary due to the different appearances of the vaccines. However, it was unclear what measures were in place to ensure blinding of the subject. The applicant explained that to ensure blinding of the subject, the route of administration was not discussed with the participant and evaluation of the safety reports was done by a blinded study personnel. Since it is unlikely that potential unblinding has an impact on the immunogenicity endpoints and from a safety perspective except for an increased frequency of solicited injection site reactions, no differences in safety profile are observed between the two study groups, no further concerns remained.

The inclusion and exclusion criteria were in general comparable over all pivotal studies and specific aspects are adequately reflected. The eligible age of the subjects differs between studies resulting in population ranging from toddlers (12 to 23 months) up to older adults (≥ 56 years). Although the whole age range is adequately represented, the population of subjects previously primed with a meningococcal vaccine is limited. Primed subjects have only been included in two studies: Study MET56 included adolescent and adult subjects (15-55 years) previously vaccinated with a meningococcal quadrivalent conjugate vaccine and study MET51 included toddlers who received a monovalent meningococcal C conjugate (MenC) vaccination during infancy. In multiple European countries MenC vaccination is recommended for toddlers and later quadrivalent MenACWY vaccination for adolescents. No data for MenQuadfi are available from primed adolescents or adults previously vaccinated with MenC. Moreover, in study MET56 subjects who previously received quadrivalent MenACWY vaccination were included with the majority of subjects primed with Menactra, a vaccine that is not licensed in the EU. Only very limited data of subjects previously vaccinated with Menveo are available and no data of subjects previously vaccinated with Nimenrix. In addition, no data are available to assess the ability of MenQuadfi to boost itself. This is adequately reflected in the SmPC and will be addressed in the planned postmarketing studies.

Overall, data generated in the EU is limited. Only one of the seven pivotal studies (MET51) and one supportive study (MET54) were conducted in the EU. Both studies included healthy toddlers aged 12 to 23 months. No EU data is available for children, adolescents or adults. From other (EU-licensed) meningococcal vaccines, it is known that the ethnic background and also the geographical region can have significant influence on the circulating serotypes and the potential degree of carriage. The impact of intrinsic and extrinsic factors on study results and their potential to limit the interpretation and applicability of the results, has also been addressed in respective ICH and EMA guidance documents (EMEA/CHMP/EWP/692702/2008). Different baseline seroprotection rates have been observed in the regions included in the developmental programme. An additional comparison of seroresponse rates in toddlers based on data obtained in study MET51 (EU) and study MET57 (Russia, Mexico, South Korea and Thailand) showed comparable seroresponse data despite baseline differences. Although no comparative data are available for subjects beyond the toddler age, presented data provided some reassuring evidence that immunogenicity of MenQuadfi derived from subjects outside EU can be extrapolated to EU subjects

Different comparators have been used in the presented studies. The comparators - Menveo and Nimenrix - chosen for toddlers, children and adolescents are both licensed in the EU and contain the same serogroups as MenQuadfi. On the other hand, the chosen comparators Menactra and Menomune used in adolescents, adults and elderly, are not considered optimal from an EU point of view. Both vaccines are not licensed in the EU and it would have been preferred at least some comparative immunogenicity data against an EU licensed vaccine in adults and elderly, which has been also addressed during a preceding scientific advice (EMA/CHMP/SAWP/467602/2015). It was also mentioned that Menactra is not a particularly good conjugate vaccine. Moreover, Menomune is a polysaccharide vaccine with generally known drawbacks regarding immunogenicity. As mentioned in the scientific advice, the assessment will focus on seropositivity and seroconversion rates rather than on non-inferiority against Menactra or Menomune (although meeting non-inferiority would still be expected). Consequently, the assessment in adolescents (10-17) was also focused on the comparison against Menveo in study MET50. The applicant submitted a network meta-analysis comparing the immunogenicity of MenACYW in adult and elderly subjects to Menveo by extrapolation from historical studies of the corresponding comparator vaccines (Menactra, Menomune) with Menveo. However, as stated by the applicant, the analysis has several methodological shortcomings leaving a large margin of uncertainty. Consequently, the results were not considered conclusive.

The immunogenicity of MenQuadfi has also been studied in combination with different concomitant vaccinations (MET50, MET57). In toddlers, concomitant vaccination with MMR, Varicella, hexavalent vaccine (DTaP-IPV-HB-Hib) and PCV13 (pneumococcal vaccine) (MET57) and in adolescents, concomitant vaccination with TdaP and HPV was investigated (MET50). Although both studies were conducted outside the EU, all used concomitant vaccinations are also licensed in the EU. The obtained results are therefore relevant for the EU population. Nevertheless, it was not considered straightforward to extrapolate data from one particular vaccine to all vaccines containing the same antigens. Notably, variable enhancement or depression of immune responses to conjugated saccharides has been observed when the carrier proteins for co-administered products are the same or different, so that generalisations cannot be made beyond the specific vaccines studied as also stated in the respective EMA guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1). The SmPC was revised accordingly.

Initially no Statistical Analysis Reports were submitted. Corresponding documents were provided on request. Protocol amendments occurred in all studies, except MET51 and were mainly clarifications and updates of logistical issues or amendments concerning the addition of hSBA immunogenicity on the request of CBER/FDA. In study MET43 non GCP conform findings have been made at one study site. Affected subjects were excluded from the analysis, and results of respective sensitivity analyses showed no apparent

differences in immune responses across the treatment groups. A GCP inspection was performed in 2019 for this study by the FDA together with study MET35. The final report is still pending but based on preliminary report,s no inspection findings were identified. Further, a routine GCP inspection for study MET57 was performed in Q1 2020 by EMA. No critical findings were identified. Some major findings were identified but it is not likely that the observed findings have an effect on the reported data. With the exception of underreporting of certain AEs at site #402 (local reaction at injection site within 30 minutes), for which the sponsor provided adequate corrective actions and the CSR was updated in May 2020.

The applicant presented an elaborate multiple testing strategy for the conclusion of superiority across serogroups and age strata, which is partly motivated by epidemiological arguments. Nevertheless, post-hoc the potential risk for erroneous conclusions cannot be quantified. Consequently, the applied methods were not considered adequate. Furthermore, it was not considered straightforward to use seroprotection rates for superiority testing instead of seroresponse rates that were used for NI-testing. However, no concerns were raised as these results were considered supportive only.

Efficacy data and additional analyses

In six of the seven pivotal studies, antibody response of MenQuadfi was compared to different comparators (Nimenrix, Menveo, Menactra, Menomune) in different age groups from toddlers of 12 - 23 months to adults ≥56 years. In all these studies the primary objective to demonstrate non-inferiority of MenQuadfi against the comparator vaccine was met for all serogroups. In all but one study non-inferiority was based on seroresponse rates. Only in study MET51 non-inferiority of seroprotection rate was tested. Upon request, an additional non-inferiority analysis of seroresponse was provided where non-inferiority was also met for all serogroups.

The applicant presented a post-hoc testing strategy for the conclusion of superiority across serogroups and age strata. Although partly motivated by epidemiological arguments, the potential risk for erroneous conclusions cannot be quantified and the applied methods were not considered adequate. Consequently, these results were considered supportive only.

In general, it was observed that seroresponse and seroprotection rates were higher in younger subjects (toddlers, children and adolescents) and declined with age. However, this was not unexpected and was also observed in the comparator groups. Across studies and age groups, MenQuadfi seroresponse rates for serogroup A were lower compared to C, W and Y.

In meningococcal-vaccination-naïve subjects seroresponse rates were even higher for MenQuadfi for all serogroups in all age groups compared to the comparators with only some exceptions such as for serogroup A in toddlers where the seroresponse rate was lower compared to that of Nimenrix, while still meeting non-inferiority criteria for seroprotection. For children the seroresponse rates for serogroup A were numerically higher than for Menveo, but the difference is marginal.

However, subgroup analyses for MenC-primed toddlers revealed significant differences for serogroup A between MenQuadfi and Nimenrix in favour of Nimenrix. While seroresponse rates for serogroups W, C and Y were comparable or even slightly higher for MenQuadfi compared to Nimenrix, the seroresponse rate for serogroup A was significantly lower for MenQuadfi: 76.1% (69.6; 81.9) vs 90.8% (83.3; 95.7). The same was also observed for serogroup A post vaccination GMTs in MenC-primed toddlers: 31.8 (26.5; 38.1) vs 64 (50.9; 80.5). This observation is mainly driven by higher seroresponse rates and GMTs observed after the

administration of Nimenrix. Overall, seroresponse rates were comparable between MenC-primed and meningococcal-vaccination-naïve toddlers receiving MenQuadfi.

However, distinct differences were observed depending on the previously received MenC vaccination conjugate protein (TT or CRM). In the MenQuadfi group, seroresponse rates for serogroups A and W were distinctly lower for MenC-CRM primed subjects than for MenC-TT primed subjects with non-overlapping CIs (A: 50.0% (35.2; 64.8) vs 84.6% (77.7; 90.0); W: 44.7% (30.2; 59.9) vs 85.2 (78.5; 90.5)). Such differences were not as pronounced in the control group (Nimenrix) with only numerically lower seroresponse rates. Although the results should be interpreted cautiously, since the study was not powered for this subgroup analysis and the number of subjects in the respective subgroups is low (MenC-CRM: (MenQuadfi 48, Nimenrix 25), it has to be noted that this difference has not been observed with Nimenrix. Overall, an impact of the conjugate used for priming cannot be ruled out and respective amendments to the SmPC were made in order to include warnings for subjects at high risk for a MenA infection who previously received a Men-C-CRM vaccination.

An analysis of seroresponse rate in primed toddlers according to the number of doses (1 or 2) of previous MenC vaccination (NeisVac-C) showed lower response for subjects with one priming dose with slightly overlapping CIs for MenQuadfi. This was not observed for Nimenrix. However, seroprotection rates were comparable across all subgroups.

In quadrivalent meningococcal primed adolescents and adults the analyses of seroresponse rates and GMT according to previous vaccination (Menactra, Menveo or unknown) did not reveal any concerns. However, the number of patients previously vaccinated with Menveo were limited and need therefore be interpreted cautiously.

For meningococcal-vaccination-naïve subjects it was observed across studies that seroresponse rates were lower in subjects with seroprotective titres at baseline. Interestingly, this was not observed in meningococcal-primed subjects.

It has been also noted in general that baseline seroprotection rates for serogroup A were much higher than for all other serogroups but differed between studies. As mentioned above this issue was addressed by the applicant by a comparison of seroresponse rates in toddlers based on data obtained in study MET51 (EU) and study MET57 (Russia, Mexico, South Korea and Thailand) which showed comparable seroresponse data despite baseline differences. Further, considering the balanced randomization and stratification by country and, most important, the definition of seroresponse, no further concerns arised.

In study MET56 non-inferiority of seroresponse rates was demonstrated for MenQuadfi when administered as booster vaccination to subjects (adolescents and adults) who previously received a quadrivalent meningococcal conjugate vaccine 4 to 10 years before, compared to Menactra with even (numerically) higher seroresponse rates and GMTs for all serotypes in favour of MenQuadfi. As most subjects previously received Menactra, a concern was raised in how far data mainly derived from subjects who previously received a vaccine not licensed in the EU can be extrapolated to the European population. Furthermore, no data from adults and adolescents who were primed with a MenC vaccine were available. However, data from the toddler study are reassuring to some degree that MenQuadfi can elicit a sufficient immune response in subjects primed with EU-licensed vaccines. As there is no clinically plausible reason to assume that there might be a difference between toddlers and older age groups, this issue was considered resolved. Furthermore, additional data will be gathered in the postmarketing by the planned/ongoing studies. Additionally, it would have been informative to compare boosting between subjects that have been primed with different conjugates, as also recommended by the WHO. Available data from study MET56 didn’t allow meaningful

evaluation in this regard, since mainly Menactra primed subjects were included. As mentioned above, in toddlers some differences were observed depending on the piming vaccine. Although these data had some limitations due to the low number of subjects in the subgroups, this observation should be described in the SmPC. Respective amendments were made.

In addition, no data are currently available to assess the ability of MenQuadfi to boost itself. This is planned for the postmarketing, which was considered acceptable. The planned studies have been included in Annex II. Concomitant vaccination: Study MET57 investigated the immunogenicity of concomitant vaccination of MenQuadfi with paediatric vaccines (MMR+V, DTaP-IPV-HB-Hib, or PCV13). Although the study was performed outside of the EU, the used concomitant vaccinations are also licensed in the EU. Seroresponse rates achieved with MenQuadfi alone compared to concomitant vaccination with MMR+V and DTaP-IPV-HB-Hib do not give rise to concern on concomitant vaccination. Results didn't suggest a negative effect of MenQuadfi on the immunogenicity of the concomitantly administered vaccines. However, the clinical relevance of rather low seroresponse rates and significantly lower GMTs for serogroup A when MenQuadfi is concomitantly administered with PCV13 for both seronegative and seropositive subjects at baseline, was unclear (seroresponse rate S+ and S-: 56.1% (48.9; 63.2) vs. 71.9% (61.8; 80.6); seroresponse rate S+: 37.5% (27.8; 48.0) vs. 57.7% (43.2; 71.3); GMT: 24.6 (20.2; 30.1) vs. 49.0 (36.8; 65.3). In consequence, a respective warning for subjects at high risk for a MenA infection was included in the SmPC.

Study MET50 investigated concomitant vaccination of MenQuadfi and TdaP and HPV in adolescents. While no concerns arised for Tetanus, Diphterie and HPV, the concomitant vaccination had negative consequences on the immune response to pertussis antigens, as shown by non-inferiority analysis of GMCs. The lower limit of the 2-sided 95% CI for the ratio of GMCs in Group 3 (MenQuadfi+TdaP+HPV) and Group 4 (TdaP+HPV) was >2/3 in only one (PT) of the 4 pertussis antigens (PT, FHA, PRN, and FIM). Even though the clinical consequences of a decreased immune response for 3 of 4 pertussis antigens was not entirely clear, and similar observations were reported for other meningococcal vaccines, this result was considered relevant for practical use and thus, has been providedin the product information. This effect was not observed in other studies addressing concomitant vaccinations with vaccines containing Pertussis antigens (MET57 and MET28 (supportive)). However, the administered vaccines differed between studies as did the age of study subjects (adolescents, toddlers and infants).

Lot-to-lot consistency was demonstrated in study MET43 for all three lots based on hSBA GMTs. However, significant differences between lot 1 and lot 2 were observed in terms of seroresponse rate against serogroup A (difference of -5.4; 95% CI: -9.59; -1.16). While GMT was considered more sensitive to detect differences between lots, this finding raised the concern whether the chosen equivalence criteria for the primary analysis based on GMTs were adequate. The applicant argued that no concern regarding a potentially relevant difference in terms of immunogenicity between lots should be raised as "the 95% CIs between the two study groups overlap (73.5; 79.4 vs 67.9; 74.2) even with large sample size around 800 per lot." However, for the comparison of averages between groups the confidence interval around the estimate of the between group difference was a more sensitive approach (due to the more efficient variance estimate) and therefore the relevant procedure for the conclusion of equivalence. While formally meeting the equivalence margin of +-10%, the result may indicate a significant difference in serorespones rates, and the lower CI limit is very close to the pre-defined margin. It was acknowledged that this was a secondary analysis and that the primary equivalence objective was met. Furthermore, there were no concerns regarding inconsistency between lots from a quality assessment perspective. In addition, the applicant provided upon request results from a re-analysis of pre-/post-vaccination titres using an ANCOVA type model. The presented model adjusted comparisons of post-vaccination titres between lots of MenACYW for differences in baseline titre between subjects. Estimates of two-sided 95% confidence intervals for the average log difference do not

exceed -0.105 or 0.138 (corresponding to titre ratios of 0.78 and 1.37) and therefore meet an equivalence margin excluding larger that two-fold differences in post-vaccination titre between lots. In contrast to the results from an analysis of lot to lot consistency with regard to seroprotection, no confidence interval excludes 0 (i.e. no difference in post-vaccination titre between lots)

The applicant initially claimed the following indication for MenQuadfi: "MenQuadfi is indicated for active primary and booster immunisation for the prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W, and Y. MenQuadfi is indicated for use in individuals 12 months of age and older." However, including the wording "primary and booster" immunisation was not considered appropriate. Some amendments were therefore required also to be consistent with both comparable quadrivalent meningococcal vaccines already approved in the EU (Menveo since 2010 and Nimenrix since 2012). The applicant proposed the new indication: "*MenQuadfi is indicated for active immunisation of individuals from the age of 12 months and older, against invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W, and Y.*" This proposal was considered acceptable.

Assessment of paediatric data on clinical efficacy

The paediatric population (older than 12 month of age) is part of the marketing authorization application. The presented respective studies are already assessed in other parts of the report. Please refer to the assessment of studies:

MET51 for toddlers: 12-23 months

MET35 for children: 2-9 years

MET57 for toddlers 12-23 months

MET54 toddlers 12-23 months

Met32 toddlers of 12 months +- 21 days

MET28 infants 2 months + 28 days and toddlers 12-<19months

2.5.3. Conclusions on the clinical efficacy

In all main clinical studies, the primary endpoints were met and non-inferior immunogenicity of MenQuadfi 30 days after vaccination against different comparators across age groups was demonstrated for all serogroups in all age groups except for serogroup A in the subgroup of MenC-primed toddlers. Overall, immunogenicity of MenQuadfi across age groups has been sufficiently demonstrated.

Important missing information is long-term persistence of immunogenicity beyond 30 days as well as the ability of MenQuadfi to boost itself, which will be addressed in the postmarketing studies, reflected in Annex II as category I post-marketing obligations.

2.6. Clinical safety

Patient exposure

There was a total of 7116 subjects who received any formulation of MenACYW conjugate vaccine in the completed 11 clinical studies (209 subjects in the Phase I study, 1494 subjects in the Phase I/II and II studies, and 5413 subjects in the Phase III studies). 6398 subjects received a single dose of the final formulation of MenACYW conjugate vaccine (alone [5417 subjects] or with at least one concomitant vaccine [981 subjects]) in the 9 studies supporting the Summary of Clinical Safety.

Of the 5417 subjects, there were 691 toddlers, 498 children 2 through 9 years, 1897 adolescents 10 through 17 years, 1684 adults 18 through 55 years, 298 older adults 56 through 64 years, and 349 elderly adults 65 years and older) receiving a single dose of MenACYW conjugate vaccine given alone and included in the SafAS.

Table 26: Overall extent of exposure - Safety Analysis Set

			Comparators			
Age group	Study	MenACYW Conjugate vaccine* N	Menactra® N	Menveo® N	Menomune® N	Nimenrix® N
All	All	5417	1042	995	553	400
	MET35	498	-	494	-	-
	MET43	2676	635	-	-	-
	MET44	199	-	-	100	-
	MET49	448	-	-	453	-
	MET50	503	-	501	-	-
	MET51	303	-	-	-	306
	MET54	94	-	-	-	94
	MET56	402	407	-	-	-
	MET57	294	-	-	-	-
All Toddlers (12 through 23 months old)	Pooled MET51 and MET54	397	-	-	-	400
	Pooled MET51, MET54 and MET57	691	-	-	-	400
All Children (2 through 9 years old)	MET35	498	-	494	-	-
All Adolescents (10 through 17 years old)	Pooled MET43, MET50 and MET56	1897	536	501	-	-
All Adults (18 years old and above)	Pooled MET43, MET44, MET49 and MET56	2331	506	-	553	-

			Comparators			
Age group	Study	MenACYW Conjugate vaccine* N	Menactra® N	Menveo® N	Menomune® N	Nimenrix® N
Adults (18 through 55 years old)	Pooled MET43 and MET56	1684	505	-	-	-
Older Adults and Elderly (56 years old and above)	Pooled MET44, MET49 and MET56	647	1	-	553	-
Older Adults (56 through 64 years old)	Pooled MET44, MET49 and MET56	298	1	-	249	-
Elderly (65 years old and above)	Pooled MET44 and MET49	349	-	-	304	-
65 through 74 years old	Pooled MET44 and MET49	258	-	-	224	-
75 years old and above	Pooled MET44 and MET49	91	-	-	80	-

		MenACYW conjugate vaccine and co-administered vaccines							
Age group	Study	MenACYW +Tdap+HPV N	Tdap+ HPV N	MenACYW +MMR+V N	MMR+V N	MenACYW +DTaP-IPV-HB-Hib N	DTaP-IPV-HB-Hib N	MenACYW +PCV13 N	PCV13 N
All	All	392	296	189	95	200	100	200	99
	MET50	392	296	-	-	-	-	-	-
	MET57	-	-	189	95	200	100	200	99
All Toddlers (12 through 23 months old)	Pooled MET51, MET54 and MET57	-	-	189	95	200	100	200	99
All Adolescents (10 through 17 years old)	Pooled MET43, MET50 and MET56	392	296	-	-	-	-	-	-

Abbreviations: N: number of subjects in the Safety Analysis Set
The Safety Analysis Set is defined as those subjects who have received at least one dose of the study vaccine and have any safety data available.

Adverse events

Solicited Reactions

Solicited Injection Site Reactions

For **toddlers** 12 through 23 months of age, the percentage of subjects with solicited injection site reactions after meningococcal vaccine injection was comparable between the MenACYW conjugate vaccine group and the Nimenrix group (56.4% and 57.6%, respectively). The percentage of subjects with at least 1 Grade 3 injection site reaction was low and comparable between the 2 groups (4.5% and 3.8%, respectively). The most commonly reported solicited injection site reactions were erythema and tenderness in both groups.

Table 27: Any and Grade 3 solicited injection site reaction after meningococcal vaccine injection, by maximum intensity during the solicited period – Toddlers (MET51, MET54) – Safety Analysis Set

		MenACYW conjugate vaccine (N=397)			Nimenrix (N=400)		
Subjects experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited injection site reaction	Any	224/397	56.4	(51.4; 61.4)	230/399	57.6	(52.6; 62.5)
	Grade 3	18/397	4.5	(2.7; 7.1)	15/399	3.8	(2.1; 6.1)
Tenderness	Any	150/397	37.8	(33.0; 42.8)	144/399	36.1	(31.4; 41.0)
	Grade 3	1/397	0.3	(0.0; 1.4)	5/399	1.3	(0.4; 2.9)
Erythema	Any	151/397	38.0	(33.2; 43.0)	148/399	37.1	(32.3; 42.0)
	Grade 3	15/397	3.8	(2.1; 6.2)	8/399	2.0	(0.9; 3.9)
Swelling	Any	77/397	19.4	(15.6; 23.6)	69/399	17.3	(13.7; 21.4)
	Grade 3	7/397	1.8	(0.7; 3.6)	5/399	1.3	(0.4; 2.9)

n: number of subjects experiencing the endpoint
M: number of subjects with available data for the relevant endpoint
N: number of subjects in Safety Analysis Set
Percentages are based on M.
MenC-primed subjects from MET51 were excluded from the safety analysis.
Contributing studies: MET51 and MET54
Modified from 5.3.5.3 Integrated Summary of Safety Report Table 3.1.6, and Table 3.1.1.

MenC-primed toddlers the frequency of solicited reactions tended to be higher in the MenACYW conjugate vaccine group (70.4%) compared to those who received Nimenrix (60.8%). While the rates are comparable in MenC-CRM primed toddlers between Nimenrix and MenQuadfi, in MenC-TT primed toddlers solicited reactions tend to be reported with higher frequency in the MenQuadfi group (66.9% vs 55.3%). The percentage of subjects experiencing any Grade 3 solicited injection site reaction or systemic reaction remained low after MenACYW conjugate vaccine (2.5% and 4.4%, respectively). The frequency of solicited reactions, particularly injection site reactions, tended to be lower in MenC-primed toddlers (70.4%) than in meningococcal vaccine-naïve toddlers (80.9%) after administration of MenACYW conjugate vaccine. The same observation applied to subjects who had received Nimenrix (60.8% and 81.6%, respectively). There were no immediate AEs, no discontinuations due to an SAE or other AE, no deaths, and no related SAEs. One unrelated AESI was reported following administration of MenACYW conjugate vaccine: this case corresponded to post-traumatic seizure (subject accidently fell of his cradle).

Table 28: Summary of solicited reactions within 7 days vaccine injection - Safety Analysis Set

	Group 1 MenACYW–naïve (N=303)			Group 3 MenACYW–MenC primed (N=203)			Group 2 Nimenrix–naïve (N=306)			Group 4 Nimenrix–MenC primed (N=102)		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Solicited reaction	245/303	80.9	(76.0; 85.1)	143/203	70.4	(63.7; 76.6)	249/305	81.6	(76.8; 85.8)	62/102	60.8	(50.6; 70.3)
Grade 3 solicited reaction	28/303	9.2	(6.2; 13.1)	13/203	6.4	(3.5; 10.7)	22/305	7.2	(4.6; 10.7)	2/102	2.0	(0.2; 6.9)
Solicited injection site reaction	178/303	58.7	(53.0; 64.3)	83/203	40.9	(34.1; 48.0)	180/305	59.0	(53.3; 64.6)	34/102	33.3	(24.3; 43.4)
Grade 3 injection site reaction	15/303	5.0	(2.8; 8.0)	5/203	2.5	(0.8; 5.7)	11/305	3.6	(1.8; 6.4)	1/102	1.0	(0.0; 5.3)
Solicited systemic reaction	198/303	65.3	(59.7; 70.7)	120/203	59.1	(52.0; 65.9)	186/305	61.0	(55.3; 66.5)	51/102	50.0	(39.9; 60.1)
Grade 3 systemic reaction	14/303	4.6	(2.5; 7.6)	9/203	4.4	(2.0; 8.2)	14/305	4.6	(2.5; 7.6)	1/102	1.0	(0.0; 5.3)

n: number of subjects experiencing the endpoint listed in the first column.
M: number of subjects with available data for the relevant endpoint.
N: number of subjects in safety analysis set.
Percentages are based on M.
Source: Section 9, Table 9.14.

For **children** 2 through 9 years of age, the percentages of subjects reporting solicited injection site reactions tended to be lower in the MenACYW conjugate vaccine group (46.8%) than in the Menveo group (53.9%). There was a lower percentage of subjects in the MenACYW conjugate vaccine group experiencing Grade 3 injection site reactions (3.7%) compared to the Menveo group (11.1%). The same observations were made for children 2 to 5 years of age and for children 6 to 9 years of age. In addition, similar percentages of subjects reporting solicited injection site reactions were observed in children 2 to 5 years of age and in children 6 to 9 years of age following MenACYW conjugate vaccine injection. Pain was the most commonly reported solicited injection site reaction in children, followed by erythema, irrespective of the age group considered (2 through 9 years of age, 2 through 5 years of age, and 6 through 9 years of age).

For **adolescents** 10 through 17 years of age, the percentages of subjects with solicited injection site reactions were comparable between the MenACYW conjugate vaccine group (40.2%) and the corresponding comparator vaccine groups, Menactra (43.0%) and Menveo (45.7%). The percentage of subjects experiencing Grade 3 injection site reactions was low in the MenACYW conjugate vaccine, Menactra, and Menveo groups (1.8% to 2.2%). Pain was the most commonly reported solicited injection site reaction.

For **adults** 18 through 55 years of age, the percentages of subjects with solicited injection site reactions were comparable between the MenACYW conjugate vaccine group (43.4%) and Menactra group (43.7%). The percentage of subjects experiencing Grade 3 injection site reactions was low in both vaccine groups (2.1% and 2.2%). Pain was the most commonly reported solicited injection site reaction.

In the **older adults** (56 through 64 years of age) and elderly adults (65 years of age and older) the percentages of subjects who reported at least 1 solicited injection site reaction were higher in the MenACYW conjugate vaccine group compared to the Menomune – A/C/Y/W-135 vaccine group (38.0% versus 17.0% for older adults 56 through 64 years of age; 22.2% versus 11.8% for elderly adults 65 years of age and older). This difference was also observed in the 2 age subgroups, 65 to 74 years, and 75 years and above.

The observed rate at the MenACYW conjugate vaccine injection site tended to be lower when age increases (38.0%, 23.3%, and 18.9%, in older adults 56 through 64 years of age, in elderly 65 to 74 years, and in elderly 75 years and above, respectively). The observed rate of solicited injection site reactions in all the older adults and elderly adults was also lower than the rates observed in the younger age groups and only a low percentage of subjects reported a Grade 3 injection site reaction. Pain was the most commonly reported solicited injection site reaction irrespective of the age group considered (older adults 56 through 64 years of age, elderly 65 to 74 years, or elderly 75 years and above).

Table 29: Any and Grade 3 solicited injection site reactions after meningococcal vaccine injection, by maximum intensity during the solicited period – subjects aged 2 years and above – Safety Analysis Set

Subjects experiencing at least one:	MenACYW Conjugate Vaccine*			Menactra®			Menveo®			Menomune®		
	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Solicited Injection Site Reaction												
Any	1882/4643	40.5	(39.1; 42.0)	440/1016	43.3	(40.2; 46.4)	487/978	49.8	(46.6; 53.0)	78/551	14.2	(11.4; 17.3)
Grade 3	94/4643	2.0	(1.6; 2.5)	21/1016	2.1	(1.3; 3.1)	65/978	6.6	(5.2; 8.4)	3/551	0.5	(0.1; 1.6)
Pain												
Any	1779/4641	38.3	(36.9; 39.7)	431/1016	42.4	(39.4; 45.5)	415/978	42.4	(39.3; 45.6)	75/550	13.6	(10.9; 16.8)
Grade 3	67/4641	1.4	(1.1; 1.8)	19/1016	1.9	(1.1; 2.9)	10/978	1.0	(0.5; 1.9)	3/550	0.5	(0.1; 1.6)
Erythema												
Any	328/4642	7.1	(6.3; 7.8)	31/1016	3.1	(2.1; 4.3)	190/976	19.5	(17.0; 22.1)	5/551	0.9	(0.3; 2.1)
Grade 3	27/4642	0.6	(0.4; 0.8)	2/1016	0.2	(0.0; 0.7)	54/976	5.5	(4.2; 7.2)	0/551	0.0	(0.0; 0.7)
Swelling												
Any	255/4636	5.5	(4.9; 6.2)	28/1014	2.8	(1.8; 4.0)	136/974	14.0	(11.8; 16.3)	2/551	0.4	(0.0; 1.3)
Grade 3	13/4636	0.3	(0.1; 0.5)	1/1014	<0.1	(0.0; 0.5)	29/974	3.0	(2.0; 4.2)	0/551	0.0	(0.0; 0.7)

n: number of subjects experiencing the endpoint; M: number of subjects with available data for the relevant endpoint; Percentages are based on M.

*MenACYW includes the subjects who received MenACYW only without concomitant vaccines at V01, and excludes the subjects who received MenACYW+Tdap+HPV at V01 in MET50.

Contributing studies: MET35, MET43, MET44, MET49, MET50, and MET56

Modified from 5.3.5.3.Integrated Summary of Safety Report Table 2.2.82, and Table 2.2.113

Solicited Systemic Reactions

In the age group pool for **toddlers** 12 through 23 months of age, the percentage of subjects with solicited systemic reactions was comparable between the MenACYW conjugate vaccine group (64.5%) and the Nimenrix group (62.9%). A low percentage of these subjects experienced at least 1 Grade 3 systemic reaction. The most commonly reported solicited systemic reactions were irritability followed by abnormal crying.

Table 30: Any and Grade 3 solicited systemic reactions after vaccine injection, by maximum intensity during the solicited period – Toddlers (MET51, MET54) – Safety Analysis Set

		MenACYW conjugate vaccine (N=397)			Nimenrix (N=400)		
Subjects experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited systemic reaction	Any	256/397	64.5	(59.6; 69.2)	251/399	62.9	(58.0; 67.7)
	Grade 3	17/397	4.3	(2.5; 6.8)	17/399	4.3	(2.5; 6.7)
Fever	Any	36/397	9.1	(6.4; 12.3)	42/395	10.6	(7.8; 14.1)
	Grade 3	5/397	1.3	(0.4; 2.9)	3/395	0.8	(0.2; 2.2)
Vomiting	Any	25/397	6.3	(4.1; 9.2)	18/399	4.5	(2.7; 7.0)
	Grade 3	0/397	0.0	(0.0; 0.9)	0/399	0.0	(0.0; 0.9)
Abnormal crying	Any	137/397	34.5	(29.8; 39.4)	147/399	36.8	(32.1; 41.8)
	Grade 3	7/397	1.8	(0.7; 3.6)	7/399	1.8	(0.7; 3.6)
Drowsiness	Any	96/397	24.2	(20.0; 28.7)	81/399	20.3	(16.5; 24.6)
	Grade 3	1/397	0.3	(0.0; 1.4)	0/399	0.0	(0.0; 0.9)
Appetite lost	Any	112/397	28.2	(23.8; 32.9)	127/399	31.8	(27.3; 36.6)
	Grade 3	3/397	0.8	(0.2; 2.2)	3/399	0.8	(0.2; 2.2)
Irritability	Any	193/397	48.6	(43.6; 53.7)	180/399	45.1	(40.2; 50.1)
	Grade 3	3/397	0.8	(0.2; 2.2)	7/399	1.8	(0.7; 3.6)

n: number of subjects experiencing the endpoint
M: number of subjects with available data for the relevant endpoint
N: number of subjects in Safety Analysis Set
Percentages are based on M.
MenC-primed subjects from MET51 were excluded from the safety analysis.
Contributing studies: MET51 and MET54
Modified from 5.3.5.3 Integrated Summary of Safety Report Table 3.1.1 and Table 3.1.10.

In the age group of **children** 2 through 9 years of age, the percentages of subjects with solicited systemic reactions were comparable between the MenACYW conjugate vaccine group (34.5%) and the Menveo group (37.0%). A low percentage of these subjects experienced at least 1 Grade 3 systemic reaction. The same observations were made in the age subgroups 2 to 5 years, and 6 to 9 years. Following MenACYW conjugate vaccine injection, the percentages of subjects with solicited systemic reactions was generally similar in subjects aged 2 to 5 years (30.9%) and in subjects aged 6 to 9 years (38.1%), except a higher frequency of headache in the 6 to 9 years age group compared to the 2 to 5 years age group (18.0% versus 7.0% of subjects). Of note, headache was also reported with a higher frequency in the 6 to 9 years age group compared to the 2 to 5 years age group following Menveo injection. The most commonly reported solicited systemic reactions were malaise and myalgia irrespective of the age group considered (2 through 9 years of age, 2 through 5 years of age, and 6 through 9 years of age). Headache was also frequently reported in the 6 to 9 years age group.

In the age group pool for **adolescents** 10 through 17 years of age, the percentages of subjects with solicited systemic reactions were largely comparable between the MenACYW conjugate vaccine group (45.9%), the Menactra group (50.1%), and the Menveo group (51.0%). A low percentage of these subjects experienced at least 1 Grade 3 systemic reaction. The most commonly reported solicited systemic reactions were myalgia and headache followed by malaise.

In the age group pool for **adults** 18 through 55 years of age, the percentages of subjects with solicited systemic reactions were similar in the MenACYW conjugate vaccine group (47.6%) and in the Menactra group (47.9%); the percentages of subjects with at least 1 Grade 3 systemic reaction were the same in both groups

(5.7%). The most commonly reported solicited systemic reactions were myalgia and headache, followed by malaise.

In the pool of **older adults** 56 through 64 years of age, the percentages of subjects who reported at least 1 solicited systemic reaction was higher in the MenACYW conjugate vaccine group (42.5%) compared to the Menomune – A/C/Y/W-135 vaccine group (29.6%). There were a low percentage of subjects experiencing at least 1 Grade 3 systemic reactions in both groups. The most commonly reported solicited systemic reactions were myalgia and headache, followed by malaise.

In the pool **of elderly adults** aged 65 years of age and above, the percentages of subjects with solicited systemic reactions were largely comparable in the MenACYW conjugate vaccine group (30.5%), and in the Menomune – A/C/Y/W-135 vaccine group (25.3%). This was also observed in the age subgroups 65 to 74 years and 75 years and above. There was a low percentage of subjects experiencing at least 1 Grade 3 systemic reaction in both vaccine groups. Similar percentages of subjects reporting solicited systemic reactions were observed in elderly adults aged 65 to 74 years and in elderly adults aged 75 years and above following MenACYW conjugate vaccine injection. The most commonly reported solicited systemic reactions were myalgia and headache, followed by malaise in the pool of elderly adults aged 65 years and above, and in elderly adults aged 65 to 74 years. In the elderly adults aged 75 years and above, the most commonly reported solicited systemic reactions following MenACYW conjugate vaccine injection were myalgia and malaise, followed by headache.

Table 31: Any and Grade 3 solicited systemic reactions after vaccine injection, by maximum intensity during the solicited period – subjects aged 2 years and above – Safety Analysis Set

Subject with at least 1:	MenACYW Conjugate Vaccine*			Menactra®			Menveo®			Menomune®		
	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Solicited Systemic Reaction												
Any	2039/4641	43.9	(42.5; 45.4)	499/1017	49.1	(46.0; 52.2)	431/978	44.1	(40.9; 47.2)	150/551	27.2	(23.5; 31.1)
Grade 3	189/4641	4.1	(3.5; 4.7)	47/1017	4.6	(3.4; 6.1)	32/978	3.3	(2.2; 4.6)	14/551	2.5	(1.4; 4.2)
Fever												
Any	56/4572	1.2	(0.9; 1.6)	9/1002	0.9	(0.4; 1.7)	19/967	2.0	(1.2; 3.1)	3/548	0.5	(0.1; 1.6)
Grade 3	7/4572	0.2	(0.1; 0.3)	3/1002	0.3	(0.1; 0.9)	5/967	0.5	(0.2; 1.2)	0/548	0.0	(0.0; 0.7)
Headache												
Any	1223/4640	26.4	(25.1; 27.7)	305/1017	30.0	(27.2; 32.9)	208/978	21.3	(18.7; 24.0)	94/551	17.1	(14.0; 20.5)
Grade 3	90/4640	1.9	(1.6; 2.4)	28/1017	2.8	(1.8; 4.0)	11/978	1.1	(0.6; 2.0)4	4/551	0.7	(0.2; 1.8)
Malaise												
Any	1009/4640	21.7	(20.6; 23.0)	240/1017	23.6	(21.0; 26.3)	229/978	23.4	(20.8; 26.2)	66/551	12.0	(9.4; 15.0)
Grade 3	95/4640	2.0	(1.7; 2.5)	28/1017	2.8	(1.8; 4.0)	19/978	1.9	(1.2; 3.0)	10/551	1.8	(0.9; 3.3)
Myalgia												
Any	1424/4641	30.7	(29.4; 32.0)	348/1017	34.2	(31.3; 37.2)	285/978	29.1	(26.3; 32.1)	95/551	17.2	(14.2; 20.7)
Grade 3	102/4641	2.2	(1.8; 2.7)	22/1017	2.2	(1.4; 3.3)	13/978	1.3	(0.7; 2.3)	8/551	1.5	(0.6; 2.8)

n: number of subjects experiencing the endpoint; M: number of subjects with available data for the relevant endpoint; Percentages are based on M.

*MenACYW includes the subjects who received MenACYW only without concomitant vaccines at V01, and excludes the subjects who received MenACYW+Tdap+HPV at V01 in MET50.

Contributing studies: MET35, MET43, MET44, MET49, MET50, and MET56

Modified from 5.3.5.3 Integrated Summary of Safety Report Table 2.2.82, and Table 2.2.117

Non-Serious Unsolicited Adverse Events and Reactions

Immediate Non-Serious Adverse Events

Very few immediate adverse events were observed within 30 minutes after vaccination. None were observed in **toddlers**, **children**, **older adults** 56 through 64 years, and one event in **elderly adults** 65 years of age and older (dysgeusia).

In **adolescents**, the percentage of subjects reporting at least 1 immediate unsolicited AE assessed as related to vaccination (ie, immediate unsolicited AR) was 0.4% in the MenACYW conjugate vaccine group, 0.0% in the Menactra group, and 0.2% in the Menveo vaccine group. The most commonly reported immediate unsolicited AR was dizziness (5 subjects; 0.3%) in the MenACYW conjugate vaccine group.

In **adults** 18 through 55 years, the percentage of subjects reporting at least 1 immediate unsolicited AR following vaccine injection was low (0.2% in the MenACYW conjugate vaccine and Menactra vaccine groups). The most commonly reported immediate unsolicited AR was dizziness (3 subjects [0.2%] in the MenACYW conjugate vaccine group and 1 subject [0.2%] in the Menactra vaccine group). No safety concerns were identified from the review of these reports.

Unsolicited Non-Serious Adverse Events

The percentages of subjects in each age group reporting at least 1 unsolicited non-serious AE were comparable between the MenACYW conjugate vaccine group and the corresponding comparator vaccine groups.

Unsolicited Reactions

The percentages of **toddlers** reporting at least 1 unsolicited non-serious AR within 30 days of vaccination were low and comparable between both vaccine groups (5.0% in the MenACYW conjugate vaccine group and 4.5% in the Nimenrix vaccine group). The most frequently reported unsolicited non-serious AR in both groups was diarrhea. Overall, most of the unsolicited non-serious ARs were of Grade 1 or Grade 2 intensity, most started and resolved within 3 days of vaccination. There were no subjects with Grade 3 unsolicited non-serious ARs within 30 days of vaccination in the MenACYW conjugate vaccine group.

The percentages of **children** 2 through 9 years of age reporting at least 1 unsolicited non-serious AR within 30 days of vaccination were low and comparable between both vaccine groups (2.0% in the MenACYW conjugate vaccine group and 3.4% in the Menveo vaccine group). The most frequently reported unsolicited non-serious ARs in the MenACYW conjugate vaccine group were vomiting, and abdominal pain (upper) for subjects 2 through 5 years of age, and injection site bruising for subjects 6 through 9 years of age. Overall, most of the unsolicited non-serious ARs were of Grade 1 or Grade 2 intensity, most started and resolved within 3 days of vaccination. One subject in each group (0.2%) reported a Grade 3 non-serious AR within 30 days of vaccination.

The percentages of **adolescents** with at least 1 unsolicited non-serious AR were comparable between the MenACYW conjugate vaccine, Menactra, and Menveo groups: 3.1%, 1.3%, and 3.4%, respectively. The most frequently reported unsolicited non-serious ARs included injection site pruritus, injection site warmth, dizziness, and nausea. Overall, the majority of unsolicited non-serious ARs were of Grade 1 or Grade 2 intensity, most started and resolved within 3 days of vaccination. There was a low proportion (≤ 1.3%) of subjects experiencing Grade 3 unsolicited non-serious ARs within 30 days of vaccination across all vaccine groups.

In **adults 18 through 55 years of age** the percentages of adults reporting at least 1 unsolicited non-serious AR within 30 days of vaccination were low and comparable between MenACYW conjugate vaccine group (2.2%) and the Menactra group (2.4%). The most frequently reported unsolicited non-serious ARs were injection site pruritus and injection site warmth (at the MenACYW conjugate vaccine injection site), fatigue, nausea, and dizziness. Overall, most of the unsolicited non-serious ARs were of Grade 1 or Grade 2 intensity, most started and resolved within 3 days of vaccination. There was a low proportion (≤ 0.6%) of subjects experiencing Grade 3 unsolicited non-serious ARs within 30 days of vaccination in both the vaccine groups.

In **older adults 56 through 64 years of age** the percentages of older adults reporting at least 1 unsolicited non-serious AR within 30 days of vaccination were low: 3.4% in the MenACYW conjugate vaccine group and 1.6% in the Menomune − A/C/Y/W-135 group. The most frequently reported unsolicited non-serious ARs were injection site pruritus (at the MenACYW conjugate vaccine site), injection site bruising (at the Menomune − A/C/Y/W-135 site), and fatigue. Overall, most of the unsolicited non-serious ARs were of Grade 1 or Grade 2 intensity, most started and resolved within 3 days of vaccination. There was a low proportion (0.3%) of older adults experiencing Grade 3 unsolicited non-serious ARs within 30 days of vaccination in the MenACYW conjugate vaccine group.

In **elderly adults 65 years of age** and older the percentages of elderly adults with at least 1 unsolicited non-serious AR were low in the MenACYW conjugate vaccine group (5.2%) and the Menomune − A/C/Y/W-135 vaccine group (2.6%). The most frequently reported unsolicited non-serious ARs was injection site pruritus (2.3% in the MenACYW conjugate vaccine group and 0.7% in the Menomune − A/C/Y/W-135 group). Overall, most of the unsolicited non-serious ARs were of Grade 1 or Grade 2 intensity, most started and resolved within 3 days of vaccination. There was only 1 subject (0.3%) in the Menomune − A/C/Y/W-135 group and no subjects in the MenACYW conjugate vaccine group who experienced a Grade 3 unsolicited non-serious AR within 30 days of vaccination.

Concomitant vaccines

A total of 392 adolescents received a single dose of MenACYW conjugate vaccine administered concomitantly with Tdap + HPV in Study MET50, and 296 adolescents received Tdap + HPV alone.

A total of 589 toddlers received a single dose of MenACYW conjugate vaccine administered concomitantly with a licensed paediatric vaccine (MMR + V, DTaP-IPV-HB-Hib, or PCV13) in Study MET57, and 294 toddlers received MMR + V, DTaP-IPV-HB-Hib, or PCV13 vaccines alone.

Solicited Reactions

In **toddlers**, the percentages of subjects who reported at least 1 solicited injection site reaction at any vaccination site within 7 days post-vaccination were comparable when MMR + V or DTaP-IPV-HB-Hib vaccines were given with or without MenACYW conjugate vaccine. This percentage was higher in subjects who received PCV13 concomitantly with MenACYW conjugate vaccine (31.5%) compared to subjects who received PCV13 without MenACYW conjugate vaccine (13.1%). Grade 3 injection site reactions were reported at a similar frequency in subjects who received the concomitant vaccines with or without MenACYW conjugate vaccine.

Table 32: Solicited injection site reaction after vaccine injection(s), by maximum intensity during the solicited period – Toddlers– Safety Analysis Set (MET51, MET54 and MET57)

		MenACYW conjugate vaccine* (N=691)			MenACYW + MMR + V (N=189)			MenACYW + DTaP- IPV-HB-Hib (N=200)			MenACYW + PCV13 (N=200)		
Subjects experiencing at least one:	Maximum intensity	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
MenACYW conjugate vaccine													
Tenderness	Any	215/689	31.2	(27.8; 34.8)	53/189	28.0	(21.8; 35.0)	68/191	35.6	(28.8; 42.8)	28/200	14.0	(9.5; 19.6)
	Grade 1	177/689	25.7	(22.5; 29.1)	43/189	22.8	(17.0; 29.4)	45/191	23.6	(17.7; 30.2)	18/200	9.0	(5.4; 13.9)
	Grade 2	35/689	5.1	(3.6; 7.0)	9/189	4.8	(2.2; 8.8)	17/191	8.9	(5.3; 13.9)	6/200	3.0	(1.1; 6.4)
	Grade 3	3/689	0.4	(0.1; 1.3)	1/189	0.5	(0.0; 2.9)	6/191	3.1	(1.2; 6.7)	4/200	2.0	(0.5; 5.0)
Erythema	Any	209/689	30.3	(26.9; 33.9)	48/189	25.4	(19.4; 32.2)	40/191	20.9	(15.4; 27.4)	43/200	21.5	(16.0; 27.8)
	Grade 1	172/689	25.0	(21.8; 28.4)	43/189	22.8	(17.0; 29.4)	34/191	17.8	(12.7; 24.0)	42/200	21.0	(15.6; 27.3)
	Grade 2	17/689	2.5	(1.4; 3.9)	5/189	2.6	(0.9; 6.1)	3/191	1.6	(0.3; 4.5)	1/200	0.5	(0.0; 2.8)
	Grade 3	20/689	2.9	(1.8; 4.4)	0/189	0.0	(0.0; 1.9)	3/191	1.6	(0.3; 4.5)	0/200	0.0	(0.0; 1.8)
Swelling	Any	111/689	16.1	(13.4; 19.1)	31/189	16.4	(11.4; 22.5)	23/191	12.0	(7.8; 17.5)	8/200	4.0	(1.7; 7.7)
	Grade 1	92/689	13.4	(10.9; 16.1)	30/189	15.9	(11.0; 21.9)	17/191	8.9	(5.3; 13.9)	8/200	4.0	(1.7; 7.7)
	Grade 2	10/689	1.5	(0.7; 2.7)	1/189	0.5	(0.0; 2.9)	4/191	2.1	(0.6; 5.3)	0/200	0.0	(0.0; 1.8)
	Grade 3	9/689	1.3	(0.6; 2.5)	0/189	0.0	(0.0; 1.9)	2/191	1.0	(0.1; 3.7)	0/200	0.0	(0.0; 1.8)

The percentages of subjects who reported at least 1 solicited systemic reaction were comparable when MMR + V, DTaP-IPV-HB-Hib, or PCV13 vaccines were given concomitantly with MenACYW conjugate vaccine compared to when MMR + V, DTaP-IPV-HB-Hib, or PCV13 vaccines were given without MenACYW conjugate vaccine. A comparable percentage of subjects reported at least 1 Grade 3 systemic reaction when MMR + V, DTaP-IPV-HB-Hib, or PCV13 vaccines were given with or without MenACYW conjugate vaccine.

Table 33: Solicited systemic reactions after vaccine injection(s), by maximum intensity during the solicited period – Toddlers– Safety Analysis Set (MET51, MET54 and MET57)

		MenACYW conjugate vaccine* (N=691)			MenACYW + MMR + V (N=189)			MenACYW + DTaP- IPV-HB-Hib (N=200)			MenACYW + PCV13 (N=200)		
Subjects experiencing at least one:	Maximum intensity	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Fever	Any	56/689	8.1	(6.2; 10.4)	23/189	12.2	(7.9; 17.7)	32/191	16.8	(11.8; 22.8)	12/200	6.0	(3.1; 10.2)
	Grade 1	34/689	4.9	(3.4; 6.8)	15/189	7.9	(4.5; 12.8)	16/191	8.4	(4.9; 13.2)	7/200	3.5	(1.4; 7.1)
	Grade 2	13/689	1.9	(1.0; 3.2)	7/189	3.7	(1.5; 7.5)	12/191	6.3	(3.3; 10.7)	5/200	2.5	(0.8; 5.7)
	Grade 3	9/689	1.3	(0.6; 2.5)	1/189	0.5	(0.0; 2.9)	4/191	2.1	(0.6; 5.3)	0/200	0.0	(0.0; 1.8)
Vomiting	Any	38/689	5.5	(3.9; 7.5)	11/189	5.8	(2.9; 10.2)	15/191	7.9	(4.5; 12.6)	0/200	0.0	(0.0; 1.8)
	Grade 1	30/689	4.4	(3.0; 6.2)	8/189	4.2	(1.8; 8.2)	8/191	4.2	(1.8; 8.1)	0/200	0.0	(0.0; 1.8)
	Grade 2	7/689	1.0	(0.4; 2.1)	3/189	1.6	(0.3; 4.6)	7/191	3.7	(1.5; 7.4)	0/200	0.0	(0.0; 1.8)
	Grade 3	1/689	0.1	(0.0; 0.8)	0/189	0.0	(0.0; 1.9)	0/191	0.0	(0.0; 1.9)	0/200	0.0	(0.0; 1.8)
Abnormal crying	Any	189/689	27.4	(24.1; 30.9)	35/189	18.5	(13.3; 24.8)	46/191	24.1	(18.2; 30.8)	8/200	4.0	(1.7; 7.7)
	Grade 1	124/689	18.0	(15.2; 21.1)	30/189	15.9	(11.0; 21.9)	34/191	17.8	(12.7; 24.0)	3/200	1.5	(0.3; 4.3)
	Grade 2	57/689	8.3	(6.3; 10.6)	5/189	2.6	(0.9; 6.1)	11/191	5.8	(2.9; 10.1)	3/200	1.5	(0.3; 4.3)
	Grade 3	8/689	1.2	(0.5; 2.3)	0/189	0.0	(0.0; 1.9)	1/191	0.5	(0.0; 2.9)	2/200	1.0	(0.1; 3.6)
Drowsiness	Any	132/689	19.2	(16.3; 22.3)	25/189	13.2	(8.7; 18.9)	31/191	16.2	(11.3; 22.2)	25/200	12.5	(8.3; 17.9)
	Grade 1	122/689	17.7	(14.9; 20.8)	21/189	11.1	(7.0; 16.5)	26/191	13.6	(9.1; 19.3)	24/200	12.0	(7.8; 17.3)
	Grade 2	9/689	1.3	(0.6; 2.5)	4/189	2.1	(0.6; 5.3)	4/191	2.1	(0.6; 5.3)	0/200	0.0	(0.0; 1.8)

		MenACYW conjugate vaccine* (N=691)			MenACYW + MMR + V (N=189)			MenACYW + DTaP- IPV-HB-Hib (N=200)			MenACYW + PCV13 (N=200)		
Subjects experiencing at least one:	Maximum intensity	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
	Grade 3	1/689	0.1	(0.0; 0.8)	0/189	0.0	(0.0; 1.9)	1/191	0.5	(0.0; 2.9)	1/200	0.5	(0.0; 2.8)
Appetite lost	Any	171/689	24.8	(21.6; 28.2)	40/189	21.2	(15.6; 27.7)	51/191	26.7	(20.6; 33.6)	19/200	9.5	(5.8; 14.4)
	Grade 1	124/689	18.0	(15.2; 21.1)	33/189	17.5	(12.3; 23.6)	36/191	18.8	(13.6; 25.1)	14/200	7.0	(3.9; 11.5)
	Grade 2	42/689	6.1	(4.4; 8.2)	6/189	3.2	(1.2; 6.8)	7/191	3.7	(1.5; 7.4)	4/200	2.0	(0.5; 5.0)
	Grade 3	5/689	0.7	(0.2; 1.7)	1/189	0.5	(0.0; 2.9)	8/191	4.2	(1.8; 8.1)	1/200	0.5	(0.0; 2.8)
Irritability	Any	266/689	38.6	(35.0; 42.4)	45/189	23.8	(17.9; 30.5)	64/191	33.5	(26.9; 40.7)	26/200	13.0	(8.7; 18.5)
	Grade 1	144/689	20.9	(17.9; 24.1)	21/189	11.1	(7.0; 16.5)	39/191	20.4	(14.9; 26.8)	11/200	5.5	(2.8; 9.6)
	Grade 2	117/689	17.0	(14.3; 20.0)	24/189	12.7	(8.3; 18.3)	21/191	11.0	(6.9; 16.3)	11/200	5.5	(2.8; 9.6)
	Grade 3	5/689	0.7	(0.2; 1.7)	0/189	0.0	(0.0; 1.9)	4/191	2.1	(0.6; 5.3)	4/200	2.0	(0.5; 5.0)

The percentages of **adolescents** who reported at least 1 solicited **injection site** reaction were comparable between subjects who received the licensed Tdap and HPV vaccines with or without MenACYW conjugate vaccine (84.5% and 82.4%, respectively). At the MenACYW conjugate vaccine injection site, the percentages of subjects were higher in subjects who received MenACYW conjugate vaccine concomitantly with Tdap and HPV (49.0%) versus subjects who received MenACYW conjugate vaccine alone (40.2%). Also Grade 3 injection site reactions at the MenACYW conjugate vaccine site were slightly higher in subjects who received MenACYW conjugate vaccine concomitantly with Tdap and HPV (2.8%) as compared to subjects who received MenACYW conjugate vaccine alone (1.8%). Pain was the most common solicited injection site reaction for MenACYW conjugate vaccine, Tdap, and HPV vaccines in both groups, with 2.3% of subjects who experienced Grade 3 injection site pain for MenACYW conjugate vaccine.

The percentage of **adolescent** subjects who reported at least 1 solicited **systemic** reaction were higher in subjects who received MenACYW conjugate vaccine concomitantly with Tdap and HPV (70.6%) versus subjects who received MenACYW conjugate vaccine alone (45.9%) and slightly higher versus subjects who received Tdap and HPV alone (65.9%). Slightly more subjects reported at least 1 Grade 3 systemic reaction in the MenACYW+ Tdap + HPV (7.5%) compared to the Tdap + HPV vaccine groups (5.5%) or the MenACYW alone group (4%). Myalgia was the most commonly reported solicited systemic reaction, followed by headache and malaise.

Unsolicited Non-Serious Adverse Reactions

In **toddlers** 12 to 23 months of age, the percentage of subjects who reported at least 1 unsolicited non-serious AR was low when MMR + V, DTaP-IPV-HB-Hib, or PCV13 vaccines were given concomitantly with or without MenACYW conjugate vaccine (≤ 2.1%).

The percentage of **adolescents** reporting at least 1 unsolicited non-serious AR were slightly higher when Tdap and HPV were given concomitantly with MenACYW conjugate vaccine than when Tdap and HPV were given without MenACYW conjugate vaccine (8.7% and 4.1%, respectively) or when MenACYW was given alone (3.1%). The most frequently reported unsolicited non-serious ARs were injection site pruritus, injection site bruising, nausea, and vomiting, which also occurred more frequently in the MenACYW/Tdap/HPV group compared to Tday/HPV given alone (except injection site bruising). The frequency of reported Grade 3 unsolicited non serious ARs increased when subjects were concomitantly vaccinated with HPV and Tdap (1.3%) and were also higher when compared to HPV+Tdap alone (0%). In particular grade 3 nausea and vomiting were more frequently reported when MenACYW was administered with Tdap+HPV (0.5% each, versus 0% for MenACYW alone). Dizziness was not reported more frequently than when MenACYW was vaccinated alone. The unsolicited non serious AR tended to be of longer duration when MenACYW was concomitantly administered with Tdap+HPV compared to Tdap and HPV alone (4-7days: 1.8% versus 0%, 8 days and more 0.8% versus 0.3%).

Serious adverse events and deaths

There were no deaths in subjects who received the MenACYW conjugate vaccine.

Serious Adverse Events

In each age group, the rates of SAEs were comparable between the MenACYW conjugate vaccine group and the corresponding comparative control groups:

In **toddlers**: 0.8% in the MenACYW conjugate vaccine group and 0.3% in the Nimenrix vaccine group between D0 and D30; and none in any group from D31 to the end of the study.

In **children**: 0.4% in the MenACYW conjugate vaccine group and 0.2% in the Menveo vaccine group between D0 and D30; and 1.0% in the MenACYW conjugate vaccine group and 0.4% in the Menveo vaccine group from D31 to the end of the study.

In **adolescents**: 0.2% in the MenACYW conjugate vaccine group, 0.0% in the Menactra group, 0.2% in the Menveo group between D0 and D30; and 0.4% in the MenACYW conjugate vaccine group, 0.6% in the Menactra group, and 0.6% in the Menveo group from D31 to the end of the study.

In **adults** 18 through 55 years of age: 0.2% in the MenACYW conjugate vaccine group and 0.4% in the Menactra vaccine group between D0 and D30; and 1.4% in the MenACYW conjugate vaccine group and 0.6% in the Menactra vaccine group from D31 to the end of the study.

In **older adults** 56 through 64 years of age: 0.3% in the MenACYW conjugate vaccine group and 0.8% in the Menomune – A/C/Y/W-135 vaccine group between D0 and D30; and 1.3%in the MenACYW conjugate vaccine group and 1.6% in the Menomune – A/C/Y/W-135 vaccine group from D31 to the end of the study.

In **elderly adults** ≥ 65 years of age: 0.6% in the MenACYW conjugate vaccine group and 0.3%in the Menomune – A/C/Y/W-135 vaccine group between D0 and D30; and 2.3% in the MenACYW conjugate vaccine group and 3.0% in the Menomune – A/C/Y/W-135 vaccine group from D31 to the end of the study.

None were considered related to MenACYW vaccination by the Sponsor or Investigator. All SAEs were collected up to D30 in studies MET44, MET51, MET54, and MET57, while in studies MET35, MET50, MET43, MET49, and MET56, SAEs were collected up to 6-month after vaccination.

Adverse Events of Special Interest

A total of 5 AESIs were reported in subjects from the active-controlled studies included in the integrated analysis and all corresponded to reports of seizures: 4 (N=5417) were reported in subjects who received MenACYW conjugate vaccine alone and 1 (N=2990) was reported in a subject who received a comparator vaccine. None of the AESIs were considered related to study vaccination by the Investigator or Sponsor or reported within 7 days of vaccination. In subjects who received MenACYW conjugate vaccine alone, AESIs were reported in one toddler (febrile convulsion), 1 adolescent (seizure), and 2 adults (status epilepticus and seizure). Temporal relationship for the febrile seizure case was inconsistent with causal association with vaccination. The other reports of seizures were confounded by the subject's underlying condition or had an alternative cause.

There were no reports of Kawasaki disease, GBS, or idiopathic thrombocytopenic purpura in any of the studies among the subjects who received MenACYW conjugate vaccine or a comparator vaccine. As stated by the applicant, no confirmed cases of GBS occurred within 6 weeks after vaccination (this window is a commonly used post-vaccination period which may be consistent with vaccine associated GBS). However, subjects in Studies MET44, MET51, MET54 and MET57 were only observed for 30 days after vaccination.

Concomitant vaccines

SAEs and AESIs

In **toddlers**, the percentage of subjects who reported at least 1 SAE was low when MMR + V, DTaP-IPV-HB-Hib, or PCV13 vaccines were given concomitantly with or without MenACYW conjugate vaccine (≤ 3.2%). None of the SAEs were assessed as related to study vaccination and no deaths were reported. No AESIs were reported when MenACYW conjugate vaccine was given concomitantly with MMR + V, DTaP-IPV-HB-Hib, or PCV13 vaccines. One unrelated AESI (febrile convulsion) was reported 22 days after vaccination with DTaP-IPV-HB-Hib vaccine alone.

In **adolescents**, the percentage of subjects who reported at least 1 SAE during the study was low and comparable when Tdap and HPV vaccines were given concomitantly with or without MenACYW conjugate vaccine (1.0% and 1.4%, respectively). None were assessed as related to study vaccination either by the Investigator or Sponsor and no deaths were reported.

One subject reported an unrelated AESI (Grand Mal seizure) following administration of MenACYW conjugate vaccine with Tdap and HPV vaccines. The case was confounded by the subject's underlying condition (history of autism, attention deficit hyperactivity disorder, and seizure disorder treated with carbamazepine).

Laboratory findings

Neither of the studies included safety laboratory evaluations as part of routine study procedures for the safety evaluation of MenACYW.

Safety in special populations

Table 34 below displays AEs according to age categories <65, 65-74, 75-84 and above 85 years of age.

Table 34: Unsolicited ARs overview by MedDRA category – All subjects – MenACYW group – Safety Analysis Set

MedDRA Terms	**Age <65** number (percentage)		**Age 65-74 number (percentage)**		**Age 75-84 number (percentage)**		**Age 85+ number (percentage)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Unsolicited ARs	136	2.7	15	5.8	2	2.6	1	6.7
Related SAEs	0	0	0	0	0	0	0	0
- Death	0	0	0	0	0	0	0	0
- Life-threatening	0	0	0	0	0	0	0	0
- Required or prolonged inpatient hospitalization	0	0	0	0	0	0	0	0
- Persistent or significant disability/incapacity	0	0	0	0	0	0	0	0
Congenital anomaly/birth defect	0	0	0	0	0	0	0	0
Other: important medical event	0	0	0	0	0	0	0	0
Unsolicited ARs leading to drop-out	0	0	0	0	0	0	0	0
Psychiatric disorders	4	<0.1	0	0	0	0	0	0
Nervous system disorders	14	0.3	2	0.8	0	0	0	0
Accidents and injuries	0	0	0	0	0	0	0	0
Cardiac disorders	0	0	0	0	0	0	0	0
Vascular disorders	0	0	0	0	0	0	0	0
Cerebrovascular disorders	0	0	0	0	0	0	0	0

MedDRA Terms	Age <65 number (percentage)		Age 65-74 number (percentage)		Age 75-84 number (percentage)		Age 85+ number (percentage)	
	n	%	n	%	n	%	n	%
Infections and infestations	2	<0.1	0	0	0	0	0	0
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	12	0.2	1	0.4	0	0	0	0

n: number of subjects fulfilling the first column; N: Number of subjects in the safety analysis set; Percentages are based on N; ARs: Reactions related to Investigational product. Unsolicited ARs withing 30 days after V01 vaccination injection(s) and related SAEs during the study; One subject could be present in several categories but only be counted once in each category; Other unsolicited ARs appearing more frequently in older subjects>64 years; unsolicited ARs not in the pre-listed categories but with a higher percentage in the pooling subjects aged >65 years than that in subjects <65 yeaars; MenACYW group only includes the subjects who received MenACYW alone at V01, and excludes the subjects who received MenACYW + concomitant vaccines at V01; MenC-primed subjects from MET51 were excluded from the safety analysis.; Contributing studies: MET35, MET43, MET44, MET49, MET50, MET51, MET54, MET56 and MET57

Intrinsic Factors

No apparent differences were observed in the safety profile of MenACYW conjugate vaccine compared to the licensed vaccines when race and gender were considered.

The higher rates of solicited injection site reactions, including Grade 3 reactions, in toddlers and children are possibly confounded by the intensity scale used in these age groups. In these age groups, erythema/and swelling were of Grade 3 severity when above 5 cm while in the older age group they were of Grade 3 when above 10 cm. Also, in toddlers and children any erythema/ and swelling were collected and considered as injection site reaction; while in the other age groups, measurement had to be above 2.5 cm to be considered in the analysis. Overall, the rates were comparable between adolescents, adults, and older adults.

In elderly, a lower local and systemic reactogenicity was noted compared to the younger age groups; while the rate of SAEs was higher (as expected and remained comparable to that of Menomune – A/C/Y/W-135 vaccine).

Extrinsic Factors

No clinical outcome data associated with extrinsic factors (eg, the use of tobacco or alcohol and food habits) have been collected in the studies included in the clinical development program. The potential interaction of extrinsic factors is not expected with vaccines.

Pregnancies during the studies

The following is the distribution of the 12 pregnancies reported in subjects who had received MenACYW conjugate vaccine):

- 7 unexposed

- 4 exposed, but not yet pregnant (injection received during the interval between 30 days before her last menstrual period (LMP) and 7 days after her LMP)

- 1 exposed and pregnant (injection received 7 days after her LMP)

Table 35: MenACYW conjugate vaccine pregnancy exposure and pregnancy outcomes

	MenACYW conjugate vaccine (n=12)		
Pregnancy exposure	**Unexposed**	**Exposed but not yet pregnant**	**Exposed and pregnant**
Pregnancy Outcome	**n**	**n**	**n**
Spontaneous abortion	2	0	0
Ectopic pregnancy	0	0	0
Elective termination	0	0	0
Live birth	5	4	1
Stillbirth†	0	0	0
Death in utero‡	0	0	0
Unknown	0	0	0
Total	**7**	**4**	**1**

n: number of pregnancy cases ; † at or after 20 weeks of gestation ‡ before 20 weeks of gestation

No cases of congenital abnormalities were reported in either category of exposed pregnancies.

Immunological events

No specific analyses were provided, and evaluation of immunological events was part of the safety and efficacy documentation above.

Safety related to drug-drug interactions and other interactions

Vaccination in patients receiving immunosuppressive treatment may not elicit an adequate immune response.

Data on concomitant administration with other vaccines is integrated in the safety documentation above (MMR [M-M-RII], V [VARIVAX], DTaP-IPV-HB-Hib [Hexaxim/Hexyon/Hexacima], and PCV13 [Prevenar 13/Prevnar 13 were investigated in toddlers and Tdap [Adacel/Covaxis] and HPV [Gardasil] in adolescents).

Discontinuation due to adverse events

One subject experienced an AE that led to discontinuation among the MenACYW conjugate vaccine recipients. The parents of subject 301-05001, an 18-month old male, withdrew their consent due to a nonserious Grade 2 AE (Gastroenteritis) experienced by the subject on D0, and lasted 5 days after receiving MenACYW conjugate vaccine administered alone in study MET57. The event was considered as not related to the vaccine by the Investigator and Sponsor. The subject was treated and recovered from the event.

Post marketing experience

No post-marketing data are available for MenACYW conjugate vaccine as the vaccine is not yet marketed in any country.

2.6.1. Discussion on clinical safety

The safety of one dose of MenACYW conjugate vaccine (MenQuadfi) was evaluated in subjects aged 12 months and older (toddlers, children, adolescents, and adults including those 56 years and older). The safety was evaluated descriptively in eleven clinical trials: two phase I/II studies for selection of the final formulation and nine pivotal phase II/III studies investigating the to be marketed formulation. The safety profile of MenACYW was compared to the currently available and well characterised MCV4 vaccines Menveo and Menactra (in children 2-9 years, adolescents 10-17 years and adults 18-55years) and Nimenrix (in toddlers) as well as to the no longer available, unconjugated vaccine Menomune (in older adults; 56 years and older).

An integrated safety summary, summarised by age category and vaccine type, formed the basis of this full application, which was acceptable based on the similar design and conduct of the studies. MenC primed toddlers from Study MET51 were excluded from the integrated/pooled safety analysis, which was also acceptable based on different rates of solicited reactions, different number of MenC priming doses and time point of priming up to one month before study vaccination. Of note, MCV-4 primed subjects from study MET56 were included in the integrated analysis as priming occurred at least 4 to 10 years prior to study vaccination.

As regards the different types of vaccines used in children, adolescents and adults, it should be noted that only Menveo is an EU-licensed vaccine (Menactra and Menomune are US-licensed). Overall, 995 subjects received Menveo, among which 494 were children 2-9 years of age and 501 were adolescents 10-17 years of age, but none were adults. No concern was however raised on the use of only non EU-licensed comparator vaccines in adults for the following reasons: The two conjugated vaccines Menveo and Menactra are expected to show largely comparable safety profiles (despite containing a different amount of antigen and different carrier proteins). Indeed, only small differences in the safety profiles were observed between the different treatment arms that were considered not to influence the benefit risk conclusion (see results below). Further, adolescents and adults were expected to show comparable safety profiles based on mechanistic considerations, which was supported by the results (see also below). The unconjugated Menomune vaccine, however, has a lower reactogenicity potential than the other, more comparable, conjugated vaccines. Hence, the established safety profile in older adults (above 56 years of age) could only be indirectly compared to the safety profile observed in MenACYW vaccinated younger adults. Reassuringly, however, elderly overall reported less frequently AEs compared to younger adults (see below). Importantly, the safety assessments were considered appropriate and sufficiently similar across studies to allow pooling of the results by age group and by vaccine type. Therefore, a within treatment-group comparison by age group for the pooled MenACYW anaylsis as well as the between-treatment group comparison of MenACYW to Menveo and Menactra within the ISS was overall sufficient.

The overall safety database of MenACYW consists of 7116 subjects. 6398 subjects received the final MenACYW formulation in the 9 pivotal studies included in the safety analysis, thereof 5417 alone and 981 subjects with a concomitant vaccine. Out of the 5417 subjects exposed to MenACYW, there were 691 toddlers, 492 children (2 through 9 years), 1897 adolescents, 1684 adults, 298 older adults (56 to 64 years), and 349 elderly adults (65 years and above). The overall safety database fulfils the recommendations as set out in the Guideline for Vaccines (EMA/CHMP/VWP/164653/2005) and was considered acceptable to support registration of MenQuadfi.

Safety analysis was stratified by age, gender and race. The demographic and baseline characteristics were generally comparable between vaccine groups. In toddlers there were more male (56.2%) than female

(43.8%) subjects in the MenACYW group. Most of the study subjects were white and not Hispanic or Latino, the number of subjects belonging to racial groups other than white (roughly 80%) or black/African American (roughly 10 to 20%) were underrepresented in the studies.

The method for safety collection was comparable across all studies and was in line with the EMA guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1), although different duration of follow up in the studies were reported. Immediate unsolicited adverse reactions were collected within 30 minutes after the vaccine injection. A diary card was used to collect all information about solicited reactions (injection site: pain, erythema, swelling, redness; systemic: fever, headache, myalgia, malaise) from D0 to D7 after vaccination and about unsolicited AEs/ARs (including medically attended adverse events; MAAEs) from Day 0 to Day 30 (Visit 2; V02). Serious AEs and MAAEs were collected during the entire study (1-month follow-up for studies MET 44, MET 51, and MET 54; 6 months- follow-up for studies MET 35, MET 43, MET 49, MET 50, Met 56). Adverse events of special interest (generalized seizures, Guillain-Barré syndrome, Kawasaki disease and idiopathic thrombocytopenic purpura) were prospectively collected in toddlers in studies MET 35 and MET 51 and for other studies retrieved based on MedDRA coding.

Concomitant medications that might have influenced the study results were recorded in each study and summarized per Category (per study and vaccine arm). No notable differences were observed between study groups within the different studies.

The MedDRA coding version was updated during the course of the trials and the same version of MedDRA was not used to code AEs in all studies. Although the applicant was asked to indicate how the changes affected the tabulations, no details on the changes between different MedDRA versions were provided. The provided data in the pooled analysis include the solicited, unsolicited non-serious and serious AEs/ARs among all studies and all age groups, re-coded according to the last MedDRA version (21.0) available at that time.

The safety profile was comparable to the currently available EU- or US-licensed MCV4 vaccines Menveo, Menactra, and Nimenrix. The age cut-off used for older adults (56 years) was justified as since, at the time of study conduct, Menomune was the only licensed vaccine in the older age group 56 years and older in the US. As expected, in older adults, Menomune vaccinated subjects showed a less reactogenic profile than MenACYW vaccinated subjects. In particular, solicited ARs were reported less frequently in older (56 years and above) compared to younger adults (18 to 55 years), while a larger proportion of older adults reported unsolicited (injection site) ARs. These differences were reflected in the SmPC. The frequency of reported immediate unsolicited ARs (within 30 minutes after vaccination) was low in all age cohorts: no immediate AEs were reported in toddlers and children, while in adolescents 0.4% (7/1987), in adults 18-55 years 0.2% (4/1684) and in older adults 0.2% (1/647) of subjects reported immediate ARs in the MenACYW arm. These were mostly driven by dizziness. Dizziness was considered related and is reflected in the SmPC. There were no serious immediate unsolicited ARs (including any anaphylactic or life-threatening events.)

Solicited ARs within 7 days:

In **toddlers**, overall, solicited **injection site** reactions were reported by 56.4% of subjects in the MenACYW group and comparable to the Nimenrix group. The most reported local reactions were erythema (38.0%) and tenderness (37.8%), followed by swelling (19.4%). The number of Grade 3 reactions was low (4.5%) and comparable to Nimenrix.

Safety of 305 **MenC primed toddlers** was not included in the integrated safety analysis and presented separately. Compared to meningococcal vaccine naïve toddlers, solicited reactions tended to be reported with lower frequency in MenC-primed toddlers after the administration of MenACYW (70.4 vs 80.9%) or Nimenrix (60.8 vs 81.6%). In MenC-primed toddlers, solicited reactions, especially solicited injection site reactions,

tended to be reported with higher frequency in toddlers vaccinated with MenACYW conjugate vaccine as compared to toddlers vaccinated with Nimenrix. This was still in an acceptable range. While the rates are comparable in MenC-CRM primed toddlers between Nimenrix and MenQuadfi, in MenC-TT primed toddlers solicited reactions tend to be reported with higher frequency in the MenQuadfi group (66.9% vs 55.3%). Although the point estimate for solicited injection site reactions and systemic reactions tended to be higher in the MenACYW group, no statistical significance was reached, and the intensity of the reactions were mostly Grade 1.

In **children**, 46.8% of subjects reported solicited **injection site** reactions which was comparable to Menveo. Pain was reported most commonly (38.6%) followed by erythema (22.6%) and swelling (13.8%). Most of the reported solicited events were of grade 1 and 2, while the number of Grade 3 reactions for solicited events was lower in the MenACYW group compared to Menveo (3.7 % vs 11.1% respectively).

In **adolescents and adults**, the percentages of subjects reporting solicited **injection site** reactions following MenACYW vaccination were comparable (any intensity: 40.2% and 43.4%, respectively; Grade 3: 1.8% and 2.1%, respectively). Pain was most commonly reported (38.3% resp. 42.7%), followed by erythema (4.8% resp. 5%) and swelling (4.4 % resp. 4.3%). These events occurred mostly in the three days after the vaccination, were mainly of Grade 1 or 2 and there were no significant differences compared to Menactra or Menveo (including Grade 3 events).

A comparable percentage of **older adults 56 to 64 years** of age reported solicited **injection site** ARs (38%; grade 3: 1.7%). As for adolescents and adults 18-55 years, pain was reported most commonly (35.6%), followed by erythema (8.8%) and swelling (7.1%). These ARs were mostly grade 1 or 2 and most resolved within 3 days. In **elderly** subjects (**65 years and above**), injection site reactions were less frequently reported in the MenACYW group (22.2%, grade 3 0.9%) compared to older adults: pain 19.9%, erythema 5.8% and swelling: 4%.

Solicited systemic ARs:

In **toddlers**, overall, 64.5% reported solicited **systemic reactions**, which was comparable to the Nimenrix group. Irritability was most commonly reported (48.6%), followed by abnormal crying (34.5%), appetite lost (28.2%), and drowsiness (24.2%) with a similar pattern in the Nimenrix group. Most of the reactions were Grade 1 and 2, number of Grade 3 reactions was low and comparable (4.3% in both groups).

In **children,** 34.5% of subjects reported solicited **systemic** reactions, which was comparable to the Menveo group. Malaise was most commonly reported (21.1%) followed by myalgia (20.1%) and headache (12.5%). Most reactions were of grade 1 and 2 intensity, while the number of Grade 3 reactions was low (1.8%) and comparable to Menveo.

In **adolescents and adults**, 45.9% and 47.6%, respectively, reported solicited **systemic** ARs. Myalgia was most commonly reported (by 30.5% resp. 35.8 % of subjects) followed by headache (28.8% resp. 30%) and malaise (21.7% resp. 23.9%). Fever was reported by 0.8% and 1.2% of MenACYW vaccinated subjects, respectively. Most reactions occurred and resolved within the first days and were mostly Grade 1 and 2. Grade 3 reactions were overall low (4% resp. 5.7%, lowest for fever). There were no significant differences to the comparator arms Menveo or Menactra.

A comparable percentage of **older adults 56-64 years** reported solicited systemic ARs (42.5%; grade 3, 2.4%), while in **elderly** subjects, these were reported less frequently (30.5%; grade 3, 1.4%). Otherwise, the pattern was similar (most commonly myalgia, followed by headache and malaise, fever less frequently).

The reported local and systemic reactions were consistent with those expected after vaccine administration and are adequately reflected in SmPC section 4.8

Unsolicited AEs and ARs (within 30 days): In **toddlers** 54.7% of subjects reported at least 1 unsolicited non-serious AE, which was comparable to Nimenrix. The number of unsolicited adverse reactions was low (5%, no Grade 3). Most of the reported reactions belong to the SOC 'Gastrointestinal disorders' with diarrhoea reported by 2.3% of subjects in the MenACYW conjugate group. Other preferred terms were mostly reported as single cases.

In **children** 23.9% reported unsolicited non-serious AEs, which was comparable to the Menveo group. The percentage of subjects reporting unsolicited non-serious ARs was low (2%). Most of the reported reactions belong to the SOC 'General Disorders and administration site conditions' with reports of injections site bruising, crying and injection site warmth among others. Beside 'Gastrointestinal Disorders' including vomiting, upper abdominal pain and nausea, other preferred terms were reported as single cases. Most of the ARs were grade 1 or 2, 1 subject in each vaccine group (0.2%) experienced at least 1 Grade 3 unsolicited non-serious AR within 30 days of vaccine injection. Overall MenACYW and Menveo groups were comparable.

For **adolescents and adults 18-55 years**, 19.2% of adolescents and 12.7% of adults 18-55 years reported at least 1 unsolicited non-serious AE in the MenACYW group, which was comparable to Menveo or Menactra. The percentages of subjects reporting at least 1 unsolicited non-serious AR (by SOC and PT) were low and similar for adolescents and adults (in the MenACYW arm 3.1% and 2.2%, respectively). This was also comparable to the comparator arms (Menveo or Menactra). The most frequently reported ARs were in the SOC 'General disorders and administration site conditions' and were most frequently 'injection site pruritus' and 'injection site warmth', followed by 'dizziness' and 'nausea' in adolescents and 'fatigue' in adults. The unsolicited non-serious ARs were mostly Grade 1 or 2 and mostly resolved within 3 days. Grade 3 unsolicited non-serious ARs were reported in a very low number of patients (<0.1% and 0.2%, in adolescents and adults, respectively, in the MenACYW arm).

In older **adults 56-64 years**, the percentages of subjects reporting at least 1 unsolicited non-serious AR within 30 days of vaccination was comparable to adolescents/adults in the MenACYW group (3.4%). Similarly, the most frequently reported ARs were from the SOC 'general disorders and administration site conditions' (2.7% in the MenACYW arm) and mostly injection site pruritus (2%). Dizziness was not reported, and neither were nausea or vomitus. Only one grade 3 unsolicited non-serious AR (0.3%) was reported for the MenACYW group (i.e. chills).

In contrast, in **elderly** subjects (aged 65 years and older), slightly more subjects reported at least 1 unsolicited non-serious AR within 30 days of vaccine injection (5.2%) compared to the 'older adults' (3.4%) in the MenACYW group, respectively. As for the older adults, this was driven by the SOC 'General disorders and administration site conditions' (most frequently 'injection site pruritus'). Most unsolicited non serious ARs were of Grade 1 or 2 and most resolved within 3 days after the injection. No subject experienced Grade 3 unsolicited AR in the MenACYW group.

The tabulated summary of adverse reactions in Section 4.8 of the SmPC was updated during the last round with the removal of the use of any threshold of frequency of occurrence of adverse reactions, thereby now also including AR's that were rarely (≥1/10,000 to <1/1,000) observed. Yet, the tabulated summary had previously already been outlined to show AR's occurring with a frequency of at least 0.1% (including only very common, common and uncommon AR's). The applicant explained the discrepancies and provided enough justification. All adverse reactions which were considered related to vaccination with a reasonable possibility were included, i.e. also including unsolicited adverse reactions or MAAEs considered related to

vaccination (e.g. urticaria, pruritus, rash,; for the complete list see related SmpC comment). The applicant clarified how the frequencies were calculated.

Serious AEs:

There were no deaths reported in the MenACYW conjugate vaccine group.

Overall, the incidence of SAEs was low and comparable between MenACYW and the corresponding active control vaccine group: 0.8% of **toddlers**, 1% of **children** (mostly single cases in the SOC 'Respiratory, thoracic and mediastinal disorders'), 0.5% of **adolescents** (with comparable results for the concomitant vaccination groups, i.e. 1.0% and 1.4% for Tdap + HPV with and without MenACYW, respectively) and 1.6% of **adults reported** at least 1 SAE**.** These were mostly single cases with no evident pattern. None of these events were considered related by the investigator or sponsor. The narratives were provided and there is no indication of a causal relationship to the vaccine in any age group. The applicant was asked to discuss the different duration of follow up in the different studies and justify why safety data (especially SAES and AESIs) in toddlers were not collected for a 6-month period after vaccination. Difference in safety follow up duration were only based on the standard requirements for the US conducted studies. In all other studies safety endpoints were followed for 30 days; MAAEs and SAEs were followed up till end of 6 months post vaccination.

The number of AESIs that might potentially have been associated with MenACYW vaccination was low across the clinical development programme with reports in 4 subjects who received the MenACYW vaccine (febrile convulsion, temporal partial seizure). None of the events was considered as related, which is acknowledged. As stated by the applicant, no confirmed cases of GBS occurred within 6 weeks after vaccination (this window is a commonly used post-vaccination period which may be consistent with vaccine associated GBS). Subjects in Studies MET44, MET51, MET54 and MET57 were only observed for 30 days after vaccination. GBS should be included as a safety concern for the PSURs, but not the RMP.

No significant differences for MAAEs between treatment arms were noted in the individual studies. However, since some of these MAAEs were considered related to treatment by the investigator, the applicant was asked to provide listings, summarized by treatment and study, of those MAAEs that were considered related to the vaccination and discuss in how far they needed to be reflected in the SmPC . These MAAEs were summarised and the applicant clarified that the nature and frequency of those events were similar to the unsolicited adverse events and that therefore no particular advice should be added to the SmPC.

MCV4- primed subjects (aged 15 years and older) showed no notable differences to MCV4-vaccine naïve subjects (slightly more solicited injection site and systemic reactions in MC4-primed subjects [<10% difference in proportion of subjects], but no difference in grade 3 solicited ARs, unsolicited ARs or MAEEs).

Concomitant vaccines:

In study MET57 the safety profile of MenACYW was evaluated in **toddlers** with **concomitant administration of different vaccines**, including either DTaP-IPV-HB-Hib, MMR+V or PCV13. The frequency of reported AEs (solicited and unsolicited events) was in general lower, especially in Russian study sites where PCV13 was used as concomitant vaccine, than in studies MET51 and MET54 conducted in the EU, in the same age group. As there were fewer reports from the Russian study sites it is difficult to compare the results of the concomitant vaccines. The applicant discussed possible reasons for the low frequency of reported AEs in study MET57 and provided arguments, including a comparable low frequency across different study sites in Russia, possible influence by genotypic/phenotypic profiles and the cultural differences in medical practice in the Russian Federation against underreporting.

Percentage of subjects reporting at least one **injection site** reaction or **systemic** reaction at the MenACYW injection site was comparable between the groups receiving MenACYW alone or in combination with either MMR+V or DTaP-IPV-HB-Hib (46.3%, 40.7 % and 44.5% and 54%, 46.6% and 51.3%, respectively). In subjects who received MenACYW + PCV13 the number was lower with 26.0% and 20%. Reporting of injection site reactions at any vaccine injection site was comparable with slight differences with or without MenACYW. In the PCV13 + MenACYW group the percentage was higher (31.5%) than in PCV13 alone (13.1%). Although the reports of injection site reactions and systemic reactions tended to be higher when PCV13 was administered in combination with MenACYW than PCV13 alone, the corresponding 95% CI were overlapping and the overall numbers with PCV13 were lower than in combination with other vaccines.

Tdap and HPV (adolescents): When MenACYW was concomitantly administered with Tdap and HPV vaccines, more adverse reactions were reported (including grade 3): approximately 10% and 25% more subjects reported solicited injection site and systemic reactions, respectively, compared to MenACYW alone (driven by myalgia and fever). Unsolicited ARs were also more frequently reported, especially injection site pruritus, injection site bruising, nausea and vomiting (still remained low, below 2%), and were of longer duration. When compared to vaccination of Tdap and HPV alone, solicited systemic (61.3 versus 55.4%) and unsolicited ARs (8.5 versus 4.1%) tended to be more frequently reported with the vaccination of the three components.

Although concomitant vaccination was tolerated without unexpected or serious safety concerns, more adverse reactions are generally to be expected with concomitant vaccination. The higher rates of adverse reactions in toddlers who received PCV13 given conconmitantly with MenQuadfi than in toddlers who received PCV13 alone was reflected in the SmPC.

Pregnancy and lactation:

Concerning the use of the product during pregnancy and lactation, data is very limited. Despite pregnancy being an exclusion criterion, 12 pregnancies were reported, of which one was considered 'exposed to the study vaccine when pregnant', four 'exposed when not pregnant' and seven as 'not exposed'. No pregnancy complications or cases of congenital abnormalities were reported in either category. Experience with the product from pregnant women is however limited, and women in their childbearing years will potentially receive the vaccine. The applicant will establish a pregnancy registry in the US to collect data on the outcome of exposure during pregnancy and to monitor for any potential safety signals that may arise. 'Use during pregnancy' was included as missing information in the RMP and the pregnancy registry was included as a Category 3 study in the PhV plan of the RMP. The applicant has committed to submit the final protocol of the pregnancy registry (MEQ00070) to the EMA in a next RMP update or in a stand-alone procedure. The applicant has also commited to provide a discussion on alternative EU data sources in case a signal is raised from the pregnancy registry or spontaneous reported data.

2.6.2. Conclusions on the clinical safety

The nature and frequency of the reported adverse events are considered to be consistent with those expected after vaccine administration, are comparable as observed with the comparator vaccines and do not give rise to concern.

In conclusion, the safety profile of MenQuadfi is considered acceptable.

2.7. Risk Management Plan

Safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Long-term persistence of the vaccine response, and safety and immunogenicity of booster in individuals primed with MenACYW conjugate vaccine Co-administration with MenB vaccine Use during pregnancy

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Booster study in children (MET62) Ongoing	To evaluate antibody persistence following the primary dose of MenACYW conjugate vaccine To evaluate the safety and immunogenicity of a single dose of MenACYW conjugate vaccine in children in Finland who had been vaccinated 3 years earlier as toddlers at 12 to 23 months of age with either MenACYW conjugate vaccine or Nimenrix	Waning of protection over time Need for booster	Planned submission of final study report	30 June 2021
Booster study in adolescents and adults (MET59) Ongoing	To evaluate antibody persistence following the primary dose of MenACYW conjugate vaccine To evaluate the safety and immunogenicity of a single dose of MenACYW conjugate vaccine given alone or concomitantly with MenB vaccine in adolescents and adults ≥ 13 to < 26 years in The United States who had been vaccinated 3-6 years earlier with either MenACYW conjugate vaccine or Menveo	Waning of protection over time Need for booster Co-administration with MenB vaccine	Planned submission of final study report	30 June 2022
Booster study in older adults (MEQ00066) Ongoing	To evaluate antibody persistence following the primary dose of MenACYW conjugate vaccine To evaluate the safety and immunogenicity of a single dose of MenACYW conjugate vaccine in subjects in the United States who received a dose of Menomune vaccine or MenACYW conjugate vaccine ≥ 3 years previously, at ≥ 56 years of age	Waning of protection over time Need for booster	Planned submission of final study report	31 March 2024

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information on long term persistence of the vaccine response, and safety and immunogenicity of booster in individuals primed with MenACYW conjugate vaccine	**Routine risk minimisation measures:** SmPC section 5.1 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Booster study in children (MET62) / Planned submission of final study report: Q1 2021 Booster study in adolescents and adults (MET59) / Planned submission of final study report: Q1 2022 Booster study in older adults (MEQ00066) / Planned submission of final study report: Q4 2023
Missing information on co-administration with MenB vaccine	**Routine risk minimisation measures:** SmPC section 4.5 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Booster study in adolescents and adults (MET59) / Planned submission of final study report: Q1 2022 Safety, immunogenicity and co-administration with MenB vaccine study in infants and toddlers (MET52) / Planned submission of final study report: Q3 2023
Missing information on use during pregnancy	**Routine risk minimisation measures:** SmPC section 4.6 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Pregnancy registry (MEQ00070) / Planned submission of final study report: Q2 2029

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, MenQuadfi (meningococcal group A, C, W135 and Y conjugate vaccine) is included in the additional monitoring list.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant initially applied for the following indication:

"MenQuadfi is indicated for active primary and booster immunisation for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y. MenQuadfi is indicated for use in individuals 12 months of age and older.

The use of this vaccine should be in accordance with available official recommendations."

The virulence of Neisseria meningitides is mostly based on the biochemical structure of capsular polysaccharides. So far 12 distinct meningococcal serogroups have been classified, with serogroups A, B, C, W, X and Y being responsible for most cases of meningococcal disease. Dynamics of meningococcal transmission, acquisition, and carriage in humans are a major influence on the incidence and likelihood of meningococcal disease and vary world-wide greatly among regions. The European population is mostly affected by serogroup B, but also C and Y have been reported. At present, the best prevention known against meningococcal disease is the up-front immunization with vaccines targeting the relevant serogroups.

3.1.2. Available therapies and unmet medical need

Meningococcal vaccines induce the production of bactericidal antibodies specific to the capsular polysaccharides of N meningitidis serogroups. In multiple European countries MenC vaccination is recommended for toddlers, even though the favoured timing of vaccination differs among countries.

MenQuadfi is intended to induce antibody production specific for serogroups A, C, Y, and W-135.

Currently two quadrivalent MenACWY vaccinations are licensed in the EU: Nimenrix (since 2012) indicated for the immunization from the age of 6 weeks, and Menveo (since 2010) indicated for the immunization of children from 2 years of age, adolescents and adults.

Menveo is also available in the US but not Nimenrix. In addition, other MenACWY vaccinations are available in the US: Menactra is approved from infants as young as 9 months of age to adults 55 years of age, and Menomune-A/C/Y/W-135, a polysaccharide vaccine, which was licensed for persons 2 years of age and older at the time of the clinical trials. The production was discontinued in 2017 by the applicant (MAH of Menomune). According to the applicant, the decision was strategic and not based on any quality, safety, or efficacy issues.

3.1.3. Main clinical studies

For this MAA eleven clinical studies have been submitted of which seven were considered pivotal (MET35, MET43, MET49, MET50, MET51, MET56 and MET57). The remaining five studies are considered supportive evidence (MET28, MET32, MET44, MET54, MET39).

Six of the seven pivotal studies intended to demonstrate non-inferiority of seroresponse rates or seroprotection rates (MET51) following administration of MenQuadfi compared to different comparator vaccines (Nimenrix, Menveo, Menactra, and Menomune) in different age groups:

- Toddlers (12-23 months): MET51, compared to Nimenrix
- Children (2-9 years): MET35, compared to Menveo
- Adolescents (10-17 years): MET50, compared to Menveo
- Adolescents and adults (10-17 and 18-55 years): MET43, compared to Menactra
- Adolescents and adults (≥15 years): MET56, compared to Menactra
- Older adults (>56 years): MET49, compared to Menomune

Furthermore, lot consistency (MET43), booster dose (MET56) and administration of concomitant vaccinations (toddlers: MET57, adolescents: MET50) were investigated.

Subjects were meningococcal-vaccination naïve in studies MET35, MET50, MET43 and MET49. In MET51 both naive and MenC primed toddlers were included. In study MET56 subjects who previously received a quadrivalent meningococcal vaccine were included.

Overall, the design of the presented studies was similar. In all studies, the subjects received one dose of MenQuadfi or a comparator vaccine. Immunogenicity was evaluated immediately before vaccination and 30 days after vaccination.

Primary analyses were conducted in the per-protocol analysis sets (PPAS) but the respective analyses have also been performed in the full analysis set (FAS) with comparable results.

In line with the relevant EMA (EMA guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) and WHO guidelines (WHO Guidelines on clinical evaluation of vaccines: regulatory expectations), it was agreed in a preceding scientific advice (EMA/CHMP/SAWP/467602/2015) that no efficacy studies are necessary and that the clinical development programme of MenQuadfi is based on immunogenicity studies. This is based on the fact that a widely accepted immunological correlate of protection for meningococcal vaccines containing serogroups A, C, W and Y exists, which has also been applied in previous licensing procedures of conjugated meningococcal vaccines (e.g. Menveo, Nimenrix). The best established and scientifically proven correlate of protection against meningococcal disease to date appears to be hSBA titers ≥1:4. rSBA titers ≥1:8 are generally also considered to correlate with protection for MenACWY vaccines, although formally only correlated with effectiveness for serogroup C. Each assay has its merits and overall the serological assays together are considered appropriate to generate sufficient data to support the likely protective efficacy of the vaccine. The use of hSBA titres for primary immunogenicity analyses was adequately justified by the applicant and accepted in a previous SA. As supportive evidence, the applicant also provided data derived from rSBA for all patients in studies MET 50, 56 and 35 and for a subset of subjects in studies MET 43, 49, 51 and 57.

The main endpoints for the evaluation of immunogenicity were: seroprotection rates, seroresponse rates and geometric mean titers (GMTs). Seroprotection is defined as the percentage of subjects with an hSBA titer ≥1:8 while seroresponse extends this definition by taking into account prevaccination titers: For subjects with a pre-vaccination titer ≥1:8, an at least 4-fold increase of titer needs to be demonstrated. In addition, GMTs were presented for all serogroups, allowing the assessment of differences in immune response between

vaccines. Furthermore, percentages of subjects achieving an at least 4-fold increase of titres and reverse cumulative distribution curves of antibody titers (RCDs) were presented.

3.2. Favourable effects

The MenACYW conjugate vaccine is prepared by using tetanus toxoid as the carrier protein. Conjugation of polysaccharide antigens to a protein carrier can induce T-cell-dependent immune responses, which are anticipated to give rise to higher antibody titers, longer duration of the immune response, and enhanced immunologic memory that allows for a booster response.

All the core components of the MenACYW conjugate vaccine have been used extensively in licensed vaccines and have been shown to be safe. The meningococcal polysaccharides are the same as those used in Menactra (Meningococcal [Serogroups A, C, Y, and W] Polysaccharide Diphtheria Toxoid Conjugate Vaccine), Menveo (Meningococcal [Groups A, C, Y, and W] Oligosaccharide Diphtheria CRM197 Conjugate Vaccine), and Menomune - A/C/Y/W-135 (Meningococcal Polysaccharide Vaccine, Groups A, C, Y, and W) vaccines. The source of tetanus toxoid protein used as a protein carrier in MenACYW conjugate vaccine is the same as that used in ActHIB (a vaccine against Haemophilus influenzae type b [Hib]), as a carrier in the Hib portion of all Sanofi Pasteur paediatric combination vaccines containing Hib such as Pentaxim (diphtheria, tetanus, pertussis [acellular, component], poliomyelitis [inactivated] vaccine [adsorbed], and Hib conjugate vaccine [DTaP2-IPV/Hib]), Pentacel (DTaP5-IPV/Hib), Hexaxim / Hexacima / Hexyon (DTaP, hepatitis B [HB], IPV, and Hib conjugate vaccine [DTaP2-IPV-HB-Hib]), and as the tetanus component of the 2-component pertussis-containing combination vaccines such as Tetraxim, Pentaxim, Hexaxim / Hexacima / Hexyon. The safety of the combination of these components as they appear in the MenACYW conjugate vaccine has been evaluated in clinical trials conducted as part of the development program in the populations of the claimed indication (individuals 12 months of age and older: toddlers, children, adolescents, and adults including older adults and the elderly).

In all seven pivotal studies antibody response to MenQuadfi was compared to different comparators (Nimenrix, Menveo, Menactra, Menomune) in different age groups from toddlers of 12 - 23 months to adults ≥56 years. In all these studies the primary objective to demonstrate non-inferiority of MenQuadfi against the comparator vaccine was met for all serogroups. In all but one study non-inferiority was based on seroresponse rates. Only in study MET51 non-inferiority of seroprotection rate was tested. A requested analysis of non-inferiority of seroresponse was also successful for this study. The respective results for seroresponse and seroprotection are listed in the table below.

Seroresponse and seroprotection rates were higher in younger subjects (toddlers, children and adolescents) and declined with age. Across studies and age groups, MenQuadfi seroresponse rates for serogroup A were lower compared to C, W and Y.

In meningococcal-vaccination-naïve subjects seroresponse rates were higher for MenQuadfi for all serogroups in all age groups compared to the comparators with only some exceptions such as for serogroup A in toddlers where the seroresponse rate is lower compared to that of Nimenrix, while still meeting non-inferiority criteria for seroprotection. For children the seroresponse rates for serogroup A are only numerically higher than for Menveo.

In adolescents and adults, non-inferiority of seroresponse rates was demonstrated for MenQuadfi when administered as booster vaccination to subjects who previously received a quadrivalent meningococcal

conjugate vaccine 4 to 10 years before, compared to Menactra with even (numerically) higher seroresponse rates and GMTs for all serotypes in favour of MenQuadfi.

Concomitant vaccinations: In toddlers, immune response to MenQuadfi and MMR and Varicella or hexavalent vaccine (DTaP-IPV-HB-Hib) was comparable for each vaccine when given alone or concomitantly. In adolescents, concomitant vaccination with TdaP and HPV revealed comparable results for Tetanus and Diphtheria antigens and HPV.

Lot-to-lot consistency was demonstrated in study MET43 for all three lots based on hSBA GMTs.

Table 36: Results of non-inferiority studies

Study Comparator	**Age group**	**Seroresponse rates MenQuadfi (95% CI)** **Difference to comparator: MenQuadfi – comparator (95% CIs)**							
		Serogroup A		***Serogroup C***		***Serogroup Y***		***Serogroup W***	
MET51 [1)] Nimenrix	Naïve toddlers 12-23 months	76.8 %	(71.5; 81.5)	98.3 %	(96.1; 99.4)	81.9 %	(77.0; 86.1)	67.6 %	(61.9; 72.9)
	MenC-primed toddlers	76.1 %	(69.6; 81.9)	95.4 %	(91.5; 97.9)	89.2 %	(84.0; 93.2)	75.5 %	(68.9; 81.4)
Stratified difference [2)]		-2.20	(-7.70; 3.30)	17.9	(13.4; 22.5)	5.43	(0.289; 10.6)	1.11	(-4.95; 7.17)
MET35 Menveo	Children 2-9 years	55.4 % 7.6	(50.7; 60.0) (1.1, 14.0)	95.2 % 47.4	(92.8; 97.0) (42.2, 52.2)	91.5 % 12.2	(88.5; 93.9) (7.7, 16.7)	78.8 % 14.8	(74.8; 82.5) (8.9, 20.5)
MET50 Menveo	Adolescents 10-18 years	75.6 9.2	(71.4; 79.4) (3.4; 15.0)	97.2 24.6	(95.2; 98.5) (20.3; 29.0)	97.0 16.2	(95.0; 98.3) (12.3; 20.2)	86.2 19.6	(82.7; 89.2) (14.2; 24.8)
MET43 Menactra	Adolescents, Adults 10-55 years	73.8 % 19.1	(72.0; 75.5) (14.8; 23.5)	88.8 % 40.9	(87.5; 90.0) (36.7; 45.0)	91.4 % 18.1	(90.3; 92.5) (14.5; 21.9)	80.3 % 19.1	(78.7; 81.8) (14.9; 23.3)
MET49 Menomune	adults >56 years	58.2 % 15.7	(53.4; 62.9) (9.08; 22.2)	77.1 % 27.5	(72.9; 81.0) (21.2; 33.5)	74.4 % 31.0	(70.0; 78.4) (24.6; 37.0)	62.6 % 17.8	(57.8; 67.2) (11.2; 24.2)

MET56 Menactra	Men4-primed Adolescents and Adults ≥ 15 years	92.2 % 5.0	(89.0; 94.7) (0.74; 9.38)	97.1 % 5.4	(94.9; 98.6) (2.16; 8.76)	97.4 % 1.8	(95.3; 98.7) (-0.91; 4.55)	98.2 % 7.4	(96.3; 99.3) (4.30; 10.9)
Study Comparator	**Age group**	**Seroprotection rates MenQuadfi (95% CI)** **Difference to comparator: MenQuadfi – comparator (95% CIs)**							
		Serogroup A		***Serogroup C***		***Serogroup Y***		***Serogroup W***	
MET51 Nimenrix	Naïve toddlers	90.8 % 1.3	(86.9; 93.8) (-3.60; 6.20)	99.3 % 18.0 %	(97.6; 99.9) (13.6; 22.8)	93.2 % 1.6	(89.7; 95.8) (-2.76; 6.03)	83.6 % 0.2	(78.9; 87.7) (-5.85; 6.18)
	MenC-primed toddlers	89.8 %	(84.8; 93.7)	99.0 %	(96.4; 99.9)	95.9 %	(92.2; 98.2)	86.7 %	(81.2; 91.1)
Stratified difference [2)]		-2.03	(-5.84; 1.78)	12.1	(8.16; 16.1)	2.42	(-1.34; 6.19)	0.458	(-4.37; 5.28)

[1)] seroresponse was initially only included as observational objective; NI analysis was provided as requested

[2)] NI was tested for toddlers who either were meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy (MenC-primed)

Although the cut-off for definition of hSBA seroprotection was ≥1:8, the applicant changed the cut-off for the definition of seroresponse in most of the pivotal studies from ≥1:8 to ≥1:16 (reaching an hSBA titer of ≥1:16 if <1:8 pre-vaccination or achieving a 4-fold increase in hSBA titer if ≥1:8 pre-vaccination) during the development programme. Higher titers as proposed by the applicant provide a more conservative approach and were thus considered acceptable.

According to the applicant's submitted data the methods were found to fulfil the set criteria for the different properties and are therefore regarded suitable for measuring clinical samples for documentation of immunogenicity.

3.3. Uncertainties and limitations about favourable effects

Different cut offs for hSBA titers were used for the definition of hSBA seroprotection and hSBA seroresponse during the development (≥1:8 vs ≥1:16). Although the use of higher titers can be considered as more conservative approach, a clinical justification for the chosen NI margins was missing as well as a justification whether the chosen NI margins are equally applicable for the different definitions of seroresponse used

during the development. However, the chosen NI-margins were also applied in the development programme of other MenACWY vaccines licensed in the EU.

The chosen comparators Menactra and Menomune used in adolescents, adults and elderly, are both not licensed in the EU. In a preceding SA, it was stated that Menactra is not a particularly good conjugate vaccine. Menomune is an unconjugated polysaccharide vaccine with generally known drawbacks regarding immunogenicity.

Overall, data generated in the EU is limited. Only one of the seven pivotal studies (MET51) and one supportive study (MET54) were conducted in the EU. Both studies included healthy toddlers aged 12 to 23 months. No EU data is available for older subjects.

No immunogenicity data beyond 30 days after vaccination are available to determine immune persistence. From other licensed quadrivalent meningococcal vaccines, rapid waning of antibodies against serogroup A is known. Due to absence of any long-term data, it remains unknown if this would also apply to MenQuadfi.

In toddlers (MET51), differences were observed depending on the previously received MenC vaccination conjugate protein (TT or CRM). In the MenQuadfi group, seroresponse rates for serogroups A and W were lower for MenC-CRM primed subjects than for MenC-TT primed subjects with non-overlapping CIs (A: 50.0% (35.2; 64.8) vs 84.6% (77.7; 90.0); W: 44.7% (30.2; 59.9) vs 85.2 (78.5; 90.5)). Of note, the study was not designed to formally evaluate such differences and the number of subjects in the respective subgroups is low. In the control group (Nimenrix) only numerically lower seroresponse rates were observed.

Booster vaccination

Primed subjects have only been included in two studies: Study MET56 included adolescent and adult subjects (15-55 years) previously vaccinated with a meningococcal quadrivalent conjugate vaccine and study MET51 included toddlers who received a monovalent meningococcal C conjugate (MenC) vaccination during infancy. No data for MenQuadfi are available from primed adolescents or adults previously vaccinated with MenC. The majority of subjects in study MET56 previously received a vaccine not licensed in the EU (Menactra) (327/384 in the MenQuadfi group and 340/389 in the Menactra group). Additionally, data from study MET56 do not allow meaningful comparison of boosting between subjects that have been primed with different conjugates as also recommended by the WHO due to the limited number of subjects previously vaccinated with Menveo (48/384 in the MenQuadfi group and 39/389 in the Menactra group).

No data are available for MenQuadfi to boost itself.

Concomitant vaccinations

In study MET57, lower seroresponse rates and significantly lower GMTs for serogroup A, when MenQuadfi is concomitantly administered with PCV13 compared to MenQuadfi alone, were observed (seroresponse rate S+ (=seropositive at baseline) and S- (=seronegative at baseline): 56.1% (48.9; 63.2) vs. 71.9% (61.8; 80.6); seroresponse rate S+: 37.5% (27.8; 48.0) vs. 57.7% (43.2; 71.3); GMT: 24.6 (20.2; 30.1) vs. 49.0 (36.8; 65.3).

In study MET50 the concomitant vaccination of MenQuadfi and TdaP reduced the immune response to 3 of 4 pertussis antigens as shown by non-inferiority analysis of GMCs. The lower limit of the 2-sided 95% CI for the ratio of GMCs in Group 3 (MenQuadfi+TdaP+HPV) and Group 4 (TdaP+HPV) was >2/3 in only one (PT) of the 4 pertussis antigens (PT, FHA, PRN, FIM).

- Quality aspects:

Serogroup A differs from the other three serogroups C, Y and W135 in several basic aspects (e.g. binding to conjugate, process residuals). Additionally, dissociation rates of the conjugate differ between serogroup A and the other three serogroups. Free polysaccharide of serogroup A is elevated, compared to the other serogroups, in the accelerated stability study of the Drug Substance. In the real time stability study for the Drug Product, a higher increase of free polysaccharides can be observed for serogroup A in the course of time.

The applicant introduced a release specification of not more than 20% free saccharides and an end-of-shelf-life specification that allows 30% free saccharides. These specifications were not justified. At day 150, two studies were presented, reflecting immunogenicity data derived from a new batch (MET49) and an older batch (MET44). However, these data are not considered useful to further justify the specification limits. The definition of seroresponse differs between the two studies and makes any comparisons unfeasible. Furthermore, the actual amount of free polysaccharide is only known for serogroup Y in one of the studies and not known at all for the other study. For serogroup A, the applicant additionally justifies the proposed limit based on phase III lot results and stability trend analysis. This can in principle be accepted, however, the respective results do not support the proposed acceptance criteria for the other strains. The mouse immunogenicity data seem to confirm the applicants proposed specification limit. However, the unit of the ELISA data provided is not clear, considering also the fact that for serogroups Y and W135, the result doubled after 6 months under accelerated conditions.

It was acknowledged that the applicant has experience with other quadrivalent meningococcal vaccines, but the data presented didn't fully justify the proposed specification limits of NMT 20% free PS for release and NMT 30% free PS for end of shelf life for MenQuadfi.

Clarification on the mouse immunogenicity data was provided upon request. An arbitrary value in MEU was assigned to the reference standard serum based on the dilution and absorbance in ELISA. The release specification for free polysaccharide is reduced to NMT 13 % and the stability specifications of NMT 30 % will be reassessed for all serogroups, which was considered acceptable.

The end of shelf life was claimed at 48 months. However, no stability data is available for 48 months yet. The currently available stability data for the drug product show clear signs of degradation of the Meningococcal Polysaccharide Serogroup A Tetanus Toxoid Conjugate after 36 months (3 batches; 15%, 15% and 17%) while after 24 months, the measured free polysaccharide content was below the LOQ. In order to justify the shelf life claim of 48 months, the applicant was asked to provide an update to ongoing stability studies, which was provided up to 42 months. Data of three lots of drug product was presented until the time point of 42 months. All parameters were inside the acceptance criteria. Since no data is available for the 48-month time point, the proposed shelf life of 48 months was not endorsed. The applicant revised the shelf life of the drug product form 48 months to 42 months as requested.

3.4. Unfavourable effects

The overall safety database of MenACYW consists of 7116 subjects. 6398 subjects received the final MenACYW formulation, thereof 5417 alone and 981 subjects with a concomitant vaccine. Out of the 5417 subjects exposed to MenACYW, there were 691 toddlers, 492 children (2 through 9 years), 1897 adolescents, 1684 adults, 298 older adults (56 to 64 years), and 349 elderly adults (65 years and above). Toddlers and subjects above 2 years of age are separately described in the SmPC based on different rates of solicited reactions, different number of MenC priming doses and time point of priming up to one month before study vaccination. Children, adolescents, adults (aged 18-55 years and above 56 years of age) were separately

evaluated, but may be described integratively in the SmPC due to the comparability in design and conduct of the studies and the similar nature of reported adverse events.

In toddlers (12 through 23 months of age), 56.4% of subjects who received MenACYW and 57.6% of subjects who received Nimenrix reported any solicited injection site reaction. The most commonly reported solicited injection site reactions were erythema and tenderness in both groups. Among the subjects above 2 years of age, 41.3% of subjects reported solicited injection site reactions in the MenACYW conjugate vaccine group, with pain (38.3%) as the most commonly reported.

In the age group pool for toddlers, the percentage of subjects who experienced at least one solicited systemic reaction was comparable between the MenACYW conjugate vaccine group (64.5%) and the Nimenrix group (62.9%). The most commonly reported solicited systemic reactions were irritability followed by abnormal crying. In subjects above 2 years of age, the percentage of subjects who reported at least 1 solicited systemic reaction within 7 days of vaccine injection was 45.2% in the MenACYW conjugate vaccine group. The most commonly reported solicited systemic reactions were myalgia (30.7%), headache (26.4%) followed by malaise (21.7%).

The rates of each of the injection site and systemic ARs were in general similar between MenACYW and the respective comparator vaccine, and the majority of solicited reactions were Grade 1 or Grade 2 intensity. The percentage of subjects experiencing Grade 3 solicited injection site or systemic reactions was low in the MenACYW conjugate vaccine group (up to 4.5% and 2% experienced Grade 3 injection site reactions and up to 4.3% and 4.1% experienced Grade 3 systemic reactions in toddlers and in subjects above 2 years of age, respectively).

The percentage of unsolicited AEs reported by toddlers was 54.7% and in subjects above 2 years of age 20.7% in the MenACYW conjugate vaccine group. The majority of unsolicited AEs were in the SOCs of 'Infections and infestations' followed by 'Gastrointestinal disorders', 'Respiratory, thoracic and mediastinal disorders', and 'General disorders and administration site conditions'. In these SOCs, the most frequently reported PTs were upper respiratory tract infection, nasopharyngitis, cough, diarrhea, vomiting, injection site pruritus, rhinitis and fever, corresponding mainly to common respiratory or gastrointestinal ailments and infections.

The percentage of subjects reporting at least 1 unsolicited AR within 30 days of vaccine injection was low in toddlers (5%) and in subjects above 2 years of age (2.8%) in the MenACYW conjugate vaccine group. The most frequently reported unsolicited non-serious ARs were in the SOC 'General disorders and administration site conditions' (1.6%). The most frequently reported unsolicited non-serious ARs in this SOC were injection site pruritus (0.7%) and injection site warmth (0.4%) followed by fatigue, injection site bruising and injection site rash (0.1% each) reported in the MenACYW conjugate vaccine group. Other unsolicited ARs reported by at least 0.1% of subjects were diarrhea and dizziness (0.2% each), and nausea (0.1%) in the MenACYW conjugate vaccine group. No unexpected ARs were identified.

In toddlers, the frequency of SAEs was 0.8% in the MenACYW and 0.3% in the Nimenrix vaccine group. Among subjects above 2 years of age, the percentage of SAEs were 0.4% in the MenACYW group. There were no noteworthy differences in the incidence of any preferred terms between the vaccine groups.

There were no deaths reported in the MenACYW conjugate vaccine group.

3.5. Uncertainties and limitations about unfavourable effects

As regards the different types of vaccines used in children, adolescents and adults, it should be noted that only Menveo is an EU-licensed vaccine (Menactra and Menomune are US-licensed). Overall, 995 subjects received Menveo, among which 494 were children 2-9 years of age and 501 were adolescents 10-17 years of age, but none were adults.

Further of note, all adults above 56 years of age received either MenACYW (n=647) or the comparator Menomune (n=553), an unconjugated MCV4 vaccine that is no longer available (formerly US-licensed). A higher reactogenicity profile (in terms of solicited and unsolicited adverse reactions) was observed after MenACYW compared to Menomune vaccination, which could possibly be attributed to the different pharmaceutical form. Hence, the established safety profile in older adults (above 56 years of age) is more reasonably indirectly compared to the safety profile observed in MenACYW vaccinated younger adults. Reassuringly, however, older adults showed a lower reactogenicity profile compared to younger adults (except for the unsolicited adverse reactions (mostly injection site ARs). The age cut-off used for older adults (56 years) was justified as due to the fact that at the time of study conduct, Menomune was the only licensed vaccine in the older age group 56 years and older in the US. Observed differences between older/elderly subjects and younger adults are reflected in the SmPC.

The adverse events table as presented in the SmPC seems incomplete and differs from the Menveo AE profile. It cannot be followed which adverse reactions (that were per definition related to vaccination) were considered irrelevant enough not to be mentioned in the SmPC (SmPC comment).

SAEs and any pre-specified AESIs should be collected from all trial subjects for at least 6 months after the last dose of assigned treatment, however, in toddlers and elderly there are no 6 months safety data available as the trial duration was substantially shorter.

In study MET57, the frequency of reported AEs (solicited and unsolicited events) was in general lower, especially in Russian study sites where PCV13 was used as concomitant vaccine, than in studies MET51 and MET54 conducted in the EU, in the same age group. As there were fewer reports from the Russian study sites it is difficult to compare the results of the concomitant vaccines.

Although concomitant vaccination was tolerated without unexpected or serious safety concerns, more adverse reactions are to be expected with concomitant vaccination. This is adequately reflected in the SmPC.

Experience with the product from pregnant women is limited, and women in their childbearing years will potentially receive the vaccine. Therefore 'Use during pregnancy' is included as missing information in the RMP and a pregnancy registry was established.

No data is available concerning concomitant administration of MenQuadfi with MenB vaccines in adolescents. However, this is listed as missing information in the RMP, and the applicant will initiate a study to explore this issue.

There are currently only limited data on the safety of booster doses (810 adolescents and adults ≥ 15 years of age).

During the assessment of the non-clinical development the following concern arose: The fact that dark faeces were found in all cages of treated animals strongly suggests that this observation is treatment-related. It is unclear whether these findings may have been caused by a transient toxicological adverse effect (that was consequently not observed during later histological investigations). Considering that the relevance of the rat

repeated dose study for humans was doubted, it is unclear whether this finding also bears relevance for the clinical use of MenQuadfi.

3.6. Effects Table

Table 37: Effects Table for MenQuadfi.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Seroresponse rate	Non-inferiority in children 2-10 years	%	MenQuadfi	Menveo	NI met for all serogroups	MET35
	Non-inferiority in adolescents 10-18 years	%	MenQuadfi	Menveo	NI met for all serogroups	MET50
	Non-inferiority In adolescents and adults 10-55 years	%	MenQuadfi	Menactra	NI met for all serogroups	MET43
	Non-inferiority In adults >56 years	%	MenQuadfi	Menomune	NI met for all serogroups	MET49
	Non-inferiority In Men4-primed adolescents and adults ≥ 15 years	%	MenQuadfi	Menactra	NI met for all serogroups	MET56

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Seroprotection rate and seroresponse rate	Non inferiority in toddlers (naïve and MenC-primed) 12-23 months	%	MenQuadfi	Nimenrix	NI met for all serogroups MenC-primed toddlers were not tested for NI separately. They show, however, lower seroresponse rates for serogroup A.	MET51
	Non inferiority in naïve toddlers 12-23 months		MenQuadfi	Nimenrix	NI met for all serogroups	MET51
Unfavourable Effects ()						
Immediate unsolicited AR[1)]	**Toddlers**	%	0			MET 51, MET 54, MET 57
	Subjects 2 years and older *Most common:* Dizziness	%	0.2 0.1			ISS [5)]
Solicited injection site reactions[2)]	**Toddlers** Erythema Tenderness Swelling	%	 38 37.8 19.4		In **toddlers** the frequency of injection site ARs was higher compared to older subjects	ISS[4)]

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	Subjects 2 years and older Pain Erythema Swelling Grade 3	%	 38.3 7.1 5.5 2		Adults above **56-64 years** of age comparable to adolescents/adults 18-55 years Adults **65 years and above** reported less frequently injection site ARs (pain 19.9%, erythema 5.8% and swelling 4%)	ISS [5)]
Solicited systemic reactions[2)]	**Toddlers** Irritability Anormal crying Appetite loss Drowsiness Fever Vomiting	%	 48.6 34.5 28.2 24.2 9.1 6.2		In **toddlers** the frequency of systemic ARs was higher compared to older subjects	ISS[4)]
	Subjects 2 years and older Myalgia Headache Malaise Fever *Grade 3*	%	 30.7 26.4 21.7 1.2 4.1		Adults above **56-64 years** of age comparable to adolescents/adults 18-55 years Adults **65 years and above** reported less frequently systemic ARs (Myalgia 22.2%, Headache 15.9%, Malaise 14.1%, Fever 1.7%)	ISS [5)]
Unsolicited ARs[3)]	**Toddlers** *Most common:* Diarrhea flatulence constipation	%	5 2.3 0.5 0.3			ISS[4)]

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	Subjects 2 years and older *Most common:* Injection site pruritus Injection site warmth Diarrhoea dizziness Fatigue nausea injection site bruising injection site rash *Grade 3*	%	2.8 0.7 0.4 0.2 0.2 0.1 0.1 0.1 0.1 0.1		Adults above **56-64 years** of age comparable to adolescents/adults 18-55 years Adults **65 years and above** reported more frequently unsolicited ARs (5.2%, most frequently injection site pruritus; no grade 3 AR, reported)	ISS [5)]

Abbreviations:

Notes: 1) within 30 minutes after vaccination 2) within 7 days after vaccination 3) within 30 days after vaccination 4) Contributing studies: MET51 and MET54 5) Contributing studies MET35, MET43, MET44, MET49, MET50 and MET56

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In all main clinical studies, the primary endpoints were met and non-inferior seroresponse rates or seroprotection rates, respectively, of MenQuadfi 30 days after vaccination against different comparators was demonstrated for all serogroups in all age groups except for serogroup A in the subgroup of MenC-primed toddlers. The applicant justifies the applied non-inferiority margins mainly based on precedence from other development programs, as well as feasibility concerns. A justification based on clinical considerations (e.g.

relevance of a 10% lower seroresponse rate in terms of vaccine efficacy) or statistical considerations (e.g. assay sensitivity) is missing. Given the reference to other development programmes as well as the clear demonstration of NI against various comparator vaccines across studies this issue is not further pursued.

Although seroprotection is considered clinically relevant for the individual subject, seroresponse is considered more relevant for the immunogenicity assessment, especially since a rather high percentage of subjects with seroprotective titres at baseline was included in the submitted studies. In all but one study non-inferiority analyses were based on seroresponse rates. However, demonstration of non-inferiority in children was based on seroprotection rates. An additional analysis based on seroresponse rates was provided upon request and showed non-inferiority for all serogroups.

The lower seroresponse rates against serogroup A as observed with concomitant vaccination with PCV13 and the lower seroresponse rates against serogroup A in toddlers primed with a CRM-conjugate vaccine compared to a TT-conjugate vaccine are considered relevant to be described in the SmPC. Although the latter finding is based on data from subgroup analysis in a rather low number of subjects and should therefore be interpreted cautiously, this effect was not observed for the comparator vaccine. Especially for vaccinees at high risk for MenA infection, this information is considered relevant. Overall, an impact of the vaccine conjugate used for priming cannot be ruled out based on the presented data.

The investigation of long-term persistence data in the postmarketing is considered acceptable. Nevertheless, the absence of such data so far needs to be adequately stated in the SmPC.

From both other licensed quadrivalent meningococcal vaccines rapid waning of antibodies against serogroup A is known and is described in their SmPCs. Due to the absence of any data beyond D30 following vaccination with MenQuadfi, it remains unknown if this is also applicable for MenQuadfi or not. A general statement on this effect known from other licensed vaccines should therefore be added in the SmPC.

Declining seroresponse and seroprotection rates with age are not unexpected and were also observed in the comparator groups.

Several concerns have initially been raised whether the presented data are representative for the European population. Only two studies have been conducted in the EU and it is known also from other (EU-licensed) meningococcal vaccines, that a variety of factors can have significant influence on the circulating serotypes and the potential degree of carriage. A comparison of data from toddlers from studies MET51 (EU) and MET57 (Russia, Mexico, South Korea, Thailand) showed comparable seroresponse rates despite different seroprotection rates at baseline. Data for older subjects is still not available but the presented results for toddlers are reassuring.

The identified uncertainties concerning concomitant vaccinations have an impact on the SmPC wordings. This concerns on the one hand the observed differences (Pertussis antigens, PCV13). Even though the clinical consequences of a decreased immune response to 3 of 4 pertussis antigens is not entirely clear and similar observations were reported for other meningococcal vaccines, this result is relevant for practical use and thus should be provided in the product information. Concomitant use of MenQuadfi and PCV13 can be recommended but a respective warning for subjects at risk of MenA infections has to be included in the SmPC. On the other hand, this concerns extrapolation of available data into general recommendations in section 4.5 of the SmPC. It is not considered straightforward to extrapolate data from one particular vaccine to all vaccines containing the same antigens. Notably, variable enhancement or depression of immune responses to conjugated saccharides has been observed when the carrier proteins for co-administered products are the same or different, so that generalizations cannot be made beyond the specific vaccines studied and respective detailed information about the used vaccines have to be added to the SmPC. However,

the concerns on concomitant vaccination are not considered to affect the benefit risk balance. Upon request, these findings were adequately reflected in the SmPC.

For a comprehensive assessment of immunogenicity of MenQuadfi data on long-term persistence and on the ability of MenQuadfi to boost itself are necessary. The applicant plans to address this with three postmarketing studies, which are included in Annex II as category I post marketing studies.

The applicant introduced a release specification of not more than 20% free saccharides and an end-of-shelf-life specification that allows 30% free saccharides. Whereas the theoretical concern that an increased rate of free saccharides might cause hyporesponsiveness to further doses of conjugate vaccine will be investigated in the postmarketing by booster studies, there is still insufficient justification for the proposed end-of-shelf-life specifications. The release limits for free PS have been lowered to NMT 13%. The applicant commits to reassess stability specifications of NMT 30 % for all serogroups, which is acceptable.

The ability of MenQuadfi to boost other quadrivalent meningococcal vaccines was investigated. However, as the majority of adolescent subjects previously received Menactra it is unclear in how far data mainly derived from subjects who previously received a vaccine not licensed in the EU can be extrapolated to the European population. Three postmarketing studies are planned for further evaluation of immunogenicity of MenQuadfi in primed subjects (included in Annex II). Furthermore, no data from adults and adolescents who were primed with a MenC vaccine are available. However, respective data from toddlers are reassuring to some degree that MenQuadfi is able to elicit a sufficient immune response in subjects primed with EU-licensed vaccines as well as in MenC primed subjects. As there is no clinically plausible reason to assume that there might be a difference between toddlers and older age groups, the postponing of further investigation in adolescents and adults to the postmarketing is acceptable.

The concerns raised concerning the stability of the conjugate could impact the intended shelf life claim of 48 months. So far (day 150), stability data have been provided until the time point of 42 months. All parameters tested meet the specifications. As no data is available for 48 months, the proposed shelf life claim of 48 months could not currently be endorsed and was revised to 42 months.

Overall, the nature and frequency of the reported adverse events are considered to be consistent with those expected after meningococcal vaccine administration. There were no serious or unexpected safety findings with a suspected causal relationship to the vaccine.

No concern is raised on the use of non EU-licensed comparator vaccines from a safety perspective for the following reasons: Comparative data to an EU-licensed vaccine are available in a proportion of subjects and both conjugated vaccines Menveo and Menactra are expected to show largely comparable safety profiles, despite containing a different amount of antigen and different carrier proteins. Indeed, only small differences in the safety profiles were observed between the different treatment arms that are considered not to influence the benefit risk conclusion. Further, adolescents and adults are expected to show comparable safety profiles based on mechanistic considerations, which was also confirmed by the results. In addition, the safety assessments are considered appropriate and sufficiently similar across studies to allow pooling of the results by age group and by vaccine type. Therefore, a within treatment-group comparison by age group for the pooled MenACYW analysis as well as the between-treatment group comparison of MenACYW to Menveo and Menactra within the ISS is overall sufficient. Reassuringly, older adults, in whom more adverse reactions were reported compared to Menomune, showed a lower reactogenicity profile when compared to younger adults. This is appropriately reflected in the SmPC.

3.7.2. Balance of benefits and risks

From an immunogenicity point of view, the results are overall favourable. In all clinical studies the primary endpoints were met. There was even a trend towards higher seroresponse rates for MenQuadfi compared to other quadrivalent meningococcal vaccines. Also, secondary endpoints do in general support the results from the primary endpoints. Nevertheless, some uncertainties remain but could be adequately reflected in the SmPC or addressed in the postmarketing.

The safety profile of MenQuadfi is considered acceptable.

The applicant initially claimed the following indication for MenQuadfi: "MenQuadfi is indicated for active primary and booster immunisation for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y. MenQuadfi is indicated for use in individuals 12 months of age and older.

The use of this vaccine should be in accordance with available official recommendations."

Including the wording, "primary and booster" immunisation, was not considered appropriate. Two comparable quadrivalent meningococcal vaccines are already approved in the EU (Menveo since 2010 and Nimenrix since 2012). The indication of MenQuadfi should be consistent with these other vaccines. Therefore, rewording of the indication was needed.

The applicant revised the wording of indication as follows: "MenQuadfi is indicated for active immunisation of individuals from the age of 12 months and older, against invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y." This wording is considered acceptable.

Taken together, MenQuadfi could be approvable in the revised indication.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of MenQuadfi is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of MenQuadfi is favourable in the following indication:

"MenQuadfi is indicated for active immunisation 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".

The CHMP therefore recommends the granting of the marketing authorisation subject to the following

conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Study MET62: Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered as a Booster Dose in Children Vaccinated 3 Years Earlier as Toddlers	Q2 2021
Study MET59: Immunogenicity and safety of a booster dose of an investigational quadrivalent MenACYW conjugate vaccine in adolescents and adults	Q2 2022

Description	Due date
Study MEQ00066: Safety and immunogenicity of a single dose of MenACYW conjugate vaccine at least 3 years following initial vaccination with either Menomune vaccine or MenACYW conjugate vaccine in Older Adults	Q1 2024

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0164/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.