19 September 2024
EMA/464092/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Penbraya

Common name: Meningococcal groups A, C, W, Y conjugate and group B vaccine (recombinant, adsorbed)

Procedure No. EMEA/H/C/006165/0000

Note

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

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List of abbreviations

ACWY	*Neisseria meningitidis* groups A, C, W, and Y
ADH	adipic acid dihydrazide
ADHD	attention deficit hyperactivity disorder
ADR	adverse drug reaction
AE	adverse event
AR	assessment report
AS	active substance
ASI	active substance intermediate
BI-RCV	Boehringer-Ingelheim, Austria
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine (Trumenba)
CDAP	1-cyano-4-dimethylamino-pyridinium tetrafluoroborate
CE	Conformité Européenne certificate
cHAP	ceramic hydroxyapatite chromatography
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CoP	correlate of protection
COVID-19	coronavirus disease 2019
CPP	critical process parameters
CQA	critical quality attributes
CRF	case report form
CSR	clinical study report
DMAB	dimethylaminobenzaldehyde
DMAP	4-dimethylaminopyridine
DNA	deoxyribonucleic acid
DOE	design of experiments
DTap	diphtheria, tetanus, acellular pertussis
EDAC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
e-diary	electronic diary
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
EVA	ethylene vinyl acetate
FDA	Food and Drug Administration
fHbp	factor H binding protein
FIH	first-in-human
FMEA	failure modes and effects analysis
FP	finished product
G1	group 1
G2	group 2
GCP	good clinical practice
GMP	good manufacturing practice
GMTs	geometric mean titres
GSK	Glaxo Smithkline
HCP	host cell protein
HDPE	high density polyethylene
HPLC	high-performance liquid chromatography
hSBA	serum bactericidal assay using human complement
ICD	informed consent document
ICE	intercurrent event
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICP–OES	inductively coupled plasma – optical emission spectrometry
IgG	immunoglobulin G
IMD	invasive meningococcal disease
IPT-C	in-process tests for control
IPT-M	in-process tests for monitoring
IRM	interim reference standard
IRT	interactive response technology
IVP	*in vivo* potency
IVRP	*in vitro* relative potency

IVRA	*in vitro* relative antigenicity method
kDa	kilo dalton
L	litre
LL	lower limit
LLOQ	lower limit of quantification
LOD	limit of detection
MAA	marketing authorisation application
mAb	monoclonal antibody
MAE	medically attended adverse events
MAH	marketing authorisation holder
MCAR	missing completely at random
MCB	master cell bank
MCC	monovalent MenC conjugate
Men	meningococcal
MenA	*Neisseria meningitidis* group A
MenAAH-TT	meningococcal serogroup A - tetanus toxoid conjugate
MenABCWY	*Neisseria meningitidis* Group A, B, C, W, and Y vaccine (i.e. Penbraya)
MenACWY	*Neisseria meningitidis* groups A, C, Y, and W-135
MenACWY-CRM	Meningococcal (groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (Menveo)
MenACWY-CRM197	MenACWY vaccine conjugated to Corynebacterium diphtheriae CRM197 protein (Menveo)
MenACWY-TT	MenACWY vaccine conjugated to tetanus toxoid carrier protein (Nimenrix)
MenB/ MnB	*Neisseria meningitidis* group B
MenB-fHbp	Trumenba
HFV-MnB	high fill volume MenB FP component (MnB Bivalent rLP2086 FP)
MenC	*Neisseria meningitidis* group C
MenCAH-TT	meningococcal serogroup C - tetanus toxoid conjugate
MenW	*Neisseria meningitidis* group W
MenW-TT	meningococcal serogroup W - tetanus toxoid conjugate
MenY	*Neisseria meningitidis* group Y
MenY-TT	meningococcal serogroup Y - tetanus toxoid conjugate
MF	microfluidisation
mITT	modified intention to treat
MMR	measles, mumps, rubella vaccine
N. meningitidis	*Neisseria meningitidis*
N	Neisseria
N	number of participants
NA	not applicable
NDCMC	newly diagnosed chronic medical conditions
NE	non estimable
NI	noninferiority
NIP	national Immunisation programme
No.	number
NOR	normal operating ranges
OMV	outer membrane vesicle
PAR	proven acceptable range
PFS	pre-filled syringe
Ph. Eur.	European Pharmacopeia
PASS	post-authorisation safety studies
PD	protocol deviation
PD1, PD2	post-dose 1, post-dose 2
PDCO	paediatric committee
PETG	polyethylene terephthalate
PFS	pre-filled syringe
PIP	paediatric investigation plan
PorA	porin A
PP	polypropylene
PPQ	process performance qualification
PS80	polysorbate 80
PSUR	periodic safety update report
PT	preferred term
PV1E	post-vaccination 1 evaluable population
PV2E	post-vaccination 2 evaluable population

QFF	Q sepharose fast flow
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
RP-HPLC	reverse phase high-performance liquid chromatography
RRI	research related injuries
rSBA	serum bactericidal assay using rabbit complement
SAE	serious adverse events
SAP	statistical analysis plan
SBA	serum bactericidal assay
Sd-hSBA	single-dilution serum bactericidal assays
SEC	size exclusion chromatography
SmPC	summary of product characteristics
SOC	system organ class
SRM	Study reference manual
TMAE	trimethylaminoethyl
TSE	transmissible spongiform encephalopathy
TT	tetanus toxoid
np-TT	non-precipitated-TT solution.
pTT	purified precipitated-TT solution
UFDF	ultrafiltration/diafiltration
US	United States
USP	United States Pharmacopeia
vs	versus
WCB	working cell bank
WHO	World Health Organization
WRM	working reference material
YoA	years of age

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 2 February 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Penbraya, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication "*TRADENAME is indicated for active immunisation of individuals 10 years of age and older to prevent invasive disease caused by Neisseria meningitidis groups A, B, C, W, and Y.*"

1.2. Legal basis, dossier content

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 studies.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0055/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0055/2023 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP P/0055/2023.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

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

Date	Reference	SAWP co-ordinators
24 June 2021	EMA/SA/0000058078	*Rune Kjeken, Jens Reinhardt*

27 January 2022	EMA/SA/0000071412	*Jens Reinhardt, Johannes Hendrikus Ovelgönne*

The scientific advice pertained to the following *quality and clinical* aspects:

- Acceptability of proposed strategy for separation of release and stability testing of DP components.
- Data requirements and label wording regarding antipyretic (paracetamol) administration together with the vaccine in infants.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Ingrid Wang

The application was received by the EMA on	2 February 2023
The procedure started on	15 June 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 September 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 September 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 September 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 October 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	5 June 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 June 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 June 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	04 September 2024
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 Penbraya on	19 September 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The gram-negative diplococci bacterium *N. meningitidis* is a human pathogen that colonizes the upper respiratory tract, which, in some individuals, can cause serious, life-threatening invasive meningococcal disease (IMD), which clinically presents as septicaemia, meningitis, or both. The bacteria can spread rapidly through contact with saliva or nasal secretions.

Serogroups are defined by chemically and immunologically distinctive polysaccharides. Multiple serogroups are known to cause IMD.

Asymptomatic colonization of the upper respiratory tract by encapsulated *Neisseria meningitidis* is common, observed in 5–10% of persons and up to 25% in certain age groups. However, only a small percentage of colonized persons develop IMD.

2.1.2. Epidemiology and risk factors, screening tools/prevention

The vast majority of cases of meningococcal disease worldwide is caused by 5 serogroups (A, B, C, Y and W-135). Most common causes of IMD in Europe are serogroups B and C, however recently there has been an increase of IMD due to serogroup W. In 2018 the overall notification rate for IMD was 0.6 cases per 100,000 population in 30 EU/EEA countries, which was similar to previous years (ECDC, 2022) with slight increase compared to 2015. Children under one year of age experience the highest rates of IMD (8.3/100 000), followed by 1-4 years old (2.4/100,000) and adolescents and young adults 15-24 years old (0.9/100,000).

The prevalence of serogroups varies with geography, calendar time, and subject age group. In Europe, the dominating serogroups in 2018 were serogroup B (51%), C (15%), W (18%) and Y (12%) (ECDC, 2022). Serogroup C was most prominent in 25-49 years old, while serogroup W and Y were most prominent in those aged 65 years and above. Although the proportion of serogroup C remained stable from 2013 to 2018 (ECDC, 2022), the incidence rate of serogroup C has decreased following the introduction of immunisation programmes across European countries (Nuttens, 2022). Serogroup W notification rate increased 3-fold from 2013 to 2018. The increase was mostly due to increases among children less than 5 years old and adults 50 years old and above and was driven by an hypervirulent serogroup W strain belonging to clonal complex 11 (Krone, 2019). The proportion of serogroup Y increased from 2% in 2000 to over 12% in 2018 (ECDC, 2007; ECDC, 2022).

After birth, neonates remain relatively protected against IMD by the presence of maternal antibodies acquired trans-placentally in utero. As the material antibodies decrease, infants become relatively susceptible, with the lowest antibody levels found in infants between 6 months and 2 years of age; natural immunity begins to be acquired after 2 years of age (Pollard, 2001; Goldschneider, 1969a; Goldschneider, 1969b). Overcrowding and social behaviour are other risk-factors for IMD. Age, and social behaviour explain the age-related incidence peaks seen for IMD.

2.1.3. Clinical presentation, diagnosis and stage/prognosis

Patients with invasive meningococcal infection often present initially with flu-like symptoms. Other signs of meningococcal meningitis may include headache, stiff neck, fever, chills, malaise, and shock.

Despite the availability of medical treatment and effective antibiotics, the mortality rate of IMD has been reported to be 8-16%, even when promptly diagnosed and treated. Up to 10-19% of survivors have lifelong sequelae (Kirsch, 1996, Edmond, 2010), including hearing loss, speech disorders, loss of limbs, mental retardation, paralysis, and skin scarring.

2.1.4. Management

Treatment

Treatment of IMD involves prompt recognition of disease and administration of antibiotics, usually beta-lactam antibiotics. However, despite prompt and adequate treatment, IMD still has a high rate of morbidity and mortality.

Prophylactic vaccines

For the primary prevention of invasive meningococcal vaccines several monovalent vaccines are currently registered for the active immunisation against serogroups B and C. In addition also quadrivalent meningococcal vaccines against serogroups A, C, W and Y are available. (Table 1)

Table 1. Overview of vaccines for active immunisation against invasive meningococcal disease currently licensed in Europe

Serogroups	Product	Indicated for
ACWY	MenQuadfi, Sanofi Pasteur	12 months and older
	Menveo, GSK	2 years and older
	Nimenrix, Pfizer	6 weeks and older
B	Bexsero, GSK	2 months and older
	Trumenba, Pfizer	10 years and older
C	NeisVacC, Pfizer	2 months and older

2.2. About the product

Penbraya is a pentavalent vaccine using the components from Nimenrix (EMEA/H/C/002226, meningococcal groups A, C, W-135 and Y conjugate vaccine) and Trumenba (EMEA/H/C/004051, meningococcal group b vaccine (recombinant, adsorbed)), which are currently both authorised in the European Union. Nimenrix is not authorised for co-administration with any other Meningococcal vaccine. Trumenba is authorised for concomitant use with MenACWY conjugated vaccine.

The pentavalent vaccine consists of 5 micrograms each of polysaccharides of *N. meningitidis* group A, C, W-135 and Y conjugated to 44 micrograms tetanus, toxoid carrier protein and 60 micrograms each of *N. meningitidis* group B fHbp subfamily A and B absorbed on aluminium phosphate (0.25 milligrams of aluminium. After reconstitution this is administered as a 0.5 mL dose.

The pentavalent MenABCWY vaccine was designed to induce the production of bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* groups A, C, W, and Y and to the surface-exposed lipoprotein fHbp subfamilies A and B of *N. meningitidis* group B. Anti-meningococcal antibodies protect against invasive meningococcal disease via complement mediated bactericidal activity.

The claimed indication is active immunisation of individuals 10 years of age and older to prevent invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y.

The proposed posology is to 1) administer 2 doses (0.5 mL each) at least 6 months apart for prevention of meningococcal disease caused by groups A, B, C, W, and Y and 2) administer 1 dose (0.5 mL) for prevention of meningococcal disease caused by groups A, C, W, and Y.

2.3. Quality aspects

2.3.1. Introduction

2.3.2. Active Substance MnB rLP2086 Subfamily A and Subfamily B

2.3.2.1. General information MnB rLP2086 Subfamily A and Subfamily B

The finished product is composed of two Meningococcal Serogroup B active substances (Subfamily A and Subfamily B), both of which are recombinant MnB rLP2086 lipoproteins expressed in and purified from *Escherichia coli.*

The active substance components of bivalent rLP2086 antigens are both members of the *Neisseria meningitidis* family of proteins called factor H binding proteins (fHBP). Based on primary amino acid sequence, fHBP variants can be segregated into two subfamilies, designated subfamily A and B. To ensure that the vaccine elicits a broad functional immune response, one component of bivalent rLP2086 corresponds to an fHBP variant from subfamily A (variant A05) and the second from subfamily B (variant B01).

The subfamily A and B proteins are tri-lipidated at the N-terminus with the three fatty acids covalently linked to the protein.

2.3.2.2. Manufacture, characterisation and process controls MnB rLP2086 Subfamily A and Subfamily B

The MnB rLP2086 Subfamily A and Subfamily B active substances are manufactured at Pfizer, Strängnäs, Sweden.

Description of manufacturing process and process controls MnB rLP2086 Subfamily A and Subfamily B

The MnB rLP2086 antigens (subfamily A and B) are individually expressed in *E. coli* and the fermentation and recovery processes are identical for both subfamily proteins. The production consists of 3 stages: shake flask, seed fermenter and production fermentation. The cells are harvested by centrifugation and lysed. The cellular fragments are recovered by a second centrifugation step and the protein is extracted from the cellular fragments. The extract is centrifuged and clarified. The clarified protein extract is then transferred to purification.

The purification process of MnB rLP2086 subfamily A and subfamily B are different.

Both purification processes comprise chromatography purification , acid precipitation and depth filtration. These steps are then followed by higher resolution purification steps. Then the AS pool is concentrated, diafiltered, filtered and filled. The bags containing purified active substance are stored frozen. MnB rLP2086 subfamily A and B ASs are stored in specified storage containers for storage. Leachable testing has been performed and the provided information is satisfactory.

The active substance manufacturing process is considered acceptable process in-process controls are adequately set to control the process. There are no reprocessing procedures for the purification of MnB rLP2086 subfamily A or B.

The same active substance manufacturing process is licensed for Trumenba. Process validation data from Trumenba were used to support the MenABCWY application.

Control of materials MnB rLP2086 Subfamily A and Subfamily B

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human materials are used in the active substance manufacturing process. See the adventitious agents section for details of materials of biological origin used.

rLP2086 Subfamily A and B are produced by plasmid in *E. coli*. The construction of the plasmids is sufficiently well described.

The same cell banks are used as for Trumenba. The MnB rLP2086 subfamily A and B master cell banks (MCB) were prepared in accordance with ICH Q5B and Q5D. The MCBs testing provided confirmation that the MnB rLP2086 producing cell lines are free from microbial and bacteriophage contamination and also that they are of an *E. coli* lineage. Plasmid integrity was also demonstrated. Working cell banks (WCB) are suitably tested. MCBs as well as the WCBs are enrolled in a stability programme and tested according to a pre-approved stability protocol. Overall, the source, history and generation of the cell banks is sufficiently described. Genetic stability of the Subfamily A and B protein expression strains has been demonstrated on end of production cells. Protocols for the establishment of future WCBs is provided.

Control of critical steps and intermediates MnB rLP2086 Subfamily A and Subfamily B

Process parameters and tests are used to control the process during manufacture. All critical process parameters (CPPs) are described as well as relevant non-CPPs that have an impact on quality attributes. Both types of process parameters have acceptable ranges. In-process tests for control (IPT-C) used in the manufacture of the active substances have associated acceptance criteria. The monitoring tests may have action limits. These in-process controls (process parameters and in-process tests) are used to ensure control of the individual process steps, process consistency and product quality.

Process validation MnB rLP2086 Subfamily A and Subfamily B

The AS manufacturing processes were validated by successfully manufacturing four full scale rLP2086 subfamily A AS batches and three full scale rLP2086 subfamily B AS batches. Results of operational parameters, in process controls for select quality attributes, and impurities are reported as well as regeneration and cleaning results of resins and ultrafiltration/diafiltration (UFDF) units, and a deviation summary. Shipping validation has also been conducted. The data provided are satisfactory and consistent, indicating that each step has been appropriately validated at the commercial AS manufacturing site, Pfizer Strängnäs.

Manufacturing process development MnB rLP2086 Subfamily A and Subfamily B

A comprehensive understanding of the MnB rLP2086 active substance manufacturing process has been developed through commercial-scale runs and process characterisation studies that include design of experiments (DOE), using scale-down models of individual unit operations. A structured quality risk management programme was applied, including a Failure Modes and Effects Analysis (FMEA).

Comparability between the MnB AS used in clinical studies, manufacturing processes through commercial was adequately shown.

Characterisation MnB rLP2086 Subfamily A and Subfamily B

The active substance has been sufficiently characterised by physicochemical and biological methods. Characterisation of the active substances was performed on one lipoprotein batch subfamily A and one batch subfamily B which were derived from the full scale commercial process. These studies confirmed

that the MnB rLP2086 subfamily A and B lipoproteins exhibit the expected amino acid sequence and fatty acids. The results demonstrate that MnB rLP2086 subfamily A and B have the expected structure and biological activity.

The applicant has appropriately identified a number of process-related and product-related impurities that could be present in the active substances. These include proteins (e.g. host cell protein), nucleic acids (host cell DNA), metals and organic compounds that were derived from the host cells, medium, and purification process. The removal of process-related impurities was demonstrated through supplemental testing during process validation. Specified impurities have been present in materials used in clinical trials.

2.3.2.3. Specification MnB rLP2086 Subfamily A and Subfamily B

The commercial specifications for MnB rLP2086 active substance for both subfamily A and subfamily B include appropriate physicochemical tests and tests for identity, purity, potency, physicochemical attributes and microbiological properties.

The specifications (including test methods) are aligned with Trumenba specification except for the removal of endotoxin on stability samples since it is not considered as a stability indicating test. This is supported.

Analytical methods MnB rLP2086 Subfamily A and Subfamily B

Compendial methods are used for appearance, bioburden, pH and endotoxin. Non-compendial methods comprise *in vitro* relative antigenicity method (IVRA), RP-HPLC, protein concentration determination, Polysorbate 80 (to calculate PS80 to protein molar ratio), residual DNA and residual HCP. Validation of these methods was performed in conformance with ICH guidelines.

The analytical methods used have been sufficiently described and non-compendial methods were appropriately validated in accordance with ICH guidelines.

Batch analysis MnB rLP2086 Subfamily A and Subfamily B

Batch Analyses results are provided for batches used in Phase 2, Phase 3, process performance qualification (three PPQ lots), and primary and supportive stability studies. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials MnB rLP2086 Subfamily A and Subfamily B

A bivalent reference material and monovalent reference materials are used in the testing of MnB AS and FP. The reference lots are linked to material used in clinical trials. Protocols for qualification of future reference standards are provided.

2.3.2.4. Stability MnB rLP2086 Subfamily A and Subfamily B

The proposed shelf life for MnB rLP2086 AS is 48 months when stored at the recommended temperature of -55±8°C.

The shelf-life claim is based on 48 months of real time stability data generated at the long-term condition of –55±8°C from the three commercial PPQ/primary stability batches. Tested parameters include those that are stability-indicating. The stability programme is designed to follow ICH Guideline Q5C: Quality of Biotechnological Products, Stability Testing of Biotechnological/Biological Products.

A shelf-life of 48 months when stored at the recommended temperature of –55 ± 8°C, is considered acceptable.

2.3.3. Active Substance MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

2.3.3.1. General information MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

The MenACWY-TT finished product component is marketed as Nimenrix and is composed of four active substances, all of which are polysaccharides conjugated to tetanus toxoid (TT).

Dried bulk meningococcal polysaccharides of the bacterium Neisseria meningitidis serogroups A, C, W and Y form the active substance intermediates (ASIs) MenA, MenC, MenW and MenY, respectively. The polysaccharides are isolated from the Neisseria meningitidis strains, as recommended by the WHO for the manufacture of meningococcal vaccine.

MenA and MenC are first activated and derivatised to form the MenAAH and MenCAH intermediates, which are coupled to TT to form the ASs MenAAH and MenCAH-TT. MenW and MenY are activated and then directly coupled to TT to form the ASs MenW-TT and MenY-TT.

The exact conjugation positions of the polysaccharides to TT have not been determined due to inherent complexity of the conjugates. Chemical analyses are used to determine the apparent size distributions as well as the presence of free and conjugated protein and polysaccharide. As part of the formulated finished product, meningococcal serogroup A/C/W/Y-TT conjugate induces a protective immune response against meningococcal serogroup A/C/W-135/Y bacteria in immunised individuals.

2.3.3.2. Manufacture, characterisation and process controls MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

The commercial manufacture of the ASIs takes place at Pfizer Sanford, NC, USA, and the commercial manufacture of the conjugated ASs takes place at Pfizer Grange Castle, Clondalkin, Ireland. Process validation data were used to support recent Nimenrix variations for the introduction of the Pfizer Sanford site and for the introduction of the high capacity AS process at Pfizer Grange Castle.

The manufacture of the different polysaccharides follows the same basic principle with slight adaptations between the serogroups.

Each meningococcal polysaccharide serogroup ASI is individually produced from a single fermentation. The fermentation process consists of 4 stages: plate pre-culture, shake flask pre-culture, fermentation and inactivation by heating. It starts with the thawing of one vial of working cell bank (WCB) to inoculate agar plates. Polysaccharide is purified from the inactivated fermentation broth. This involves two precipitation steps, a UFDF step, a selective alcohol precipitation step and a drying step. The dried bulk polysaccharide ASIs are dispensed into specified storage containers for storage and shipped frozen for manufacture of the ASs.

Prior to use in the conjugation process, the tetanus toxoid (TT) ASI is subjected to an additional purification to remove potential aggregates and to achieve the appropriate concentration. TT for use in the MenAAH and MenCAH-TT AS manufacturing processes is precipitated, centrifuged, clarified, ultrafiltered, Chromatography treated to separate TT-monomers from the TT aggregates, ultrafiltered and concentrated to obtain the purified precipitated-TT (pTT) solution. TT for use in the MenW-TT and MenY-TT AS is manufactured by the same process except for the precipitation step, which results in the purified non-precipitated-TT (npTT) solution. Purified pTT/npTT is filtered and stored until conjugation to the polysaccharides.

The conjugation for the manufacture of MenAAH and MenCAH-TT consists of a microfluidisation (MF) process to reduce the size of the polysaccharide via mechanical action, a derivatisation process, and a conjugation process involving the activation of a fraction of TT carboxylic acid groups) and subsequent

conjugation with the derivatised MenAAH/MenCAH. The conjugation for the manufacture of MenW-TT and MenY-TT involves the MF and conjugation processes but lacks the derivatisation process. Microfluidised MenW-135/MenY hydroxyl groups are activated in the presence of npTT. MenAAH-TT/MenCAH-TT/MenW-TT/MenY-TT conjugate is separated by clarification and chromatography. The purified conjugates are sterile filtered into specified storage containers for storage and stored at 2 – 8°C in a long-term storage area before shipment for use in the FP manufacturing. Testing has adequately shown that leachable studies did not need to be performed.

The manufacturing processes for ASIs and ASs are identical to what is registered for Nimenrix, however the descriptions of process parameters and acceptable ranges are slightly changed to accommodate the re-evaluated control strategy for the MenABCWY vaccine. As requested, the applicant included additional process parameters with acceptance criteria in the manufacturing process descriptions.

Control of materials MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human materials are used in the active substance manufacturing process. See the adventitious agents section for details of materials of biological origin used.

The origin of each strain of *Neisseria meningitidis* serogroups A, C, W and Y used to produce the respective cell banks is described, The same working cell banks (WCBs) are used for Nimenrix and the MenACWY component of the MenABCWY vaccine. When Nimenrix was acquired from GSK, the GSK master cell bank (MCB) was used to generate the Pfizer MCB, which was then used to generate WCBs to be used in Pfizer Sanford for active substance intermediate (ASI) production. The cell banks were prepared in accordance with ICH Q5D. Culture purity, identity, and viability testing is performed on the MCBs and WCBs. Results show that the polysaccharide producing cell lines are free from microbial contamination and produce polysaccharides of the correct serogroups. MCBs as well as the WCBs are enrolled in a stability programme and tested according to a pre-approved stability protocol. Overall, the source, history and generation of the cell banks is sufficiently described. Protocols for the generation of future WCBs are provided.

Control of critical steps and intermediates MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

The purified bulk polysaccharides (MenA/MenC/MenW-135/MenY) and additional purified tetanus toxoid (pTT) and non-precipitated tetanus toxoid (npTT) are defined as process intermediates and have each been provided with in-process test methods and validations, release and stability specifications, batch analyses, container closure information, and stability studies and commitments. The release and stability specifications and testing procedures for the ASIs are identical to those registered for Nimenrix. The control strategy for the ASIs and ASs has been re-evaluated based on additional Pfizer generated process development study data. Process parameters and tests are used to control the process during manufacture. All critical process parameters (CPPs) are described as well as relevant non-CPPs that have an impact on quality attributes. Both types of process parameters have acceptable ranges. In-process tests for control (IPT-C) used in the manufacture of the active substances used to control the active substance intermediates (ASI) and active substance quality attributes within a specified range and have associated acceptance criteria. In-process tests for monitoring (IPT-Ms) are used to monitor polysaccharide's quality attributes and may have action limits. These in-process controls (process parameters and in-process tests) are used to ensure control of the individual process steps, process consistency and product quality. The information related to the tetanus toxoid intermediate which is used to produce the purified tetanus toxoid intermediate is actually provided as a separate AS section (see later).

Process validation MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

The manufacturing processes for MenA/C/W-135/Y ASIs and MenAAH/CAH/W/Y-TT ASs were validated by successfully manufacturing three consecutive full-scale batches of each meningococcal serogroup polysaccharide at Pfizer Sanford as well as three consecutive full scale batches of pTT/npTT and TT-conjugates for each serogroup at Pfizer Grange Castle. For MenAAH-TT and MenCAH-TT, one additional derivatisation batch was manufactured from one microfluidisation batch and forward processed into an additional AS batch. Results of operational parameters, in process controls, yield, bioburden, endotoxin and impurities are reported as well as dispense uniformity reports, and a deviation summary. The data provided are satisfactory and consistent and indicate that each step has been appropriately validated at the manufacturing sites. In addition, the proposed hold times and lifetime studies for reusable membranes and resins and the shipping validation are considered appropriately validated.

Manufacturing process development MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

A comprehensive understanding of the ASIs and ASs manufacturing processes has been developed through commercial-scale runs and process characterisation studies that include design of experiments (DOE), using scale-down models of individual unit operations. A structured quality risk management programme was applied, including a Failure Modes and Effects Analysis (FMEA). The list of critical quality attributes (CQAs), which are attributes established by an iterative process of quality risk, criticality assessment and experimentation to have an impact on the quality of the vaccine finished product, is significantly reduced compared to what is currently registered for Nimenrix. However, all the attributes are considered in the control strategy and their control is established by means of release, stability and in-process testing. It is therefore considered not necessary to request the addition of further specific attributes.

Comparability between the ASI/AS during clinical through commercial manufacturing processes by GSK and Pfizer was adequately shown.

Characterisation MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

Characterisation of the meningococcal polysaccharide serogroups from Nuclear Magnetic Resonance (NMR) spectroscopic measurements of proton, carbon, and phosphorous chemical shift and internuclear correlation between proximal nuclei was conducted to elucidate serogroup A/C/W/Y repeat unit solution structures were presented. This is considered state-of-the-art. The presented data is in accordance with characterisation currently registered for Nimenrix and with published structures. For the conjugates, no chemical structures are provided due to the inherent complexity and reference is made to batch analysis data with regard to physicochemical characteristics, this is acceptable. As requested, information has been provided that sufficiently assures the suitability of the polysaccharide serogroup-specific antibodies and anti-tetanus toxoid antibody applied for the biological and immunological characterisation of the active substance MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT.

The applicant has appropriately identified a number of process-related and product-related impurities that could be present in the active substances. The removal of these process-related impurities was demonstrated through supplemental testing during process validation. These include proteins (host cell protein), nucleic acids (host cell DNA), metals and organic compounds that were derived from the host cells, medium, and purification process. The removal of process-related impurities was demonstrated through supplemental testing during process validation. Specified impurities have been present in materials use in clinical trials.

2.3.3.3. Specification MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

The commercial specifications for meningococcal serogroup A/C/W/Y-tetanus toxoid (TT) conjugates active substances include appropriate tests for identity, purity, potency, physicochemical attributes and microbiological properties..

The specifications (including test methods) are aligned with the Nimenrix specification except for the release acceptance criteria for free Polysaccharide, which has been tightened by the applicant based on statistical analyses in scope for the MenABCWY vaccine, with a harmonised approach across the serogroups. This is supported.

Analytical methods MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

Compendial methods are used for appearance, endotoxin, pH, and sterility. Non-compendial methods comprise inductively coupled plasma – optical emission spectrometry (ICP-OES), para dimethylaminobenzaldehyde (DMAB) colorimetric method. DMAB, and resorcinol for determination of free polysaccharide and polysaccharide concentration, HPLC for free protein, ELISA for identity, HPLC for molecular size distribution, and Lowry for protein concentration. The analytical methods used have been described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

Batch analysis results are provided for batches used in Phase 2, Phase 3 and primary and supportive stability studies and include three process performance qualification batches. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

Reference materials used in the testing of the ASs include bulk polysaccharide powder for each serogroup and non-precipitated TT. The reference lots are linked to material used in clinical trials. Tests and acceptance criteria for the qualification and acceptance criteria for stability of future working reference materials are provided.

2.3.3.4. Stability MenAAH-TT, MenCAH-TT, MenW-TT, MenY-TT

The proposed shelf life for MenAAH-TT AS and MenCAH-TT AS is 12 months and for MenW-TT AS and MenY-TT AS is 24 months when stored at the recommended temperature 2-8°C.

For each serogroup the shelf-life claim is based on real time/real temperature stability data from three batches manufactured at commercial scale, including one batch that was used for manufacturing FP for clinical phase 2b/3 clinical study. Tested parameters include those that are stability-indicating. In addition, 12- and 24-month stability data at 2-8°C are available from three PPQ batches of the respective serotype. The stability programme is designed to follow ICH Guideline Q5C: Quality of Biotechnological Products, Stability Testing of Biotechnological/Biological Products. Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA

All results remain within the protocol and commercial stability acceptance criteria. Furthermore, presented data have demonstrated stability for 3 weeks for MenAAH-TT AS at 25°C, 1 month for MenCAH-TT and MenY-TT at 25°C, and 3 months for MenW-TT at 25°C, and at specified thermal cycling conditions.

The shelf life proposed for all ASs are considered acceptable.

2.3.4. Active Substance Tetanus Toxoid

2.3.4.1. General information tetanus toxoid

The active substance intermediate (ASI) tetanus toxoid (TT) is a multi-domain tetanus toxin protein isolated from a strain of *Clostridium tetani* and subsequently detoxified with formalin treatment. TT is conjugated to the ASIs MenAAH, MenCAH, MenW-135 and MenY to form the ASs MenAAH-TT, MenCAH-TT, MenW-TT and MenY-TT.

2.3.4.2. Manufacture, characterisation and process controls Tetanus Toxoid

The commercial manufacture of the TT ASI takes place at Pfizer Sanford, NC, USA.

Description of manufacturing process and process controls Tetanus Toxoid

The manufacturing process for TT ASI is identical to what is registered for Nimenrix, however the descriptions with process parameters and acceptable ranges are slightly changed to accommodate the re-evaluated control strategy for MenABCWY vaccine. Upon request, the applicant further justified the registered controls strategy of the TT intermediate, including the PP acceptance criteria for the specific process parameters. Whilst not all non-CPPs are registered in the MA dossier, all non-CPPs and CPPs are controlled/maintained within the defined NORs as specified in the manufacturing records. The proposed control strategy is sufficiently justified.

The fermentation process consists of 5 stages: tube pre-culture, flask pre-culture, fermentation, clarification/ultrafiltration/formalin addition, and detoxification, and starts with the thawing of two vials of working cell bank (WCB) to inoculate pre-culture tubes. Tetanus toxin is released into the culture through natural cell lysis and detoxified via incubation with formalin to form native TT, which is the input of the subsequent purification process.

The purification process begins with concentration of the tetanus toxoid from fermentation batches by ultrafiltration. The concentrated TT is then purified by precipitation steps. Ultrafiltration and diafiltration are then performed. and the concentrated purified TT is filtered, dispensed into specific storage containers (as for Nimenrix), which are stored at 2-8°C and shipped refrigerated for manufacture of the ASs. Extractable testing for the bags has adequately shown that leachable studied did not need to be performed.

Control of materials tetanus toxoid

The compositions of media and solutions used in the manufacturing process are listed, and for non-compendial (Ph. Eur., USP or NF) raw materials, specifications with acceptance criteria are provided. Where applicable, non-compendial raw materials are tested in accordance with their Ph. Eur. monographs. No human derived materials are used in production. Materials of biological origin are listed and additional information is provided (see Adventitious agents section).

The same *Clostridium tetani* cell banks are used for Nimenrix and the MenACWY component of the MenABCWY vaccine. The cell banks were prepared in accordance with ICH Q5D. Culture purity and identity testing performed on the MCBs provided confirmation that the polysaccharide producing cell lines are free from microbial contamination. MCB and WCBs are tested for viability, purity and identity. MCBs as well as the WCBs are enrolled in a stability programme and tested according to a pre-approved stability protocol. A protocol for establishment of new WCBs is described. Overall, the source, history and generation of the cell banks is sufficiently described.

Control of critical steps and intermediates tetanus toxoid

The control strategy for the TT ASI has been re-evaluated based on additional Pfizer generated process development study data. Process parameters and tests are used to control the process during manufacture. All critical process parameters (CPPs) are described as well as relevant non-CPPs that have an impact on quality attributes. Both types of process parameters have acceptable ranges. In-process tests for control (IPT-C) used in the manufacture of the active substances are used to control ASI quality attributes and have associated acceptance criteria. In-process tests for monitoring (IPT-Ms) are used to monitor the ASI quality attributes and may have action limits. These in-process controls (process parameters and in-process tests) are used to ensure control of the individual process steps, process consistency and product quality.

Process validation tetanus toxoid

Process validation data from Nimenrix were used to support the MenABCWY application.

The manufacturing process was validated by successfully manufacturing five full scale TT ASI batches at Pfizer Sanford, of which three were produced consecutively. Each batch was executed within the NORs established for commercial manufacture. Results of operational parameters, in-process controls, yield, batches dispensing uniformity, bioburden, endotoxin and impurities are reported as well as filter qualification and validation, hold time validations, UFDF membrane lifetime validations, shipping qualification, and an additional post-PV qualification for the combination of up to 2 low-yielding fermentation batches at the post-detoxification hold stage to be used as a single input to the purification process. The data provided are satisfactory and indicate that the TT ASI manufacturing process has been appropriately validated at the Pfizer Sanford site.

Manufacturing process development tetanus toxoid

A comprehensive understanding of the TT ASI manufacturing process has been developed through commercial-scale runs and process characterisation studies that include design of experiments (DOE), using scale-down models of individual unit operations. A structured quality risk management programme was applied, including a Failure Modes and Effects Analysis (FMEA). Compared to Nimenrix, the list of critical quality attributes (CQAs), which are attributes established by an iterative process of quality risk and criticality assessment, and experimentation to have an impact on the quality of the vaccine finished product, is significantly reduced compared to what is currently registered for Nimenrix. However, all relevant quality attributes are considered in the control strategy and their control is established by means of release, stability and in-process testing. It is therefore considered not necessary to request for the addition of specific attributes.

Comparability between the ASI/AS manufacturing processes from clinical through commercial by GSK and Pfizer was adequately shown.

Characterisation tetanus toxoid

Characterisation was performed on six batches of TT ASI manufactured at Pfizer Sanford, i.e. five process validation batches and one clinical batch, and on three representative reference material batches manufactured at GSK Gödöllő. Results from characterisation analyses with all of the above batches included are presented for non-reducing SDS-PAGE, reducing SDS-PAGE, non-reducing Western Blot, reducing Western Blot, and isoelectric focusing, and indicate structural and molecular consistency across the tested batches.

The applicant has appropriately identified a number of process-related and product-related impurities that could be present in the active substances. The removal of these process-related impurities was demonstrated through supplemental testing during process validation. Specified impurities include substances derived from the host cells and from the recovery and purification processes.

2.3.4.3. Specification tetanus toxoid

The TT ASI release and stability specifications included in the dossier are appropriate .

The specifications are aligned with the Nimenrix specification except for the removal of endotoxin and identity on stability samples since these are not considered as stability indicating tests, which is endorsed.

Analytical methods tetanus toxoid

The test methods are aligned with those used for Nimenrix. Compendial methods are used for appearance, absence of toxin, antigen activity, bioburden, endotoxin, identity, NaCl content, and pH. Non-compendial methods comprise formaldehyde content and purity. Validation was performed in conformance with ICH guidelines. The analytical methods used have been described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis tetanus toxoid

Batch Analyses results are provided for batches used in Phase 2, Phase 3, process performance qualification, and primary and supportive stability studies. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials tetanus toxoid

Reference materials are not required for the testing of the TT ASI.

2.3.4.4. Stability tetanus toxoid

The proposed shelf life for TT ASI is 36 months when stored at the recommended temperature of 2-8°C.

The shelf life claim is based on real time/real temperature stability data from four process validation batches manufactured at commercial scale, including two batches that were used for manufacturing of FP for clinical phase 2b/3 clinical study. The stability programme is designed to follow ICH Guideline Q5C: Quality of Biotechnological Products, Stability Testing of Biotechnological/Biological Products. Testing includes stability including test methods. All results remained within the protocol and commercial stability acceptance criteria except for NaCl content which was above the acceptance criteria at 36 months long-term or thermal cycling storage for batches with silicone tubing. This is attributed to the higher vapor transmission rate of silicone tubing compared to C-flex tubing, and since NaCl content is not a stability indicating assay and only included in the stability programme for the PPQ batches, this result is not considered to impact the stability conclusions. In addition, presented data have demonstrated stability for 3 weeks for MenAAH-TT AS at 25°C, 1 month for MenCAH-TT and MenY-TT at 25°C, and 3 months for MenW-TT at 25°C, and at specified thermal cycling conditions.

The proposed shelf life is considered acceptable.

2.3.5. Finished Medicinal Product MnB bivalent rLP2086 component

2.3.5.1. Description of the product and pharmaceutical development MnB bivalent rLP2086 component

The MnB Bivalent rLP2086 finished product component, also referred to as high fill volume MnB (HFV-MnB), is a sterile liquid suspension composed of rLP2086 subfamily A and B proteins formulated at 120

µg/mL/subfamily in histidine buffer, sodium chloride, polysorbate 80, with 0.5 mg/mL aluminium as aluminium phosphate (AlPO4). There is no manufacturing overage.

HFV-MnB was designed to reconstitute the lyophilised MenACWY-TT finished product component through a vial adapter to obtain the final MenABCWY vaccine. The HFV-MnB is filled into 1 mL syringes.

The 1 mL syringes are constructed of Type I borosilicate glass and are pre-assembled with a Luer lock adapter, a tip cap and either a plastic rigid tip cap or a syriQ Rigid Cap overseal. The closure for the syringes is a plunger stopper composed of latex-free chlorobutyl rubber.

Development of the HFV-MenB FP was built upon the development of Trumenba vaccine and results of a comprehensive development programme are presented. No excipients of human or animal origin and no novel excipients are used. These data support compatibility of the two proteins with each other and with the formulation components. Binding to aluminium is necessary to stabilise the formulation and histidine buffer was chosen for its high buffering capacity. Sodium chloride is added to the histidine buffer to ensure the administered finished product is isotonic. Polysorbate affects the degree of adsorption and *in vitro* relative antigenicity and the optimal ratio of PS80 to MnB rLP2086 is developed for both quality attributes. A DOE study was performed to assess the influence of formulation excipients and pH on the stability of the formulation and robustness has been sufficiently demonstrated. The fill volume for commercial Trumenba syringes was appropriately modified to ensure delivery of a single 0.5 mL dose of reconstituted vaccine. A series of studies were conducted to confirm the required HFV-MnB syringe fill volume to reconstitute the MenACWY-TT finished product component and subsequently deliver the required dose volume and antigen concentrations in the MenABCWY vaccine. The compatibility of the MnB Bivalent rLP2086 finished product component with the syringe container closure system has been determined based on the stability studies.

In process hold/processing times and maximum TOR are defined. These are adequately supported by results of development studies, full scale in-process hold time performance qualification or stability studies and media runs, if applicable.

Changes to the manufacturing process throughout clinical development to commercial manufacture were justified. There have been no major changes to the FP component manufacturing process with the exception of an increase in fill volume and stopper placement for Phase 3, process validation and commercial. It is agreed that the increase in fill volume and stopper placement does not impact the quality attributes of the FP component. Therefore, a comparability assessment is not needed between the MenB FP component used in clinical studies and the commercial process.

Leachables studies have been completed and these studies did not give rise to any concerns. Break loose force and extrusion force were monitored. All measured HFV-MnB results are within the functionality and performance requirement. These studies are considered adequate and, together with other data, ensure that the container closure system is suitable.

The syringe barrels are sterilised according to ISO requirements. The plunger stoppers are also sterilised. Leachables studies have been completed and these studies does not give rise to any concerns. Break loose force and extrusion force were monitored. All measured HFV-MnB results are within the functionality and performance requirement. These studies are considered adequate and, together with other data, ensure that the container closure system is suitable.

Information on quality control testing and sterilisation of the syringe barrels and plunger stoppers is considered sufficient.

2.3.5.2. Manufacture of the product and process controls MnB bivalent rLP2086 component

The HFV-MnB component is manufactured at Pfizer Grange Castle, Clondalkin, Ireland.

The manufacturing process starts with preparation of histidine/NaCl formulation buffer. The buffer is filtered into the formulation vessel. Aluminium phosphate is added aseptically. MnB subfamily A and B active substances are filtered directly into the formulation vessel. The sterile final formulated finished product is aseptically filled into syringes and stoppered. The syringes are visually inspected and are stored at 2-8°C. The different steps of the FP manufacturing process are described in sufficient detail and appropriately controlled.

A number of studies were performed to understand the FP medicinal product production process and to define normal operating ranges (NORs) and proven acceptable ranges (PARs) for each manufacturing step. These studies are adequately designed and sufficiently support the proposed NORs and PARs.

The control strategy has been adequately explained. A summary of the outputs from the control strategy is provided. This includes an overview of the controls in place for each of the quality attributes for the HFVMnB finished product component. The combined elements assure product quality (i.e., that quality attributes are within the demonstrated acceptable ranges) and mitigate risks of failures in process performance.

Four consecutive HFV-MnB full scale process performance qualification runs were successfully performed to demonstrate that the commercial manufacturing process performs as expected. Validation included syringes and stoppers from different suppliers. Some hold times and Time of Refrigerator of the formulation vessel were challenged during validation, whereas other process conditions were set on target. Results of process parameters, routine in process testing and extended in-process testing and batch release testing indicate a consistent FP manufacturing process. Deviations were properly handled and do not impact the process validation. The formulation, associated hold times, filling and inspection of the filled syringes is considered adequately validated. Filter qualification data and shipping qualification data are also satisfactory. The media fill studies presented support the formulation, transfers and syringe filling operations.

The aluminium phosphate suspension used as adsorbent for the MnB rLP208 antigens is also manufactured by Pfizer Ireland. Adequate information has been provided on the development, manufacture, quality control and stability of the aluminium phosphate suspension.

2.3.5.3. Product specification MnB bivalent rLP2086 component

Finished product release and stability tests and acceptance criteria for commercial assays are established and include appropriate physico-chemical tests and also assays for identity, purity and potency.

Overall, the specifications are adequate to verify the identity, potency, purity, microbial properties and pharmaceutical properties of the product. Specifications are aligned with Trumenba specification with the exception of the extractable volume and the endotoxin testing removal during stability. Endotoxin testing of stability samples is removed since this is not considered as a stability indicating test. This is agreed. The applicant has satisfactorily justified the release limit for extractable volume.

The proposed commercial acceptance criteria are justified by compendial limits (Ph. Eur.), results of formulation robustness studies, calculated tolerance intervals of FP batches and stability testing. The same batches are used as presented in the batch analysis section and encompasses clinical lots. With exception of the fill volume the acceptance criteria for Trumenba are considered suitable to control the HFV-MnB finished product.

Analytical methods MnB bivalent rLP2086 component

The test methods are the same as used for Trumenba at the Pfizer Strängnäs site and are described in sufficient detail. The tests for bacterial endotoxin, modified rabbit pyrogenicity, osmolality, pH, sterility and extractable volume are performed according to Ph. Eur. The sterility, endotoxin and container closure integrity tests have been properly verified. Non-compendial methods are described in sufficient detail and were validated in conformance with ICH guidelines.

The murine *in vivo* potency assay is used to determine the immunogenicity of *Neisseria meningitidis* serogroup B (MnB) bivalent rLP2086 FP component. Relative potency is determined by comparing the immune response in mice of test FP lots to that of a reference standard FP lot..

The batch release panel for HFV-MnB FP comprises an additional *in vivo* test, i.e. a modified pyrogenicity test in rabbits. The inherent variability of *in vivo* assays can make them less suitable than appropriately designed *in vitro* assays for batch release (e.g., Walstijn et al., Variability of *in vivo* potency assays of whole-cell pertussis, inactivated polio, and Meningococcal B vaccines, Vaccine 41(38): 5603-5613), and it is the intention of the applicant to replace them. This is fully supported.

The vitro relative antigenicity method (IVRA, sandwich ELISA) is used to determine the antigenicity of the subfamily A and B proteins in release and stability samples of the MnB bivalent rLP2086 finished product component. It is recommended to develop a supplemental binding ELISA antigenicity assay that uses a full dose response curve for samples and an antibody that binds to the N-terminal region of the subfamily A lipoprotein. This assay will replace the *in vivo* potency (IVP) assay **(recommendation 1)**. It is also recommended to replace the modified rabbit pyrogenicity test with the monocyte activation test for the MnB bivalent rLP2086 component **(recommendation 2)**.

Batch analysis MnB bivalent rLP2086 component

Batch analysis results are presented for Trumenba batches and HFV-MnB finished product batches used in clinical through commercial. All batches were manufactured at commercial scale and comply with the commercial acceptance criteria. No additional impurities are introduced by the finished product component manufacturing process. A summary of the risk assessment for elemental impurities in accordance with International Council on Harmonisation (ICH) Q3D(R2) Guideline for Elemental Impurities has been provided. All elements are below the limit of detection or control threshold. It is agreed that an additional risk assessment for MenABCWY is not required and sufficiently covered by the risk assessment for the two finished product components.

Reference materials MnB bivalent rLP2086 component

The reference materials used for analysis of the HFV-MnB finished product component are the same as those used for MnB rLP2086 Subfamily A and Subfamily B active substances.

2.3.5.4. Stability of the product MnB bivalent rLP2086 component

A shelf life of 2 years at 2°C to 8°C is proposed. Stability is assessed in accordance with ICH Q5C, Stability Testing of Biotechnological /Biological Products, 1995 using stability-indicating test methods.

Long term 2 years data (2 – 8°C) are available for HFV-MnB batches manufactured at commercial scale (primary batches, which represents the PPQ batches). In addition, supportive long term data are provided for batches manufactured at commercial scale, including batches used in clinical studies. During long term storage (2-8°C) a slight decrease in purity was observed over the time points tested for all lots. Variation in results is observed for *in vivo* potency for all lots. All other quality attributes show little to no change over time and indicate that there have been no significant changes in terms of quality of the HFV-MnB FP. All data remain within the stability acceptance criteria and the decrease in

purity was within the difference between the release and shelf-life specification. A 24-month shelf life at 2-8°C is deemed acceptable. Data are also presented showing that the HFV-MnB finished product component is stable through 3 months at 25±2°C, thermal cycling with cumulative storage at 30°C for 9 days and -5±3 °C for 9 days followed by 5±3°C for at least 24 month, 1 month at 25±2°C followed by long term storage at 5±3 °C for at least 24 months, 1 month at 30±2°C, and ICH requirements for Photostability. The unopened vaccine should be stored in a refrigerator (2°C – 8°C). The carton should be stored horizontally to minimise pre-filled syringe re-suspension time. The product should not be frozen. There is also an instruction in the PI to discard the product if the carton has been frozen.

A shelf life of 2 years at 2°C to 8°C is agreed.

2.3.6. Finished Medicinal Product MenACWY-TT component

2.3.6.1. Description of the product and pharmaceutical development

MenACWY-TT finished product component is a sterile lyophilised powder for injection composed of the purified polysaccharides of Neisseria meningitidis serogroups A, C, W and Y, each conjugated to tetanus toxoid (TT). The finished product component is formulated in trometamol buffer containing sucrose. 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 bulk MenACWY-TT finished product component is filled into vials for reconstitution with HFV-MnB to ensure a final dose concentration of 10 µg/mL/serogroup.

The MenACWY-TT finished product component is packaged in a 2 mL Type I clear glass vial, with a 13 mm finish, a bromobutyl-rubber lyophilisation stopper and an aluminium seal with a plastic flip-off cap (crimp seal).

One vial of MenACWY-TT is reconstituted with one HFV-MnB prefilled syringe to deliver 5 µg of each of the conjugates in a 0.5 mL administered dose of MenABCWY vaccine (in addition to the contents of the HFV-MnB finished product component).

The composition and container closure of the MenACWY-TT Finished product is the same as for the Nimenrix vaccine. A development scale study was conducted to evaluate FP component formulation robustness by varying the pH and sucrose levels. The finished product component is robust to variation of excipient levels beyond what was targeted in process validation batches and is stable during long term storage.

A number of studies were performed to understand the FP medicinal product production process and to define normal operating ranges (NORs) and proven acceptable ranges (PARs) for each manufacturing step. These studies are adequately designed and sufficiently support the proposed NORs and PARs. The development studies demonstrated that the bulk finished product cannot be filtered due to loss of antigens during filtration. Therefore, the bulk finished product is not filtered prior to filling and formulation is performed under aseptic conditions. For some parameters only the NORs are presented in section 3.2.P.3.3 instead of PARs.

The manufacturing site, filling lines and lyophilisers that are used during development for MenACWY-TT are also registered for the Nimenrix vaccine. The process changes have been adequately described and comparability between the Phase 2 clinical batches, Phase 3 clinical batches and batches manufactured according to the commercial manufacturing process has been adequately shown.

Extractable studies were performed, and leachable studies are in progress to support the MenACWY-TT finished product component commercial container closure system.

Sterilisation of the stoppers is performed under conditions described in Ph. Eur. 5.1.1.. The sterilisation used for the vials is not performed under conditions stated in the Ph. Eur., but the validation data for the sterilisation process demonstrate > 3 log reduction of endotoxin, and therefore considered acceptable. Compatibility of the container closure and MenACWY-TT finished product has been investigated.

2.3.6.2. Manufacture of the product and process controls MenACWY-TT component

Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs-Sint-Amands, 2870 in Belgium is also licensed for Nimenrix and is responsible for the manufacture of MenACWY-TT FP component.

The batch formula and batch size for MenACWY-TT is identical to Nimenrix. Also, the FP manufacturing process for MenACWY-TT FP is the same as for Nimenrix FP. The manufacturing process starts with preparation of the formulation buffer. The buffer is sterilised by filtration after preparation. The active substances are added aseptically during formulation. No additional filtration takes place prior to filling and lyophilisation.

Three consecutive MenACWY-TT full scale process performance qualification runs were successfully performed to demonstrate that the commercial manufacturing process performs as expected. Results of process parameters, in-process testing, and batch release testing indicate a consistent FP manufacturing process. The PV lots were challenged with cumulative maximum allowable process hold times to confirm the process step hold times for the FP component manufacturing process. No relevant protocol deviations occurred with impact on the process validation outcome. An additional lyophiliser was added for the manufacturing and confirmatory PV was successfully conducted.

The control strategy has been adequately explained. A summary of the outputs from the control strategy is provided. This includes an overview of the controls in place for each of the quality attributes for the MenACWY-TT finished product component.

The Company's policy on what actions are taken in case of NORs, PARs, IPCs or IPMs are exceeded has been summarised.

Validation of the sterilising filter, used for sterilisation of the formulation buffer, was performed. The filter validation fulfils the requirements as state in Table 3 of EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015). The formulation process and subsequent filling is performed under aseptic conditions. The media fill studies presented support the aseptic conditions used.

2.3.6.3. Product specification MenACWY-TT component

The release specifications for the MenACWY-TT bulk component are provided to ensure sterility of the bulk.

The release and stability specifications for the MenACWY-TT finished product (FP) component are appropriate to ensure the identity, purity , potency, physicochemical attributes and microbiological properties of the commercial finished product component.

The acceptance criteria align with the Nimenrix specification. Compared to Nimenrix, the MenACWY-TT FP component specification includes additional release and stability testing (i.e., conjugated antigenicity, CCIT, content uniformity, osmolality, reconstitution time, visible and subvisible particulates). The panel of specifications for release and stability testing is considered adequate.

The proposed commercial acceptance criteria are justified by compendial limits (Ph. Eur.), manufacturing experience, and clinical evaluation. The same batches are used as presented in the batch analysis section all Pfizer MenACWY-TT FP component batches relevant to MenABCWY clinical development and PV batches. The approach is considered acceptable.

Analytical methods MenACWY-TT component

The test methods are the same as used for Nimenrix and are described in sufficient detail. The additional methods used for content uniformity, osmolality, visible and subvisible particles are compendial methods. The additional non-compendial methods for conjugated antigenicity, CCIT and reconstitution time are described in sufficient detail and were validated in conformance with ICH guidelines.

Quantification of the conjugated antigenicity of the MenACWY-TT FP component is performed by rate nephelometry. Specific assays to quantify the meningococcal polysaccharide serogroup A, C, W and Y content in the finished product are used.

Batch analysis MenACWY-TT component

Batch analysis include a Nimenrix batch and MenACWY-TT FP component batches designated for clinical trials and process validation/confirmatory batches. All batches comply with the commercial acceptance criteria. No additional impurities are introduced by the finished product component manufacturing process. A risk assessment for elemental impurities for MenACWY-TT has been provided. All elements are below the limit of detection or control threshold. It is agreed that an additional risk assessment for MenABCWY is not required and sufficiently covered by the risk assessment for the two FP components.

Reference materials MenACWY-TT component

The Reference materials used for polysaccharide content assays are the same as used for Nimenrix. The qualification of the reference standards is described, as well as bridging of the reference standards. A protocol for qualification of future reference standards is provided. Furthermore, information on the Reference standards that are used for the conjugated antigenicity assay are included.

2.3.6.4. Stability of the product MenACWY-TT component

A shelf life of 2 years at 2°C to 8°C is proposed. Stability is assessed in accordance with ICH Q5C, Stability Testing of Biotechnological /Biological Products (CPMP/ICH/138/95). Stability-indicating methods are used.

Long term stability studies in line with ICH guidelines were performed and presented. In addition, supportive long term data are provided for respectively batches manufactured according to the commercial manufacturing process. All results remain within specifications. Based on these data a 2-year shelf life at 2-8°C is acceptable. In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA. It is noted that for Nimenrix, the shelf-life claim is also supported by batches manufactured at GSK and is 48 months at 5 ± 3°C.

Data are also presented showing that the MenACWY-TT finished product component is stable through 6 months at 25±2°C, thermal cycling with cumulative storage at 30°C for 9 days and -5±3 °C for 9 days followed by 5±3°C for at least 12 month, 1 month at 25±2°C followed by long term storage at 5±3 °C for at least 12 months, 1 month at 40±2°C, and ICH requirements for Photostability. The unopened vaccine should be stored in a refrigerator (2°C – 8°C). The carton should be stored

horizontally to minimise pre-filled syringe re-suspension time. The product should not be frozen. There is also an instruction in the PI to discard the product if the carton has been frozen.

In conclusion, a 2-year shelf life at 2-8°C is acceptable.

2.3.7. Finished Medicinal Product MenABCWY vaccine (reconstituted)

2.3.7.1. Description of the product and pharmaceutical development MenABCWY vaccine (reconstituted)

The MenABCWY vaccine finished product is composed of two finished product components: MenACWY-TT and MnB Bivalent rLP2086. The MenACWY-TT finished product component is a sterile lyophilised powder for injection supplied in a 2 mL glass vial. The MnB Bivalent rLP2086 finished product component, also referred to as high fill volume MnB (HFV-MnB), is a sterile liquid suspension pre-filled into 1 mL syringes.

A sterile vial adapter body, constructed of polycarbonate, is included in the vaccine kit. One side of the vial adapter is designed for attachment to a Luer lock connection. The other side is designed to snap onto a 13 mm vial with a spike designed to puncture the vial septum. A 25G x 5/8" (0.5 x 16 mm) needle or 25G x 1” (0.5 x 25 mm) needle can also be included in the packaging.

A notified body opinion has been provided for the MenABCWY medicinal product-device combination vaccine and this does not give rise to any concerns on the device parts. CE certificates are provided for the co-packaged vial adapter and needles.

Prior to use, the MenABCWY finished product is generated by reconstituting the MenACWY TT finished product component with the HFV-MnB finished product component in a single use prefilled syringe using a vial adapter and the entire extractable content is withdrawn to enable a dose of 0.5 mL for intramuscular administration. A 0.5 mL dose of MenABCWY vaccine delivers rLP2086 subfamily A and B proteins at 60 µg /subfamily and MenAAH-TT, MenCAH-TT, MenW-TT, and MenY-TT at 5 µg/serogroup using the same 1 mL syringe that contained the HFV-MnB. The MenABCWY finished product contains no preservatives and is for single use only.

The applicant has addressed some key issues of the combined vaccine prepared according to the directions in the SmPC and using combinations of different syringes and vial adapters. Dosage verification studies were performed to address that the MenACWY-TT FP component and MnB Bivalent rLP2086 FP component are compatible when mixed together, are compatible with the administration components and that the MenABCWY vaccine is stable in the dosing syringe for a period of time adequate to perform the dose preparation and administration operation.

The study results demonstrate stability of MenABCWY for 4 hours at 2°C to 30°C. The results have not shown any relevant clinical impact on the immunogenicity of the MenACWY components of the vaccine during its proposed in-use time. The binding of MenACWY antigens to an adjuvant is not critical to the immunogenicity of those conjugates.

A risk assessment to identify potential risk factors for nitrosamine formation in the active substances, finished product components, finished product and primary packaging processes to identify risk for small molecule nitrosamine formation was performed. No risk for small molecule nitrosamine formation was identified.

2.3.7.2. Manufacture of the product and process controls MenABCWY vaccine (reconstituted)

Secondary packaging and batch release is performed by Pfizer, Puurs-Sint-Amands, Belgium. The assembly, labelling and packaging of MenABCWY vaccine has been sufficiently described and qualified. Normal operating ranges have been provided for the time outside refrigeration for each step after the end of fill at Grange Castle till shipment of final packaged MenABCWY product as well as a cumulative TOR at ambient temperature. This cumulative TOR is supported by accelerated stability data of both components.

2.3.7.3. Product specification MenABCWY vaccine (reconstituted)

The release and stability testing specifications for MenABCWY finished product is controlled at the individual finished product component level. This approach is acceptable given that compatibility is sufficiently shown. Reference is made to the description of the product and Pharmaceutical Development section above.

Analytical methods MenABCWY vaccine (reconstituted)

Analytical procedures used to control the quality and consistency of MenABCWY FP are controlled at the individual finished product component level.

Batch analysis MenABCWY vaccine (reconstituted)

Reference is made to these sections in the MnB Bivalent rLP2086 FP and MenACWY-TT FP.

Reference materials MenABCWY vaccine (reconstituted)

Reference is made to this section in the Men B AS and Men ACWY-TT AS.

2.3.7.4. Stability of the product MenABCWY vaccine (reconstituted)

Stability of the final vaccine in the kit is based on the stability of the individual MenACWY-TT and MnB bivalent rLP2086 finished product components. This approach is acceptable. After reconstitution, the MenABCWY vaccine should be administered immediately or within 4 hours if stored between 2°C and 30°C to ensure chemical and physical in-use stability. The product must not be frozen. From a microbiological point of view, unless the method of opening and reconstituting precludes the risks of microbial contamination, the MenABCWY vaccine should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

2.3.7.5. Adventitious agents MenABCWY vaccine (reconstituted)

Multiple mechanisms, procedures, and assays are used to minimise the entry of adventitious agents into the process stream and detect those agents that do enter the process stream. MenABCWY vaccine, comprising MnB bivalent rLP2086 and MenACWY-TT finished product components, is composed of components derived from microbial fermentation and is not a viral product. The animal derived ingredients used in MnB bivalent rLP2086 vaccine production are casamino acids or acid hydrolysate of casein used in the media for the production of the working cell banks, Tryptone N1 used in tetanus toxoid fermentation. Several materials used in the manufacture of the MenABCWY vaccine may contain traces of stearate materials derived from animal tallow. Tallow derivatives are processed under rigorous conditions. Starting material of the casamino acids, casein Peptone and Tryptone N1 is bovine milk deemed fit for human consumption from healthy animals from Australia and/or New Zealand. The

information provided does not give rise to any concerns on adventitious agents. The absence of adventitious agents has been sufficiently demonstrated.

2.3.8. Discussion on chemical, pharmaceutical and biological aspects

Active Substance MnB rLP2086 Subfamily A and Subfamily B

The manufacturing processes, control strategy and analytical test methods for the MnB rLP2086 subfamily A and subfamily B active substances for use in the Trumenba vaccine and the MenABCWY vaccine are almost identical. The applicant has provided a completely updated dossier, tailored for the MenABCWY vaccine. Information on development, manufacture and control of the MnB rLP2086 Subfamily A and Subfamily B have been presented in a satisfactory manner and meets current standards.

Active substance $MenA_{AH}$-TT, $MenC_{AH}$-TT, MenW-TT, MenY-TT

The manufacturing processes and analytical test methods for the $MenA_{AH}$-TT, $MenC_{AH}$-TT, MenW-TT, MenY-TT active substances for use in the Nimenrix vaccine and the MenABCWY vaccine are identical, however the control strategy has been re-evaluated for the MenABCWY vaccine. The proposed control strategy is well supported by additional process development studies and the manufacturing processes are considered adequately controlled. The applicant has provided updated dossier modules, tailored for the MenABCWY vaccine. Information on development, manufacture and control of the $MenA_{AH}$-TT, $MenC_{AH}$-TT, MenW-TT, MenY-TT active substances have been presented in a satisfactory manner.

Active substance tetanus toxoid intermediate

The manufacturing process and analytical test methods for the TT active substance intermediate for use in the Nimenrix vaccine and the MenABCWY vaccine are identical, however the control strategy has been re-evaluated for the MenABCWY vaccine. The proposed control strategy is well supported by additional process development studies and the manufacturing processes are considered adequately controlled. The applicant has provided an updated dossier module, tailored for the MenABCWY vaccine. Information on development, manufacture and control of the TT active substance intermediate have been presented in a satisfactory manner and meets current standards.

Finished Medicinal Product High Fill Volume MnB Bivalent rLP2086 component

The MnB Bivalent rLP2086 FP component is based on the Trumenba vaccine. It is designed to have a higher fill volume than Trumenba to ensure that a target dose of the MenABCWY vaccine can be administered. This increase in fill volume for the HFV-MnB component is required to account for hold-up volume within the MenACWY-TT vial and adapter post reconstitution to ensure that the target final dose of 0.5 mL of the combined MenABCWY vaccine can be withdrawn for administration.

A complete process validation campaign was successfully executed at the commercial scale to validate the buffer preparation, formulation of bulk vaccine, associated hold times, the filling of the bulk FP component into syringes and the automated visual inspection of the filled syringes. Data generated during the development to support the increased fill volume and the extensive experience from routine manufacturing of Trumenba were leveraged in the development of HFV-MnB. Release and stability testing of MnB bivalent rLP2086 FP component is performed with the same methods as for the Trumenba vaccine. The presented data are satisfactory. Two recommendations are made. The batch release panel for HFV-MnB FP comprises two *in vivo* tests, i.e., an *in vivo* potency assay to determine the immunogenicity of the HFV-MnB FP in CBA/J mice and a modified pyrogenicity test in rabbits. The inherent variability of *in vivo* assays can make them less suitable than appropriately designed *in vitro* assays for batch release and it is the intention of the applicant to replace them. It is recommended to

develop a supplemental binding ELISA antigenicity assay that uses a full dose response curve for samples and an antibody that binds to the N-terminal region of the subfamily A lipoprotein. This assay will replace the *in vivo* potency assay (**recommendation 1**). It is also recommended to replace the modified rabbit pyrogenicity test with the monocyte activation test for the MnB bivalent rLP2086 component (**recommendation 2**).

Finished Medicinal Product MenACWY component

The MenACWY FP component is essentially identical to the Nimenrix vaccine, however the control strategy has been re-evaluated for the MenABCWY vaccine. The proposed control strategy is well supported by additional process development studies and the manufacturing process is considered adequately controlled. Process validations from recently approved Nimenrix FP variations were leveraged to support the validation of the FP manufacturing process for the MenABCWY vaccine, which is acceptable. The applicant has provided an updated dossier module, tailored for the MenABCWY vaccine. Information on development, manufacture and control of the MenACWY FP component have been presented in a satisfactory manner and meets current standards.

Finished Medicinal Product MenABCWY vaccine

Dosage verification studies were performed and appropriate data were presented to address that the MenACWY-TT FP component and MnB Bivalent rLP2086 FP component are compatible when mixed together, are compatible with the administration components and that the MenABCWY vaccine is stable in the dosing syringe for a period of time adequate to perform the dose preparation and administration operation.

Validation of the MenABCWY FP process relates to the secondary packaging of the MnB bivalent rLP2086 FP component, the MenACWY-TT FP component and the vial adapter into the final carton. These data are satisfactory.

2.3.9. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be 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.

2.3.10. 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:

1. Development of a supplemental binding ELISA antigenicity assay that uses a full dose response curve for samples and an antibody that binds to the N-terminal region of the subfamily A lipoprotein is recommended. This assay should replace the *in vivo* potency (IVP) assay for the MnB Bivalent rLP2086 Finished product component.
2. It is recommended that the modified rabbit pyrogenicity test is replaced with the monocyte activation test for the MnB bivalent rLP2086 Finished Product component.

2.4. Non-clinical aspects

2.4.1. Introduction

The currently proposed vaccine MenABCWY consists of MenACWY-TT (i.e. Nimenrix, composed of the four meningococcal capsular polysaccharides A, C, W-135 and Y, each conjugated to tetanus toxoid) and MenB-FHbp/bivalent rLP2086 (i.e. Trumenba, composed of subfamily A and B proteins absorbed on aluminium phosphate). For marketing authorisation of Nimenrix and Trumenba, the applicant conducted several pharmacology studies, which have also been submitted for the current MAA. No additional non-clinical studies have been conducted for the current MenABCWY vaccine, as the quantitative and qualitative composition of the combination vaccine is the same as the two individual vaccines.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

For the authorisation of the MenACWY-TT component, Several pharmacology studies have been conducted in mice and rabbits. These studies showed that the most immunogenic response (i.e. IgG levels and SBA response) was obtained when the individual polysaccharides were conjugated to tetanus toxoid (protein carrier) and when MenA and MenC polysaccharides contained an adipic acid dihydrazide (AH) spacer between the polysaccharide and the protein carrier. The resulting composition of the vaccine that was tested clinically was therefore $MenA_{AH}C_{AH}WY$-TT.

For the selection of the most immunogenic MenB antigen, the immunogenicity of several outer membrane proteins was evaluated. This led to the identification of lipoprotein LP2086 (complement factor H binding protein, FHbp), which is a bacterial virulence factor and elicited the broadest bactericidal antibody responses. Based on subsequent studies in mice, rabbits and rhesus macaques, the most immunogenic variant consisted of a combination of lipidated FHbp antigens from both subfamily A and B (i.e. bivalent vaccine). Subsequently, non-clinical studies were conducted to select MenB isolates that could be used as test strains in the clinic. This selection was amongst others based on the level of FHbp surface expression *in vitro*, as there was a relation between FHbp expression levels and susceptibility to hSBA killing.

2.4.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been performed, which is in accordance with applicable guidelines.

2.4.2.3. Safety pharmacology programme

No safety pharmacology studies have been performed with Penbraya, which is in accordance with applicable guidelines.

During the development of Nimenrix, the applicant conducted a GLP-compliant safety pharmacology study in male Wistar rats to evaluate the effect of IM- or IV-administered MenACWY-TT on cardiovascular and respiratory parameters. The study did not indicate any relevant safety issues. Additional safety data has been obtained in repeat-dose toxicity studies for both MenACWY-TT and MenB-FHbp.

2.4.2.4. Pharmacodynamic drug interactions

No studies on the pharmacodynamic drug interactions have been performed, which is in accordance with applicable guidelines.

2.4.3. Pharmacokinetics

In accordance with WHO guidelines on non-clinical evaluation of vaccines (WHO 2005) and vaccine adjuvants and adjuvanted vaccines (WHO 2014), traditional absorption, distribution, metabolism, and excretion (ADME) evaluations are not generally needed for vaccines. The safety concerns associated with vaccines are generally not related to the pharmacokinetics but are related to the potential induction of an immune response.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

Single-dose toxicity of 3rd generation MenACWY-TT (generation of the vaccine where the manufacture used direct conjugation for MenWY, and for both the MenA and the MenC polysaccharides first coupled to a spacer and then conjugated to TT, i.e. $MenA_{AH}C_{AH}WY$-TT) was evaluated after a single IM injection in New Zealand White rabbits (dose equivalent to the human dose) and after the first dose in a repeated dose toxicity study in rabbits with IM administration of MenACWY-TT (dose of 0.2 ml compared to intended human dose of 0.5 ml). In both studies, no (adverse) effects were observed, except for a slight mononuclear-type inflammation at the injection site, which was similar to the inflammation induced by the saline control.

No single dose toxicity studies were performed with bivalent rLP2086. Evaluation of safety after the first dose in a repeated dose toxicity study in rabbits with IM administration of 3.3x the human dose resulted in effects that are to be expected for a vaccine, including increases in mean body temperature, fibrinogen, and total globulins, as well as mild injection site oedema and/or erythema.

2.4.4.2. Repeat dose toxicity

Following repeated administration of 3rd generation MenACWY-TT (5 IM doses of 0.2 ml with a 2-week interval) to male and female rabbits, no distinct treatment-related changes were observed in general and in local clinical signs, ophthalmoscopy, rectal body temperature, haematology, clinical chemistry or organ weights. Very slight to slight inflammation in the injected muscles was observed, which diminished distinctly over time. The administered dose (0.2 ml) was lower than the intended human dose (0.5 ml).

Two repeated dose toxicity studies were performed with bivalent rLP2086: one with 5 doses (1 dose/2 weeks) of 100 µg or 400 µg and one with 400 µg (i.e. 3.3x human dose) of the final formulation. Observations after multiple doses were mostly similar to the observations after one dose administration, i.e. slight oedema and erythema at the injection site, slightly increased body temperature, increased fibrinogen and total globulins. Histopathologically, slight to moderate inflammatory changes were observed at the injection site, which clearly diminished over time.

2.4.4.3. Genotoxicity

No genotoxicity studies have been performed in accordance with the WHO Guidelines on Non-clinical Evaluation of Vaccines (2005) and Guidelines on the Non-clinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines (2014). The absence of these studies is considered acceptable.

2.4.4.4. Carcinogenicity

No carcinogenicity studies have been performed in accordance with the WHO Guidelines on Non-clinical Evaluation of Vaccines (2005) and Guidelines on the Non-clinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines (2014). The absence of these studies is considered acceptable.

2.4.4.5. Reproductive and developmental toxicity

A reproductive toxicity study was performed in which female rats received IM injections with 0.2 mL $MenA_{AH}C_{AH}WY$-TT or saline 42 and 28 days before mating, and on GDs 6, 8, 11 and 15. No treatment-related effects were observed on maternal toxicity, fertility, prenatal development (including external, visceral and skeletal abnormalities), or postnatal development of the pups up to 25 days after birth. The administered dose (0.2 ml) was lower than the intended human dose (0.5 ml).

Two combined fertility and developmental toxicity studies were performed in rabbits with IM injections of 200 µg bivalent rLP2086 (1.7x the human dose) at 17 and 4 days prior to mating and on GDs 10 and 24. In the natural delivery group, a slight increase in the number of stillborn pups was observed in groups given adjuvant or vaccine compared to saline controls, as well as a slight increase in pup mortality on post-partum days 1-4 in the vaccine-treated group compared to the adjuvant- or saline-treated groups. The incidences of stillborn pups and post-partum mortality were however within historical control range. It is therefore concluded that no treatment-related effects were observed on mating, female fertility, or embryo/foetal viability, growth, or development of F1 foetuses and pups.

2.4.4.6. Local Tolerance

The final formulation of the $MenA_{AH}C_{AH}WY$-TT candidate vaccine was examined for its local reactogenicity after a single intramuscular injection in New Zealand White rabbits at a dose equivalent to the human dose. Local examination of the injection sites only revealed a mild mononuclear-type inflammation, which was similar to saline control.

No dedicated local tolerance studies were performed for bivalent rLP2086, which is acceptable. Results from repeat-dose toxicity and fertility and developmental toxicity studies in rabbits did not reveal (adverse) local effects other than those observed after control injections.

2.4.4.7. Other toxicity studies

In the production of MenACWY-TT, 4-dimethylaminopyridine (DMAP) is formed as a by-product (process-related impurity) and residual DMAP (<3.5 ng/10 µg polysaccharide) may be present in the final vaccine formulation. Therefore, the acute systemic toxicity, *in vitro* mutagenicity, and skin sensitization potential of DMAP was investigated. None of these studies revealed a cause for concern for the residual levels of DMAP in the vaccine.

2.4.5. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100), due to their nature vaccines are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this application for Marketing Authorisation, which is considered acceptable.

2.4.6. Discussion on non-clinical aspects

Overall, the non-clinical package is adequate to support the current MenABCWY application and there are no pharmacological, pharmacokinetic or toxicological concerns raised.

In most studies performed to evaluate the safety of MenACWY-TT (acute, repeated dose and reproductive toxicology studies), the dose used was lower than the absolute intended human dose (0.2 ml versus 0.5 ml). However, since the vaccine is already registered and no risks with regard to local reactogenicity have emerged from clinical use, this is considered acceptable.

2.4.7. Conclusion on the non-clinical aspects

Overall, the toxicology programme revealed no treatment related adverse effects in acute, repeated dose and reproductive toxicology studies. This information has been included in the SmPC.

The non-clinical programme is considered approvable.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

• **Protocol No** • **(Country)**	**Design**	**Posology and # of subjects by group**	**Study population**	**Key immunogenicity objective(s)**
0- and 6-month Vaccination Schedule				
C3511001 ***(US, EU)*** ***(completed)***	A Phase 3 Randomized, Active-Controlled, Observer Blinded Trial to Assess the Safety, Tolerability, and Immunogenicity of MenABCWY in Healthy Participants ≥10 to <26 years old	Two doses (6 month interval) **MenABCWY+Saline (0 months) and MenABCWY (6 months)** *(Group 1 (ACWY- naïve) and 3 (ACWY-experienced))* Randomized: 1778 **Trumenba + Menveo (0 months) and Trumenba (6 months)**	Adults and adolescents ≥10-<26 years old Sex Male 48% Female 52% Age (Years) Mean 16.0 Range 10.0-25.0 Sex Male 50.8% Female 49.2%	To demonstrate that the immune response: * for Men A, C, W and Y induced by two doses of MenABCWY is noninferior to the immune response induced by 1 dose of Menveo in both ACWY-naïve and ACWY-experienced participants separately. * for MenB induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba.

		(Group 2 (ACWY- naïve) and 4 (ACWY-experienced)) Randomized: 653	Age (Years) Mean 16.0 Range 10.0-25.0	
B1971057 Stage 1 ***(US, EU)*** ***(completed)***	A 1st-In-Human Study to Describe the Immunogenicity, Safety, and Tolerability of a Bivalent rLP2086–Containing Pentavalent Vaccine (MenABCWY) in Healthy Subjects ≥10 to <26 Years of Age	Two doses (6 month interval) **MenABCWY+Saline (0 months) and MenABCWY (6 months)** *(Group 1 (ACWY- naïve) and 3 (ACWY-experienced))* Randomized: 544 **Bivalent rLP2086 + Menveo (0 months) and bivalent rLP2086 (6 months)** *(Group 2 (ACWY- naïve) and 4 (ACWY-experienced))* Randomized: 1066	Adults and adolescents ≥10-<26 years old Sex Male 45.5% Female 54.5% Age (Years) Mean 17.0 Range 10.0-25.0 Sex Male 41.2% Female 58.8% Age (Years) Mean 17.0 Range 10.0-25.0	To describe the immune response induced by: * 1 dose of MenABCWY compared to the immune response induced by 1 dose of Menveo * 2 doses of MenABCWY compared to the immune response induced by 1 dose of Menveo, as measured by hSBA performed with ACWY test strains, in ACWY-naïve/experienced subjects separately. * MenABCWY compared to the immune response induced by bivalent rLP2086 as measured by hsBA performed with 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the 2nd vaccination.
Extended interval (0- and 12-month and 0- and 36-month) Vaccination schedule				
C3511004 ***(US)*** ***(ongoing)***	A Phase 2b, Randomized, Observer-Blinded Trial to Describe the Safety, Tolerability, and Immunogenicity of MenABCWY Administered on 2 Different Dosing Schedules in Healthy Participants ≥11 to <15 Years of Age	Two doses (12 or 36 month interval [a]) **0- and 12- Month Schedule (Group 1)** Randomized: 155 **0- and 36- Month Schedule (Group 2)** Randomized: 154	Adolescents ≥11-<15 years old Sex Male 55.5% Female 44.5% Age (Years) Mean 11.0 Range 11.0-14.0 Sex Male 55.4% Female 44.6% Age (Years) Mean 11.0 Range 11.0-14.0	To describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 12-month schedule.
Immunopersistence Following Primary Series and Booster Vaccination				
B1971057 Stage 2 [c] ***(open-label)*** ***(US, EU)*** ***(ongoing)***	A 1st-In-Human Study to Describe the Immunogenicity, Safety, and Tolerability of a Bivalent rLP2086–Containing Pentavalent Vaccine (MenABCWY) in Healthy Subjects ≥10 to <26 Years of Age	*Immunepersistence* **ACWY naïve participants** Group 1: MenABCWY + Saline (n=114) or Group 2: Menveo + bivalent rLP2086 (n=65) **ACWY experienced participants** Group 3: MenABCWY + Saline (n=101) or Group 4: Menveo + bivalent rLP2086 (n=73) *Booster dose* **MenABCWY** approximately 4 years following completion of a 2-dose primary series (n=144)	Adults and adolescents ≥10-<26 years old Sex Male 47.9% Female 52.1% Sex Male 42.7% Female 57.3% Age at booster vaccination (years) Mean 20.0 Range 14.0-30.0	To describe the immune response induced by: * MenABCWY compared to the immune response induced by MenACWYCRM and bivalent rLP2086, as measured by hSBA performed with ACWY test strains and 4 primary MenB test strains, at 12, 24, 36 and 48 months after vaccination. * MenABCWY as measured by hSBA performed with ACWY and 4 primary MenB test strains, 1 month after a booster vaccination in Groups 1 and 3.

Menveo + bivalent rLP2086 approximately 4.5 years after a single dose of Menveo co-administered with bivalent rLP2086 (n=98)	Age at booster vaccination (years) Mean 20.0 Range 14.0-30.0	* bivalent rLP2086, as measured by hSBA performed with 4 primary MenB test strains, measured 1 month after the booster vaccination in Groups 2 and 4.

[a] For this submission, immunogenicity data through Month 13 (1 month after the 2nd dose of MenABCWY in Group 1 and 13 months after the 1st dose of MenABCWY in Group 2) is available. Group 2 received saline at Month 12.
[b] Vaccination phase is defined as the time from each vaccination through 1 month after that vaccination.
[c] The Stage 2 interim CSR presents results of key analyses of immunogenicity performed for this submission. This is composed of immunopersistence through 48 months following completion of the primary vaccination series and immunogenicity at 1 months after booster vaccination.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

No pharmacokinetic studies have been conducted with Penbraya, nor Trumenba or Nimenrix. This is because pharmacokinetic studies are generally not considered informative for the evaluation of vaccines, consistent with current Guidelines on clinical evaluation of vaccines.

2.5.2.2. Pharmacodynamics

The pharmacodynamic profile of vaccines is defined by their immunogenicity, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005 Rev. 1).

Mechanism of action

Penbraya consists of 5 micrograms each of polysaccharides of *N. meningitidis* group A, C, W-135 and Y conjugated to 44 micrograms tetanus toxoid carrier protein and 60 micrograms each of *N. meningitidis* group B fHbp subfamily A and B absorbed on aluminium phosphate (0.25 milligrams of aluminium).

It was designed to induce the production of bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* groups A, C, W, and Y and to the surface-exposed lipoprotein fHbp subfamilies A and B of *N. meningitidis* group B. Anti-meningococcal antibodies protect against invasive meningococcal disease via complement mediated bactericidal activity.

The immunological correlate of protection (CoP) is established at hSBA titres ≥ 1:4.

Primary and Secondary pharmacology

The immune response to both Trumenba and Nimenrix has been investigated in numerous clinical investigations that include Phase 1, Phase 2, and Phase 3 studies. This has been performed by measuring serum bactericidal assay (SBA) titres for specific meningococcal test strains and also by evaluating immunoglobulin G (IgG) binding antibodies specific to the components of the respective vaccines. As part of the current MAA for the pentavalent vaccine, only hSBA titres were measured. The hSBA for *N. meningitidis* is designed to quantify functional antibodies in human serum samples that bind to bacteria and, in the presence of functional human complement, initiate the complement cascade that ultimately results in the formation of a membrane attack complex and destruction of the bacteria.

To support the Penbraya clinical testing (studies C3511001, C3511004, and B1971057), for the MenA, C, W and Y the applicant indicated that new proprietary assays were developed. Pfizer validated proprietary hSBAs using human immune sera at Pharmaceutical Product Development (PPD) in Richmond, VA, USA. The validation reports covered relative accuracy/dilutional linearity, precision, upper and lower limits of quantitation (ULOQ and LLOQ), range, limit of detection (LOD) and false-positive rate. Since accuracy cannot be formally addressed as there is no accepted reference standard

available, relative accuracy will be addressed as part of the dilutional linearity assessments. In addition, a specificity report was showed that the hSBA assays are capable of specifically measuring polysaccharide antibodies in the presence of heterologous or irrelevant competitors.

The validation reports for MenB hSBA included are identical to the reports included during MAA application for Trumenba. Bridging reports have been included for the validation of transfer of the method from the Thermo PlateMate Plus robotic system to the Agilent Bravo Liquid Handler. The bridging reports indicate that the assay the mean titre bias between Bravo and PMP platforms was 95.30% for PMB2707 (B44), 103.76% PMB2948 (B24), 107.42% for PMB2001 (A56) and 91.24% for PMB80 (A22), and the 90% confidence interval of the GMR was contained within the acceptance limits of 67% to 150% meeting pre-set acceptance criteria. These seem to be acceptable. Therefore MenB hSBA assays for the four primary strains can be considered fully validated.

The MnB rLP2086 subfamily A and subfamily B bio-analytical methods are unchanged from those that are currently approved in the Trumenba MAA.

2.5.3. Discussion on clinical pharmacology

No human pharmacokinetic studies have been performed. This can be agreed upon as pharmacokinetic studies are not usually required for vaccines. The pharmacodynamic profile of vaccines is defined by their immunogenicity, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005 Rev. 1).

For the MenA, C, W and Y the applicant indicated that new proprietary assays were developed. The validation exercise for MenA, C, W and Y included assessment of relative accuracy/dilutional linearity, precision, upper and lower limits of quantitation (ULOQ and LLOQ), range, limit of detection (LOD) and false-positive rate. Since accuracy cannot be formally addressed as there is no accepted reference standard available, relative accuracy was addressed as part of the dilutional linearity assessment. The specificity report showed that the hSBA assays are capable of specifically measuring antibodies against polysaccharides in the presence of heterologous or irrelevant competitors, which is appreciated.

The validation reports for MenB hSBA included in the current submission are identical to the reports included during MAA application for Trumenba. Bridging reports have been included for the validation of transfer of the method from the Thermo PlateMate Plus robotic system to the Agilent Bravo Liquid Handler. The bridging reports indicate that the assay mean titre bias and the 90% confidence interval of the GMR between Bravo and PMP platforms was contained within the acceptance limits of 67% to 150% meeting pre-set acceptance criteria. These seem to be acceptable. Therefore, MenB hSBA assays for the four primary strains can be considered fully validated.

Considering that the current submission contains studies in which head-to-head comparisons between groups are made, the MenA, C, W, and Y hSBA and MenB hSBA can be considered fit for purpose.

2.5.4. Conclusions on clinical pharmacology

The assays used to determine the immunogenicity results can be considered fit for the purpose.

2.5.5. Clinical efficacy

The overall objective of the clinical development programme was to evaluate the immunogenicity, safety and tolerability of the candidate pentavalent vaccine administered to adults and adolescents ≥10 to <26 years of age. No efficacy studies were submitted as part of this application. The pivotal

study providing information on the immunogenicity and safety of the MenABCWY vaccine is Study C3511001, a Phase 3 randomised, active-controlled trial in healthy participants ≥10 to <26 years old.

2.5.5.1. Dose response study

No dose response studies have been submitted as part of this MAA.

2.5.5.2. Main study

A Phase 3, Randomised, Active-Controlled, Observer-Blinded Trial to Assess the Safety, Tolerability, and Immunogenicity of MenABCWY in Healthy Participants ≥10 to <26 Years of Age

Methods

Study C3511001 is a Phase 3 randomised, active-controlled, observer-blinded multicentre study. The study aim was to determine the immunologic noninferiority of MenABCWY, an investigational pentavalent (serogroups A, B, C, W, Y) meningococcal vaccine, to concomitantly administered licensed vaccines Trumenba (serogroup B; bivalent recombinant lipoprotein 2086 vaccine [bivalent rLP2086]) and Menveo (meningococcal groups A, C, Y, and W-135 oligosaccharide diphtheria conjugate vaccine [Menveo]) in healthy participants ≥10 to <26 years of age. An overview of the study design is shown in the table below. Randomisation is stratified by prior vaccination history (ACWY status naïve or experienced). All participants are meningococcal group B vaccine naïve prior to enrolment.

Table 2. Study design of immunogenicity subset of study C3511001 (vaccination groups and activities regarding immunogenicity)

	Visit Number	*1*		*2*	*3*	*4*
	Approximate Month	*0*		*1*	*6*	*7*
	Activity	***Blood draw***	***Vaccination 1***	***Blood draw***	***Vaccination 2***	***Blood draw***
ACWY-naïve participants	**Group 1 (n=450)**	25 mL	MenABCWY + saline	25 mL	MenABCWY	25 or 50 mL
	Group 2 (n=225)		Trumenba + Menveo		Trumenba	
ACWY-experienced participants	**Group 3 (n=675)**		MenABCWY + saline		MenABCWY	
	Group 4 (n=338)		Trumenba + Menveo		Trumenba	

- **Study Participants**

The trial included healthy male or female participants ≥10 and <26 years of age at the time of randomisation who did not have a previous vaccination with a meningococcal B vaccine. Both ACWY-naïve and ACWY-experienced participants were included. ACWY-naïve participants were participants who have never received a prior dose of a meningococcal vaccine containing ACWY serogroups. ACWY-experienced participants were participants who have received not more than 1 prior dose, no sooner than 4 years prior to the date of randomisation of Menactra (a meningococcal Groups A, C, Y and W-135 Polysaccharide Diphtheria Toxoid Conjugate Vaccine licensed in the US) or Menveo. Written

confirmation of vaccination history must be obtained prior to randomisation.

Exclusion criteria included participants who were immunocompromised, had a history of microbiologically proven disease caused by *N. meningitidis* or *Neisseria gonorrhoeae*, had a neuroinflammatory or auto-immune condition and administration of treatments that might modify immune responses, as well as previous vaccination with any meningococcal group B vaccine or any purely polysaccharide (non-conjugate) meningococcal vaccine.

In addition, normal in- and exclusion criteria appropriate for vaccine trials were in place.

- **Treatments**

Participants in groups 1 and 3 will receive the candidate MenABCWY vaccine in the left arm at Visit 1 (Month 0) and 3 (Month 6) and placebo in the right arm at Visit 1. Participants in groups 2 and 4 will receive Trumenba in the left arm at Visit 1 and 3 and Menveo in the right arm at Visit 1. All products are intended to be administered intramuscularly by appropriately qualified GCP trained and vaccine-experienced members of the study staff.

- **Objectives**

Primary objectives:

- To demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of Menveo in both ACWY-naïve and ACWY-experienced participants, separately.
    - The lower limit of the 2-sided 95% CI for the difference in seroresponders (Group 1 - Group 2, ACWY-naïve) is > -10% for all of the MenACWY test strains at 1 month after the 2nd vaccination for Group 1 and at 1 month after the 1st vaccination for Group 2; and
    - The lower limit of the 2-sided 95% CI for the difference in seroresponders (Group 3 - Group 4, ACWY-experienced) is > -10% for all of the MenACWY test strains at 1 month after the 2nd vaccination for Group 3 and at 1 month after the 1st vaccination for Group 4;

      Seroresponse is defined as:

        - For participants with a baseline hSBA titre below the LOD (or an hSBA titre of <1:4), a 4-fold response is defined as an hSBA titre of ≥1:16.
        - For participants with a baseline hSBA titre of ≥ LOD (i.e., hSBA titre of ≥1:4) and < LLOQ (i.e., hSBA titre of 1:8), a 4-fold response is defined as an hSBA titre of ≥4 times LLOQ.
        - For participants with a baseline hSBA titre of ≥ LLOQ, a 4-fold response is defined as an hSBA titre of ≥4 times the baseline titre
- To demonstrate that the immune response for MenB induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba.
    - The lower limit of the 2-sided 95% CI for the differences in 4-fold rises and composite responses (Groups 1+3 - Groups 2+4) is >-10% for all of the primary MenB test strains at 1 month after the 2nd vaccination.

      Composite response is defined as hSBA titres ≥ LLOQ for all 4 primary strains.

Secondary objectives:

- To demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY is noninferior to the immune response induced by 1 dose of Menveo, in both ACWY-naïve and ACWY-experienced participants, separately.

Tertiary/exploratory objectives:

- To describe the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY compared to the immune response induced by 1 dose of Menveo, in both ACWY-naïve and ACWY-experienced participants, separately.
- To describe the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY compared to the immune response induced by 1 dose of Menveo, in both ACWY-naïve and ACWY-experienced participants, separately.
- To describe the immune response for MenB, as measured by hSBA performed with primary MenB test strains, induced by 2 doses of MenABCWY compared to the immune response induced by 2 doses of Trumenba.
- To describe the immune response for MenB, as measured by hSBA performed with secondary MenB test strains, induced by 2 doses of MenABCWY.

In addition a primary immunogenicity estimand based on a hypothetical strategy is used for the analyses of the primary immunogenicity endpoints.

- **Outcomes/endpoints**

Primary immunogenicity endpoints

- In ACWY-naïve participants receiving at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants): Difference in the percentage of seroresponders (defined as participants achieving at least a 4-fold rise in hSBA titre from baseline for each ACWY test strain) 1 month after Vaccination 2 in Group 1 compared to 1 month after Vaccination 1 in Group 2.
- In ACWY-experienced participants receiving at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants): Difference in the percentage of seroresponders 1 month after Vaccination 2 in Group 3 compared to 1 month after Vaccination 1 in Group 4.
- In participants receiving at least 2 doses of investigational product and who are in compliance with the key protocol criteria (evaluable participants):
  - Difference in the percentage of participants achieving at least a 4-fold rise in hSBA titre from baseline for each of the 4 primary MenB test strains, in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2
  - Differences in the percentage of participants achieving an hSBA titre ≥ LLOQ (1:16 for strain A22 and 1:8 for strains A56, B24, and B44) for all 4 primary MenB test strains combined (composite response), in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2.

Secondary endpoint

- In ACWY-naïve participants: Difference in the percentage of seroresponders 1 month after Vaccination 1 in Group 1 compared to 1 month after Vaccination 1 in Group 2.
- In ACWY-experienced participants: Difference in the percentage of seroresponders 1 month after Vaccination 1 in Group 3 compared to 1 month after Vaccination 1 in Group 4.

- **Sample size**

With a sample size of 1688 (450, 225, 675, and 338 participants in Groups 1, 2, 3, and 4, respectively), assuming the expected differences in percentage of seroresponders of 0, 15%, 15%, 15% for each of the ACWY strains, resp. in the ACWY-naïve subjects, expected differences of -1%, -1%, -2%,-2% for each of the ACWY strains, resp. in the ACWY-experienced subjects and expected differences of 0% for each of the four MenB strains and composite response, based on an unknown method for calculating confidence intervals, a two-sided Type I error of 0.05, a non-inferiority margin of 10%, and a non-evaluable rate of 20%, the combined power to show non-inferiority of MenABCWY versus Menveo+Trumenba regarding the percentage of seroresponders will be at least 91%.

- **Randomisation and Blinding (masking)**

The randomisation for the immunogenicity set was stratified by prior vaccination history and by geographic region (US vs non-US) with a 2:1 ratio to either MenABCWY group or the Menveo+Trumenba group and used an interactive response technology (IRT) system. Among the subjects in the immunogenicity subset, approximately 80% is planned to be enrolled in US investigative sites, and approximately 20% is planned to be enrolled in other regions. To achieve age representation, enrolment slots were allocated to two age groups (56% for 10 to <18 years of age and 44% for 18 to <26 years of age).

For subjects enrolled into the safety subset, the randomisation ratio between active and control was 10:1 for the ACWY-naïve participants or 5:2 for the ACWY-experienced participants.

The study is observer-blind. Administration of the vaccine was performed by unblinded personnel. All other study and site personnel, participants and participants' parent(s)/legal guardian(s) are blinded to investigational product assignment. Laboratory testing is performed blinded.

- **Statistical methods**

Analysis sets

ITT population: All participants who are randomised in the IRT system

mITT population: All participants who receive at least 1 study vaccination and have at least 1 MenB or MenACWY assay result available at any time point from Visit 1 to Visit 4.

Post–Vaccination 1 evaluable immunogenicity population: All participants who are eligible through Visit 2; receive the investigational products at Visit 1 as randomised; has blood drawn for assay testing within the required time frames at Months 0 (Visit 1: before Vaccination 1) and at Month 1 (Visit 2: 1 month after the first vaccination: window 28-49 days); has at least 1 valid and determinate MenACWY assay result at Visit 2; has no important protocol deviations through Visit 2.

Post–Vaccination 2 evaluable immunogenicity population: All participants who are eligible through Visit 4; receive the investigational products at Visit 1 and Visit 3 as randomized; has blood drawn for assay testing within the required time frames at Months 0 (Visit 1: before Vaccination 1) and 7 (Visit 4: 1 month after the second vaccination: window 28-49 days); has at least 1 valid and determinate MenACWY or MenB assay result at Visit 4; has no important protocol deviations through Visit 4.

Evaluable population: Defined according to post–Vaccination 1 evaluable and post–Vaccination 2 evaluable criteria.

Safety population: All randomised participants who receive at least 1 dose of the investigational product and have safety data reported after vaccination.

Primary immunogenicity endpoints and primary immunogenicity analyses

The **primary immunogenicity endpoints are:**

- In ACWY-naïve participants: Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titre from baseline for each ACWY test strain, 1 month after Vaccination 2 in Group 1 compared to 1 month after Vaccination 1 in Group 2.
- In ACWY-experienced participants: Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titre from baseline for each ACWY test strain, 1 month after Vaccination 2 in Group 3 compared to 1 month after Vaccination 1 in Group 4.
- For all participants: Difference in the percentage of participants achieving at least a 4-fold rise in hSBA titre from baseline for each of the 4 primary MenB test strains, in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2.
- For all participants: the difference in the percentage of participants achieving an hSBA titre ≥ LLOQ (1:16 for strain A22 and 1:8 for strains A56, B24, and B44) for all 4 primary MenB test strains combined (composite response), in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2.

4-fold responder or 4-fold rise:

- For participants with a baseline hSBA titre below the LOD (or an hSBA titre of <1:4), a 4-fold response is defined as an hSBA titre of ≥1:16.
- For participants with a baseline hSBA titre of ≥ LOD (i.e., hSBA titre of ≥1:4) and < LLOQ (i.e., hSBA titre of 1:8), a 4-fold response is defined as an hSBA titre of ≥4 times LLOQ
- For participants with a baseline hSBA titre of ≥ LLOQ, a 4-fold response is defined as an hSBA titre of ≥4 times the baseline titre.

Missing or non-evaluable measurements are not imputed for the primary analysis and are considered missing (completely) at random.

The primary immunogenicity analyses:

The number and percentage of participants in each category are summarised. The 95% CI for percentages per group are constructed by the Clopper-Pearson method and the difference in the percentage of seroresponders is calculated using the Miettinen and Nurminen method. The lower limit of the CI is used in the hypothesis test for noninferiority.

The primary hypotheses for MenACWY endpoints and the primary hypotheses for MenB endpoints are tested simultaneously. The primary objectives of noninferiority is met only if all statistical criteria for the objectives are met. Hypothesis testing for the secondary objective are performed only if the primary objectives are successful.

Sensitivity analysis

A post-hoc sensitivity analysis requested by the CHMP is performed for the primary immunogenicity estimand using a generalised linear mixed model with repeated measurements, adjusted for the geographical location.

Supportive analyses

- Main analyses are also performed for the mITT population
- For the primary immunogenicity endpoints, analyses are performed using a generalised linear mixed model based on the mITT population.
- For each of the serogroups A, C, W and Y, a post-hoc analysis is performed based on an alternative estimand requested by CHMP where all subjects vaccinated with at least one dose of MenABCWY or Menveo+Trumenba are included. The endpoint is the same as the primary immunogenicity endpoint, however missing values for subjects with only one vaccination were handled by a hypothetical strategy using a multiple imputation model including fixed effects of vaccine group, age group, location, vaccine group by age group interaction and vaccine group by location interaction. Reason behind this estimand is that by considering all subjects with at least one vaccination, the subjects between the arms are expected to be comparable at baseline, due to randomisation.
- For each of the serogroups A, C, W and Y, two other post-hoc analyses are performed also based on the primary immunogenicity endpoint. For one analysis only subjects who received two vaccinations are included and for the other analysis all subjects with at least one vaccination are included, where in the last analysis all subjects with only one vaccination are considered as non-responder. The last analysis is considered a conservative one.

Subgroup analyses

Subgroup analyses are performed by age strata (10 to <18 years; 18 to <26 years), sex, race and ethnicity.

Secondary immunogenicity endpoints and analyses

- For ACWY-naïve participants: Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titre from baseline for each MenACWY test strain, 1 month after Vaccination 1 in Group 1 compared to Group 2.
- For ACWY-experienced participants: Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titre from baseline for each MenACWY test strain, 1 month after Vaccination 1 in Group 3 compared to Group 4.

The number and percentage of participants in each category are summarised. The 95% CIs for percentages per group and for the difference in the percentage of seroresponders are calculated in analogue to the primary immunogenicity endpoints. The lower limit of the CI is used in the hypothesis test for noninferiority.

Results

- **Participant flow**

A total of 2431 participants were randomised: 1778 participants to MenABCWY, 653 to MenACWY + Trumenba. Of these:

- 2413 (99.3%) received Vaccination 1;
- 2120 (87.2%) received Vaccination 2;
- 2074 (85.3%) completed the vaccination phase (defined from the date of the first study vaccination through 1 month after the second study vaccination);
- 2061 (84.8%) completed the follow-up phase (defined as the time from 1 month after the second study vaccination through 6 months after the second study vaccination) and completed the study.

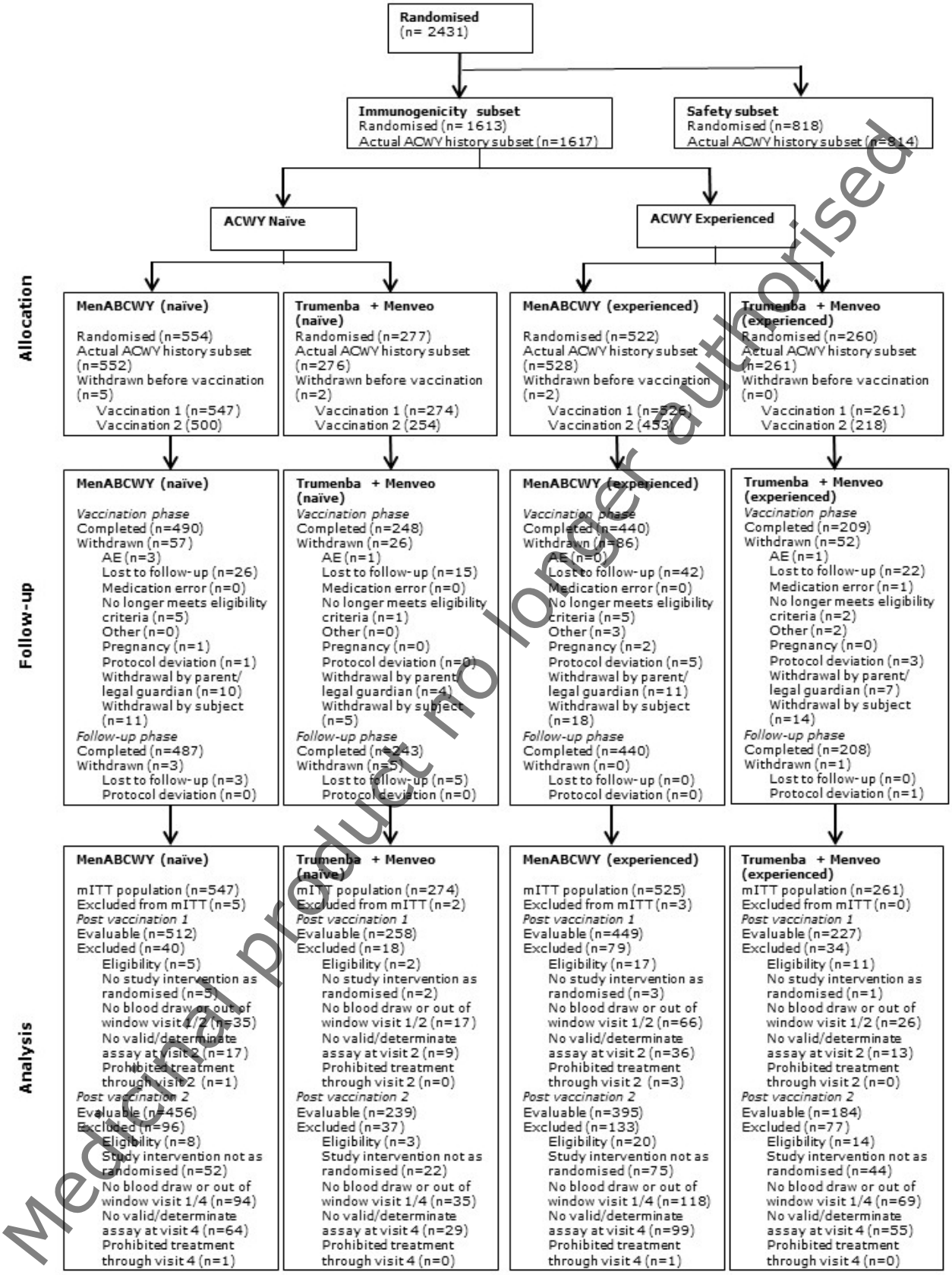

Figure 1: Participant flow

- **Recruitment**

The study began in June 2020 (1st participant 1st visit of 17 June 2020), completed recruitment in August 2021 and was completed in July 2022 (last subject last visit of 24 July 2022).

The study was conducted in 75 sites across 5 countries: the United States, Czech Republic, Denmark, Hungary and Poland. The majority of participants was located in the United States (72.5%), with the European sites representing 27.5% of participants.

- **Conduct of the study**

The original protocol (12 December 2019) was amended twice:

Protocol amendment 1 (30 April 2021)

- Add an optional increase in the volume of the blood draws at Visit 4 for the immunogenicity subset from 25 to 50 mL, to support assay development.
- Replace throughout the protocol the term "CT SAE Report Form" with "Vaccine SAE Reporting Form".
- The definition of postmenopausal state was amended with regard to woman of childbearing potential.
- Two administrative clarifications were made.
- Text was updated to comply with mandatory protocol template text ("Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.").

Protocol amendment 2 (13 June 2022)

- Move MenB secondary strain immunogenicity objective from the secondary immunogenicity objectives to tertiary/exploratory objectives.
- Made allowance for coronavirus disease 2019 (COVID-19) vaccinations within 8 days of study vaccination instead of 14 days.

- **Baseline data**

This study included individuals ≥10 to <26 years of age. Demographic characteristics were generally similar between participants who received MenABCWY versus participants who received Trumenba + Menveo. (Table 3) Also in the immunogenicity population demographic characteristics were generally similar between the study arms both among ACWY-naïve participants and ACWY-experienced participants (*Table 4*), as well as in the mITT population (data not shown) and post-vaccination 2 in the different immunogenicity study arms (*Table 5*).

Table 3. Demographic characteristics-safety population (as administered [actual ACWY history and actual immunogenicity subset[a]])- Study C3511001

	ACWY naïve		***ACWY experienced***	
	MenABCWY	**Menveo+Trumenba**	**MenABCWY**	**Menveo+Trumenba**
	N[b]=547	**N[b]=274**	**N[b]=526**	**N[b]=260**
Sex				
Male	258 (47.2)	134 (48.9)	247 (47.0)	129 (49.6)

	Female	289 (52.8)	140 (51.1)	279 (53.0)	131 (50.4)
Race					
	White	467 (85.4)	239 (87.2)	370 (70.3)	195 (75.0)
	Black or African American	26 (4.8)	19 (6.9)	74 (14.1)	32 (12.3)
	Asian	19 (3.5)	4 (1.5)	18 (3.4)	6 (2.3)
	American Indian or Alaska Native	2 (0.4)	2 (0.7)	2 (0.4)	2 (0.8)
	Native Hawaiian or other Pacific Islander	1 (0.2)	0	2 (0.4)	0
	Multiracial	9 (1.6)	3 (1.1)	12 (2.3)	3 (1.2)
	Not reported	23 (4.2)	7 (2.6)	48 (9.1)	22 (8.5)
Ethnicity					
	Hispanic/Latino	93 (17.0)	53 (19.3)	156 (29.7)	86 (33.1)
	Non-Hispanic/non-Latino	450 (82.3)	217 (79.2)	366 (69.6)	173 (66.5)
	Not reported	4 (0.7)	4 (1.5)	4 (0.8)	1 (0.4)
Age group					
	≥10 to <18 years	259 (47.3)	132 (48.2)	370 (70.3)	187 (70.0)
	≥18 to <26 years	288 (52.7)	142 (51.8)	156 (29.7)	78 (30.0)
Age at 1st vaccination (years)					
	N	547	274	526	260
	Mean (SD)	16.7 (5.49)	16.7 (5.39)	17.3 (3.17)	17.4 (3.28)
	Median	18.0	18.0	16.0	16.0
	Min, Max	(10,25)	(10,25)	(10,25)	(10,25)
Geographic location					
	US	281 (51.4)	141 (51.5)	517 (98.3)	255 (98.1)
	Ex-US	266 (48.6)	133 (48.5)	9 (1.7)	5 (1.9)

[a]. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. "Actual "subset" refers to either immunogenicity or safety subset.

[b]. N = number of participants in the specified group, or the total sample. This value is used as the denominator for the percentage calculations.

Table 4. Demographic characteristics- (study C3511001)- post-vaccination 2 evaluable immunogenicity population for groups 1 and 3; post-vaccination 1 evaluable immunogenicity population for groups 2 and 4

	Vaccine Group (as Randomized [Actual ACWY History and Subset[a]]) Immunogenicity Subset			
	ACWY-Naive		ACWY-Experienced	
	Group 1 MenABCWY + Saline (N[b]=456) n[c] (%)	Group 2 Trumenba+ MenACWY-CRM (N[b]=258) n[c] (%)	Group 3 MenABCWY + Saline (N[b]=395) n[c] (%)	Group 4 Trumenba+ MenACWY-CRM (N[b]=227) n[c] (%)
Sex				
Male	218 (47.8)	127 (49.2)	191 (48.4)	115 (50.7)
Female	238 (52.2)	131 (50.8)	204 (51.6)	112 (49.3)
Race				
White	394 (86.4)	230 (89.1)	293 (74.2)	171 (75.3)
Black or African American	18 (3.9)	16 (6.2)	44 (11.1)	25 (11.0)
Asian	15 (3.3)	4 (1.6)	14 (3.5)	6 (2.6)
American Indian or Alaska Native	1 (0.2)	2 (0.8)	2 (0.5)	2 (0.9)
Native Hawaiian or other Pacific Islander	1 (0.2)	0	1 (0.3)	0
Multiracial	9 (2.0)	3 (1.2)	11 (2.8)	2 (0.9)
Not reported	18 (3.9)	3 (1.2)	30 (7.6)	21 (9.3)
Ethnicity				
Hispanic/Latino	70 (15.4)	45 (17.4)	104 (26.3)	77 (33.9)
Non-Hispanic/non-Latino	383 (84.0)	209 (81.0)	289 (73.2)	149 (65.6)
Not reported	3 (0.7)	4 (1.6)	2 (0.5)	1 (0.4)
Age group				
≥10 Years to <18 years	209 (45.8)	117 (45.3)	297 (75.2)	162 (71.4)
≥18 Years to <26 years	247 (54.2)	141 (54.7)	98 (24.8)	65 (28.6)
Age at first vaccination (years)				
n	456	258	395	227
Mean (SD)	16.8 (5.48)	17.0 (5.34)	17.0 (2.87)	17.4 (3.19)
Median	18.0	18.0	16.0	16.0
Min, max	(10.0, 25.0)	(10.0, 25.0)	(10.0, 25.0)	(10.0, 25.0)
Geographic location				
US	218 (47.8)	125 (48.4)	390 (98.7)	225 (99.1)
Ex-US	238 (52.2)	133 (51.6)	5 (1.3)	2 (0.9)

	Vaccine Group (as Randomized [Actual ACWY History and Subset[a]])			
	Immunogenicity Subset			
	ACWY-Naive		ACWY-Experienced	
	Group 1 MenABCWY + Saline (N[b]=456) n[c] (%)	Group 2 Trumenba+ MenACWY-CRM (N[b]=258) n[c] (%)	Group 3 MenABCWY + Saline (N[b]=395) n[c] (%)	Group 4 Trumenba+ MenACWY-CRM (N[b]=227) n[c] (%)

Abbreviation: Ex-US = global not including the United States.
Note: Groups 1 and 3 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2 and 4 received Trumenba + MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination.
Note: For Group 1 and Group 3, the post-vaccination 2 evaluable immunogenicity population is used; for the Group 2 and Group 4, post-vaccination 1 evaluable immunogenicity population is used.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. "Actual subset" refers to either immunogenicity or safety subset.
b. N = number of participants in the specified group, or the total sample. This value is used as the denominator for the percentage calculations.
c. n = Number of participants with the specified characteristic.

Table 5. Demographic characteristics- (Study C3511001)- Post-vaccination 2 evaluable immunogenicity population for groups 1 and 3 combined and groups 2 and 4 combined

	Vaccine Group (as Randomized [Actual ACWY History and Subset[a]])	
	Groups 1+3 Combined MenABCWY + Saline (N[b]=851)	Groups 2+4 Combined Trumenba+ MenACWY-CRM (N[b]=423)
	n[c] (%)	n[c] (%)
Sex		
Male	409 (48.1)	219 (51.8)
Female	442 (51.9)	204 (48.2)
Race		
White	687 (80.7)	351 (83.0)
Black or African American	62 (7.3)	36 (8.5)
Asian	29 (3.4)	9 (2.1)
American Indian or Alaska Native	3 (0.4)	4 (0.9)
Native Hawaiian or other Pacific Islander	2 (0.2)	0
Multiracial	20 (2.4)	5 (1.2)
Not reported	48 (5.6)	18 (4.3)
Ethnicity		
Hispanic/Latino	174 (20.4)	92 (21.7)
Non-Hispanic/non-Latino	672 (79.0)	327 (77.3)
Not reported	5 (0.6)	4 (0.9)
Age group		
≥10 Years to <18 years	506 (59.5)	251 (59.3)
≥18 Years to <26 years	345 (40.5)	172 (40.7)

	Vaccine Group (as Randomized [Actual ACWY History and Subset[a]])	
	Groups 1+3 Combined MenABCWY + Saline (N[b]=851)	Groups 2+4 Combined Trumenba+ MenACWY-CRM (N[b]=423)
	n[c] (%)	n[c] (%)
Age at first vaccination (years)		
n	851	423
Mean (SD)	16.9 (4.46)	16.9 (4.49)
Median	16.0	16.0
Min, max	(10.0, 25.0)	(10.0, 25.0)
Geographic location		
US	608 (71.4)	296 (70.0)
Ex-US	243 (28.6)	127 (30.0)

Abbreviation: Ex-US = global not including the United States.
Note: Groups 1 and 3 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2 and 4 received Trumenba + MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. "Actual subset" refers to either immunogenicity or safety subset.
b. N = number of participants in the specified group, or the total sample. This value is used as the denominator for the percentage calculations.
c. n = Number of participants with the specified characteristic.

In all study groups in the immunogenicity subset, over 99% of those randomised received the 1st vaccine dose. Over 90% of ACWY-naïve participants received also the 2nd dose, in the ACWY-experienced group this was respectively 85.8% for the MenABCWY group and 83.5% for the Trumenba + Menveo group.

- **Numbers analysed**

The participant flow, including participants randomised, vaccinated, discontinued and evaluable, is presented above.

The primary immunogenicity analyses will be performed on the post-vaccination evaluable immunogenicity populations 1 and 2. An overview of the participants included in the different analyses groups is presented in Table 6.

Table 6: Number of participants in the immunogenicity subset by populations for analysis

Actual vaccination history	***ACWY naïve***		***ACWY experienced***	
	MenABCWY n(%)	**Menveo+Trumenba n(%)**	**MenABCWY n(%)**	**Menveo+Trumenba n(%)**
Randomised	552	276	528	261
mITT	547 (99.1)	274 (99.3)	525 (99.4)	261 (100.0)
Post-vaccination 1 evaluable	512 (92.8)	258 (93.5)	449 (85.0)	227 (87.0)

Post-vaccination 2 evaluable	456 (82.6)	239 (86.6)	395 (74.8)	184 (70.5)

- **Outcomes and estimation**

Primary outcome (proportion of seroresponders)

Immune responses (% of seroresponders: ≥4-fold rise in hSBA titres from baseline) for MenA, C, W and Y observed 1 month after 2 doses of MenABCWY given at 0 and 6 months are noninferior to those observed 1 month after 1 dose of Menveo in both ACWY-naïve and ACWY-experienced participants, using a noninferiority margin 10% (Table 7).

Table 7. Number (%) of participants achieving ⩾4-fold rise in hSBA titre from baseline for MenACWY strains – 1 month after vaccination 2 in the MenABCWY + saline groups compared to 1 month after vaccination 1 in the trumenba + menveo groups – evaluable immunogenicity populations. Study C3511001

	ACWY naïve[a]		***ACWY experienced[a]***			
Sero-group	***Group 1 MenABCWY n[b]/N[c] % (95%CI)) N=456*** [a]	***Group 2 Menveo+ Trumenba n[b]/N[c] % (95%CI)[d] N=258*** [a]	***Group 3 MenABCWY n[b]/N[c] % (95%CI) N=395*** [a]	***Group 4 Menveo+ Trumenba % (95%CI)[d] N=227*** [a]	***Difference[e] Group 1 – Group 2 (95% CI)[f]***	***Difference[e] Group 3 - Group 4 (95% CI)[f]***
MenA	437/447	242/254	361/385	220/227	2.5 (-0.2,6.0)	-3.2 (-6.5,0.5)
	97.8 (95.9,98.9)	95.3 (91.9,97.5)	93.8 (90.9,96.0)	96.9 (93.7,98.8)		
MenC	421/451	132/252	362/386	214/226	41.0 (34.4,47.5)	-0.9 (-4.6,3.3)
	93.3 (90.6,95.5)	52.4 (46.0,58.7)	93.8 (90.9,96.0)	94.7 (90.9,97.2)		
MenW	427/439	178/244	365/376	214/222	24.3 (18.8,30.4)	0.7 (-2.2,4.3)
	97.3 (95.3,98.6)	73.0 (66.9,78.4)	97.1 (94.8,98.5)	96.4 (93.0,98.4)		
MenY	421/446	175/248	360/387	209/223	23.8 (18.0,30.1)	-0.7 (-4.6,3.8)
	94.4 (91.8,96.3)	70.6 (64.5,76.2)	93.0 (90.0,95.4)	93.7 (89.7,96.5)		

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; MenA, MenC, MenW, and MenY = Neisseria meningitidis group A, group C, group W, and group Y. Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups. Note: The immunogenicity analyses for MenA, MenC, MenW, and MenY were done separately for ACWY-naïve and ACWY-experienced participants. Note: The 4-fold increase is defined as follows: (1) For participants with a baseline hSBA titre below the LOD (hSBA titre <1:4), a response is defined as an hSBA titre ≥1:16. (2) For participants with a baseline hSBA titre ≥ LOD and < LLOQ, a response is defined as an hSBA titre ≥4 times the LLOQ. (3) For participants with a baseline hSBA titre ≥ LLOQ, a response is defined as an hSBA titre ≥4 times the baseline titre. Note: For Group 1 and Group 3, the post-Vaccination 2 evaluable immunogenicity population is used; for the Group 2 and Group 4, post-Vaccination 1 evaluable immunogenicity population is used. Note: Groups 1 and 3 received MenABCWY + saline at the 1st study vaccination and MenABCWY at the 2nd study vaccination; Groups 2 and 4 received Trumenba + Menveo at the 1st study vaccination and Trumenba at the 2nd study vaccination.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
b. n = Number of participants who achieved hSBA titre fold rise ≥4 from baseline for the given strain.
c. N = number of participants with valid and determinate hSBA titres for the specified strain at both the given sampling time point and baseline. These values are used as the denominators for the percentage calculations.
d. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.
e. Difference in proportions (Group 1 MenABCWY + saline – Group 2 Trumenba + Menveo) or (Group 3 MenABCWY + saline – Group 4 Trumenba + Menveo), expressed as a percentage.
f. 2-Sided CI (based on Miettinen and Nurminen) for the difference in proportions, expressed as a percentage.

In addition, seroresponses for MenB observed after 2 doses of MenABCWY given at 0 and 6 months are noninferior to those observed after 2 doses of Trumenba. Also for the composite response (hSBA titre ≥LLOQ for all four primary MenB strains) noninferiority was shown (Table 8).

Table 8. Number (%) of participants achieving ⩾4-fold rise in hSBA titre and composite response at 1 month after vaccination 2 for primary MenB strains (MenABCWY + saline combined vs Trumenba + Menveo combined) – post-vaccination 2 evaluable immunogenicity population. Study C3511001

Endpoint MenB Strain	Group 1+ 3 Combined MenABCWY+saline[b] N=851 *n[d]/N[e]* *% (95%CI)[f]*	Groups 2+4 Combined Trumenba + Menveo[c] N=423 *n[d]/N[e]* *% (95%CI)[f]*	*Difference[g]*	*95%CI[h]*
hSBA titre fold rise ≥4 from baseline				
PMB80 (A22)	646/778 83.0 (80.2,85.6)	313/396 79.0 (74.7,82.9)	4.0	(-0.7, 8.9)
PMB2001 (A56)	774/807 95.9 (94.3,97.2)	378/400 94.5 (91.8,96.5)	1.4	(-1.0, 4.3)
PMB2948 (B24)	567/833 68.1 (64.8,71,2)	239/418 57.2 (52.3,62.0)	10.9	(5.2, 16.6)
PMB2707 (B44)	731/845 86.5 (84.0,88.7)	332/419 79.2 (75.0,83.0)	7.3	(2.9, 11.9)
Composite hSBA response [a]				
Before vaccination 1	10/812 1.2 (0.6,2.3)	8/403 2.0 (0.9,3.9)		
1 Month after Vaccination 2	591/755 78.3 (75.2,81.2)	263/383 68.7 (63.8,73.3)	9.6	(4.2, 15.2)

a. hSBA titre ≥ LLOQ for all 4 MenB strains
b. Groups 1 and 3 received MenABCWY + saline at the 1st study vaccination and MenABCWY at the 2nd study vaccination
c. Groups 2 and 4 received Trumenba + Menveo at the 1st study vaccination and Trumenba at the 2nd study vaccination.
d. n = Number of participants who achieved hSBA titre fold rise ≥4 from baseline for the given strain.
e. N = number of participants with valid and determinate hSBA titres for the specified strain at both the given sampling time point and baseline. These values are used as the denominators for the percentage calculations.
f. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.
g. Difference in proportions (Group 1 and 3 MenABCWY + saline – Group 2 and 4 Trumenba + Menveo), expressed as a percentage.
f. 2-Sided CI (based on Miettinen and Nurminen) for the difference in proportions, expressed as a percentage.

Sensitivity analyses

The post-hoc sensitivity analyses requested by the CHMP for the primary estimand using a generalized linear mixed model with repeated measurements adjusted for the geographical location showed comparable results to the primary immunogenicity analyses.

Supportive analyses

Results of the supportive analyses of the noninferiority assessment based on the mITT population for each serogroup A, B, C, W and Y are comparable to the results of the primary immunogenicity analyses for the evaluable immunogenicity population. In addition, the post-hoc analysis results of the alternative estimand requested by the CHMP are presented in Table 9 and are comparable to the results of the primary immunogenicity analyses.

Table 9. Number (%) of Participants Achieving ≥4-Fold Rise in hSBA Titre From Baseline for MenACWY Strains – 1 Month After Vaccination 2 in the MenABCWY + Saline Groups Compared to 1 Month After Vaccination 1 in the Trumenba + Menveo Groups – Using Multiple Imputation Model – Post-Vaccination 1 Evaluable Immunogenicity Populations. Study C3511001; Modified by Assessor

	ACWY naïve[a]		*ACWY experienced[a]*			
Sero-group	*Group 1 MenABCWY* *n[c]/N[d]* *% (95%CI[e]))*	*Group 2 Menveo+ Trumenba* *n[c]/N[d]* *% (95%CI[e])*	*Group 3 MenABCWY* *n[c]/N[d]* *% (95%CI[e])*	*Group 4 Menveo+ Trumenba* *% (95%CI[e])*	*Difference[-] Group 1 – Group 2 (95% CI[g])*	*Difference[e] Group 3 - Group 4 (95% CI[g])*
MenA	474/487 97.3 (95.9,98.6)	242/254 95.3 (91.9,97.5)	394/420 93.8 (91.1,95.9)	220/227 96.9 (93.7,98.8)	2.1 (-0.7,5.6)	-3.1 (-6.3,0.5)
MenC	457/492 92.9 (90.2,95.0)	132/252 52.4 (46.0,58.7)	393/421 93.3 (90.5,95.5)	214/226 94.7 (90.9,97.2)	40.5 (34.0,47.0)	-1.3 (-5.0,2.9)
MenW	464/480 96.7 (94.6,98.1)	178/244 73.0 (66.9,78.4)	397/409 97.1 (94.9,98.5)	214/222 96.4 (93.0,98.4)	23.7 (18.2,29.8)	0.7 (-2.1,4.2)

MenY	457/485 94.2 (91.8,96.1)	175/248 70.6 (64.5,76.2)	394/423 93.1 (90.3,95.4)	209/223 93.7 (89.7,96.5)	23.7 (17.9,29.9)	-0.6 (-4.4,3.9)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; MenA, MenC, MenW, and MenY = Neisseria meningitidis group A, group C, group W, and group Y.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups.
Note: The immunogenicity analyses for MenA, MenC, MenW, and MenY were done separately for ACWY-naïve and ACWY-experienced participants.
Note: The 4-fold increase is defined as follows: (1) For participants with a baseline hSBA titre below the LOD (hSBA titre <1:4), a response is defined as an hSBA titre ≥1:16. (2) For participants with a baseline hSBA titre ≥ LOD and < LLOQ, a response is defined as an hSBA titre ≥4 times the LLOQ. (3) For participants with a baseline hSBA titre ≥ LLOQ, a response is defined as an hSBA titre ≥4 times the baseline titre.
Note: Groups 1 and 3 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2 and 4 received Trumenba + MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination.
Note: Participants in Group 1 and Group 3 in Post Vaccination 1 Evaluable Population with valid baseline titers that are missing Vaccination 2 have had the missing result imputed using multiple imputation model including fixed effects of vaccine group, age group, location, vaccine group by age group interaction and vaccine group by location interaction.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. Vaccine group as randomized
b. Multiple imputations using a logistic model.
c. n = Number of participants who achieved hSBA titre fold rise ≥4 from baseline for the given strain.
d. N = number of participants with valid and determinate hSBA titres for the specified strain at both the given sampling time point and baseline. These values are used as the denominators for the percentage calculations.
e. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.
f. Difference in proportions (Group 1 MenABCWY + saline – Group 2 Trumenba + Menveo) or (Group 3 MenABCWY + saline – Group 4 Trumenba + Menveo), expressed as a percentage.
g. 2-Sided CI (based on Miettinen and Nurminen) for the difference in proportions, expressed as a percentage.

Secondary analyses (Percentage of seroresponders after one dose of MenABCWY vaccine)

Immune responses for MenA, C, W and Y observed after 1 dose of MenABCWY in both ACWY-naïve and experienced are noninferior to those observed after 1 dose of Menveo. The lower limit of the 2-sided 95% CI for the difference in percentage of participants achieving a ≥4-fold rise from baseline for each serogroup is greater than -10% (Table 10).

Table 10. Number (%) of Participants Achieving ≥4-Fold Rise in hSBA Titre From Baseline for MenACWY Strains – 1 Month After Vaccination 1 in the MenABCWY + Saline Groups Compared to the Trumenba + MenACWY-CRM Groups – Post-Vaccination 1 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized [Actual ACWY History and Subset[a]])					
	ACWY-Naive		ACWY-Experienced			
Serogroup	**Group 1 MenABCWY + Saline n[b]/ N[c] (%) (95% CI[d])**	**Group 2 Trumenba + MenACWY-CRM n[b]/ N[c] (%) (95% CI[d])**	**Group 3 MenABCWY + Saline n[b]/ N[c] (%) (95% CI[d])**	**Group 4 Trumenba + MenACWY-CRM n[b]/ N[c] (%) (95% CI[d])**	**Difference[e] (Group 1 MenABCWY + Saline - Group 2 Trumenba + MenACWY-CRM (95% CI[f])**	**Difference[e] (Group 3 MenABCWY + Saline - Group 4 Trumenba + MenACWY-CRM (95% CI[f])**
MenA	484/499 (97.0) (95.1, 98.3)	242/254 (95.3) (91.9, 97.5)	416/439 (94.8) (92.2, 96.7)	220/227 (96.9) (93.7, 98.8)	1.7 (-1.0, 5.3)	-2.2 (-5.2, 1.4)
MenC	315/501 (62.9) (58.5, 67.1)	132/252 (52.4) (46.0, 58.7)	410/439 (93.4) (90.7, 95.5)	214/226 (94.7) (90.9, 97.2)	10.5 (3.0, 17.9)	-1.3 (-4.9, 2.9)
MenW	390/492 (79.3) (75.4, 82.8)	178/244 (73.0) (66.9, 78.4)	417/428 (97.4) (95.4, 98.7)	214/222 (96.4) (93.0, 98.4)	6.3 (-0.1, 13.1)	1.0 (-1.6, 4.6)
MenY	405/494 (82.0) (78.3, 85.3)	175/248 (70.6) (64.5, 76.2)	417/442 (94.3) (91.8, 96.3)	209/223 (93.7) (89.7, 96.5)	11.4 (5.0, 18.2)	0.6 (-3.0, 5.0)

Serogroup	Vaccine Group (as Randomized [Actual ACWY History and Subset[a]]) ACWY-Naive Group 1 MenABCWY + Saline n[b]/ N[c] (%) (95% CI[d])	ACWY-Naive Group 2 Trumenba + MenACWY-CRM n[b]/ N[c] (%) (95% CI[d])	ACWY-Experienced Group 3 MenABCWY + Saline n[b]/ N[c] (%) (95% CI[d])	ACWY-Experienced Group 4 Trumenba + MenACWY-CRM n[b]/ N[c] (%) (95% CI[d])	Difference[e] (Group 1 MenABCWY + Saline - Group 2 Trumenba + MenACWY-CRM (95% CI[f])	Difference[e] (Group 3 MenABCWY + Saline - Group 4 Trumenba + MenACWY-CRM (95% CI[f])

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* group A, group C, group W, and group Y.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups.
Note: The immunogenicity analyses for MenA, MenC, MenW, and MenY were done separately for ACWY-naïve and ACWY-experienced participants.
Note: The 4-fold increase is defined as follows: (1) For participants with a baseline hSBA titer below the LOD (hSBA titer <1:4), a response is defined as an hSBA titer ≥1:16. (2) For participants with a baseline hSBA titer ≥ LOD and < LLOQ, a response is defined as an hSBA titer ≥4 times the LLOQ. (3) For participants with a baseline hSBA titer
≥ LLOQ, a response is defined as an hSBA titer ≥4 times the baseline titer.
Note: Groups 1, 3, 5, and 7 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2, 4, 6, and 8 received Trumenba + MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. "Actual subset" refers to either immunogenicity or safety subset.
b. n = Number of participants who achieved hSBA titer fold rise ≥4 from baseline for the given strain.
c. N = number of participants with valid and determinate hSBA titers for the specified strain at both the given sampling time point and baseline. These values are used as the denominators for the percentage calculations.
d. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.
e. Difference in proportions (Group 1 MenABCWY + saline – Group 2 Trumenba + MenACWY-CRM) or (Group 3 MenABCWY + saline – Group 4 Trumenba + MenACWY-CRM), expressed as a percentage.
f. 2-Sided CI (based on Miettinen and Nurminen) for the difference in proportions, expressed as a percentage.

Exploratory analyses: Seroprotection (hSBA titres ≥LLOQ)

The accepted CoP is hSBA titre ≥ 1:4, seroprotection is defined here based on the LLOQ for the hSBA, which is 1:8 for A, C, W, Y and MenB strains A56, B24, and B44 and 1:16 for MenB strain A22. Therefore, some individual participants in either group who did not achieve titres ≥ LLOQ may still have achieved titres above the accepted CoP, but could not be reliably quantified based on the limits of the assay.

When comparing serogroups A, C, W, and Y hSBA titres after 2 doses of MenABCWY to 1 dose of Menveo, for both ACWY-naïve and ACWY-experienced participants, the proportions of participants achieving hSBA titres ≥1:8 approached 100% seroprotection for the 4 serogroups except in Group 2 for MenC (74.4%) at 1 month after Vaccination 1 (*Table 11*).

When comparing serogroups A, C, W, and Y hSBA titres after 1 dose of MenABCWY to 1 dose of Menveo, for both ACWY-naïve and ACWY-experienced participants, proportions of MenABCWY recipients achieving seroprotective titres ≥1:8 at 1 month after Vaccination 1 for the 4 serogroups were similar to those for Trumenba + Menveo recipients. Among ACWY-naïve participants proportions achieving seroprotective titres ≥1:8 for MenC were higher for MenABCWY (82.4%) recipients than Menveo (74.4%). Among ACWY-experienced participants, proportions achieving seroprotective titres ≥1:8 at 1 month after Vaccination 1 approached 100% regardless of whether participants received MenABCWY or Trumenba + Menveo (Table 11).

Table 11. Number (%) of participants with hSBA Titre ≥1:8 for MenACWY strains at baseline and 1 month after vaccination 1 and 1 month after vaccination 2 in the MenABCWY + Saline groups compared to the Trumenba + Menveo groups at baseline and 1 month after vaccination 1 –evaluable immunogenicity population (modified by the assessor). Study C3511001

		Vaccine Group (as Randomised [Actual ACWY History and Subset[a]])			
		ACWY-naïve		ACWY-Experienced	
		Group 1 MenABCWY N=512	Group 2 Trumenba + Menveo N=258	Group 3 MenABCWY N=449	Group 4 Trumenba + Menveo N=227
Serogroup	**Sampling Time Point**	**n[b]/ N[c] (%) (95% CI[d])**	**n[b]/ N[c] (%) (95% CI[d])**	**n[b]/ N[c] (%) (95% CI[d])**	**n[b]/ N[c] (%) (95% CI[d])**
MenA	Before Vaccination 1	91/499 (18.2) (14.9, 21.9)	53/254 (20.9) (16.0, 26.4)	233/439 (53.1) (48.3, 57.8)	125/227 (55.1) (48.3, 61.7)
	1 Month after Vaccination 1	506/509 (99.4) (98.3, 99.9)	254/258 (98.4) (96.1, 99.6)	445/445 (100.0) (99.2, 100.0)	225/227 (99.1) (96.9, 99.9)
	1 Month after Vaccination 2[e]	454/455 (99.8) (98.8, 100.0)		391/391 (100.0) (99.1, 100.0)	
MenC	Before Vaccination 1	150/503 (29.8) (25.9, 34.0)	78/252 (31.0) (25.3, 37.1)	204/441 (46.3) (41.5, 51.0)	103/226 (45.6) (39.0, 52.3)
	1 Month after Vaccination 1	418/507 (82.4) (78.8, 85.7)	192/258 (74.4) (68.6, 79.6)	441/443 (99.5) (98.4, 99.9)	221/227 (97.4) (94.3, 99.0)
	1 Month after Vaccination 2[e]	451/455 (99.1) (97.8, 99.8)		386/390 (99.0) (97.4, 99.7)	
MenW	Before Vaccination 1	198/492 (40.2) (35.9, 44.7)	103/244 (42.2) (35.9, 48.7)	299/428 (69.9) (65.3, 74.2)	162/222 (73.0) (66.6, 78.7)
	1 Month after Vaccination 1	503/509 (98.8) (97.5, 99.6)	250/258 (96.9) (94.0, 98.7)	445/445 (100.0) (99.2, 100.0)	226/227 (99.6) (97.6, 100.0)
	1 Month after Vaccination 2[e]	454/455 (99.8) (98.8, 100.0)		390/390 (100.0) (99.1, 100.0)	
MenY	Before Vaccination 1	233/496 (47.0) (42.5, 51.5)	134/248 (54.0) (47.6, 60.4)	337/442 (76.2) (72.0, 80.1)	172/223 (77.1) (71.1, 82.5)
	1 Month after Vaccination 1	503/507 (99.2) (98.0, 99.8)	256/258 (99.2) (97.2, 99.9)	445/445 (100.0) (99.2, 100.0)	227/227 (100.0) (98.4, 100.0)
	1 Month after Vaccination 2[e]	453/455 (99.6) (98.4, 99.9)		391/391 (100.0) (99.1, 100.0)	

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* group A, group C, group W, and group Y.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups.
Note: The immunogenicity analyses for MenA, MenC, MenW, and MenY were done separately for ACWY-naïve and ACWY-experienced participants.
Note: Groups 1 and 3 received MenABCWY + saline at the 1st study vaccination and MenABCWY at the 2nd study vaccination; Groups 2 and 4 received Trumenba + Menveo at the 1st study vaccination and Trumenba at the 2nd study vaccination.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. "Actual subset" refers to either immunogenicity or safety subset.
b. n = Number of participants with observed hSBA titre ≥1:8 for the specified serogroup at the given sampling time point.
c. N = number of participants with valid and determinate hSBA titres for the specified serogroup at the given sampling time point. These values are used as the denominators for the percentage calculations.
d. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.
e. At Vaccination 2 (7 months after the 1st dose of Menveo), participants in Groups 2 and 4 were to receive bivalent rLP2086 only.

The proportions of MenABCWY recipients achieving a seroprotective hSBA titre (hSBA titre ≥ LLOQ) at 1 month after Vaccination 2 compared to those of Trumenba + Menveo recipients were similar for PMB80 (A22) and PMB2001 (A56) and were notably higher among MenABCWY versus Trumenba + Menveo recipients for test strains PMB2948 (B24) (83.4% vs 74.0%) and PMB2707 (B44) (94.3% vs 87.4%) (Table 12).

Table 12. Number (%) of Participants With Defined hSBA Titres (≥1:4 and ≥ LLOQ) for Primary MenB Strains at Baseline and 1 Month After Vaccination 2 (MenABCWY + Saline Combined vs Trumenba + Menveo Combined) – Post-Vaccination 2 Evaluable Immunogenicity Population. Study C3511001

MenB Strain (Variant)	Sampling Time Point	Titre	Groups 1+3 Combined MenABCWY				Groups 2+4 Combined Trumenba + Menveo			
			N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])
PMB80 (A22)	Before Vaccination 1	4	834	171	20.5	(17.8, 23.4)	414	84	20.3	(16.5, 24.5)
		LLOQ	834	142	17.0	(14.5, 19.8)	414	74	17.9	(14.3, 21.9)
	1 Month after Vaccination 2	4	794	734	92.4	(90.4, 94.2)	405	358	88.4	(84.9, 91.3)
		LLOQ	794	732	92.2	(90.1, 94.0)	405	357	88.1	(84.6, 91.1)
PMB2001 (A56)	Before Vaccination 1	4	831	113	13.6	(11.3, 16.1)	413	65	15.7	(12.4, 19.6)
		LLOQ	831	89	10.7	(8.7, 13.0)	413	51	12.3	(9.3, 15.9)
	1 Month after Vaccination 2	4	825	814	98.7	(97.6, 99.3)	409	403	98.5	(96.8, 99.5)
		LLOQ	825	814	98.7	(97.6, 99.3)	409	401	98.0	(96.2, 99.2)
PMB2948 (B24)	Before Vaccination 1	4	848	67	7.9	(6.2, 9.9)	422	44	10.4	(7.7, 13.7)
		LLOQ	848	44	5.2	(3.8, 6.9)	422	29	6.9	(4.7, 9.7)
	1 Month after Vaccination 2	4	836	738	88.3	(85.9, 90.4)	419	332	79.2	(75.0, 83.0)
		LLOQ	836	697	83.4	(80.7, 85.8)	419	310	74.0	(69.5, 78.1)
PMB2707 (B44)	Before Vaccination 1	4	849	54	6.4	(4.8, 8.2)	423	28	6.6	(4.4, 9.4)
		LLOQ	849	31	3.7	(2.5, 5.1)	423	20	4.7	(2.9, 7.2)
	1 Month after Vaccination 2	4	847	820	96.8	(95.4, 97.9)	419	382	91.2	(88.0, 93.7)
		LLOQ	847	799	94.3	(92.6, 95.8)	419	366	87.4	(83.8, 90.4)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = *Neisseria meningitidis* group B.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
Note: Groups 1 and 3 received MenABCWY + saline at the 1st study vaccination and MenABCWY at the 2nd study vaccination; Groups 2 and 4 received Trumenba + Menveo at the 1st study vaccination and Trumenba at the 2nd study vaccination.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. "Actual subset" refers to either immunogenicity or safety subset.
b. N = number of participants with valid and determinate hSBA titres for the specified strain at the given sampling time point. These values are used as the denominators for the percentage calculations.
c. n = Number of participants achieving the defined hSBA titre for the specified strain at the given sampling time point.
d. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

Exploratory analyses: hSBA titres (GMTs)

hSBA titres among ACWY-experienced participants were higher compared to ACWY-naïve participants. In ACWY-naïve participants hSBA GMTs after 2 doses of MenABCWY vaccine were markedly higher for compared with those at 1 month after Vaccination 1 with Trumenba + Menveo. In contrast, GMTs were also lower in ACWY-experienced MenABCWY recipients (group 3) 1 month after the 2nd dose (266.7 to 542.8) compared to 1 month after a single dose of Menveo (454.5 to 824.4).

Among ACWY-experienced individuals who received MenABCWY (group 3), GMTs for the 4 serogroups A, C, W, and Y did decline 1 month after the 2nd dose compared to GMTs 1 month after the 1st dose of MenABCWY.

An overview of the GMTs at different timepoints in the mITT population can be found in table 13.

Table 13. hSBA GMTs at all time points for MenACWY Strains – mITT population. Study C3511001

	Vaccine Group (as Randomised [Actual ACWY History and Subset[a]])							
	ACWY-naive				**ACWY-experienced**			
Serogroup Sampling time point	**Group 1 MenABCWY+saline**		**Group 2 Trumenba + Menveo**		**Group 3 MenABCWY+saline**		**Group 4 Trumenba + Menveo**	
	n	GMT (95%CI)	n	GMT (95%CI)	N	GMT (95%CI)	n	GMT (95%CI)
MenA								
Before Vaccination 1	536	5.6 (5.3, 6.1)	270	5.9 (5.3, 6.5)	517	13.0 (11.6, 14.6)	259	12.4 (10.6, 14.5)
1 Month after Vaccination 1	535	137.5 (124.4, 151.9)	267	142.7 (121.8, 167.3)	492	412.1 (375.0, 453.0)	248	592.1 (506.2, 692.5)
1 Month after Vaccination 2[e]	487	168.9 (154.6, 184.6)	245	62.9 (54.7, 72.4)	429	307.8 (282.8, 335.0)	206	185.3 (157.5, 218.0)
MenC								
Before Vaccination 1	540	6.1 (5.7, 6.5)	268	6.5 (5.8, 7.2)	518	9.8 (8.8, 10.9)	257	9.3 (8.0, 10.8)
1 Month after Vaccination 1	533	41.5 (35.4, 48.5)	267	38.8 (30.3, 49.6)	490	396.9 (351.4, 448.3)	248	441.5 (361.7, 539.0)
1 Month after Vaccination 2[e]	487	139.8 (126.1, 155.0)	246	31.0 (25.8, 37.3)	428	256.8 (228.9, 288.1)	204	123.3 (99.5, 152.9)
MenW								
Before Vaccination 1	528	7.6 (7.0, 8.3)	259	8.0 (7.0, 9.1)	505	13.7 (12.3, 15.2)	252	13.7 (11.9, 15.8)
1 Month after Vaccination 1	535	61.9 (55.5, 69.1)	267	56.1 (47.0, 66.9)	492	803.6 (717.1, 900.7)	248	828.0 (704.7, 972.9)
1 Month after Vaccination 2[e]	487	260.4 (238.2, 284.7)	247	77.2 (68.0, 87.7)	428	516.2 (465.1, 572.8)	206	237.7 (201.7, 280.2)
MenY								
Before Vaccination 1	531	9.7 (8.8, 10.7)	264	12.3 (10.5, 14.4)	519	21.3 (18.9, 23.9)	255	20.3 (17.4, 23.7)
1 Month after Vaccination 1	533	100.5 (91.0, 111.0)	267	88.8 (74.7, 105.4)	492	884.4 (791.9, 987.8)	248	785.2 (671.2, 918.6)
1 Month after Vaccination 2[e]	487	270.6 (248.7, 294.5)	247	69.8 (61.0, 79.9)	429	547.1 (492.8, 607.4)	206	256.0 (214.8, 305.2)

[e] For the Menveo+Trumenba group this is actually at 7 months after Vaccination 2 since there is no 2nd dose of Menveo administered.

For all 4 primary MenB test strains at 1 month after Vaccination 2, hSBA GMTs in the MenABCWY group (range, 17.8 to 182.0) were consistently higher than in the Trumenba group (range, 14.4 to 148.1) (table 14).

Table 14. hSBA GMTs for Primary MenB Strains at Baseline and 1 Month After Vaccination 2 (MenABCWY + Saline Combined vs Trumenba + Menveo Combined) – Post-Vaccination 2 Evaluable Immunogenicity Population. Study C3511001

		Groups 1+3 MenABCWY + Saline			**Groups 2+4 Trumenba + Menveo**		
MenB Strain (Variant)	**Sampling Time Point**	**n**	**GMT**	**(95% CI)**	**n**	**GMT**	**(95% CI)**
PMB80 (A22)	Before Vaccination 1	834	10.3	(9.9, 10.8)	414	10.6	(9.9, 11.3)
	1 Month after Vaccination 2	794	65.4	(61.1, 70.0)	405	54.3	(49.2, 59.9)
PMB2001 (A56)	Before Vaccination 1	831	5.1	(4.9, 5.4)	413	5.3	(4.9, 5.7)
	1 Month after Vaccination 2	825	182.0	(169.5, 195.4)	409	148.1	(133.0, 164.9)
PMB2948 (B24)	Before Vaccination 1	848	4.3	(4.2, 4.4)	422	4.4	(4.2, 4.5)
	1 Month after Vaccination 2	836	17.8	(16.7, 19.0)	419	14.4	(13.0, 15.9)
PMB2707 (B44)	Before Vaccination 1	849	4.2	(4.1, 4.3)	423	4.3	(4.2, 4.4)
	1 Month after Vaccination 2	847	33.9	(31.6, 36.3)	419	26.2	(23.7, 29.1)

- **Ancillary analyses**

According to the results provided, subgroup analyses for the percentage of seroresponders for A, C, W and Y and the four primary MenB strains by race and ethnicity did not show any differences that are considered clinically relevant.

Some differences were observed in the percentage of seroresponders by age group. In general the proportion of seroresponders was higher in the younger age group (≥10-<18 years versus ≥18-<26 years), for serogroups A, C, W and Y this was more apparent in the ACWY-naïve group since among ACWY-experienced the percentage of seroresponders was in general higher.

Table 15. Number (%) of Participants By Age Group Achieving ≥4-Fold Rise in hSBA Titer From Baseline for MenACWY Strains by Subgroups – 1 Month After Vaccination 2 in the MenABCWY + Saline Groups Compared to 1 Month After Vaccination 1 in the Trumenba + MenACWY-CRM Groups – Evaluable Immunogenicity Populations

	Vaccine Group (as Randomised [Actual ACWY History and Subset[a]])			
	ACWY-naive		ACWY-experienced	
	Group 1 MenABCWY n[b]/ N[c] (%) (95% CI[d])	Group 2 Trumenba + Menveo n[b]/ N[c] (%) (95% CI[d])	Group 3 MenABCWY n[b]/ N[c] (%) (95% CI[d])	Group 4 Trumenba + Menveo n[b]/ N[c] (%) (95% CI[d])
MenA				
≥10 to <18 years	204/208 (98.1) (95.1, 99.5)	112/114 (98.2) (93.8, 99.8)	282/289 (97.6) (95.1, 99.0)	159/162 (98.1) (94.7, 99.6)
≥18 to <26 years	233/239 (97.5) (94.6, 99.1)	130/140 (92.9) (87.3, 96.5)	79/96 (82.3) (73.2, 89.3)	61/65 (93.8) (85.0, 98.3)
MenC				
≥10 to <18 years	203/207 (98.1) (95.1, 99.5)	69/115 (60.0) (50.4, 69.0)	276/291 (94.8) (91.6, 97.1)	154/161 (95.7) (91.2, 98.2)
≥18 to <26 years	218/244 (89.3) (84.8, 92.9)	63/137 (46.0) (37.4, 54.7)	86/95 (90.5) (82.8, 95.6)	60/65 (92.3) (83.0, 97.5)
MenW				
≥10 to <18 years	196/197 (99.5) (97.2, 100.0)	77/110 (70.0) (60.5, 78.4)	286/288 (99.3) (97.5, 99.9)	157/160 (98.1) (94.6, 99.6)
≥18 to <26 years	231/242 (95.5) (92.0, 97.7)	101/134 (75.4) (67.2, 82.4)	79/88 (89.8) (81.5, 95.2)	57/62 (91.9) (82.2, 97.3)
MenY				
≥10 to <18 years	198/202 (98.0) (95.0, 99.5)	85/114 (74.6) (65.6, 82.3)	279/290 (96.2) (93.3, 98.1)	151/158 (95.6) (91.1, 98.2)
≥18 to <26 years	223/244 (91.4) (87.1, 94.6)	90/134 (67.2) (58.5, 75.0)	81/97 (83.5) (74.6, 90.3)	58/65 (89.2) (79.1, 95.6)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; MenA, MenC, MenW, and MenY =Neisseria meningitidis group A, group C, group W, and group Y; NE = not estimable; NA= not applicable.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups.
Note: The immunogenicity analyses for MenA, MenC, MenW, and MenY were done separately for ACWY-naïve and ACWY-experienced participants.
Note: The 4-fold increase is defined as follows: (1) For participants with a baseline hSBA titre below the LOD (hSBA titre <1:4), a response is defined as an hSBA titer ≥1:16. (2) For participants with a baseline hSBA titre ≥ LOD and < LLOQ, a response is defined as an hSBA titre ≥4 times the LLOQ. (3) For participants with a baseline hSBA titre ≥ LLOQ, a response is defined as an hSBA titre ≥4 times the baseline titre.
Note: For Group 1 and Group 3, the post-Vaccination 2 evaluable immunogenicity population is used; for the Group 2 and Group 4, post-Vaccination 1 evaluable immunogenicity population is used.
Note: Groups 1 and received MenABCWY + saline at the 1st study vaccination and MenABCWY at the 2nd study vaccination; Groups 2and 4 received Trumenba + Menveo at the 1st study vaccination and Trumenba at the 2nd study vaccination.
Note: Race categories other than "White", "Black", "Asian" or "Not Reported" have been reported in the "Other" category.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. "Actual subset" refers to either immunogenicity or safety subset.
b. n = Number of participants who achieved hSBA titre fold rise ≥4 from baseline for the given strain.
c. N = number of participants with valid and determinate hSBA titres for the specified strain at both the given sampling time point and baseline. These values are used as the denominators for the percentage calculations.
d. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

Table 16. Number (%) of participants achieving ⩾4-fold rise in hSBA titer and composite response at 1 month after vaccination 2 for primary MenB strains by subgroups (MenABCWY + saline combined vs Trumenba + Menveo combined) – post-vaccination 2 evaluable immunogenicity population

	Vaccine Group (as Randomised [Actual ACWY History and Subset[a]])							
	Groups 1+3 Combined MenABCWY + saline				Groups 2+4 Combined Trumenba + Menveo			
	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])
PMB80 (A22)								
≥10 Years to <18 years	468	403	86.1	(82.6, 89.1)	236	197	83.5	(78.1,88.0)
≥18 Years to <26 years	310	243	78.4	(73.4, 82.8)	160	116	72.5	(64.9-79.3)
PMB2001 (A56)								
≥10 Years to <18 years	486	470	96.7	(94.7, 98.1)	240	230	95.8	(92.5, 98.0)
≥18 Years to <26 years	321	304	64.7	(91.7, 96.9)	160	148	92.5	(87.3, 96.1)
PMB2948 (B24)								
≥10 Years to <18 years	491	345	70.3	(66.0, 74.3)	247	151	61.1	(54.7, 67.2)
≥18 Years to <26 years	342	222	64.9	(59.6, 70.0)	171	88	51.5	(43.7, 59.2)

PMB2707 (B44)								
≥10 Years to <18 years	502	446	88.8	(85.8, 91.5)	249	212	85.1	(80.1, 89.3)
≥18 Years to <26 years	343	285	83.1	(78.7, 86.9)	170	120	70.6	(63.1, 77.3)
Composite hSBA response (hSBA titer ≥ LLOQ for all 4 MenB strains)								
≥10 Years to <18 years	452	362	80.1	(76.1, 83.7)	227	171	75.3	(69.2, 80.8)
≥18 Years to <26 years	303	229	75.6	(70.3, 80.3)	156	92	59.0	(50.8, 66.8)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; MenB = Neisseria meningitidis group B; NE = not estimable; NA= not applicable.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
Note: The 4-fold increase is defined as follows: (1) For participants with a baseline hSBA titer below the LOD (hSBA titer <1:4), a response is defined as an hSBA titer ≥1:16. (2) For participants with a baseline hSBA titer ≥ LOD and < LLOQ, a response is defined as an hSBA titer ≥4 times the LLOQ. (3) For participants with a baseline hSBA titer ≥ LLOQ, a response is defined as an hSBA titer ≥4 times the baseline titer.
Note: Participants from Groups 1 and 2 are ACWY-naïve; participants from Groups 3 and 4 are ACWY-experienced.
Note: Groups 1 and 3 received MenABCWY + saline at the 1st study vaccination and MenABCWY at the 2nd study vaccination; Groups 2 and 4 Trumenba + Menveo at the 1st study vaccination and Trumenba at the 2nd study vaccination.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. "Actual subset" refers to either immunogenicity or safety subset.
b. For hSBA titer fold rise ≥4 from baseline, N = number of participants with valid and determinate hSBA titers for the specified strain at baseline. For composite hSBA response (hSBA ≥ LLOQ for all 4 primary strains), N = number of participants with valid and determinate hSBA results for all 4 strains.
c. For hSBA titer fold rise ≥4 from baseline, n = number of participants who achieved hSBA titer fold rise ≥4 from baseline for the given strain. For composite hSBA response
(hSBA ≥ LLOQ for all 4 primary strains), n = number of participants with observed hSBA titer ≥ LLOQ for all 4 primary strains.
d. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

Slight differences were observed in the percentage of seroresponders by sex. The immune responses were higher in men compared to women in both arms to all five antigens (see Tables 17 and 18).

Table 17. Number (%) of participants achieving ⩾4-fold rise in hSBA Titer from baseline for MenACWY strains by subgroups – 1 month after vaccination 2 in the MenABCWY + saline groups compared to 1 Month After Vaccination 1 in the Trumenba + MenACWY-CRM groups – evaluable immunogenicity populations

	Vaccine Group (as Randomised [Actual ACWY History and Subset[a]])			
	ACWY-naive		ACWY-experienced	
	Group 1 MenABCWY n[b]/ N[c] (%) (95% CI[d])	**Group 2 Trumenba + Menveo** n[b]/ N[c] (%) (95% CI[d])	**Group 3 MenABCWY** n[b]/ N[c] (%) (95% CI[d])	**Group 4 Trumenba + Menveo** n[b]/ N[c] (%) (95% CI[d])
MenA				
female	226/232 (97.4) (94.5, 99.0)	126/131 (96.2) (91.3, 98.7)	184/199 (92.5) (87.9, 95.7)	108/112 (96.4) (91.1, 99.0)
male	211/215 (98.1) (95.3, 99.5)	116/123 (94.3) (88.6, 97.7)	177/186 (95.2) (91.0, 97.8)	112/115 (97.4) (92.6, 99.5)
MenC				
female	219/236 (92.8) (88.7, 95.7)	69/131 (52.7) (43.8, 61.5)	191/200 (95.5) (91.6, 97.9)	104/112 (92.9) (86.4, 96.9)
male	202/215 (94.0) (89.9, 96.7)	63/121 (52.1) (42.8, 61.2)	171/186 (91.9) (87.0, 95.4)	110/114 (96.5) (91.3, 99.0)
MenW				
female	224/230 (97.4) (94.4, 99.0)	87/123 (70.7) (61.9, 78.6)	189/192 (98.4) (95.5, 99.7)	104/110 (94.5) (88.5, 98.0)
male	203/209 (97.1) (93.9, 98.9)	91/121 (75.2) (66.5, 82.6)	176/184 (95.7) (91.6, 98.1)	110/112 (98.2) (93.7, 99.8)
MenY				
female	221/233 (94.8) (91.2, 97.3)	92/128 (71.9) (63.2, 79.5)	188/199 (94.5) (90.3, 97.2)	100/109 (91.7) (84.9, 96.2)
male	200/213 (93.9) (89.8, 96.7)	83/120 (69.2) (60.1, 77.3)	172/188 (91.5) (86.5, 95.1)	109/114 (95.6) (90.1, 98.6)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; MenA, MenC, MenW, and MenY =Neisseria meningitidis group A, group C, group W, and group Y; NE = not estimable; NA= not applicable.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups.
Note: The immunogenicity analyses for MenA, MenC, MenW, and MenY were done separately for ACWY-naïve and ACWY-experienced participants.
Note: The 4-fold increase is defined as follows: (1) For participants with a baseline hSBA titre below the LOD (hSBA titre <1:4), a response is defined as an hSBA titer ≥1:16. (2) For participants with a baseline hSBA titre ≥ LOD and < LLOQ, a response is defined as an hSBA titre ≥4 times the LLOQ. (3) For participants with a baseline hSBA titre ≥ LLOQ, a response is defined as an hSBA titre ≥4 times the baseline titre.
Note: For Group 1 and Group 3, the post-Vaccination 2 evaluable immunogenicity population is used; for the Group 2 and Group 4, post-Vaccination 1 evaluable immunogenicity population is used.
Note: Groups 1 and received MenABCWY + saline at the 1st study vaccination and MenABCWY at the 2nd study vaccination; Groups 2and 4 received Trumenba + Menveo at the 1st study vaccination and Trumenba at the 2nd study vaccination.
Note: Race categories other than "White", "Black", "Asian" or "Not Reported" have been reported in the "Other" category.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. "Actual subset" refers to either immunogenicity or safety subset.
b. n = Number of participants who achieved hSBA titre fold rise ≥4 from baseline for the given strain.

c. N = number of participants with valid and determinate hSBA titres for the specified strain at both the given sampling time point and baseline. These values are used as the denominators for the percentage calculations.
d. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

Table 18. Number (%) of Participants Achieving ≥4-Fold Rise in hSBA Titer and Composite Response at 1 Month After Vaccination 2 for Primary MenB Strains by Subgroups (MenABCWY + Saline Combined vs Trumenba + MenACWY-CRM Combined) – Post-Vaccination 2 Evaluable Immunogenicity Population

	Vaccine Group (as Randomised [Actual ACWY History and Subset[a]])							
	Groups 1+3 Combined MenABCWY + saline				**Groups 2+4 Combined Trumenba + Menveo**			
	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])
PMB80 (A22)								
Female	408	331	81.1	(77.0, 84.8)	188	144	76.6	(69.9, 82.4)
Male	370	315	85.1	(81.1, 88.6)	208	169	81.3	(75.3, 86.3)
PMB2001 (A56)								
Female	421	400	95.0	(92.5, 96.9)	190	177	93.2	(88.6, 96.3)
Male	386	374	96.9	(94.6, 98.4)	210	201	95.7	(92.0, 98.0)
PMB2948 (B24)								
Female	432	271	62.7	(58.0, 67.3)	199	107	53.8	(46.6, 60.8)
Male	401	296	73.8	(69.2, 78.1)	219	132	60.3	(53.5, 66.8)
PMB2707 (B44)								
Female	440	375	85.2	(81.6, 88.4)	200	153	76.5	(70.0, 82.2)
Male	405	356	87.9	(84.3, 90.9)	219	179	81.7	(76.0, 86.6)
Composite hSBA response (hSBA titer ≥ LLOQ for all 4 MenB strains)								
Female	396	291	73.5	(68.8, 77.8)	179	114	63.7	(56.2, 70.7)
Male	359	300	83.6	(79.3, 87.2)	204	149	73.0	(66.4, 79.0)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; MenB = Neisseria meningitidis group B; NE = not estimable; NA= not applicable.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
Note: The 4-fold increase is defined as follows: (1) For participants with a baseline hSBA titer below the LOD (hSBA titer <1:4), a response is defined as an hSBA titer ≥1:16. (2) For participants with a baseline hSBA titer ≥ LOD and < LLOQ, a response is defined as an hSBA titer ≥4 times the LLOQ. (3) For participants with a baseline hSBA titer ≥ LLOQ, a response is defined as an hSBA titer ≥4 times the baseline titer.
Note: Participants from Groups 1 and 2 are ACWY-naïve; participants from Groups 3 and 4 are ACWY-experienced.
Note: Groups 1 and 3 received MenABCWY + saline at the 1st study vaccination and MenABCWY at the 2nd study vaccination; Groups 2 and 4 Trumenba + Menveo at the 1st study vaccination and Trumenba at the 2nd study vaccination.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. "Actual subset" refers to either immunogenicity or safety subset.
b. For hSBA titer fold rise ≥4 from baseline, N = number of participants with valid and determinate hSBA titers for the specified strain at baseline. For composite hSBA response (hSBA ≥ LLOQ for all 4 primary strains), N = number of participants with valid and determinate hSBA results for all 4 strains.
c. For hSBA titer fold rise ≥4 from baseline, n = number of participants who achieved hSBA titer fold rise ≥4 from baseline for the given strain. For composite hSBA response
(hSBA ≥ LLOQ for all 4 primary strains), n = number of participants with observed hSBA titer ≥ LLOQ for all 4 primary strains.
d. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

- **Summary of main efficacy results**

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19. Summary of immunogenicity efficacy for trial C3511001

Title: A Phase 3, Randomised, Active-Controlled, Observer Blinded Trial to Assess the Safety, Tolerability, and Immunogenicity of MenABCWY in Healthy Participants ≥10 to <26 Years of Age		
Study identifier	C3511001 European Clinical Trials Database (EudraCT) Number: 2019-004313-13 United States (US) Investigational New Drug (IND) Number: 17319	
Design	Phase 3, randomised, active-controlled, observer blinded, multicentre trial	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	2 years (June 17, 2020 – July 24, 2022) not applicable not applicable

Hypothesis	Non-inferiority (immunogenicity); the lower limit of the 2-sided 95% CI for the difference in seroresponders is >-10% for all of the MenACWY test strains and in 4-fold rises and composite responses for all primary MenB strains		
Treatments groups	Group 1 MenACWY-naive MenABCWY	MenABCWY + saline n= 552 randomised	Month 0: 1 dose 0.5 mL MenABCWY & 1 dose 0.5 mL saline Month 6: 1 dose 0.5 mL MenABCWY All administered intramuscularly
	Group 3 MenACWY-experienced MenABCWY	MenABCWY + saline n= 276 randomised	
	Group 2 MenACWY-naive Active comparator	Menveo + Trumenba n= 528 randomised	Month 0: 1 dose 0.5 mL Menveo & 1 dose 0.5 mL Trumenba Month 6: 1 dose 0.5 mL Trumenba All administered intramuscularly
	Group 4 MenACWY-experienced Active comparator	Menveo + Trumenba n= 261 randomised	
Endpoints and definitions	Co-Primary endpoints	Difference in the percentage of seroresponders for each A,C,W, Y strain	Separately for MenACWY-naïve and MenACWY-experienced participants: Difference in the percentage of seroresponders (participants achieving at least a 4-fold rise in hSBA titre from baseline) 1 month after Vaccination 2 in the MenABCWY arm compared to 1 month after Vaccination 1 in the Menveo arm for each ACWY strain
	Co-Primary endpoints	Difference in the percentage of seroresponders for each of the 4 primary MenB strains (A22, A56, B24, and B44) and a composite of all 4 MenB strains	Difference in the percentage of participants achieving at least a 4-fold rise in hSBA titre from baseline 1 month after Vaccination 2 for each of the 4 primary MenB test strains Differences in the percentage of participants achieving an hSBA titre ≥ LLOQ 1 month after Vaccination 2 for all 4 primary menB strains
	Secondary endpoint	Difference in the percentage of seroresponders for each of the ACWY test strains	Separately for MenACWY-naïve and MenACWY-experienced participants: Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titre from baseline for each ACWY test strain, 1 month after Vaccination 1 in the MenABCWY arm compared to 1 month after Vaccination 1 in the Menveo arm.
Database lock	18 Aug 2022		
Final Database release	25 Aug 2022		
Results and Analysis			
Analysis description	**Primary Analysis:** Differences in percentages and associated 95% CIs between study groups are based on the Miettinen and Nurminen method		

Analysis population and time point description	Post-vaccination 1 evaluable immunogenicity population / Per protocol: All treated participants randomised to group of interest; had blood drawn within the required time frames; had at least 1 valid and determinate MenACWY assay result at Visit 2; no prohibited vaccines or treatment through Visit 2 and no important protocol deviations through Visit 2. Post–Vaccination 2 evaluable immunogenicity population / Per Protocol: All treated participants randomised to group of interest; had blood drawn for assay testing within the required time frames at Months 0 (Visit 1: before Vaccination 1) and 7 (Visit 4: 1 month after the 2nd vaccination: window 28 49 days); had at least 1 valid and determinate MenACWY or MenB assay result at Visit 4; no prohibited vaccines or treatment through Visit 4 and no important protocol deviations through Visit 4. Evaluable population: Defined according to post–Vaccination 1 evaluable and post–Vaccination 2 evaluable criteria. Primary immunogenicity analyses populations: For ACWY strains: Post–Vaccination 2 evaluable immunogenicity population for the MenABCWY treatment groups (group 1 and 3) and Post–Vaccination 1 evaluable immunogenicity population for the active comparator treatment groups (group 2 and 4) For B strains: Post–Vaccination 2 evaluable immunogenicity population				
Descriptive statistics and estimate variability	Treatment group	Group 1 MenACWY-naïve MenABCWY	Group 2 MenACWY-naïve Menveo+Trumenba	Group 3 MenACWY-experienced MenABCWY	Group 4 MenACWY-experienced Menveo+Trumenba
	Number of subject	456	258	395	227
	Seroresponders, % of participants with ≥4-fold-rise from baseline (95%CI)				
	MenA	97.8 (95.9,98.9)	95.3 (91.9,97.5)	93.8 (90.9,96.0)	96.9 (93.7,98.8)
	MenC	93.3 (90.6,95.5)	52.4 (46.0,58.7)	93.8 (90.9,96.0)	94.7 (90.9,97.2)
	MenW	97.3 (95.3,98.6)	73.0 (66.9,78.4)	97.1 (94.8,98.5)	96.4 (93.0,98.4)
	MenY	94.4 (91.8,96.3)	70.6 (64.5,76.2)	93.0 (90.0,95.4)	93.7 (89.7,96.5)
	Treatment group	MenABCWY+saline (group 1&3)		Menveo+Trumenba (group 2&4)	
	Number of subjects	851		423	
	% of participants with ≥4-fold-rise from baseline (95%CI)				
	MenB PMB80 (A22)	83.0 (80.2,85.6)		79.0 (74.7,82.9)	
	MenB PMB2001 (A56)	95.9 (94.3,97.2)		94.5 (91.8,96.5)	
	MenB PMB2948 (B24)	68.1 (64.8,71.2)		57.2 (52.3,62.0)	
	MenB PMB2707 (B44)	86.5 (84.0,88.7)		79.2 (75.0,83.0)	
	MenB Composite response before vaccination 1 (95%CI)	1.2 (0.6,2.3)		2.0 (0.9,3.9)	
	MenB	78.3		68.7	

	Composite response 1 month after vaccination 2 (95%CI)	(75.2,81.2)		(63.8,73.3)	
Effect estimate per comparison	Co-Primary endpoint		Comparison groups	Group 1 and 2	
			Endpoint (variability)	Estimated difference (%) between groups (95%CI)	
			MenA	2.5 (-0.2, 6.0)	
			MenC	41.0 (34.4, 47.5)	
			MenW	24.3 (18.8, 30.4)	
			MenY	23.8 (18.0, 30.1)	
	Co-Primary endpoint		Comparison groups	Group 3 and 4	
			Endpoint (variability)	Estimated difference (%) between groups (95%CI)	
			MenA	-3.2 (-6.5, 0.5)	
			MenC	-0.9 (-4.6, 3.3)	
			MenW	0.7 (-2.2, 4.3)	
			MenY	-0.7 (-4.6, 3.8)	
	Co-Primary endpoint		Comparison groups	Group 1 and 3 combined versus group 2 and 4 combined	
			Endpoint (variability)	Estimated difference (%) between groups (95%CI)	
			MenB -PMB80 (A22)	4.0 (-0.7, 8.9)	
			MenB -PMB2001 (A56)	1.4 (-1.0, 4.3)	
			MenB -PMB2948 (B24)	10.9 (5.2, 16.6)	
			MenB -PMB2707 (B44)	7.3 (2.9, 11.9)	
			Composite MenB	9.6 (4.2, 15.2)	
Notes	• It should be noted that the ACWY component vaccine used in the active comparator arm is Menveo and not Nimenrix, which is the basis of the MenABCWY investigative vaccine. • The applicant has concluded non-inferiority for their primary immunogenicity objectives, based on a non-inferiority margin of 10%, however the choice of delta has not been justified and clinical relevance is unclear.				
Analysis description	**Secondary analysis:** Differences in percentages and associated 95% CIs between study groups are based on the Miettinen and Nurminen method				
Analysis population and time point description	Post-vaccination evaluable immunogenicity population / Per protocol 1 month after vaccination 1				
Descriptive statistics and estimate variability	Treatment group	MenACWY-naïve MenABCWY+saline	MenACWY-naïve Menveo +Trumenba	MenACWY-experienced MenABCWY+ saline	MenACWY-experienced Menveo +Trumenba
	Number of subject	512	258	449	227
	% of participants with 4-fold-rise (95%CI)				
	MenA	97.0 (95.1, 98.3)	95.3 (91.9, 97.5)	94.8 (92.2, 96.7)	96.9 (93.7, 98.8)
	MenC	62.9 (58.5, 67.1)	52.4 (46.0, 58.7)	93.4 (90.7, 95.5)	94.7 (90.9, 97.2)
	MenW	79.3 (75.4, 82.8)	73.0 (66.9, 78.4)	97.4 (95.4, 98.7)	96.4 (93.0, 98.4)
	MenY	82.0 (78.3, 85.3)	70.6 (64.5, 76.2)	94.3 (91.8, 96.3)	93.7 (89.7, 96.5)

Effect estimate per comparison	Secondary endpoint	Comparison groups	Group 1 and 2
		Endpoint (variability)	Estimated difference (%) between groups (95% CI)
		MenA	1.7 (-1.0, 5.3)
		MenC	10.5 (3.0,17.9)
		MenW	6.3 (-0.1, 13.1)
		MenY	11.4 (5.0,18.2)
	Secondary endpoint	Comparison groups	Group 3 and 4
		Endpoint (variability)	Estimated difference (%) between groups (95% CI)
		MenA	-2.2 (-5.2,1.4)
		MenC	-1.3 (-4.9,2.9)
		MenW	1.0 (-1.6,4.6)
		MenY	0.6 (-3.0,5.0)
Notes	Not applicable		

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

The combined analysis for immunogenicity included data only from the MenABCWY arms (groups 1 and 3) of studies C3511001 and B1971057.

The estimated percentage of seroresponders is very similar in both studies investigating the 0-, 6-month schedule, with ≥93% of participants being seroresponders for all serogroups in both studies for both the ACWY-naïve and ACWY-experienced population. However, after dose 1 a clear estimated difference can be observed in the ACWY-naïve population between study B1971057 and C3511001, with especially the responses for serogroup MenC being substantially higher in study B1971057 (75.5%) compared to C3511001 (62.9%) with non-overlapping 95% CI. In addition, the estimated proportion of seroresponders for both MenW and MenY were also higher in study B1971057 (86.6% and 86.0%) compared to C3511001 (79.3% and 82.0%), although the 95% CI did overlap.

2.5.5.4. Supportive studies

The supportive studies, B1971057 and C3511004, both evaluated immunogenicity of the MenABCWY vaccine. No efficacy results were obtained.

B1971057

Study B1971057 is a phase 3, randomised, active-controlled, observer-blinded study to assess the immunogenicity, safety, and tolerability of bivalent rLP2086 when administered as a 2-dose regimen and a 1st-in-human study to describe the immunogenicity, safety, and tolerability of a bivalent rLP2086-containing pentavalent Vaccine (MenABCWY) in Healthy Subjects ≥10 to <26 Years of age.

In addition to the standard exclusion criteria for, participants who had a history of microbiologically proven disease caused by *N. meningitidis* or *Neisseria gonorrhoeae*, previous vaccination with any meningococcal group B vaccine or any purely polysaccharide (non-conjugate) meningococcal vaccine were excluded. Also those with previous vaccination with >1 dose of a vaccine containing 1 or more ACWY group or subjects who received 1 prior dose of a vaccine containing 1 or more ACWY group <4 years prior to date of randomisation were excluded.

Participants were randomised to receive either two doses of MenABCWY vaccine administered concomitantly with saline at the first dose or two doses of bivalent rLP2086 administered concomitantly

with Menveo at the first dose, in both groups vaccines were administered six months apart. The study is conducted in two stages. Stage 1 is observer-blinded and examines the immune responses up to 1 month after Vaccination 2. Stage 2 is open-label and focusses on the immunopersistence following primary vaccination, as well as the safety, tolerability and immunogenicity of a booster dose of MenABCWY (administered four years later) through 1 month following the booster. Currently only an interim analysis is available.

A total of 1610 participants were randomised in stage 1 of this study. Demographic characteristics were generally similar across groups. Overall, most participants were White (85.6%). The median age at the time of Vaccination 1 was 17.0 years, and 42.6% of participants were male.

A total of 353 participants entered Stage 2 (immunopersistence evaluations followed by booster vaccination); 242 participants received booster doses. Demographic characteristics were generally similar across groups. Overall, most participants were White (92.1%). The median age at the time of study vaccination was 20.0 years, and 45.8% of participants were male.

Primary series

The proportions of MenABCWY + saline recipients (Groups 1+3 combined) for the evaluable immunogenicity population achieving at least a 4-fold rise and/or the composite response at 1 month after Vaccination 2 are shown in Table 20. The proportion of MenABCWY + saline and bivalent rLP2086 + Menveo recipients achieving a composite response for MenB at 1 month after Vaccination 2 was 79.9% and 74.3%, respectively (Table 21). hSBA GMTs among MenABCWY + saline recipients for the 4 primary MenB test strains were comparable to those observed for bivalent rLP2086 + Menveo recipients at all time points.

Table 20. Subjects Achieving ≥4-Fold Rise in hSBA Titre and Composite Response at 1 Month After Vaccinations 1 and 2 for Primary MenB Strains - MenABCWY (Groups 1+3 Combined) and Bivalent rLP2086 (Groups 2+4 Combined) - Stage 1 Evaluable Immunogenicity Population; Study B1971057

	Vaccine Group (as Randomised [Actual ACWY History[a]])					
	Groups 1+3 Combined (MenABCWY + Saline)			Groups 2+4 Combined (Bivalent rLP2086 + Menveo)		
Endpoint						
MenB Strain (Variant)						
Time Point	**N[b]**	**n[c] (%)**	**(95% CI)[d]**	**N[b]**	**n[c] (%)**	**(95% CI)[d]**
hSBA titre fold rise ≥4 from baseline						
PMB80 (A22)						
1 Month after Vaccination 1	411	150 (36.5)	(31.8, 41.4)	814	292 (35.9)	(32.6, 39.3)
1 Month after Vaccination 2	422	320 (75.8)	(71.5, 79.8)	827	610 (73.8)	(70.6, 76.7)
PMB2001 (A56)						
1 Month after Vaccination 1	402	228 (56.7)	(51.7, 61.6)	800	394 (49.3)	(45.7, 52.8)
1 Month after Vaccination 2	418	396 (94.7)	(92.1, 96.7)	823	782 (95.0)	(93.3, 96.4)
PMB2948 (B24)						
1 Month after Vaccination 1	428	173 (40.4)	(35.7, 45.2)	829	277 (33.4)	(30.2, 36.7)
1 Month after Vaccination 2	422	321 (76.1)	(71.7, 80.1)	835	563 (67.4)	(64.1, 70.6)
PMB2707 (B44)						
1 Month after Vaccination 1	422	149 (35.3)	(30.7, 40.1)	834	229 (27.5)	(24.5, 30.6)
1 Month after Vaccination 2	432	396 (91.7)	(88.6, 94.1)	850	734 (86.4)	(83.9, 88.6)
Composite hSBA response (hSBA titre ≥ LLOQ for all 4 MenB strains)						
Before Vaccination 1	403	6 (1.5)	(0.5, 3.2)	799	14 (1.8)	(1.0, 2.9)
1 Month after Vaccination 1	388	118 (30.4)	(25.9, 35.3)	769	178 (23.1)	(20.2, 26.3)
1 Month after Vaccination 2	418	334 (79.9)	(75.7, 83.6)	814	605 (74.3)	(71.2, 77.3)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
Note: The 4-fold increase is defined as follows: (1) For subjects with a baseline hSBA titre below the LOD (hSBA titre <1:4), a response is defined as an hSBA titre ≥1:16 or the LLOQ (whichever titre is higher). (2) For subjects with a baseline hSBA titre ≥ LOD and < LLOQ, a response is defined as an hSBA titre ≥4 times the LLOQ. (3) For subjects with a baseline hSBA titre ≥ LLOQ, a response is defined as an hSBA titre ≥4 times the baseline titre.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
b. For hSBA titre fold rise, N = number of subjects with valid and determinate hSBA titres for the given strain at both the specified time point and baseline. For composite hSBA response, N = number of subjects with valid and determinate hSBA results on all 4 strains at the given time point.
c. For hSBA titre fold rise, n = number of subjects who achieved hSBA titre fold rise ≥4 from baseline for the given strain. For composite hSBA response, n = number of subjects with observed hSBA titre ≥ LLOQ for all 4 primary strains at the given time point.
d. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.

Among ACWY-naive participants, estimated proportions of participants achieving titres ≥1:8 at 1 month after Vaccination 1 for the 4 serogroups ranged from 92.4% to 99.6% for MenABCWY + saline recipients and were slightly higher compared to bivalent rLP2086 + Menveo recipients. Among ACWY-experienced participants, proportions achieving titres ≥1:8 at 1 month after Vaccination 1 approached 100% regardless of whether participants received MenABCWY + saline or bivalent rLP2086 + Menveo.

One month after a 2nd dose of MenABCWY (administered 6 months after the 1st dose), estimated proportions of participants achieving titres ≥1:8 in ACWY-naive participants were 100% for serogroups A, C, W, and Y. Among ACWY-experienced participants after a 2nd dose of MenABCWY administered 6 months after the 1st dose, estimated proportions with titres ≥1:8 1 month following the 2nd dose were 99.5% to 99.6% for all 4 serogroups.

Among ACWY-naive participants, GMTs at 1 month after Vaccination 1 were higher for MenABCWY + saline recipients compared to bivalent rLP2086 + Menveo recipients, except for MenA. Among ACWY-experienced participants, hSBA GMTs for Men A, C, W and Y were higher post vaccination 1 than post vaccination 2. (Table 21).

Table 21. hSBA GMTs at All Time Points for MenA, MenC, MenW, and MenY – MenABCWY (Groups 1 and 3) and Menveo (Groups 2 and 4) – Stage 1 mITT Population; Study B1971057

	Vaccine Group (as Randomised [Actual ACWY History[a]])							
	ACWY-Naive				**ACWY-Experienced**			
	Group 1		**Group 2**		**Group 3**		**Group 4**	
Serogroup	**MenABCWY + Saline**		**Bivalent rLP2086 + Menveo**		**MenABCWY +Saline**		**Bivalent rLP2086 + Menveo**	
Time Point	N[b]	GMT[c] (95%CI)[d]	N[b]	GMT[c] (95%CI)[d]	N[b]	GMT[c] (95%CI)[d]	N[b]	GMT[c] (95%CI)[d]
MenA								
Before Vaccination 1	270	5.7 (5.1, 6.3)	528	6.3 (5.7, 6.8)	219	11.0 (9.3, 13.0)	418	10.7 (9.6, 12.0)
1 Month after Vaccination 1	264	215.8 (184.6, 252.4)	510	203.2 (178.7, 231.0)	218	568.6 (492.9, 656.0)	411	916.1 (809.1, 1037.3)
Before Vaccination 2	238	42.7 (36.1, 50.4)	463	47.2 (40.8, 54.5)	200	158.7 (132.6, 189.8)	385	214.6 (187.7, 245.3)
1 Month after Vaccination 2[e]	232	151.3 (134.1, 170.7)	463	54.9 (48.5, 62.0)	191	337.3 (291.7, 390.0)	376	224.2 (197.9, 253.9)
MenC								
Before Vaccination 1	267	7.5 (6.6, 8.5)	526	7.5 (6.8, 8.2)	264	11.9 (10.2, 13.8)	511	13.4 (11.9, 15.1)
1 Month after Vaccination 1	262	111.5 (87.2, 142.6)	509	81.4 (68.1, 97.4)	264	814.9 (689.4, 963.2)	506	827.0 (722.5, 946.6)
Before Vaccination 2	239	61.5 (49.5, 76.3)	460	32.7 (27.8, 38.5)	243	253.1 (213.0, 300.8)	474	186.7 (161.9, 215.2)
1 Month after Vaccination 2[e]	231	229.1 (194.7, 269.5)	454	58.0 (50.7, 66.5)	237	498.7 (429.1, 579.6)	466	222.6 (195.3, 253.8)
MenW								
Before Vaccination 1	268	7.0 (6.2, 7.9)	527	7.0 (6.4, 7.5)	218	10.5 (9.1, 12.2)	418	11.0 (9.8, 12.3)
1 Month after Vaccination 1	264	98.4 (80.7, 120.0)	512	71.2 (61.5, 82.4)	219	1214.9 (1032.0, 1430.1)	414	1176.7 (1017.9, 1360.2)
Before Vaccination 2	242	62.6 (53.5, 73.1)	467	39.1 (34.4, 44.5)	199	376.8 (311.4, 456.0)	385	255.5 (221.4, 295.0)
1 Month after Vaccination 2[e]	233	274.1 (242.7, 309.7)	464	80.9 (73.5, 89.1)	191	570.9 (484.3, 673.0)	376	291.3 (256.8, 330.4)
MenY								
Before Vaccination 1	265	10.5 (9.1, 12.1)	528	11.5 (10.4, 12.7)	219	19.2 (16.3, 22.5)	421	19.0 (16.8, 21.4)
1 Month after Vaccination 1	263	141.9 (118.8, 169.4)	510	96.6 (83.9, 111.2)	218	1174.0 (990.3, 1391.9)	413	1000.2 (872.1, 1147.1)
Before Vaccination 2	239	83.6 (71.4, 97.8)	463	58.6 (52.0, 66.0)	198	395.2 (327.8, 476.3)	382	264.0 (228.5, 305.0)
1 Month after Vaccination 2[e]	233	301.5 (266.6, 341.0)	461	69.8 (63.1, 77.3)	191	558.6 (470.0, 663.9)	374	268.6 (235.0, 307.1)

Abbreviations: GMT = geometric mean titre; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* serogroup A, serogroup C, serogroup W, and serogroup Y; mITT = modified intent-to-treat.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups. Titres below the LLOQ were set to 0.5 × LLOQ for analysis.

a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. Subjects who received a monovalent meningococcal group C vaccine are included in the analysis for *Neisseria meningitidis* group C (MenC) only.
b. N = number of subjects with valid and determinate hSBA titres for the given serogroup at the specified time point.
c. GMTs were calculated using all subjects with valid and determinate hSBA titres at the given time point.
d. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean of the ratio.
e. At Vaccination 2, subjects in Groups 2 and 4 were to receive bivalent rLP2086 only

Immune persistence

The estimated proportion of recipients with protective MenB hSBA titres ≥ LLOQ at different time points up to 48 months after Vaccination 2 were similar between the MenABCWY group and bivalent rLP2086 + Menveo group. The GMTs for the four primary MenB test strains drop close to baseline at 12 months after Vaccination 2 for both the MenABCWY groups (Group 1+3) and the combined Bivalent rLP2086 + MenACWY-CRM groups (Groups 2+4). However, there is no further reduction from 12 months post Vaccination 2 through 48 months post Vaccination 2 (Table 22).

Table 22. Participants With hSBA Titres ≥ LLOQ for Primary MenB Strains – MenABCWY (Groups 1+3 Combined) and Bivalent rLP2086 (Groups 2+4 Combined) – Persistence Analysis – Stage 2 mITT Population; Study B1971057

	Vaccine Group (as Randomised [Actual ACWY History[a]])							
	Groups 1+3 Combined (MenABCWY + Saline)				Groups 2+4 Combined (Bivalent rLP2086 + Menveo)			
MenB Strain (Variant)								
Time Point	**N[b]**	**n[c]**	**%**	**(95% CI[d])**	**N[b]**	**n[c]**	**%**	**(95% CI[d])**
PMB80 (A22)								
Before Vaccination 1	206	59	28.6	(22.6, 35.3)	133	30	22.6	(15.8, 30.6)
1 Month after Vaccination 2	211	193	91.5	(86.9, 94.9)	137	127	92.7	(87.0, 96.4)
12 Months after Vaccination 2	162	53	32.7	(25.6, 40.5)	83	22	26.5	(17.4, 37.3)
24 Months after Vaccination 2	196	72	36.7	(30.0, 43.9)	128	37	28.9	(21.2, 37.6)
36 Months after Vaccination 2	185	54	29.2	(22.8, 36.3)	116	30	25.9	(18.2, 34.8)
48 Months after Vaccination 2	139	39	28.1	(20.8, 36.3)	94	30	31.9	(22.7, 42.3)
PMB2001 (A56)								
Before Vaccination 1	206	28	13.6	(9.2, 19.0)	132	13	9.8	(5.3, 16.3)
1 Month after Vaccination 2	210	205	97.6	(94.5, 99.2)	136	133	97.8	(93.7, 99.5)
12 Months after Vaccination 2	162	54	33.3	(26.1, 41.2)	84	27	32.1	(22.4, 43.2)
24 Months after Vaccination 2	196	68	34.7	(28.1, 41.8)	131	44	33.6	(25.6, 42.4)
36 Months after Vaccination 2	186	54	29.0	(22.6, 36.1)	118	40	33.9	(25.4, 43.2)
48 Months after Vaccination 2	145	50	34.5	(26.8, 42.8)	98	29	29.6	(20.8, 39.7)
PMB2948 (B24)								
Before Vaccination 1	210	23	11.0	(7.1, 16.0)	137	10	7.3	(3.6, 13.0)
1 Month after Vaccination 2	205	176	85.9	(80.3, 90.3)	135	108	80.0	(72.3, 86.4)
12 Months after Vaccination 2	165	51	30.9	(24.0, 38.6)	85	24	28.2	(19.0, 39.0)
24 Months after Vaccination 2	196	65	33.2	(26.6, 40.2)	131	36	27.5	(20.0, 36.0)
36 Months after Vaccination 2	192	68	35.4	(28.7, 42.6)	120	34	28.3	(20.5, 37.3)
48 Months after Vaccination 2	145	53	36.6	(28.7, 44.9)	98	26	26.5	(18.1, 36.4)
PMB2707 (B44)								
Before Vaccination 1	210	6	2.9	(1.1, 6.1)	136	4	2.9	(0.8, 7.4)
1 Month after Vaccination 2	212	202	95.3	(91.5, 97.7)	135	130	96.3	(91.6, 98.8)
12 Months after Vaccination 2	166	31	18.7	(13.1, 25.4)	85	13	15.3	(8.4, 24.7)
24 Months after Vaccination 2	200	36	18.0	(12.9, 24.0)	132	24	18.2	(12.0, 25.8)

36 Months after Vaccination 2	193	39	20.2	(14.8, 26.6)	121	24	19.8	(13.1, 28.1)
48 Months after Vaccination 2	148	27	18.2	(12.4, 25.4)	99	16	16.2	(9.5, 24.9)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = Neisseria meningitidis serogroup B.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
b. N = number of participants with valid and determinate hSBA titres for the given strain.
c. n = Number of participants with observed hSBA titre ≥ LLOQ for the given strain at the given time point.
d. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

During the 4 years following completion of the 2-dose primary vaccination series, estimated proportions of participants with seroprotective titres ≥1:8 for serogroups A, C, W, and Y through 48 months remained relatively high for all 4 serogroups, and where there was some decline, it was gradual. At 48 months, estimated seroprotection rates among ACWY-naïve participants ranged from 62.0% to 100.0% for MenABCWY (2 doses) and from 38.1% to 95.2% for bivalent rLP2086 + Menveo (only 1 dose Menveo) recipients. Among ACWY-experienced participants, estimated seroprotection rates at 48 months ranged from 98.7% to 100.0% in MenABCWY recipients compared to 89.7% to 100.0% in bivalent rLP2086 + Menveo recipients (Table 23).

Table 23. Participants With hSBA Titres ≥1:8 for MenA, MenC, MenW, and MenY – MenABCWY (Groups 1 and 3) and Bivalent rLP2086 (Groups 2 and 4) – Persistence Analysis – Stage 2 mITT Population – Adapted by assessor (24 and 36 months results not displayed); Study B1971057

	Vaccine Group (as Randomised [Actual ACWY Historya])			
	ACWY-Naive		**ACWY-Experienced**	
	Group 1 (MenABCWY + Saline)	**Group 2 (Bivalent rLP2086 + Menveo)**	**Group 3 (MenABCWY + Saline)**	**Group 4 (Bivalent rLP2086 + Menveo)**
Serogroup Time Point	nb/ Nc (%) (95% CId)	nb/ Nc (%) (95% CId)	nb/ Nc (%) (95% CId)	nb/ Nc (%) (95% CId)
MenA				
Before Vaccination 1	12/111 (10.8) (5.7, 18.1)	10/63 (15.9) (7.9, 27.3)	31/59 (52.5) (39.1, 65.7)	16/37 (43.2) (27.1, 60.5)
1 Month after Vaccination 2[e]	112/112 (100.0) (96.8, 100.0)	60/64 (93.8) (84.8, 98.3)	59/60 (98.3) (91.1, 100.0)	38/38 (100.0) (90.7, 100.0)
12 Months after Vaccination 2	102/112 (91.1) (84.2, 95.6)	42/59 (71.2) (57.9, 82.2)	47/48 (97.9) (88.9, 99.9)	22/22 (100.0) (84.6, 100.0)
48 Months after Vaccination 2	58/71 (81.7) (70.7, 89.9)	26/41 (63.4) (46.9, 77.9)	40/40 (100.0) (91.2, 100.0)	23/23 (100.0) (85.2, 100.0)
MenC				
Before Vaccination 1	32/109 (29.4) (21.0, 38.8)	18/64 (28.1) (17.6, 40.8)	58/97 (59.8) (49.3, 69.6)	47/71 (66.2) (54.0, 77.0)
1 Month after Vaccination 2[e]	111/111 (100.0) (96.7, 100.0)	58/63 (92.1) (82.4, 97.4)	99/100 (99.0) (94.6, 100.0)	72/72 (100.0) (95.0, 100.0)
12 Months after Vaccination 2	86/112 (76.8) (67.9, 84.2)	32/62 (51.6) (38.6, 64.5)	52/54 (96.3) (87.3, 99.5)	21/23 (91.3) (72.0, 98.9)
48 Months after Vaccination 2	44/71 (62.0) (49.7, 73.2)	16/42 (38.1) (23.6, 54.4)	75/76 (98.7) (92.9, 100.0)	52/58 (89.7) (78.8, 96.1)
MenW				
Before Vaccination 1	28/109 (25.7) (17.8, 34.9)	21/63 (33.3) (22.0, 46.3)	37/59 (62.7) (49.1, 75.0)	21/36 (58.3) (40.8, 74.5)
1 Month after Vaccination 2[e]	112/112 (100.0) (96.8, 100.0)	64/64 (100.0) (94.4, 100.0)	59/60 (98.3) (91.1, 100.0)	38/38 (100.0) (90.7, 100.0)
12 Months after Vaccination 2	111/112 (99.1) (95.1, 100.0)	52/62 (83.9) (72.3, 92.0)	48/48 (100.0) (92.6, 100.0)	21/22 (95.5) (77.2, 99.9)
48 Months after Vaccination 2	64/70 (91.4) (82.3, 96.8)	29/41 (70.7) (54.5, 83.9)	40/40 (100.0) (91.2, 100.0)	21/23 (91.3) (72.0, 98.9)
MenY				
Before Vaccination 1	59/109 (54.1) (44.3, 63.7)	31/64 (48.4) (35.8, 61.3)	47/58 (81.0) (68.6, 90.1)	24/36 (66.7) (49.0, 81.4)
1 Month after Vaccination 2[e]	112/112 (100.0) (96.8, 100.0)	61/62 (98.4) (91.3, 100.0)	60/61 (98.4) (91.2, 100.0)	38/38 (100.0) (90.7, 100.0)
12 Months after Vaccination 2	112/112 (100.0) (96.8, 100.0)	61/62 (98.4) (91.3, 100.0)	48/48 (100.0) (92.6, 100.0)	22/22 (100.0) (84.6, 100.0)
48 Months after Vaccination 2	71/71 (100.0) (94.9, 100.0)	40/42 (95.2) (83.8, 99.4)	40/40 (100.0) (91.2, 100.0)	22/22 (100.0) (84.6, 100.0)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA, MenC, MenW, and MenY = Neisseria meningitidis serogroup A, serogroup C, serogroup W, and serogroup Y.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY strains.

a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. Participants who received a monovalent meningococcal group C vaccine are included in the analysis for Neisseria meningitidis group C (MenC) only.
b. n = Number of participants with observed hSBA titre ≥1:8 for the given strain at the specified time point.
c. N = number of participants with valid and determinate hSBA titres for the given strain at the specified time point.
d. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.
e. At Vaccination 2, participants in Groups 2 and 4 were to receive bivalent rLP2086 only.

Booster dose

At 1 month after a booster dose administered 48 months after Vaccination 2, the estimated proportions of MenABCWY recipients and bivalent rLP2086 + Menveo recipients achieving hSBA titres ≥LLOQ for the 4 primary MenB test strains were higher than those at 1 month after Vaccination 2 and were comparable between both vaccine groups (>93.8% for all four primary strains in both arms).

At 1 month after a booster dose administered 48 months after Vaccination 2, a substantial rise over pre-booster hSBA GMTs was demonstrated for the 4 primary Men B test strains among MenABCWY recipients and bivalent rLP2086 + Menveo recipients. hSBA GMTs before and 1 month after booster vaccination were higher in the MenABCWY group than in the bivalent rLP2086 + Menveo group, with substantially higher post-booster GMTs than post-Vaccination 2 GMTs for both groups.

Table 24. hSBA GMTs for Each of the Primary MenB Strains – MenABCWY (Groups 1+3 Combined) and Bivalent rLP2086 (Groups 2+4 Combined) – Booster Evaluable Immunogenicity Population; Study B1971057

	Vaccine Group (as Randomised [Actual ACWY History[a]])					
	Groups 1+3 Combined (MenABCWY + Saline)			Groups 2+4 Combined (Bivalent rLP2086 + Menveo)		
MenB strain (Variant)						
Time Point	**N[b]**	**GMT[c]**	**(95% CI)[d]**	**N[b]**	**GMT[c]**	**(95% CI)[d]**
PMB80 (A22)						
1 Month after Vaccination 2	129	54.8	(47.1, 63.7)	88	43.5	(36.2, 52.3)
Before booster vaccination	121	12.0	(10.5, 13.8)	83	11.6	(10.1, 13.4)
1 Month after booster vaccination	122	85.0	(70.3, 102.9)	81	74.7	(60.3, 92.5)
PMB2001 (A56)						
1 Month after Vaccination 2	128	161.6	(134.7, 193.8)	87	123.0	(97.5, 155.2)
Before booster vaccination	127	8.9	(7.2, 11.0)	86	6.6	(5.4, 8.0)
1 Month after booster vaccination	124	321.9	(272.3, 380.7)	86	223.2	(172.0, 289.7)
PMB2948 (B24)						
1 Month after Vaccination 2	126	28.8	(23.6, 35.2)	87	16.9	(13.5, 21.2)
Before booster vaccination	126	7.0	(6.0, 8.1)	86	5.9	(5.0, 7.1)
1 Month after booster vaccination	123	60.8	(50.9, 72.7)	84	40.7	(33.1, 49.9)
PMB2707 (B44)						
1 Month after Vaccination 2	130	46.7	(39.0, 56.0)	86	34.1	(27.5, 42.4)
Before booster vaccination	129	5.1	(4.6, 5.6)	87	5.0	(4.4, 5.7)
1 Month after booster vaccination	128	98.2	(81.3, 118.5)	86	66.1	(53.3, 81.9)

Abbreviations: GMT = geometric mean titre; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = *Neisseria meningitidis* serogroup B.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44. Titres below the LLOQ were set to 0.5 × LLOQ for analysis.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
b. N = number of participants with valid and determinate hSBA titres for the given strain.

Among MenABCWY recipients, estimated proportions achieving protective hSBA titres ≥1:8 for serogroups A, C, W, and Y at 1 month after the booster dose rose to 100% in both ACWY-naïve (MenACWY Dose 3) and ACWY-experienced (MenACWY Dose 4, including conjugate ACWY vaccine ≥4

years prior to 1st study dose) participants. Seroprotective titres were also achieved by 100% of bivalent rLP2086 + Menveo recipients 1 month after completing the booster dose (MenACWY Dose 2) in ACWY-naïve and ACWY-experienced participants (MenACWY Dose 3).

Among MenABCWY recipients, hSBA GMTs for serogroups A, C, W, and Y, were markedly higher compared to the pre-booster hSBA GMTs and generally higher than 1 month post-Vaccination 2 GMTs of the primary series except for serogroups W and Y in the ACWY-experienced group. GMTs were lower after booster vaccination across all serogroups in both ACWY-naïve and -experienced MenABCWY recipients compared to bivalent rLP2086 + Menveo recipients.

Table 25. hSBA GMTs for MenA, MenC, MenW, and MenY – MenABCWY (groups 1 and 3) and bivalent rLP2086 (groups 2 and 4) – booster evaluable immunogenicity population; study B1971057

	Vaccine Group (as Randomised [Actual ACWY History[a]])							
	ACWY-Naive				ACWY-Experienced			
	Group 1 (MenABCWY + Saline)		Group 2 (Bivalent rLP2086 + Menveo)		Group 3 (MenABCWY + Saline)		Group 4 (Bivalent rLP2086 + Menveo)	
Serogroup Time Point	N[b]	GMT[c] (95%CI)[d]	N[b]	GMT[c] (95%CI)[d]	N[b]	GMT[c] (95%CI)[d]	N[b]	GMT[c] (95%CI)[d]
MenA								
1 Month after Vaccination 2[e]	60	143.7 (114.3, 180.6)	37	56.1 (33.9, 93.0)	33	315.8 (223.7, 445.9)	17	236.0 (136.5, 408.0)
Before booster vaccination	60	29.9 (21.2, 42.0)	36	21.0 (11.6, 37.8)	32	125.3 (89.3, 175.8)	17	122.9 (62.0, 243.5)
1 Month after booster vaccination	60	530.1 (427.6, 657.0)	37	1043.4 (728.5, 1494.3)	33	451.4 (333.1, 611.6)	17	1024.0 (687.5, 1525.3)
MenC								
1 Month after Vaccination 2[e]	60	191.8 (143.5, 256.3)	36	50.8 (30.3, 85.2)	70	689.1 (531.2, 894.0)	51	318.2 (217.8, 464.8)
Before booster vaccination	60	17.1 (11.5, 25.6)	37	12.1 (7.0, 21.0)	68	130.6 (96.8, 176.3)	51	91.1 (57.9, 143.4)
1 Month after booster vaccination	60	383.6 (286.0, 514.4)	37	641.1 (421.8, 974.3)	70	760.8 (593.8, 974.8)	51	1272.7 (885.6, 1829.0)
MenW								
1 Month after Vaccination 2[e]	60	230.7 (185.0, 287.7)	37	84.8 (59.2, 121.4)	33	779.3 (496.3, 1223.8)	17	313.9 (141.8, 694.8)
Before booster vaccination	59	36.4 (26.4, 50.3)	37	16.0 (10.2, 25.1)	32	159.0 (94.8, 266.7)	17	92.4 (35.6, 239.4)
1 Month after booster vaccination	60	822.2 (627.1, 1077.9)	37	1189.6 (796.8, 1776.0)	33	631.7 (492.2, 810.7)	17	943.8 (479.5, 1857.7)
MenY								
1 Month after Vaccination 2[e]	60	297.5 (244.0, 362.6)	35	84.4 (54.2, 131.7)	33	522.9 (348.7, 784.1)	17	208.8 (103.8, 420.0)
Before booster vaccination	60	45.3 (34.8, 58.9)	37	27.5 (18.8, 40.4)	32	162.4 (105.3, 250.6)	16	103.1 (55.0, 193.2)
1 Month after booster vaccination	60	1012.2 (793.6, 1291.1)	37	1575.5 (1062.3, 2336.7)	33	522.9 (404.4, 676.0)	17	943.8 (538.1, 1655.3)

Abbreviations: GMT = geometric mean titre; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA, MenC, MenW, and MenY = Neisseria meningitidis serogroup A, serogroup C, serogroup W, and serogroup Y.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups. Titres below the LLOQ were set to 0.5 × LLOQ for analysis.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine. Participants who received a monovalent meningococcal group C vaccine are included in the analysis for Neisseria meningitidis serogroup C (MenC) only.
b. N = number of participants with valid and determinate hSBA titres for the given serogroup at the specified time point.
c. GMTs were calculated using all participants with valid and determinate hSBA titres at the given time point.
d. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean of the ratio.
e. At Vaccination 2, participants in Groups 2 and 4 were to receive bivalent rLP2086 only

At 1 month after a booster dose administered 48 months after Vaccination 2, the proportions of MenABCWY recipients and bivalent rLP2086 + Menveo recipients achieving hSBA titres ≥ LLOQ for the 4 primary MenB test strains were higher than those at 1 month after Vaccination 2 and were comparable between both vaccine groups.

Within the ACWY-experienced groups, monovalent MenC vaccine was previously received by 17% (46/271) of MenABCWY recipients and 18% (96/523) of Trumenba + MenACWY-CRM recipients. Table 26 and Table 27 present the proportion of participants achieving an hSBA titer ≥1:8 and the GMTs for serogroups A, C, W, and Y between MenC-experienced and the overall ACWY-experienced participants, respectively.

Table 26. Number (%) of experienced participants with hSBA Titer ⩾1:8 for Monovalent C experienced and other MenACWY experienced participants at all time points for MenA, MenC, MenW, and MenY – (study B1971057) – stage 1 mITT population

		Vaccine Group (as Randomized [Actual ACWY History[a]])					
		Mono-C Experienced[b]		Other Experienced[b]		Overall	
		Group 3 MenABCWY + Saline	Group 4 Bivalent rLP2086 + MenACWY-CRM	Group 3 MenABCWY + Saline	Group 4 Bivalent rLP2086 + MenACWY-CRM	Group 3 MenABCWY + Saline	Group 4 Bivalent rLP2086 + MenACWY-CRM
Serogroup	Sampling Time Point	n[c]/ N[d] (%) (95% CI[e])	n[c]/ N[d] (%) (95% CI[e])	n[c]/ N[d] (%) (95% CI[e])	n[c]/ N[d] (%) (95% CI[e])	n[c]/ N[d] (%) (95% CI[e])	n[c]/ N[d] (%) (95% CI[e])
MenA	Before Vaccination 1	4/45 (8.9) (2.5, 21.2)	15/96 (15.6) (9.0, 24.5)	118/219 (53.9) (47.0, 60.6)	220/418 (52.6) (47.7, 57.5)	122/264 (46.2) (40.1, 52.4)	235/514 (45.7) (41.4, 50.1)
	1 Month after Vaccination 1	45/46 (97.8) (88.5, 99.9)	92/95 (96.8) (91.0, 99.3)	218/218 (100.0) (98.3, 100.0)	408/411 (99.3) (97.9, 99.8)	263/264 (99.6) (97.9, 100.0)	500/506 (98.8) (97.4, 99.6)
	Before Vaccination 2	42/45 (93.3) (81.7, 98.6)	76/93 (81.7) (72.4, 89.0)	198/200 (99.0) (96.4, 99.9)	379/385 (98.4) (96.6, 99.4)	240/245 (98.0) (95.3, 99.3)	455/478 (95.2) (92.9, 96.9)
	1 Month after Vaccination 2	46/46 (100.0) (92.3, 100.0)	86/94 (91.5) (83.9, 96.3)	190/191 (99.5) (97.1, 100.0)	374/376 (99.5) (98.1, 99.9)	236/237 (99.6) (97.7, 100.0)	460/470 (97.9) (96.1, 99.0)
MenC	Before Vaccination 1	33/46 (71.7) (56.5, 84.0)	58/93 (62.4) (51.7, 72.2)	124/218 (56.9) (50.0, 63.6)	254/418 (60.8) (55.9, 65.5)	157/264 (59.5) (53.3, 65.4)	312/511 (61.1) (56.7, 65.3)
	1 Month after Vaccination 1	46/46 (100.0) (92.3, 100.0)	95/96 (99.0) (94.3, 100.0)	218/218 (100.0) (98.3, 100.0)	408/410 (99.5) (98.2, 99.9)	264/264 (100.0) (98.6, 100.0)	503/506 (99.4) (98.3, 99.9)
	Before Vaccination 2	45/46 (97.8) (88.5, 99.9)	93/94 (98.9) (94.2, 100.0)	194/197 (98.5) (95.6, 99.7)	373/380 (98.2) (96.2, 99.3)	239/243 (98.4) (95.8, 99.5)	466/474 (98.3) (96.7, 99.3)
	1 Month after Vaccination 2	46/46 (100.0) (92.3, 100.0)	95/95 (100.0) (96.2, 100.0)	190/191 (99.5) (97.1, 100.0)	370/371 (99.7) (98.5, 100.0)	236/237 (99.6) (97.7, 100.0)	465/466 (99.8) (98.8, 100.0)
MenW	Before Vaccination 1	20/46 (43.5) (28.9, 58.9)	37/96 (38.5) (28.8, 49.0)	135/218 (61.9) (55.1, 68.4)	254/418 (60.8) (55.9, 65.5)	155/264 (58.7) (52.5, 64.7)	291/514 (56.6) (52.2, 60.9)
	1 Month after Vaccination 1	46/46 (100.0) (92.3, 100.0)	89/96 (92.7) (85.6, 97.0)	218/219 (99.5) (97.5, 100.0)	412/414 (99.5) (98.3, 99.9)	264/265 (99.6) (97.9, 100.0)	501/510 (98.2) (96.7, 99.2)

		Vaccine Group (as Randomized [Actual ACWY History[a]])					
		Mono-C Experienced[b]		Other Experienced[b]		Overall	
Serogroup	Sampling Time Point	Group 3 MenABCWY + Saline n[c]/ N[d] (%) (95% CI[e])	Group 4 Bivalent rLP2086 + MenACWY-CRM n[c]/ N[d] (%) (95% CI[e])	Group 3 MenABCWY + Saline n[c]/ N[d] (%) (95% CI[e])	Group 4 Bivalent rLP2086 + MenACWY-CRM n[c]/ N[d] (%) (95% CI[e])	Group 3 MenABCWY + Saline n[c]/ N[d] (%) (95% CI[e])	Group 4 Bivalent rLP2086 + MenACWY-CRM n[c]/ N[d] (%) (95% CI[e])
	Before Vaccination 2	45/46 (97.8) (88.5, 99.9)	90/95 (94.7) (88.1, 98.3)	199/199 (100.0) (98.2, 100.0)	381/385 (99.0) (97.4, 99.7)	244/245 (99.6) (97.7, 100.0)	471/480 (98.1) (96.5, 99.1)
	1 Month after Vaccination 2	46/46 (100.0) (92.3, 100.0)	95/95 (100.0) (96.2, 100.0)	190/191 (99.5) (97.1, 100.0)	376/376 (100.0) (99.0, 100.0)	236/237 (99.6) (97.7, 100.0)	471/471 (100.0) (99.2, 100.0)
MenY	Before Vaccination 1	34/45 (75.6) (60.5, 87.1)	63/94 (67.0) (56.6, 76.4)	175/219 (79.9) (74.0, 85.0)	328/421 (77.9) (73.6, 81.8)	209/264 (79.2) (73.8, 83.9)	391/515 (75.9) (72.0, 79.6)
	1 Month after Vaccination 1	46/46 (100.0) (92.3, 100.0)	95/96 (99.0) (94.3, 100.0)	217/218 (99.5) (97.5, 100.0)	412/413 (99.8) (98.7, 100.0)	263/264 (99.6) (97.9, 100.0)	507/509 (99.6) (98.6, 100.0)
	Before Vaccination 2	46/46 (100.0) (92.3, 100.0)	91/94 (96.8) (91.0, 99.3)	198/198 (100.0) (98.2, 100.0)	380/382 (99.5) (98.1, 99.9)	244/244 (100.0) (98.5, 100.0)	471/476 (98.9) (97.6, 99.7)
	1 Month after Vaccination 2	46/46 (100.0) (92.3, 100.0)	94/95 (98.9) (94.3, 100.0)	190/191 (99.5) (97.1, 100.0)	374/374 (100.0) (99.0, 100.0)	236/237 (99.6) (97.7, 100.0)	468/469 (99.8) (98.8, 100.0)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* group A, group C, group W, and group Y; mITT = modified intent-to-treat.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups.
Note: Group 3 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Group 4 received Bivalent rLP2086 + MenACWY-CRM at the first study vaccination and Bivalent rLP2086 at the second study vaccination.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
b. "Mono-C Experienced" are for participants who received a prior monovalent meningococcal group C vaccine; "Other Experienced" are for participants who received other prior meningococcal group A, C, W and Y vaccine.
c. n = Number of participants with observed hSBA titer ≥1:8 for the specified serogroup at the given sampling time point.
d. N = number of participants with valid and determinate hSBA titers for the specified serogroup at the given sampling time point. These values are used as the denominators for the percentage calculations.
e. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

Table 27. hSBA GMTs for MenA, MenC, MenW, and MenY strains at all time points for Monovalent C experienced and other MenACWY experienced participants – (study b1971057) – stage 1 mITT population

		Vaccine Group (as Randomized [Actual ACWY History[a]])					
		Mono-C Experienced[b]		Other Experienced[b]		Overall	
Serogroup	Sampling Time Point	Group 3 MenABCWY + Saline n[c]/ GMT[d] (95% CI[e])	Group 4 Bivalent rLP2086 + MenACWY-CRM n[c]/ GMT[d] (95% CI[e])	Group 3 MenABCWY + Saline n[c]/ GMT[d] (95% CI[e])	Group 4 Bivalent rLP2086 + MenACWY-CRM n[c]/ GMT[d] (95% CI[e])	Group 3 MenABCWY + Saline n[c]/ GMT[d] (95% CI[e])	Group 4 Bivalent rLP2086 + MenACWY-CRM n[c]/ GMT[d] (95% CI[e])
MenA	Before Vaccination 1	45/4.6 (3.8, 5.6)	96/5.0 (4.4, 5.6)	219/11.0 (9.3, 13.0)	418/10.7 (9.6, 12.0)	264/9.5 (8.2, 11.0)	514/9.3 (8.4, 10.3)
	1 Month after Vaccination 1	46/128.0 (88.1, 185.9)	95/153.6 (111.4, 211.8)	218/568.6 (492.9, 656.0)	411/916.1 (809.1, 1037.3)	264/438.5 (377.3, 509.6)	506/655.2 (574.2, 747.6)

		Vaccine Group (as Randomized [Actual ACWY History[a]])					
		Mono-C Experienced[b]		Other Experienced[b]		Overall	
Serogroup	Sampling Time Point	Group 3 MenABCWY + Saline n[c]/ GMT[d] (95% CI[e])	Group 4 Bivalent rLP2086 + MenACWY-CRM n[c]/ GMT[d] (95% CI[e])	Group 3 MenABCWY + Saline n[c]/ GMT[d] (95% CI[e])	Group 4 Bivalent rLP2086 + MenACWY-CRM n[c]/ GMT[d] (95% CI[e])	Group 3 MenABCWY + Saline n[c]/ GMT[d] (95% CI[e])	Group 4 Bivalent rLP2086 + MenACWY-CRM n[c]/ GMT[d] (95% CI[e])
	Before Vaccination 2	45/42.9 (29.3, 62.7)	93/40.6 (29.1, 56.7)	200/158.7 (132.6, 189.8)	385/214.6 (187.7, 245.3)	245/124.8 (104.9, 148.4)	478/155.2 (135.1, 178.3)
	1 Month after Vaccination 2	46/189.4 (134.3, 267.0)	94/47.3 (35.0, 64.0)	191/337.3 (291.7, 390.0)	376/224.2 (197.9, 253.9)	237/301.6 (263.0, 345.7)	470/164.2 (144.4, 186.8)
MenC	Before Vaccination 1	46/13.2 (9.7, 17.8)	93/12.3 (9.6, 15.8)	218/11.6 (9.8, 13.8)	418/13.6 (11.9, 15.7)	264/11.9 (10.2, 13.8)	511/13.4 (11.9, 15.1)
	1 Month after Vaccination 1	46/1957.5 (1240.7, 3088.3)	96/1989.7 (1414.0, 2799.7)	218/677.3 (571.4, 802.8)	410/673.3 (585.5, 774.2)	264/814.9 (689.4, 963.2)	506/827.0 (722.5, 946.6)
	Before Vaccination 2	46/453.9 (287.1, 717.4)	94/370.1 (273.8, 500.4)	197/220.8 (184.3, 264.7)	380/157.6 (134.7, 184.4)	243/253.1 (213.0, 300.8)	474/186.7 (161.9, 215.2)
	1 Month after Vaccination 2	46/1087.6 (829.9, 1425.3)	95/423.5 (325.0, 552.0)	191/413.3 (350.4, 487.5)	371/188.8 (163.2, 218.4)	237/498.7 (429.1, 579.6)	466/222.6 (195.3, 253.8)
MenW	Before Vaccination 1	46/7.0 (5.6, 8.8)	96/6.8 (5.7, 8.1)	218/10.5 (9.1, 12.2)	418/11.0 (9.8, 12.3)	264/9.8 (8.6, 11.1)	514/10.1 (9.1, 11.1)
	1 Month after Vaccination 1	46/69.0 (53.5, 89.0)	96/66.8 (48.4, 92.2)	219/1214.9 (1032.0, 1430.1)	414/1176.7 (1017.9, 1360.2)	265/738.4 (608.8, 895.7)	510/685.8 (582.0, 808.0)
	Before Vaccination 2	46/74.4 (58.7, 94.3)	95/46.1 (35.5, 59.8)	199/376.8 (311.4, 456.0)	385/255.5 (221.4, 295.0)	245/277.9 (232.3, 332.5)	480/182.1 (158.3, 209.4)
	1 Month after Vaccination 2	46/467.7 (351.2, 623.0)	95/94.9 (78.3, 115.0)	191/570.9 (484.3, 673.0)	376/291.3 (256.8, 330.4)	237/549.2 (475.9, 633.8)	471/232.3 (207.1, 260.6)
MenY	Before Vaccination 1	45/13.1 (9.8, 17.5)	94/10.1 (8.6, 12.0)	219/19.2 (16.3, 22.5)	421/19.0 (16.8, 21.4)	264/18.0 (15.6, 20.7)	515/16.9 (15.2, 18.8)
	1 Month after Vaccination 1	46/105.2 (78.7, 140.6)	96/76.1 (57.3, 101.0)	218/1174.0 (990.3, 1391.9)	413/1000.2 (872.1, 1147.1)	264/771.2 (640.5, 928.4)	509/615.3 (529.0, 715.7)
	Before Vaccination 2	46/90.5 (69.8, 117.3)	94/57.3 (44.6, 73.6)	198/395.2 (327.8, 476.3)	382/264.0 (228.5, 305.0)	244/299.3 (251.4, 356.4)	476/195.3 (170.3, 223.9)
	1 Month after Vaccination 2	46/447.1 (330.3, 605.0)	95/75.1 (61.1, 92.5)	191/558.6 (470.0, 663.9)	374/268.6 (235.0, 307.1)	237/535.0 (460.2, 621.9)	469/207.5 (183.4, 234.8)

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* group A, group C, group W, and group Y; mITT = modified intent-to-treat; LLOQ = lower limit of quantitation.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups. Titers below the LLOQ are set to 0.5 × LLOQ for analysis.
Note: Group 3 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Group 4 received Bivalent rLP2086 + MenACWY-CRM at the first study vaccination and Bivalent rLP2086 at the second study vaccination.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
b. "Mono-C Experienced" are for participants who received a prior monovalent meningococcal group C vaccine; "Other Experienced" are for participants who received other prior meningococcal group A, C, W and Y vaccine.
c. n = Number of participants with valid and determinate hSBA titers for the specified serogroup at the given sampling time point.
d. GMTs are calculated using all participants with valid and determinate hSBA titers at the given sampling time point.
e. CIs are obtained by exponentiating the limits of CIs for the mean logarithm of the hSBA titers (based on the Student t distribution).

C3511004

Study C3511004 is a phase 2b, randomised, observer-blinded trial executed in the US to describe the safety, tolerability, and immunogenicity of MenABCWY administered on 2 different dosing schedules in healthy participants ≥11 to <15 Years Of Age. As part of only results of the interim analysis have been submitted, this includes immunogenicity and safety data up to Month 13, during this period the study remained blinded.

Participants were randomised to receive two doses of pentavalent vaccine on a 0- and 12-month schedule (Group 1) or a 0- and 36-month schedule (Group 2). In addition, participants in group 2 will receive a saline placebo at Month 12.

Among participants in Group 1 (post-vaccination 2 evaluable population) for the 4 primary MenB test strains high estimated proportions (>96.6%) achieved an hSBA titre ≥ LLOQ at 1 month after Vaccination 2 also 98.2% to 100.0% of participants achieved an hSBA titre ≥1:4 (accepted correlate of protection) at 1 month after vaccination 2.

Among participants in Group 1, across the serogroups A, C, W and Y, the estimated proportions of participants achieving hSBA titres ≥1:8 ranged from 79.3% to 99.3% 1 month after Vaccination 1 (post-vaccination 1 evaluable population) and from 99.1% to 100.0% 1 month after vaccination 2 (post-vaccination 2 evaluable population). Among Group 2 participants, for A, C, W and Y the estimated proportions of participants achieving hSBA titres ≥1:8 at 1 month after vaccination 1 ranged from 80.4% to 100.0%, and at 13 months after Vaccination 1 these ranged from 72.4% to 97.7%.

Among participants receiving MenABCWY on a 0- and 12-month schedule, hSBA GMTs increased for all 4 serogroups at 1 month after Vaccination 1 (Table 28). hSBA GMTs increased further for all 4 serogroups, ranging from 140.0 to 385.7 after Vaccination 2 (Table 29).

hSBA GMTs 1 month after Vaccination 1 were similar between Group 1 and Group 2 for all 4 serogroups.

Table 28. hSBA GMTs for MenA, MenC, MenW, MenY at baseline and 1 month after vaccination 1 in groups 1 and 2, and 13 months after vaccination 1 in group 2 – post-vaccination 1 – evaluable population

		Vaccine Group (as Randomized)								
		Group 1 MenABCWY (0- and 12-month Schedule)			Group 2 MenABCWY (0- and 36-month Schedule)			Combined (Group 1 + Group 2)		
Serogroup	**Sampling Time Point**	**n[a]**	**GMT[b]**	**(95% CI[c])**	**n[a]**	**GMT[b]**	**(95% CI[c])**	**n[a]**	**GMT[b]**	**(95% CI[c])**
MenA	Before Vaccination 1	140	4.7	(4.3, 5.1)	141	4.5	(4.1, 4.9)	281	4.6	(4.3, 4.9)
	1 Month after Vaccination 1	140	133.2	(111.1, 159.6)	144	147.9	(124.8, 175.2)	284	140.4	(124.1, 158.9)
	13 Months after first dose of MenABCWY	N/A	N/A	N/A	126	19.6	(15.7, 24.4)	N/A	N/A	N/A
MenC	Before Vaccination 1	139	4.4	(4.2, 4.7)	144	4.5	(4.2, 4.9)	283	4.5	(4.3, 4.7)
	1 Month after Vaccination 1	140	51.5	(36.5, 72.6)	143	41.8	(30.8, 56.7)	283	46.3	(36.9, 58.2)
	13 Months after first dose of MenABCWY	N/A	N/A	N/A	127	17.9	(14.0, 23.0)	N/A	N/A	N/A
MenW	Before Vaccination 1	138	4.9	(4.5, 5.3)	143	4.8	(4.4, 5.2)	281	4.8	(4.6, 5.1)
	1 Month after Vaccination 1	140	48.0	(39.2, 58.8)	144	47.7	(39.4, 57.7)	284	47.9	(41.7, 54.9)
	13 Months after first dose of MenABCWY	N/A	N/A	N/A	128	42.0	(34.8, 50.5)	N/A	N/A	N/A
MenY	Before Vaccination 1	136	6.7	(5.8, 7.6)	142	6.5	(5.7, 7.6)	278	6.6	(6.0, 7.3)
	1 Month after Vaccination 1	140	80.0	(65.8, 97.2)	143	80.8	(65.5, 99.6)	283	80.4	(69.7, 92.7)
	13 Months after first dose of MenABCWY	N/A	N/A	N/A	126	47.3	(38.6, 57.9)	N/A	N/A	N/A

		Vaccine Group (as Randomized)								
		Group 1 MenABCWY (0- and 12-month Schedule)			Group 2 MenABCWY (0- and 36-month Schedule)			Combined (Group 1 + Group 2)		
Serogroup	**Sampling Time Point**	**n[a]**	**GMT[b]**	**(95% CI[c])**	**n[a]**	**GMT[b]**	**(95% CI[c])**	**n[a]**	**GMT[b]**	**(95% CI[c])**

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* serogroup A, serogroup C, serogroup W, and serogroup Y.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups. Titers below the LLOQ were set to 0.5 × LLOQ for analysis.
a. n = Number of participants with valid and determinate hSBA titers for the specified strain at the given sampling time point.
b. GMTs were calculated using all participants with valid and determinate hSBA titers at the given time point.
c. CIs obtained by exponentiating the limits of CIs for the mean logarithm of the hSBA titers (based on the Student t distribution).

Table 29. hSBA GMTs for MenA, MenC, MenW, MenY at baseline and 1 month after second dose of MenABCWY in group 1 – post-vaccination 2 – evaluable population

		Vaccine Group (as Randomized)		
		Group 1 MenABCWY (0- and 12-month Schedule)		
Serogroup	**Sampling Time Point**	**n[a]**	**GMT[b]**	**(95% CI[c])**
MenA	Before Vaccination 1	116	4.4	(4.1, 4.7)
	1 Month after second dose of MenABCWY	116	236.9	(203.7, 275.5)
MenC	Before Vaccination 1	115	4.4	(4.1, 4.6)
	1 Month after second dose of MenABCWY	116	140.0	(114.0, 172.0)
MenW	Before Vaccination 1	114	4.9	(4.5, 5.5)
	1 Month after second dose of MenABCWY	115	385.7	(327.5, 454.2)
MenY	Before Vaccination 1	113	6.3	(5.5, 7.3)
	1 Month after second dose of MenABCWY	114	377.8	(315.7, 452.1)

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* serogroup A, serogroup C, serogroup W, and serogroup Y.
Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups. Titers below the LLOQ were set to 0.5 × LLOQ for analysis.
a. n = Number of participants with valid and determinate hSBA titers for the specified strain at the given sampling time point.
b. GMTs were calculated using all participants with valid and determinate hSBA titers at the given time point.
c. CIs obtained by exponentiating the limits of CIs for the mean logarithm of the hSBA titers (based on the Student t distribution).

2.5.6. Discussion on clinical efficacy

The proposed indication for the MenABCWY vaccine is active immunisation of individuals 10 years of age and older to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, B, C, W, and Y. Two doses of vaccine administered 6 to 12 months apart are needed for prevention of meningococcal disease caused by groups A, B, C, W, and Y. The posology to achieve the proposed indication requires two doses of the MenABCWY vaccine, as this is required to achieve optimal protection against MenB.

This application is based on the immunogenicity data from the pivotal Phase 3 trial C3511001, supported by two additional immunogenicity studies. Study B1971057 assessed immunogenicity and safety of the initial vaccination series (2 doses at a 6 month interval) including immunopersistence up

to 48 months, as well as immunogenicity and safety of a booster dose after four years. Study C3511004 evaluates the immunogenicity of extended dosing schedules (12 and 36 month intervals).

The clinical development programme has not been formally discussed with CHMP. Four national scientific advices have been given (during 2020) regarding the pivotal phase 3 trial and the study development strategy in infants, respectively (national agencies in Sweden, Spain, Germany [PEI] and Ireland). The study design of the pivotal trial was overall considered acceptable, however, with comments. Several national agencies (Spain, Germany) did not agree that the separate Trumenba and Nimerix studies in immunocompromised individuals would be sufficient as data to support the use of MenABCWY in immunocompromised patients. The applicant was recommended to add an MenABCWY arm to the planned Trumenba study in immunocompromised patients. No data in immunocompromised individuals have been included in the dossier. Based on CHMP feedback the SmPC states that efficacy, safety and immunogenicity of the vaccine have not been assessed in immunocompromised individuals.

Design and conduct of clinical studies

Both studies (C3511001 and B1971057) evaluating the proposed posology of two doses of MenABCWY vaccine administered six months apart were randomised, observer-blind, active controlled multicentre studies in ACWY-naïve and ACWY-experienced participants. This study design was considered adequate. The studies were conducted in the US and EU. The B1971057 clinical study is considered supportive since it was designed to meet an FDA post-approval commitment to verify and describe the clinical benefit of a 2-dose schedule of Trumenba administered at months 0 and 6 in healthy participants $\geq$10 years to <26 years of age.

Both studies included healthy male and female participants ≥10 and <26 years of age at the time of randomisation, which is in line with the target population. In addition to the standard exclusion criteria for vaccine trials, subjects who had a history of microbiologically proven disease caused by *N meningitidis* or *Neisseria gonorrhoeae,* previous vaccination with any meningococcal group B vaccine or any purely polysaccharide (non-conjugate) meningococcal vaccine were excluded. In addition in Study B1971057 also those with previous vaccination with >1 dose of a vaccine containing 1 or more ACWY group or subjects who received 1 prior dose of a vaccine containing 1 or more ACWY group <4 years prior to date of randomisation were excluded. Immunogenicity in MenB-experienced individuals (prior vaccination) has not been addressed in the submission as only MenB-naïve participants were eligible to the clinical trials.

The active comparators in both studies were Trumenba and Menveo, where a concomitant vaccination (in 2 arms) of Menveo and Trumenba was followed by a 2nd dose of Trumenba administered six months later. Menveo was used as a comparator rather than Nimenrix. During scientific advice, the applicant has indicated this was because most participants were recruited from the US where Nimenrix is not authorised. Within the EU Trumenba is indicated for active immunisation of individuals 10 years and older to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B. Menveo is indicated for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to *Neisseria meningitidis* groups A, C, W-135 and Y, to prevent invasive disease. Although Nimenrix and Menveo both include MenACWY antigens, they are not identical vaccines. Each component of MenACWY in Nimenrix is conjugated to tetanus toxoid whilst for Menveo they are conjugated to *Corynebacterium diphtheriae* CRM197 protein. Since both Trumenba and Menveo are registered within the EU for respectively immunisation against MenB and MenA, C, W and Y, the active comparators can in general be accepted. However, since the candidate MenABCWY vaccine consists of Trumenba and Nimenrix, ideally the applicant should have chosen Nimenrix to use as active comparator. This has also been advised to the applicant in several national scientific advices from national regulatory authorities within the EU. Although understandable, the choice of comparator, and

the differing posologies for MenACWY antigens between the active and comparator arms raised uncertainty when evaluating of the immunogenicity results which were resolved or not further pursued.

The recognized correlate of protection against meningococcal disease is an hSBA titre ≥1:4. Primary immunogenicity objectives in both studies indicate a response that was well above the established correlate of protection and took into account the LLOQ of the assays for the different serogroups. In the pivotal Phase 3 study, a NI margin of 10% was used. No justification was provided for the choice of NI margin. This would be relevant since in the context of a severe and potentially deadly disease such as invasive meningococcal disease, a more stringent margin might have been more appropriate. The choice of a NI margin should always be justified on a case by cases basis, and precedents from other vaccines approvals are not necessarily sufficient justification. However, although the MAH did not adequately address the issue, the results were such that it will not affect the overall conclusion.

For studies B1971057 and C3511004 this submission contains data from an interim analysis.

Efficacy data and additional analyses

Main results

A total of 2431 participants were randomised: 1778 participants to MenABCWY, 653 to MenACWY + Trumenba. A total of 85.3% (2074) completed the vaccination phase (from the date of the first study vaccination through 1 month after the second study vaccination) and 84.8% (2061) completed the follow up phase (time from 1 month after the second study vaccination through 6 months after the second study vaccination).

Overall, demographics were balanced between treatment arms in the safety and immunogenicity subsets.

In the pivotal phase 3 study the estimated proportion of participants achieving seroprotection (measured as hSBA titer of ≥1:8 for MenA, C, W, and Y and ≥LLOQ for MenB, as hSBA titer >1:4 could not reliably be established) after a primary series (2 doses) with MenABCWY was >83% for all MenA, C, W, Y and all 4 primary MenB test strains. Non-inferiority was shown in both ACWY-naïve and ACWY-experienced participants for the ACWY-components and for the four primary strains and composite hSBA responses for MenB. Based on the performed sensitivity and supportive analyses for each serogroup A, B, C, W and Y, the results of the primary immunogenicity analyses are considered robust.

After a single dose of MenABCWY, >82% of participants achieved an hSBA titre of ≥1:8, thereby being seroprotected for MenA, C, W and Y. No clear difference could be observed compared to the concomitant administration of Trumenba + Menveo, except for a slightly lower response for MenC in the concomitant group. This was to be expected considering Menveo was used as a comparator. Following the second dose of the pentavalent MenABCWY vaccine regarding MenA, C, W and Y a slightly higher seroprotection rate of MenC only in the ACWY-naïve population could be observed.

The estimated MenB seroprotection rate was >83% after 2 doses. It is noteworthy that the estimated response in the comparator arm was lower compared to the MenABCWY arm (estimated difference > 7%) for 2 out of 4 test strains, as well as for the composite response (>9% estimated difference). This is unexpected as the participants were randomised, were exposed to the same amount of antigen and the same number of doses. The estimates for GMTs were slightly lower in the active control arm compared with the MenABCWY arm. No clear explanation has been provided by the applicant.

In ACWY-naïve participants the estimated seroprotection appears to be slightly higher in the group receiving two doses of MenABCWY compared with a single dose of Menveo, however no formal testing was planned. Since currently a single dose of Nimenrix/Menveo is indicated and considered sufficient for the active immunisation against Men A, C, W and Y, the clinical relevance of the 2nd dose for protection against serogroups MenA, C, W and Y is unclear. In the ACWY-naïve groups GMTs after two

doses of MenABCWY vaccine were higher than after a single dose of Menveo. Among ACWY-experienced individuals who received MenABCWY, GMTs for the 4 serogroups A, C, W, and Y are lower at 1 month after the 2nd dose compared to GMTs at 1 month after the 1st dose of MenABCWY. This is observed in both studies. Also in study B1971057 among ACWY-naïve participants for MenA GMTs were lower after the second dose compared to after the first dose. No data was collected pre-vaccination of the second dose in Study C3511001, in study B1971057 GMTs post-vaccination 2 were higher compared with before vaccination 2. It should be noted that lower GMTs after the second dose in ACWY-naïve participants were not observed when an interval of at least 12 months between the two doses is applied, as GMTs for all serogroups seem higher after the 2nd than after the 1st dose in Study C3511004.

In elderly individuals it is not clear if the lower GMTs after the second administration of Nimenrix may affect protection if a fourfold increase in hSBA titre should not be reached.

Effect in subgroups (pivotal study)

Overall, the immune responses were higher in men (vs women) in both arms to all five antigens. This is not as expected according to the literature on immune responses in men vs women. However, the CIs are overlapping, and the difference will not be further pursued.

The immune responses in two age groups (≥ 10 to <18 years and ≥ 18 to < 26 years) were analysed. As expected, the immune responses were higher in the lower age subset (≥ 10 to < 18 years). The difference according to age subset was more pronounced in MenC, MenY and MenB (in both study arms). The clinical implications of this observations are unclear.

No data in individuals > 25 years of age, particularly no data in elderly (>65 years) has been provided. Although the benefit of a vaccine can largely be extrapolated to the adult population, there are uncertainties on the magnitude of benefit in elderly due to diminishing immune response. Furthermore, due to childhood vaccination there is a shift in notified cases to older adults and elderly in EU. More data on immune responses in elderly is of interest.

Immune-persistence

A total of 353 participants entered stage 2, with 242 participants completing the 48-month persistence and receiving booster dose. Demographic characteristics were overall similar.

The estimated percentage of participants with antibody persistence at 48 months after Vaccination 2 for the four primary MenB strains is low in both treatment arms (<37%). In general the proportion of participant with titres ≥LLOQ declines in the 1st 12 months and thereafter remains relatively stable to approximately 48 months in both treatment arms. A similar pattern is seen for GMTs, which decline close to baseline at 12 months after vaccination 2 for both groups, but no further reduction is seen up to 48 months after vaccination 2.

During the 4 years following completion of the 2-dose primary vaccination series, proportions of participants with seroprotective titres ≥1:8 for serogroups A, C, W, and Y through 48 months remained either relatively stable or gradually declined in both treatment arms. Estimated seroprotection rates at 48 months ACWY-experienced were higher than those observed in ACWY-naïve individuals.

Booster dose

Although the estimated percentage of participants with antibody persistence (titres ≥ LLOQ) for the four primary MenB strains was low after 48 months, after booster vaccination estimated seroprotection was high in both study groups, indicating a good anamnestic response in both groups. The same holds true for the MenACWY responses as the estimated proportions of participants achieving protective

hSBA titres ≥1:8 for serogroups A, C, W, and Y at 1 month after the booster dose rose to 100% in both ACWY-naïve and ACWY-experienced participants independent of primary immunization series.

Among MenABCWY recipients, hSBA GMTs for serogroups A, B, C, W, and Y, were markedly higher compared to the pre-booster hSBA GMTs and generally higher than 1 month post-Vaccination 2.

GMTs for A, C, W and Y were lower after booster vaccination across all serogroups in both ACWY-naïve and -experienced MenABCWY recipients compared to bivalent rLP2086 + Menveo recipients. This seems to indicate that even 4 years after the primary dose, there is still a reduced response. With regard to MenB point estimates for the GMTs in the combined administration group were lower compared with GMTs in the pentavalent vaccine arm, although with overlapping confidence intervals, except for B24.

Data regarding booster vaccination is limited and only considered supportive. The time interval (48 months) prior to boosting used in the clinical study lacks justification and there is no specified time interval for a booster dose in the SmPC. The benefit of a booster dose of Penbraya for individuals who have previously received a primary vaccination against MenACWY after 4 years is uncertain as long-term antibody persistence data following vaccination with MenA, C, W, Y vaccines are available. Penbraya as a booster should be used in line with official recommendations and it should be considered for individuals at continued risk of invasive meningococcal disease who completed primary vaccination with Penbraya or completed primary vaccination with both meningococcal group b vaccine (recombinant, adsorbed) and a meningococcal serogroups A, C, W, Y vaccine.

Subjects who had received monovalent MenC vaccine were only included in the analysis for MenC. Within the ACWY-experienced groups, monovalent MenC vaccine was previously received by 17% (46/271) of MenABCWY recipients and 18% (96/523) of Trumenba + MenACWY-CRM recipients. The immunogenicity results of the monovalent MenC experienced population was in line with the other MenACWY experienced population and the total MenACWY experienced population. The benefit for individuals previously vaccinated against MenC, vaccination with MenABCWY could potentially provide additional protection against meningococcal serogroups A, W, and Y.

2.5.7. Conclusions on the clinical efficacy

The availability of a pentavalent vaccine could potentially simplify vaccination programmes for those of ten years of age and above. The application for a marketing authorisation of a pentavalent MenABCWY vaccine proposes a posology including two doses.

The primary immunogenicity endpoints were met. The potential benefit for a second dose of A, C, W and Y components as used in the proposed posology seems limited to ACWY-naïve participants for serogroup C only. For the other serogroups and among ACWY-experienced participants the seroprotection rates seem not negatively influenced by the additional dose of A, C, W, and Y.

Booster vaccination administered at four years after the initial series resulted in a high estimated proportion of participants achieving seroprotective titres, indicating a good anamnestic response. Although it is noteworthy that the GMTs in the MenABCWY primed population were substantially lower, the clinical relevance of this finding is unknown.

2.5.8. Clinical safety

This section provides a summary description of the safety data from 3 clinical studies: 1 first in human study (Study B1971057), 1 Phase 2b study (study C3511004) and 1 Phase 3 study (Study C3511001).

The main source of safety data to support the benefit/risk profile of the MenABCWY vaccine in the target population of adolescents ≥10 years of age and adults were study C3511001 and B1971057 (Stage 1), which investigated the proposed posology of 2 vaccinations on a 0- and 6-month schedule. Study B1971057 (Stage 2) investigated the safety of a booster dose, while the ongoing study C3511004 currently provides safety information up to 13 months after the first vaccination for an extended interval vaccination schedule of 0-, 12- month and 0-, 36-months. The safety database is comprised of safety data from participants who received at least 1 dose of MenABCWY.

Safety assessments include monitoring and recording of solicited (local reactions and systemic events) adverse events (except for study C3511004), unsolicited adverse events (AEs), serious adverse events (SAEs), medically attended adverse events (MAEs), newly diagnosed chronic medical conditions (NDCMCs), and deaths.

During study C3511001 and B1971057, solicited adverse events were collected for 7 after each vaccination, with day 1 defined as the day of vaccination. Local reactions included redness, swelling, and pain at the site of investigational product administration. Local reactogenicity was measured in the left arm at the injection site of investigational product (MenABCWY or Trumenba [bivalent rLP2086]) administration. Local reactogenicity was not measured in the right arm at the injection site for saline or Menveo. The systemic events included fever, vomiting, diarrhoea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain. The use of antipyretic medication was recorded in the e-diary daily during the active safety observation periods (Day 1 to Day 7) for each vaccination. No solicited AEs were collected and no e-diary was used during study C3511004.

The following safety data was collected in Study C3511001, Study B1971057 Stage 1 and Stage 2, and Study C3511004:

- AEs (serious and nonserious);
- Medically attended adverse events (MAEs) (defined as a nonserious AE that results in an evaluation at a medical facility);
- Newly diagnosed chronic medical conditions (NDCMCs) (defined as a disease or medical condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects);
- Immediate AEs (defined as AEs occurring within the first 30 minutes after investigational product administration);
- Additional safety data that were collected included the number of days of school or work missed due to AEs and reports of neuroinflammatory and autoimmune conditions.

AEs, serious adverse events (SAEs), MAEs, NDCMCs were reported for the following intervals in Study C3511001, B1971057 Stage 1, and C3511004:

- 30 days after each vaccination and 30 days after any vaccination
- During the Vaccination Phase which was defined as:
    - Study C3511001 and Study B1971057 Stage 1: from the first study vaccination through 1 month after the second study vaccination
    - Study C3511004: Vaccination 1 vaccination phase (from Vaccination 1 through 1 month after Vaccination 1) and Vaccination 2 vaccination phase (from Vaccination 2 through 1 month after Vaccination 2)

SAEs, MAEs, NDCMCs were also reported for the following intervals in Study C3511001, B1971057 Stage 1, and C3511004:

- In Study C3511004, SAEs, MAEs, and NDCMCs were reported from Vaccination 1 through 6 months after Vaccination 1
- During the Follow-up Phase which was defined as:
    - Study C3511001 and Study B1971057 Stage 1: from 1 month after the second study vaccination through 6 months after the second study vaccination
    - Study C3511004: from 1 month after Vaccination 1 through 6 months after Vaccination 1
- Throughout the study (referred to as Throughout Stage 1 in Study B1971057 Stage 1): from the first study vaccination through 6 months after the second study vaccination in Study C3511001 and Study B1971057 Stage 1

For Study C3511001, safety endpoints will be summarized by MenABCWY groups (Groups 1, 3, 5, and 7 combined) and Trumenba + Menveo groups (Groups 2, 4, 6, and 8 combined).

For Study B1971057, safety endpoints will be presented for the MenABCWY groups (Groups 1 and 3 combined) and the Trumenba + Menveo groups (Groups 2 and 4 combined).

For Study C3511004, safety endpoints will be summarized for each individual group (Group 1 and Group 2).

The safety section as described below is focussed mainly on the pivotal Phase 3 study, as the integrated analysis of safety only provided information on the pentavalent vaccine and no information from the comparator arm was included. Where relevant, additional information from the integrated analysis of safety, study B1971057 and study C3511004 (0-, 12- month vaccination schedule) is included.

2.5.8.1. Patient exposure

The number of vaccinated participants, by study, who received at least 1 dose of MenABCWY on any dosing schedule is presented in Table 30.

Table 30. Number (%) of vaccinated participants, by study, who received at least 1 dose of MenABCWY on any dosing schedule – overall and for core

	All Sites		US Sites	
	MenABCWY on 0- and 6-Month Schedule Core	MenABCWY on any Dosing Schedule Overall	MenABCWY on 0- and 6-Month Schedule Core	MenABCWY on any Dosing Schedule Overall
	n (%)	n (%)	n (%)	n (%)
All vaccinated participants[a]	2306 (88.7)	2600 (100.0)	1708 (85.3)	2002 (100.0)
B1971057	543 (20.9)	543 (20.9)	447 (22.3)	447 (22.3)
C3511001	1763 (67.8)	1763 (67.8)	1261 (63.0)	1261 (63.0)
C3511004	0	294[b] (11.3)	0	294[b] (14.7)

	All Sites		US Sites	
	MenABCWY on 0- and 6-Month Schedule Core	MenABCWY on any Dosing Schedule Overall	MenABCWY on 0- and 6-Month Schedule Core	MenABCWY on any Dosing Schedule Overall
	n (%)	n (%)	n (%)	n (%)

Note: Core dataset includes all participants who received at least 1 dose of MenABCWY on a 0- and 6-month schedule from Studies B1971057 Stage 1 (Groups 1+3 [MenABCWY]) and C3511001 (Groups 1+3+5+7 [MenABCWY]). Overall dataset includes participants in Study C3511004 (Groups 1+2 [MenABCWY: 1-year and 3-year schedules combined] and participants in core dataset.
Note: Overall dataset includes all participants who received at least 1 dose of MenABCWY on a 0- and 6-month schedule from Studies B1971057 Stage 1 (Groups 1+3 [MenABCWY]), C3511001 (Groups 1+3+5+7 [MenABCWY]), and C3511004 (Groups 1+2 [MenABCWY: 1-year and 3-year schedules combined]).
a. The values in this row for overall dataset columns are used as the denominators for percentage calculations.
b. In total 299 participants were vaccinated during study C3511004, however, for 5 participants (3 from Group 1 and 2 from Group 2) no safety data was available and they were excluded from the safety database.

2.5.8.2. Adverse events

Reactogenicity

For studies **C3511001** and **B1971057** Stage 1, reactogenicity was collected by participants' e-diary for reporting solicited local reactions, systemic events, and use of antipyretic medication for 7 days after each vaccination. Local reactogenicity to MenABCWY was measured in the left arm, in which participants received MenABCWY or Trumenba. No solicited AEs were collected for study **C3511004** and all reactogenicity events were collected as adverse events.

Local Reactions

During study **C3511001**, local reactions (pain, swelling, and redness at the injection site) were reported in a similar percentage of MenABCWY and Trumenba+ Menveo participants (Table 31). Pain at the injection site was the most commonly reported local reaction. Most local reactions were mild or moderate in severity.

Table 31. Local reactions, by maximum severity, within 7 days after vaccination – safety population – study c3511001 (modified by the assessor)

	MenABCWY			Trumenba + Menveo		
	n[a]	%	95% CI[b]	n[a]	%	95% CI[b]
N[c]	1728			635		
Local reaction[d]						
Any	1634	94.6	93.4 – 95.6	581	91.5	89.0 – 93.5
Local reaction: Redness[e]						
Any	566	32.8	30.5 – 35.0	162	25.5	22.2 – 29.1
Severe	73	4.2	3.3 – 5.3	17	2.7	1.6 – 4.3
Local reaction: Swelling[e]						
Any	587	34.0	31.7 – 36.3	161	25.4	22.0 – 28.9
Severe	32	1.9	1.3 – 2.6	6	0.9	0.3 – 2.0
Local reaction: Pain at the injection site[f]						
Any	1627	94.2	92.9 – 85.2	574	90.4	87.8 – 92.6
Severe	199	11.5	10.0 – 13.1	60	9.4	7.3 – 12.0

Note: Local reactions are summarized for the MenABCWY or Trumenba injection site for the left arm only. At Vaccination 1, 26 participants received MenABCWY or Trumenba in the right arm and were excluded from this summary of Vaccination 1 and from summaries across Vaccinations 1 and 2.
The 6 participants who received Vaccination 2 in the right arm were excluded from this summary of Vaccination 2 and from summaries across Vaccinations 1 and 2.
Note: One (1) participant who received Trumenba + saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables.

Note: One (1) participant who received MenABCWY + Menveo at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.
a. n = Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.
b. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
c. N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are used as the denominators for the percentage calculations.
d. Any local reaction = any redness, any swelling, or any pain at the injection site.
e. Severe is >10.0 cm..
f. Severe = prevents daily activity

The median onset for most local reactions was Day 1.0 to Day 2.0 (Day 1.0 was the day of vaccination) after Dose 1 or Dose 2 for participants in the MenABCWY and Trumenba + Menveo groups and most local reactions resolved within 2.0 to 3.0 days for participants in both vaccine groups.

During Study **B1971057**, local reactions were reported in a similar percentage of MenABCWY and bivalent rLP2086 + Menveo participants during both Stage 1 (94.3% vs 91.6%) and 2 (82.7% vs 85.6%). Pain at the injection site was the most commonly reported local reaction. Most local reactions were mild or moderate in severity. Most local reactions resolved within a median duration of 1.0 to 2.0 days after Dose 1 or Dose 2 in both vaccine groups during Stage 1, while the majority of events resolved within a median duration of 2.0 to 3.0 days after the booster dose.

Systemic Events

During Study **C3511001**, systemic events were reported in a similar percentage of MenABCWY and Trumenba + Menveo participants but generally, in a lower percentage of participants following Dose 2 relative to Dose 1 (Table 32). Fatigue and headache were the most commonly reported systemic events. Most systemic events were mild or moderate in severity.

After Dose 1 and 2, use of antipyretic/pain medication was reported by 29.5% and 25.1% of participants in the MenABCWY group (respectively) compared to 28.1% and 20.5% of participants (respectively) in the Trumenba + Menveo group.

Table 32. Systemic events, by maximum severity, within 7 days after vaccination – safety population – study c3511001 (modified by the assessor)

	MenABCWY			Trumenba + Menveo		
Systemic reaction[d]	**n[a]**	**%**	**95% CI[b]**	**n[a]**	**%**	**95% CI[b]**
N[c]	**1748**			**646**		
Any	1427	81.6	79.7 – 83.4	517	81.6	78.4 – 84.5
Fever						
≥38˚C	123	7.0	5.9 – 8.3	43	6.7	4.9 – 8.9
>38.9 ˚C – 40.0 ˚C	13	0.7	0.4 – 1.3	7	1.1	0.4 – 2.2
>40.0 ˚C	0			0		
Fatigue[e]						
Any	1117	63.9	61.6 – 66.2	416	64.4	60.6 – 68.1
Severe	90	5.1	4.2 – 6.3	27	4.2	2.8 – 6.0
Headache[e]						
Any	1010	57.8	55.4 – 60.1	374	57.9	54.0 – 61.7
Severe	55	3.1	2.4 – 4.1	16	2.5	1.4 – 4.0
Chills[e]						
Any	479	27.4	25.3 – 29.6	170	26.3	23.0 – 29.9
Severe	19	1.1	0.7 – 1.7	17	2.6	1.5 – 4.2
Vomiting[f]						
Any	71	4.1	3.2 – 5.1	23	3.6	2.3 – 5.3
Severe	0			0		
Diarrhoea[g]						
Any	280	16.0	14.3 – 17.8	120	18.6	15.6 – 21.8
Severe	6	0.3	0.1 – 0.7	0		
Muscle Pain[e]						
Any	629	36.0	33.7 – 38.3	234	36.2	32.5 – 40.1
Severe	39	2.2	1.6 – 3.0	15	2.3	1.3 – 3.8

Systemic reaction[d]	MenABCWY			Trumenba + Menveo		
	n[a]	%	95% CI[b]	n[a]	%	95% CI[b]
N[c]	**1748**			**646**		
Joint Pain[e]						
Any	504	28.8	26.7 – 31.0	189	29.3	25.8 – 32.9
Severe	23	1.3	0.8 – 2.0	10	1.5	0.7 – 2.8
Use of antipyretic medication	671	38.4	36.1 – 40.7	225	34.8	31.2 – 38.6

Note: One (1) participant who received Trumenba + saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables.
Note: One (1) participant who received MenABCWY + Menveo at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.
a. n = Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.
b. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
c. N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are used as the denominators for the percentage calculations.
d. Any systemic event = any fever ≥38.0°C, any fatigue, any headache, any chills, any vomiting, any diarrhoea, any muscle pain, or any joint pain.
e. Severe = prevents daily activity.
f. Severe = requires intravenous hydration.
g. Severe = 6 or more loose stools in 24 hours.

The median onset for most systemic events was Day 1.0 to Day 3.0 (Day 1.0 was the day of vaccination) after Dose 1 or Dose 2 for participants in the MenABCWY and Trumenba + Menveo groups and most systemic events resolved within a median duration of 1.0 to 2.0 days for participants in both vaccine groups.

During study **B1971057**, the proportion of participants reporting any systemic events was similar between MenABCWY + saline recipients and bivalent rLP2086 + Menveo recipients during both Stage 1 (80.6% and 80.1%, respectively) and Stage 2 (70.6% vs 74.7% respectively). Most systemic events were mild or moderate in severity. Fatigue and headache were the most commonly reported systemic events in both MenABCWY + saline recipients and bivalent rLP2086 + Menveo recipients in both stages. The median onset for most systemic events was Day 2.0 after booster vaccination however, the onset ranged from 1.0 to 4.0 days for some systemic events. The majority of events resolved within a median duration of 1.0 to 2.0 days in both vaccine groups.

After Dose 1 and 2, use of antipyretic/pain medication was reported by 29.5% and 25.1% of participants in the MenABCWY group (respectively) compared to 28.1% and 20.5% of participants (respectively) in the Trumenba + Menveo group.

Unsolicited Adverse Events

During study **C3511001**, adverse events reported by at least 4 participants during the vaccination phase, by SOC and PT, are presented in table 33. The most commonly reported PT was COVID-19 in both vaccination groups.

There were no immediate AEs (AEs that occur within 30 minutes after vaccination) reported during the study.

Table 33. Adverse events reported by at least 4 participants during the vaccination phase, by system organ class and preferred term – safety population – study c3511001 (modified by assessor)

System Organ Class Preferred Term	MenABCWY (N[a]=1763)		Trumenba + Menveo (N[a]=649)	
	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	368	20.9	132	20.3
Ear and labyrinth disorders				
Cerumen impaction	5 (0.3)	(0.1, 0.7)	2 (0.3)	(0.0, 1.1)
Eye disorders				
Conjunctivitis allergic	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.6)
Gastrointestinal disorders				
Constipation	7 (0.4)	(0.2, 0.8)	0	(0.0, 0.6)
Vomiting	7 (0.4)	(0.2, 0.8)	1 (0.2)	(0.0, 0.9)
Gastrooesophageal reflux disease	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.6)
Nausea	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.6)
General disorders and administration site conditions				
Pyrexia	5 (0.3)	(0.1, 0.7)	0	(0.0, 0.6)
Immune system disorders				
Seasonal allergy	4 (0.2)	(0.1, 0.6)	1 (0.2)	(0.0, 0.9)
Infections and infestations				
COVID-19	69 (3.9)	(3.1, 4.9)	19 (2.9)	(1.8, 4.5)
Upper respiratory tract infection	25 (1.4)	(0.9, 2.1)	11 (1.7)	(0.8, 3.0)
Pharyngitis	19 (1.1)	(0.7, 1.7)	8 (1.2)	(0.5, 2.4)
Tonsillitis	8 (0.5)	(0.2, 0.9)	4 (0.6)	(0.2, 1.6)
Urinary tract infection	8 (0.5)	(0.2, 0.9)	2 (0.3)	(0.0, 1.1)
Hordeolum	6 (0.3)	(0.1, 0.7)	0	(0.0, 0.6)
Viral upper respiratory tract infection	5 (0.3)	(0.1, 0.7)	2 (0.3)	(0.0, 1.1)
Gastroenteritis	4 (0.2)	(0.1, 0.6)	1 (0.2)	(0.0, 0.9)
Gastroenteritis viral	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.6)
Nasopharyngitis	4 (0.2)	(0.1, 0.6)	7 (1.1)	(0.4, 2.2)
Otitis media	4 (0.2)	(0.1, 0.6)	2 (0.3)	(0.0, 1.1)
Pharyngitis streptococcal	4 (0.2)	(0.1, 0.6)	4 (0.6)	(0.2, 1.6)
Rhinitis	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.6)
Sinusitis	4 (0.2)	(0.1, 0.6)	2 (0.3)	(0.0, 1.1)
Injury, poisoning and procedural complications				
Fall	14 (0.8)	(0.4, 1.3)	6 (0.9)	(0.3, 2.0)
Contusion	10 (0.6)	(0.3, 1.0)	0	(0.0, 0.6)
Skin laceration	6 (0.3)	(0.1, 0.7)	1 (0.2)	(0.0, 0.9)
Investigations				
SARS-CoV-2 test positive	13 (0.7)	(0.4, 1.3)	6 (0.9)	(0.3, 2.0)
Metabolism and nutrition disorders				
Obesity	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.6)
Musculoskeletal and connective tissue disorders				
Arthralgia	7 (0.4)	(0.2, 0.8)	4 (0.6)	(0.2, 1.6)
Nervous system disorders				
Headache	5 (0.3)	(0.1, 0.7)	4 (0.6)	(0.2, 1.6)
Migraine	5 (0.3)	(0.1, 0.7)	0	(0.0, 0.6)
Psychiatric disorders				
Attention deficit hyperactivity disorder	5 (0.3)	(0.1, 0.7)	1 (0.2)	(0.0, 0.9)
Depression	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.6)
Respiratory, thoracic and mediastinal disorders				
Rhinitis allergic	11 (0.6)	(0.3, 1.1)	4 (0.6)	(0.2, 1.6)
Asthma	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.6)
Oropharyngeal pain	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.6)
Skin and subcutaneous tissue disorders				
Acne	13 (0.7)	(0.4, 1.3)	3 (0.5)	(0.1, 1.3)
Vascular disorders				
Hypertension	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.6)

Note: (MedDRA v25.0) coding dictionary applied.
Note: Vaccination phase is from the first study vaccination (Visit 1) through 1 month after the second study vaccination (Visit 4).
Note: One (1) participant who received Trumenba + saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables.
Note: One (1) participant who received MenABCWY + Menveo at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.

System Organ Class Preferred Term	MenABCWY (N[a]=1763)		Trumenba + Menveo (N[a]=649)	
	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
a. N = number of participants in the specified group. These values are used as the denominator for percentage calculations for the vaccine groups. b. n = Number of participants reporting at least 1 event of the type specified. c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.				

During study **B1971057**, a similar percentage of participants reported at least 1 AE in the MenABCWY and the bivalent rLP2086 + Menveo groups in both stages of the study (39.2% and 40.7%, respectively). The most commonly reported unsolicited AEs for both MenABCWY + saline and rLP2086 + Menveo recipients were in the SOC infections and infestations (133 [24.5%] and 263 [24.9%] participants, respectively).

There were no immediate AEs reported for MenABCWY recipients. In the Trumenba + Menveo group, immediate AEs within 30 minutes after Vaccination 1 and Vaccination 2 were reported by 9 (0.9%) and 3 (0.3%) participants, respectively. Immediate AEs generally included local and systemic reactogenicity events, syncope, presyncope, and procedural dizziness. No events consistent with hypersensitivity were reported as immediate AEs.

During study **C3511004**, solicited reactogenicity events (local reactions and systemic events) were not collected via participant-reported e-diary, but in case a reactogenicity event met the protocol definition of an AE, it was documented as an AE on the CRF. As a result, a large number of AEs were reported that are consistent with reactogenicity-type events. As such, the most commonly reported SOCs were general disorders and administration site conditions, nervous system disorders, and gastrointestinal disorders and the most commonly reported PTs were injection site pain, pyrexia, fatigue, headache, and vomiting during the Vaccination 1 vaccination phase in Group 1 and Group 2. Additionally, during the Vaccination 2 vaccination phase for Group 1, the most common SOC was general disorders and administration site conditions followed by infections, and the most common PTs were injection site pain and nasopharyngitis.

Related Unsolicited Adverse Events

During the vaccination phase, events considered by the investigator as related to study intervention were reported in the same percentage of MenABCWY and Trumenba + Menveo participants (0.6%) (Table 34). Most related AEs were reactogenicity events in the SOC of general disorders and administration site conditions.

Table 34. Related adverse events reported during the vaccination phase, by system organ class and preferred term – safety population – C3511001

System Organ Class Preferred Term	MenABCWY (N[a]=1763)		Trumenba + Menveo (N[a]=649)	
	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	11 (0.6)	(0.3, 1.1)	4 (0.6)	(0.2, 1.6)
Gastrointestinal disorders	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.6)
Abdominal pain upper	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)
Swollen tongue	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)
General disorders and administration site conditions	7 (0.4)	(0.2, 0.8)	1 (0.2)	(0.0, 0.9)
Injection site pain	3 (0.2)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Injection site erythema	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.6)
Injection site swelling	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.6)
Fatigue	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)
Injection site haematoma	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)
Injection site pruritus	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)
Injection site rash	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)
Injection site reaction	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)

Vaccination site haematoma	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)
Musculoskeletal and connective tissue disorders	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)
Pain in extremity	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)
Nervous system disorders	1 (0.1)	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Headache	1 (0.1)	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Skin and subcutaneous tissue disorders	1 (0.1)	(0.0, 0.3)	2 (0.3)	(0.0, 1.1)
Dermatitis	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)
Pruritus	0	(0.0, 0.2)	1 (0.2)	(0.0, 0.9)
Rash erythematous	0	(0.0, 0.2)	1 (0.2)	(0.0, 0.9)
Rash maculo-papular	0	(0.0, 0.2)	1 (0.2)	(0.0, 0.9)
Vascular disorders	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)
Haematoma	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.6)

Note: (MedDRA v25.0) coding dictionary applied.
Note: Vaccination phase is from the first study vaccination (Visit 1) through 1 month after the second study vaccination (Visit 4).
Note: One (1) participant who received Trumenba + saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables.
Note: One (1) participant who received MenABCWY + Menveo at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.
a. N = number of participants in the specified group. These values are used as the denominator for percentage calculations for the vaccine groups.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "Any event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.

For study **B1971057**, the percentage of participants who experienced any unsolicited adverse events considered related to the study interventions that occurred during the vaccination phase for Stage 1 was 3.7% in the MenABCWY group and 4.2% in the Trumenba+Menveo group. The majority of related AEs reported were reactogenicity-type events. During the booster vaccination phase, events considered by the investigator as related to study intervention were reported by 1.4% (n=2) participants in the MenABCWY group and none in the Trumenba + Menveo group. Again the related AEs reported were reactogenicity type events.

During study **C3511004**, the percentage of participants experiencing related AEs was 19% in Group 1 and 22.3% in Group 2. In Group 1, most related AEs reported during the Vaccination 1 and Vaccination 2 vaccination phases (time from each vaccination through 1 month after that vaccination) were reactogenicity-type events and generally included injection site pain, injection site erythema, pyrexia, headache, fatigue, vomiting, and chills. In Group 2, a similar trend was observed relative to Group 1 with regard to the proportion of participants with related AEs and the type of related AEs reported during the Vaccination 1 vaccination phase.

Adverse events of special interest

Newly diagnosed chronic medical conditions

In **Study C3511001**, NDCMCs were reported by 25 (1.4%) participants receiving MenABCWY and 2 (0.3%) participants receiving Trumenba + Menveo. The proportion of participants with NDCMCs for individual SOCs were generally similar between the vaccination groups apart from a higher number of events in the SOC of Psychiatric disorders in the MenABCWY group (9 events) relative to the Trumenba + Menveo group (1 event), which is the main contributor to the overall difference in NDCMCs reported between the vaccination groups, see table 35.

Table 35. Newly diagnosed chronic medical conditions reported throughout the study by >1 participant, by system organ class and preferred term – safety population – c3511001 (modified by assessor)

System Organ Class Preferred Term	MenABCWY (N[a]=1763) n[b] (%)	 (95% CI[c])	Trumenba + Menveo (N[b]=649) n[b] (%)	 (95% CI[c])
Any Event	25 (1.4)	(0.9, 2.1)	2 (0.3)	(0.0, 1.1)
Blood and lymphatic system disorders	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.6)
Iron deficiency anaemia	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.6)
Endocrine disorders	2 (0.1)	(0.0, 0.4)	1 (0.2)	(0.0, 0.9)
Metabolism and nutrition disorders	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.6)
Musculoskeletal and connective tissue disorders	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.6)
Psychiatric disorders	9 (0.5)	(0.2, 1.0)	1 (0.2)	(0.0, 0.9)
Attention deficit hyperactivity disorder	6 (0.3)	(0.1, 0.7)	1 (0.2)	(0.0, 0.9)
Skin and subcutaneous tissue disorders	3 (0.2)	(0.0, 0.5)	0	(0.0, 0.6)
Vascular disorders	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.6)
Hypertension	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.6)

Abbreviation: NDCMC = newly diagnosed chronic medical condition.
Note: (MedDRA v25.0) coding dictionary applied.
Note: Throughout the Study is from the 1st study vaccination (Visit 1) through 6 months after the 2nd study vaccination (Visit 5).
Note: One (1) participant who received Trumenba + saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables.
Note: One (1) participant who received MenABCWY + Menveo at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.
a. N = number of participants in the specified group. These values are used as the denominator for percentage calculations for the vaccine groups.
c. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "Any event," n = number of participants reporting at least 1 occurrence of any adverse event.
d. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.

ADHD was reported by 6 (0.3%) participants in the MenABCWY group vs 1 (0.2%) participant in the Trumenba + Menveo group however, this difference is not considered to be clinically meaningful. Among the 7 participants with ADHD across both vaccine groups, 5 participants, all in the MenABCWY group, had an onset of ADHD related symptoms that occurred prior to study enrolment. The remaining 2 participants, one in the MenABCWY group and 1 in the Trumenba + Menveo group, had a history of one or more psychiatric conditions prior to enrolment that commonly co-occur with ADHD including anxiety, depression, and substance use.

In **study B1971057** Stage 1, NDCMCs were reported by 3 (0.6%) MenABCWY participants and 10 (0.9%) Trumenba + MenACWY-CRM participants. None were considered by the investigator to be related to the investigational product and none were severe. The only NDCMC reported by >1 participant was ADHD reported by 2 participants in the Trumenba + Menveo arm.

In Study B1971057 Stage 2, there were no NDCMCs reported during the booster vaccination phase. There was one participant in the bivalent rLP2086 + Menveo group with an unrelated NDCMC (autoimmune thyroiditis; day 233 after vaccination 2) that was reported during the persistence phase and one participant with an unrelated NDCMC (migraine) that was reported after the booster vaccination phase.

In **Study C3511004**, NDCMCs were reported by 2 (1.4%) MenABCWY participants within 6 months after Vaccination 1 and none were reported within 1 month after Vaccination 2 in Group 1. In Group 2 (who received MenABCWY at Vaccination 1 and saline at Vaccination 2), 1 (0.7%) participant reported an NDCMC within 6 months of Vaccination 1 and 7 NDCMCs were reported by 4 participants either from 6 months after Vaccination 1 and prior to Vaccination 2, or from 1 month after Vaccination 2 through the Analysis 1 database release date of 01 July 2022. ADHD was reported as an NDCMC by 3 participants. In 1 of these 3 participants, ADHD symptoms began prior to study enrolment.

Autoimmune Conditions

In **Study C3511001**, 2 participants were diagnosed with confirmed autoimmune conditions in the Trumenba + Menveo arm: Alopecia areata (n=1, onset 38 days after Vaccination 1) and Autoimmune thyroiditis (n=1, onset 144 days after Vaccination 1). Both events were considered unrelated to vaccine by the investigators. No confirmed autoimmune AEs were reported in the MenABCWY group.

In **Study B1971057 Stage 1**, 5 participants, all receiving bivalent rLP2086 + Menveo, were diagnosed with confirmed autoimmune conditions: Crohn's disease (n=1), alopecia areata (n=1), ulcerative colitis (n=1), and autoimmune thyroiditis (n=2). No cases were reported in participants receiving MenABCWY.

There were no confirmed autoimmune conditions reported in **Study B1971057 Stage 2** or in Study **C3511004**.

No events of confirmed autoimmune conditions were considered by the investigator to be related or possibly related to study vaccine. Overall, the rates of autoimmune conditions in participants receiving MenABCWY or Trumenba + Menveo across the studies contributing to this submission were low and there is no evidence to suggest a causal relationship between MenABCWY vaccination and development of autoimmune conditions.

Neuroinflammatory Conditions

In **Study C3511001**, one Trumenba + Menveo participant reported one case of a confirmed neuroinflammatory condition which was restless leg syndrome with onset of 56 days after Vaccination 2. The event was not considered vaccine-related and was attributed to iron deficiency anaemia associated with the participant's medical history of menorrhagia.

In **Study C3511004**, one MenABCWY recipient reported one case of confirmed neuroinflammatory condition which was a case of restless leg syndrome with onset 140 days after Vaccination 1. The participant also received non-study vaccines Tdap, HPV, VZV and influenza after Vaccination 1 with MenABCWY and between 40 and 112 days prior to onset of the event. No treatment was required, and the condition was considered resolved within approximately 3 months from onset. The investigator considered that there was a reasonable possibility that the restless leg syndrome was related to the study intervention as well as the contemporaneously administered concomitant vaccines because no other cause was identified.

In **Study B1971057**, one MenABCWY recipient reported one case of confirmed neuroinflammatory condition, epilepsy with onset of 457 days after Vaccination 2. The case of epilepsy was considered unrelated to investigational product by the investigator.

Overall, the rates of neuroinflammatory conditions in participants receiving MenABCWY or bivalent rLP2086 + Menveo across the studies contributing to this submission were low and there is no evidence to suggest a causal relationship between MenABCWY vaccination and development of neuroinflammatory conditions.

2.5.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

In each of the 3 studies in the MenABCWY clinical development programme, the proportion of participants with SAEs in either intervention group was low and comparable across intervention groups, see table 36. None of the SAEs were considered by the investigator to be related to MenABCWY. SAEs were reported

across multiple SOCs, with the most commonly reported SOC being psychiatric disorder; no specific pattern of SAEs was identified.

Table 36. SAEs per study

Study	All SAEs		Vaccine-related SAE	
	MenABCWY	Trumenba + Menveo	MenABCWY	Trumenba + Menveo
C3511001	11/1763 (0.6%)	4/649 (0.6%)	0/1763 (0%)	0/649 (0%)
B19710157	10/543 (1.8%)	14/1057 (1.3%)	0/543 (0%)	0/1057 (0%)
C3511004[a]	1/300 (0.3%)		0/300 (0%)	
[a] 2 intervention groups: MenABCWY administered at 0, 12 month and 0, 36 month schedule combined. Of note: after vaccination 2 only SAE occurring within 30 days after vaccination were collected.				

Deaths

During Study C3511001, there were no deaths reported in participants who received MenABCWY or Trumenba + Menveo.

In Study B1971057 Stage 1, one (1) MenABCWY recipient died 109 days after Vaccination 2 due to a motor vehicle accident. The death was not considered by the investigator to be related to the investigational product. There were no deaths reported in bivalent rLP2086 + Menveo participants during Stage 1 of the study. No deaths were reported during Study B1971057 Stage 2.

There were no deaths reported in participants who received MenABCWY in Group 1 or Group 2 during Study C3511004.

2.5.8.4. Safety in special populations

2.5.8.4.1. ACWY experience

C3511001

There were no clinically important differences with regard to the severity of or percentage of participants who reported local reactions or systemic events by maximum severity within 7 days after vaccination in subgroup analyses by ACWY experience, see Table 37.

Table 37. Summary of reactogenicity events by ACWY experience – safety population - C3511001 (modified by assessor)

	ACWY-Naive		ACWY-Experienced	
	MenABCWY	Trumenba + Menveo	MenABCWY	Trumenba + Menveo
Local Reaction Severity	n[a]/N[b] (%) (95% CI[c])	n[a]/N[b] (%) (95% CI[c])	n[a]/N[b] (%) (95% CI[c])	n[a]/N[b] (%) (95% CI[c])
Local reactions				
Any local reaction[d]	1010/1066 (94.7) (93.2, 96.0)	298/324 (92.0) (88.5, 94.7)	624/662 (94.3) (92.2, 95.9)	283/311 (91.0) (87.3, 93.9)
Redness	370/1066 (34.7) (31.9, 37.7)	89/324 (27.5) (22.7, 32.7)	196/662 (29.6) (26.2, 33.2)	73/311 (23.5) (18.9, 28.6)
Swelling	384/1066 (36.0) (33.1, 39.0)	86/324 (26.5) (21.8, 31.7)	203/662 (30.7) (27.2, 34.3)	75/311 (24.1) (19.5, 29.3)
Pain at the injection site	1005/1066 (94.3) (92.7, 95.6)	294/324 (90.7) (87.0, 93.7)	622/662 (94.0) (91.9, 95.6)	280/311 (90.0) (86.2, 93.1)
Systemic reactions				
Any systemic event[e]	870/1078 (80.7) (78.2, 83.0)	264/328 (80.5) (75.8, 84.6)	557/670 (83.1) (80.1, 85.9)	263/318 (82.7) (78.1, 86.7)
Fever (≥38.0°C)	86/1078 (8.0) (6.4, 9.8)	27/328 (8.2) (5.5, 11.8)	37/670 (5.5) (3.9, 7.5)	16/318 (5.0) (2.9, 8.0)
Fatigue	681/1078 (63.2) (60.2, 66.1)	213/328 (64.9) (59.5, 70.1)	436/670 (65.1) (61.3, 68.7)	203/318 (63.8) (58.3, 69.1)
Headache	612/1078 (56.8)	176/328 (53.7)	398/670 (59.4)	198/318 (62.3)

Local Reaction Severity	ACWY-Naive		ACWY-Experienced	
	MenABCWY	**Trumenba + Menveo**	**MenABCWY**	**Trumenba + Menveo**
	n[a]/N[b] (%)	**n[a]/N[b] (%)**	**n[a]/N[b] (%)**	**n[a]/N[b] (%)**
	(95% CI[c])	**(95% CI[c])**	**(95% CI[c])**	**(95% CI[c])**
	(53.8, 59.8)	(48.1, 59.2)	(55.6, 63.1)	(56.7, 67.6)
Chills	285/1078 (26.4)	92/328 (28.0)	194/670 (29.0)	78/318 (24.5)
	(23.8, 29.2)	(23.3, 33.2)	(25.5, 32.6)	(19.9, 29.6)
Vomiting	44/1078 (4.1)	16/328 (4.9)	27/670 (4.0)	7/318 (2.2)
	(3.0, 5.4)	(2.8, 7.8)	(2.7, 5.8)	(0.9, 4.5)
Diarrhoea	141/1078 (13.1)	58/328 (17.7)	139/670 (20.7)	62/318 (19.5)
	(11.1, 15.2)	(13.7, 22.3)	(17.7, 24.0)	(15.3, 24.3)
Muscle Pain	365/1078 (33.9)	115/328 (35.1)	264/670 (39.4)	119/318 (37.4)
	(31.0, 36.8)	(29.9, 40.5)	(35.7, 43.2)	(32.1, 43.0)
Joint Pain	300/1078 (27.8)	87/328 (26.5)	204/670 (30.4)	102/318 (32.1)
	(25.2, 30.6)	(21.8, 31.7)	(27.0, 34.1)	(27.0, 37.5)

Note: Local reactions are summarized for the MenABCWY or Trumenba injection site for the left arm only. At Vaccination 1, 26 participants received MenABCWY or Trumenba in the right arm and were excluded from this summary of Vaccination 1 and from summaries across Vaccinations 1 and 2.
The 6 participants who received Vaccination 2 in the right arm were excluded from this summary of Vaccination 2 and from summaries across Vaccinations 1 and 2.
Note: Groups 1, 3, 5, and 7 received MenABCWY + saline at the 1st study vaccination and MenABCWY at the 2nd study vaccination; Groups 2, 4, 6, and 8 received Trumenba + Menveo at the 1st study vaccination and Trumenba at the 2nd study vaccination.
Note: One (1) participant who received Trumenba + saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables.
Note: One (1) participant who received MenABCWY + Menveo at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.
a. n = Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.
b. N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are used as the denominators for the percentage calculations.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. Any local reaction = any redness, any swelling, or any pain at the injection site.
e. Any systemic event = any fever ≥38.0°C, any fatigue, any headache, any chills, any vomiting, any diarrhoea, any muscle pain, or any joint pain.

AEs were reported by 207 (19.1%) ACWY-naive MenABCWY + saline participants and 161 (23.7%) ACWY experienced MenABCWY + saline participants during the vaccination phase. The proportion of participants reporting AEs within 30 days after Vaccination 1 and Vaccination 2 was similar for both ACWY-naive (5.1% and 5.2%, respectively) and ACWY-experienced (6.9% and 5.5%, respectively) participants.

B1971057

The proportion of MenABCWY recipients reporting local reactions was similar between ACWY-naive participants (Group 1) and ACWY-experienced participants (Group 3) (95.2% and 93.3%, respectively). The proportion of MenABCWY + saline recipients reporting any systemic event after any vaccination was similar between ACWY-naive participants and ACWY-experienced participants (83.1% and 78.1%, respectively).

AEs were reported by 113 (41.5%) ACWY-naive MenABCWY + saline participants and 100 (36.9%) ACWY experienced MenABCWY + saline participants during the vaccination phase. The proportion of participants reporting AEs within 30 days after Vaccination 1 and Vaccination 2 was similar for both ACWY-naive (15.1% and 16.1%, respectively) and ACWY-experienced (11.1% and 12.3%, respectively) participants.

2.5.8.4.2. Sex

C3511001

There were no clinically important differences with regard to the severity of or percentage of participants who reported local reactions or systemic events by maximum severity within 7 days after vaccination in subgroup analyses by sex. During the study, there were no clinically important differences with regard to the proportion of participants reporting at least 1 AE (including All, SAEs, MAEs, and NDCMCs) in subgroup analyses by sex, see Table 38.

Table 38. Summary of adverse events (solicited, all unsolicited, serious, medically attended, NDCMC) by sex – safety population - C3511001 (modified by assessor)

Interval	MenABCWY			Trumenba + Menveo		
Endpoint Sex	N[a]	n[b](%)	(95% CI[c])	N[a]	n[b](%)	(95% CI[c])
Reactogenicity						
Any local reaction						
Female	901	868 (96.3)	(94.9, 97.5)	314	292 (93.0)	(89.6, 95.6)
Male	827	766 (92.6)	(90.6, 94.3)	321	289 (90.0)	(86.2, 93.1)
Any systemic reaction						
Female	911	794 (84.5)	(84.8, 89.3)	317	268 (84.5)	(80.1, 88.3)
Male	837	633 (75.6)	(72.6, 78.5)	329	259 (78.7)	(73.9, 83.0)
During the vaccination phase[d]						
All AEs						
Female	917	218 (23.8)	(21.1, 26.7)	319	76 (23.8)	(19.3, 28.9)
Male	846	150 (17.7)	(15.2, 20.5)	330	56 (17.0)	(13.1, 21.5)
Throughout Study[e]						
All SAEs						
Female	917	7 (0.8)	(0.3, 1.6)	319	3 (0.9)	(0.2, 2.7)
Male	846	4 (0.5)	(0.1, 1.2)	330	1 (0.3)	(0.0, 1.7)
All MAEs						
Female	917	194 (21.2)	(18.6, 23.9)	319	68 (21.3)	(17.0, 26.2)
Male	846	146 (17.3)	(14.8, 20.0)	330	51 (15.5)	(11.7, 19.8)
All NDCMCs						
Female	917	15 (1.6)	(0.9, 2.7)	319	0	(0.0, 1.1)
Male	846	10 (1.2)	(0.6, 2.2)	330	2 (0.6)	(0.1, 2.2)

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition.
Note: One (1) participant who received Trumenba + saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables.
Note: One (1) participant who received MenABCWY + Menveo at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.
a. N = number of participants in the specified group. These values are used as the denominator for percentage calculations for the vaccine groups
b. n = Number of participants reporting at least 1 occurrence of the event specified.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. Vaccination phase is from the 1st study vaccination (Visit 1) through 1 month after the 2nd study vaccination (Visit 4).
e. These values include data from Visit 1 to Visit 5, inclusive

Similar results were observed in both supportive studies B1971057 and C3511004: There were no clinically important differences in the subgroup analysis by sex for local and systemic reactogenicity events, MAEs or SAEs.

2.5.8.4.3. Age

C3511001

There were no clinically important differences with regard to the severity of or percentage of participants who reported local reactions or systemic events by maximum severity within 7 days after

vaccination in subgroup analyses by age group. During the study, there were no clinically important differences with regard to the proportion of participants reporting at least 1 AE (including All, SAEs, MAEs, and NDCMCs), see Table 39.

Table 39. Summary of adverse events (solicited, all unsolicited, serious, medically attended, NDCMC) by age group – safety population - C3511001 (modified by assessor)

Interval Endpoint Sex	MenABCWY N[a]	 n[b](%)	 (95% CI[c])	Trumenba + Menveo N[a]	 n[b](%)	 (95% CI[c])
Reactogenicity						
Any local reaction						
≥10 Years to <18 years	1171	1101 (94.0)	(92.5, 95.3)	399	367 (92.0)	(88.9, 94.4)
≥18 Years to <26 years	557	533 (95.7)	(93.7, 97.2)	234	214 (90.7)	(86.2, 94.1)
Any systemic reaction						
≥10 Years to <18 years	1183	947 (80.1)	(77.7, 82.3)	407	325 (79.9)	(75.6, 83.6)
≥18 Years to <26 years	565	480 (85.0)	(81.7, 87.8)	239	202 (84.5)	(79.3, 88.9)
During the vaccination phase[d]						
All AEs						
≥10 Years to <18 years	1188	274 (23.1)	(20.7, 25.6)	409	98 (24.0)	(19.9, 28.4)
≥18 Years to <26 years	575	94 (16.3)	(13.4, 19.6)	240	34 (14.2)	(10.0, 19.2)
Throughout Study[e]						
All SAEs						
≥10 Years to <18 years	1188	10 (0.8)	(0.4, 1.5)	409	2 (0.5)	(0.1, 1.8)
≥18 Years to <26 years	575	1 (0.2)	(0.0, 1.0)	240	2 (0.8)	(0.1, 3.0)
All MAEs						
≥10 Years to <18 years	1188	274 (23.1)	(20.7, 25.6)	409	95 (23.2)	(19.2, 27.6)
≥18 Years to <26 years	575	66 (11.5)	(9.0, 14.4)	240	24 (10.0)	(6.5, 14.5)
All NDCMCs						
≥10 Years to <18 years	1188	13 (1.1)	(0.6, 1.9)	409	1 (0.2)	(0.0, 1.4)
≥18 Years to <26 years	575	12 (2.1)	(1.1, 3.6)	240	1 (0.4)	(0.0, 2.3)

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition.
Note: One (1) participant who received Trumenba + saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables.
Note: One (1) participant who received MenABCWY + Menveo at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.
a. N = number of participants in the specified group. These values are used as the denominator for percentage calculations for the vaccine groups
b. n = Number of participants reporting at least 1 occurrence of the event specified.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. Vaccination phase is from the 1st study vaccination (Visit 1) through 1 month after the 2nd study vaccination (Visit 4).
e. These values include data from Visit 1 to Visit 5, inclusive

Similar results were observed in supportive study B1971057: There were no clinically important differences in the subgroup analysis by sex for local and systemic reactogenicity events, MAEs or SAEs. Study C3511004 only enrolled participants ≥11 to <15 years of age.

2.5.8.4.4. Pregnancy

Across all studies, a total of 36 participants became pregnant during the studies or had partners who became pregnant during the studies. Information regarding pregnancy outcomes across both vaccine groups was available for 25 of the 36 pregnancies. Among the 25 pregnancies with known outcomes, live births were documented for 19 of 25 participants (76.0%), most (17 out of 19) of which were full term. Foetal loss was reported for 6 (24.0%) of the 25 cases with known outcomes; 1 (16.7%) was an elective termination and 4 (66.7%) were spontaneous abortions. There was no data for the one remaining case of foetal loss (Table 40).

Across studies where participants of child-bearing age received MenABCWY and pregnancies occurred (B1971057, C3511001), outcome information was available for 11 out of 18 pregnancies (Table 40).

Among those in the MenABCWY group, foetal loss occurred in 4 pregnancies and live births occurred in 7 pregnancies. For the 3 foetal losses due to spontaneous abortion in MenABCWY recipients, the lag time in days between last vaccination and estimated date of conception was 50, 1143, and 1244 days. The fourth was a foetal loss, cause unknown, with a lag time of 175 days between last vaccination and estimated date of conception. In the Trumenba + Menveo group, among the 14 pregnancies reported with known outcome, foetal loss occurred in 2 pregnancies, one spontaneous abortion and one elective termination, and live births occurred in 12 pregnancies.

Table 40. Summary of pregnancy outcomes by investigational product

Pregnancy Birth Type[a, b] Pregnancy Outcome	**Vaccine Group (as Administered) MenABCWY N[c]=2306**	**Control[d] N[c]=1707**	**Total N[c]=4012**
Total number of pregnancies	18	18	36
Number of pregnancies with known outcome[a]	11	14	25
Live births	7/11 (63.6)	12/14 (85.7)	19/25 (76.0)
Full term	6/7 (85.7)	11/12 (91.7)	17/19 (89.5)
Congenital anomaly	0	0	0
Normal	6/6 (100.0)	11/11 (100.0)	17/17 (100.0)
No data	0	0	0
Premature	1/7 (14.3)	1/12 (8.3)	2/19 (10.5)
Normal	0/1 (0.0)	1/1 (100.0)	1/2 (50.0)
Perinatal complication	1/1 (100.0)	0/1 (0.0)	1/2 (50.0)
No data	0	0	0
Foetal loss	4/11 (36.4)	2/14 (14.3)	6/25 (24.0)
Elective termination	0/4 (0.0)	1/2 (50.0)	1/6 (16.7)
Spontaneous abortion	3/4 (75.0)	1/2 (50.0)	4/6 (66.7)
Therapeutic abortion	0	0	0
Still birth	0	0	0
No data	1/4 (25.0)	0/2 (0.0)	1/6 (16.7)
No data[b]	7/18 (38.9)	4/18 (22.2)	11/36 (30.6)

Note: Table includes vaccinated participants from B1971057 and C3511001.
Note: To ensure accurate display of pregnancy outcomes, outcomes reported in the safety database (Argus) were supplemented with data manually derived from the case narratives within the safety database as needed. Manually derived outcomes were reviewed by two independent reviewers.
Note: Participants summarized are pregnant females and males with pregnant partners.
Note: Data are provided for individual pregnancies and their outcomes.
Note: MenABCWY includes all participants who received at least 1 dose of MenABCWY on a 0- and 6-month schedule from Studies B1971057 Stage 1 (Groups 1+3 [MenABCWY]) and C3511001 (Groups 1+3+5+7 [MenABCWY]).
Note: Control includes all participants who received at least 1 dose of Control on a 0- and 6-month schedule from Studies B1971057 Stage 1 (Groups 2+4[Trumenba + Menveo]) and C3511001 (Groups 2+4+6+8 [Trumenba + Menveo]).
a. No cases with the following birth types and/or foetal outcomes were reported in the safety database: birth type = postmature; outcome = abnormal newborn, intrauterine death, lost to follow-up, neonatal death, or outcome pending.
b. Includes participants who were lost to follow-up.
c. N = number of vaccinated participants.
d. Control = Trumenba+Menveo.

2.5.8.5. Discontinuation due to adverse events

In total 18 AEs led to withdrawal in all three studies submitted. In the studies investigating the currently proposed posology (Study C3511001 and B1971057), AEs leading to withdrawal occurred in 8 participants in the MenABCWY arm compared to 6 in the Trumenba+Menveo arm. In study C3511004 investigating an extended regimen (0, 12 and 0, 36 month schedule), 4 AEs led to withdrawal. Of the 18 AEs leading to withdrawal, 2 maculo-papular rash were considered possibly related to the study vaccine Both cases were reports of maculo-papular rash occurring in the Trumenba+Menveo arm.

2.5.8.6. Post marketing experience

At the time of submission, Penbraya had not been marketed for individuals 10 years of age and older in any country. No relevant post-marketing data was available during the procedure.

2.5.9. Discussion on clinical safety

The pentavalent MenABCWY vaccine combines two already approved vaccines: Trumenba (bivalent rLP2086) in a high fill volume and Nimenrix (MenACWY-TT). Trumenba received marketing authorisation on 24 May 2017 and Nimenrix on 20 April 2012. The safety profiles of these 2 vaccines have been studied and assessed separately. The available safety information from the 2 separate vaccines was taken into consideration within this procedure.

The clinical safety profile of the pentavalent MenABCWY vaccine was mainly derived from data obtained in study C3511001, which represents a major part of the overall exposure to the pentavalent MenABCWY vaccine and is an active comparator-controlled study conducted in the target population of healthy participants ≥10 to <26 years of age using the proposed posology (the 0-, 6-month schedule). The safety data is further supported by data from the 1st in human study investigating the proposed posology, study B1971057, and the study investigating the extended dosing schedule (0, 12-month and 0, 36-month schedule), study C3511004 (where appropriate).

Methods of collection of safety data were consistent across the 2 studies investigating the proposed posology. Reactogenicity as determined by solicited local and systemic AEs was followed for 7 days, while non-serious, unsolicited AEs were followed for 30 days. SAEs and MAEs and NDCMDs were collected up to 6 months or up to the data lock point. The strategy for collecting safety information led to a sufficient period of time to collect information on the outcome of the adverse events, for the proposed posology, also in light of the extensive safety information already available.

The information after the booster dose in Stage 2 of study B1971057 is considered limited, as SAEs were only collected for 1 month after the booster vaccination. This can be considered acceptable as the separate vaccines have been on the market for >5 years both as primary and booster vaccinations, therefore a lot of information is already available. The safety information provided by study C3511004 is considered limited. Reactogenicity was not assessed and in the current submission, due to data cut-off, SAEs were only collected for 1 month after vaccination 2 in the 0- and 12-month vaccination group. This is considered short. However, as the study is ongoing more information will become available.

Exposure

In total, 2,605 participants ≥10 to ≤25 years of age were exposed to the pentavalent vaccine in the studies submitted in the current procedure. Of these 2605 participants, 2306 subject (1763 from study C3511001 and 543 from B1971057 stage 1 received MenABCWY) on a 0- and 6 months vaccination schedule and 299 subjects on an extended vaccination schedule (1 participant who received saline instead of MenABCWY was excluded from the dataset; source: table 9 of the CSR for C3511004). 1706 subjects received at least one dose of the comparator vaccination (Trumenba + MenACWY-CRM) on a 0- and 6 months vaccination schedule. In the comparator arm dose two differed compared to dose one, as only Trumenba and saline was given as dose two compared to Trumenba and MenACWY-CRM (Menveo) as first dose. The size of the safety database is below the size recommended in the guideline on clinical evaluation of vaccines (3,000). Considering the fact that the pentavalent vaccine consists of 2 already approved vaccines, the size of the safety database can be considered sufficient for assessment of the safety profile of the combined pentavalent vaccine. However, the size of the safety database limits the detection of more rare adverse events. Information on rare but serious AEs should

be systematically collected post-licensure. The composition of the safety database appears acceptable and can be considered representative of an European population.

The demographic characteristics were generally comparable between groups included in the 3 separate studies. No clear differences were observed.

Solicited Adverse Events

Across studies observations about reactogenicity events were consistent, with the majority of participants, >80% in both studies investigating the proposed posology, experiencing 1 or more solicited AEs within 7 days. The most frequently reported solicited AEs were injection site pain, followed by fatigue and headache. In addition, most solicited AEs were mild to moderate in intensity. The most frequently reported severe solicited AE was injection site pain, experienced by 12% in the MenABCWY group. Severe solicited adverse events were experienced by ≤5% of participants for all other solicited adverse reactions. The majority of solicited AEs were of short duration (≤3 days). The safety profile of the pentavalent MenABCWY vaccine was generally comparable to Trumenba+Menveo.

Following the booster dose, the reactogenicity profile appears to be in general similar though slightly reduced compared to the profile after the primary vaccination. However, due to small numbers and selection of participants that remain in the study, no strong conclusions can be drawn.

Unsolicited Adverse Events

During the vaccination phase of study C3511001 the percentage of participants experiencing any unsolicited AEs was 20.9% in the MenABCWY group and 20.3% in the Trumenba+Menveo group, while during the vaccination phase for Stage 1 of study B1971057 any unsolicited AE was reported by 39.2% and 40.7% of participants for both groups respectively. This difference is potentially due to the studies being conducted in different time periods, with study B1971057 Stage 1 taking place prior to the COVID-19 pandemic and study C3511001 taking place during the pandemic. A clear difference in percentage of participants experiencing AEs in the SOC "Infections and infestations" was observed.

Overall, in both study C3511001 and B1971057, unsolicited AEs were experienced by a comparable percentage of participants in the MenABCWY and Trumenba+Menveo group. The most frequently reported unsolicited AEs were in the SOC Infections and infestations followed by Injury, poisoning and procedural complications.

Related unsolicited adverse events were experienced by a low percentage of participants in study C3511001, 0.6% for both the MenABCWY and Trumenba+Menveo group. In study C3511004 the percentage of related AEs is much higher, 19% in Group 1 and 22.3% in Group 2, which is mainly driven by AEs considered solicited in study C3511001. During Stage 1 of study B1971057, the percentage of participants experiencing related AEs was higher compared to study C3511001, however, similar between the treatment groups, 3.7% in the MenABCWY group and 4.2% in the Trumenba+Menveo group. The majority of related AEs reported were reactogenicity-type events. After the booster vaccination, related AEs were reported by a lower percentage of participants, 1.4% in the MenABCWY group and none in the Tumenba+Menveo group. Again the related AEs were generally considered reactogenicity events. This is in line with the general reactogenicity profile of the booster dose.

Overall, no new safety signals were observed with the pentavalent vaccine in comparison with the 2 separate vaccines.

Serious Adverse Events and Death

The proportion of participants with SAEs in the 3 studies was below 2%. In the studies investigating the 0-, and 6-month schedule (including booster vaccination), the percentage of participants

experiencing an SAE was comparable between the MenABCWY and Trumenba+Menveo groups. The majority of SAEs were single cases. The most frequently reported SAEs were in the SOC psychiatric disorders, which is not unexpected given the age of the population investigated. Upon request, the applicant provided the narratives of SAEs and it could be agreed that none of the SAEs was considered related to the investigational product.

Over the course of the 3 studies, 1 participant died in a motor vehicle accident which was not considered related to the study interventions.

AEs of special interest

No AESIs based on a predefined list of PTs were collected in the three clinical studies and analysis of AESIs/AEs of clinical interest were conducted post-hoc. This is not in accordance with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev.1).

Overall, the percentage of participants for whom a NDCMC is reported was low, <1.5%, across all groups in all studies. The majority of NDCMCs were single cases. The most frequently reported NDCMCs were in the SOC of psychiatric disorders, with ADHD being the most frequently reported PT (n=12) followed by depression (n=4). This is not unexpected for the population treated. Although the information provided by the applicant is limited, it can be agreed that none of the cases of NDCMC can be clearly linked to the investigational vaccines.

In total, 7 autoimmune conditions were confirmed during the 3 studies: 3 cases of autoimmune thyroiditis, 2 cases of alopecia areata, and 1 case each of Crohn's disease and ulcerative colitis. It can be agreed that for all events it is not possible to make a clear causal link to the investigational vaccine. Neuroinflammatory conditions were reported for 3 participants during the 3 clinical studies: restless legs in 2 participants and epilepsy in 1 participant. One case of restless leg syndrome and the case of epilepsy were not considered related to the investigational vaccines, which can be agreed. One case of restless legs, the investigator deemed that there was a reasonable possibility that the restless leg syndrome was related to the study intervention or contemporaneous vaccines. Therefore, a single case of restless leg syndrome possibly related to the MenABCWY vaccine was observed in study C3511004. As this is a single case, there is insufficient information available to determine the clinical impact of this observation. Further follow-up post-licensure is warranted to gain more insight in the potential relation between MenABCWY vaccine and restless legs syndrome. The applicant has committed to follow-up restless legs in PSURs. In addition, the applicant will closely monitor Severe cutaneous adverse reactions (SCARs) and Autoimmune and neuroinflammatory conditions, utilizing the MedDRA High Level Group Term (HLGT) Autoimmune disorders, in PSURs. The applicant has confirmed that the PT "meningitis aseptic" and related terms will be followed up as safety topics in PSURs.

Safety in special populations

MenACWY experienced

Limited information on the safety profile in MenABCWY experienced and naïve participants is available from the studies investigating the 0, and 6-month schedule. However, no clear trend in occurrence of reactogenicity events or AEs was observed.

Sex, Age and Race

The safety profile in the subgroup of sex was similar to the safety profile in the entire population and no new safety signals are observed in both study C3511001 and C3511004. Reactogenicity appears to be slightly higher in females compared to males. Sex is known to affect the response to vaccination, with women often developing more AEs compared to men. No clear trend in overall adverse event pattern was distinguished between males in females.

In the 2 studies investigating the 0-, 6-month schedule, the safety profile in the subgroup of age ≥10 to <18 YoA was similar to the safety profile in the subgroup of ≥18 -<26 YoA. The safety profile was comparable to the safety profile in the entire population and no new safety signals are observed. No trends in reactogenicity or adverse events could be clearly distinguished.

No clear trends or clinically relevant differences were observed in the safety profile between the race subgroups.

Use in pregnancy

Pregnancy data is very limited, with only 36 pregnancies reported in the 3 studies submitted. No definitive conclusions can be drawn based on these numbers. However, the data do not give rise to concern.

Use in immunocompromised subjects

No data in immunocompromised subjects were specifically collected during the studies and being immunocompromised was an exclusion criterion.

Discontinuations due to AE

It is acknowledged that the number of discontinuations due to AEs is low and comparable between intervention groups of the different studies. In total 18 AEs led to withdrawal, of which only 2 were considered possibly related to the study vaccine. These 2 cases of maculo-papular rash, which were considered possibly related, occurred in the Trumenba+Menveo group.

Single dose pentavalent vaccine

The lack of a direct head-to-head comparison to Nimenrix limits the benefit/risk discussion on the value of a single dose of pentavalent vaccine in protection against MenA, C, W, and Y compared to Nimenrix. Based on the EPAR of Nimenrix, Nimenrix appears to be less reactogenic than Trumenba. The most frequently reported local AE for Nimenrix was pain, comparable to Trumenba, however it was reported by 40% of participants in the 11-17 and 25% in the ≥ 18 years age group compared to >93% in the pentavalent group during the 2 studies. The same holds true for systemic events, with the most frequently reported systemic events for Nimenrix being comparable to Trumenba: fatigue and headache. However, the percentages reporting fatigue and headache were lower in the Nimenrix group, being at most 21% of participants, compared to >58% in the pentavalent group during the 2 studies.

Assessment of paediatric data on clinical safety

Based on the PIP, study C3511002, evaluating MenABCWY in infants (2 mths & 6 mths of age), was terminated. This decision was made following a recommendation from the external data monitoring committee (EDMC) that no further vaccinations with bivalent rLP2086 (60µg or 120 µg) or 120 µg bivalent rLP2086-containing MenABCWY should be administered in the study and was related to cases of fever requiring invasive investigations in infants 2 months of age being reported. The applicant included a warning in section 4.2 of the SmPC for MenABCWY concerning the use of the MenABCWY in children 2 to 6 months of age as agreed within Trumenba SmPC under procedure EMEA/H/C/004051/II/0052.

2.5.10. Conclusions on the clinical safety

The pentavalent MenABCWY vaccine is a reactogenic vaccine, with the vast majority of participants reporting 1 or more AEs; however, these were mostly mild or moderate in intensity and of short duration. The most frequently reported AEs by PT were solicited AEs: injection-site pain, fatigue, and

headache. The proportions of participants reporting an AE, MAEs, NDCMCs, SAEs and deaths in the MenABCWY group and discontinuations due to AEs were low and comparable to the Trumenba+Menveo group (where included).

In conclusion, the pentavalent MenABCWY vaccine is well tolerated in participants ≥10 years.

In light of serious safety concerns related to cases of high fever needing invasive intervention in 2-months infants after vaccination with Trumenba, a warning has been added in section 4.2 of the SmPC for MenABCWY concerning the use of the MenABCWY in children 2 to 6 months of age.

2.6. Risk Management Plan

2.6.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 41. Effects Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use during pregnancy

2.6.2. Pharmacovigilance plan

Protocol no/ *Status.*	**Study Title**	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	**Dates**
C3511007 *Planned*	A pregnancy registry study to evaluate the safety of PENBRAYA meningococcal vaccine exposure during pregnancy.	To estimate the proportion of MCM, SAB, elective termination, stillbirth, preterm birth, and SGA among individuals exposed to PENBRAYA during pregnancy or within 30 days prior to LMP.	This registry-based, prospective, observational cohort study will enrol and follow pregnant individuals 10 through 25 years of age in the US who are exposed to Penbraya during pregnancy. Participation in the registry is voluntary and participants can withdraw their consent to participate any time.	Pregnant individuals 10 through 25 years of age in the US who are exposed to PENBRAYA during pregnancy.	Final study report	30 April 2033

2.6.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use during pregnancy	Routine risk minimisation measures: • SmPC section 4.6 – Fertility, pregnancy and lactation. • PL section 2 – Pregnancy and breast-feeding. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaires for safety concern (Pregnancy Follow-UP Questionnaire). • If Penbraya is used as part of a national immunisation programme or in a large outbreak situation, the MAH will review and summarize, in the PSUR, national surveillance data for IMD (serogroups A, B, C, W, Y), as available. Additional pharmacovigilance activities: • C3511007: A pregnancy registry study to evaluate the safety of PENBRAYA meningococcal vaccine exposure during pregnancy. • Final study report due date: 30 April 2033.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

In addition, the following minor revisions are recommended to be taken into account with the next RMP update:

- the monitoring of national surveillance data for IMD (serogroups A, B, C, W, Y) should be removed from the Summary table of pharmacovigilance activities and risk minimisation activities provided in section V.3, as it does not address the missing information 'Use during pregnancy'.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 20.10.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. 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.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Meningococcal groups A, C, W, Y conjugate and group B vaccine (recombinant, adsorbed) is included in the additional monitoring list as it is a biological product.

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

N. meningitidis is a human pathogen that colonizes the upper respiratory tract, which, in some individuals, can cause serious, life-threatening invasive meningococcal disease (IMD), which clinically presents as septicaemia, meningitis, or both. *N. meningitidis* groups A, B, C, W, and Y are the 5 most common of the 6 meningococcal serogroups that cause the vast majority of meningococcal disease globally. Incidence of meningococcal disease in Europe is highest in infants and children younger than 5 years of age and adolescents and young adults.

Following the introduction of childhood vaccination programmes in infants and adolescents, the number of cases of IMD in adults aged >65 years appears to have increased suggesting an epidemiological shift to older age groups. Further surveillance is required to assess the need for vaccination programmes in older age groups.

Temporal variations in IMD incidence occur naturally. The incidence of meningococcal disease in Europe varies greatly across age strata, with the highest rates typically reported in children aged 4 years and younger with a notable second peak among those aged 15 to 24 years of age.

The immunological correlate of protection (CoP) is established at hSBA titres ≥1:4.

3.1.2. Available therapies

Treatment

Treatment of IMD involves prompt recognition of disease and administration of antibiotics, usually beta-lactam antibiotics. However, despite prompt and adequate treatment, IMD still has a high rate of morbidity and mortality.

Prophylactic vaccines

For the primary prevention of invasive meningococcal vaccines currently monovalent vaccines are registered for the active immunisation against serogroups B and C. In addition, also three quadrivalent meningococcal vaccines against serogroups A, C, W and Y are available.

Penbraya is a combination of two approved vaccines Trumenba (MenB) and Nimenrix (MenACWY), which are currently both authorised in the EU.

3.1.3. Main clinical studies

The main evidence of immunogenicity submitted is the pivotal phase 3 randomised, active-controlled, observer-blinded multicentre study (C3511001) comparing the MenABCWY vaccine (two doses, administered six months apart) with concomitantly administered authorised vaccines Trumenba (two doses, administered six months apart) and Menveo (single dose). The study was conducted in the EU and US. The trial was designed to demonstrate non-inferiority for the difference in seroresponders (LL 95%CI > -10%) between the study arms.

The study enrolled in healthy participants ≥10 to <26 years of age who were randomised 2:1 (based on MenACWY vaccination history) to receive candidate MenABCWY vaccine at Month 0 and 6 and placebo at Month 0 or to receive Trumenba at Month 0 and 6 and Menveo at Month 0, intramuscularly.

3.2. Favourable effects

- **Percentage of seroresponders**:
    - Both in ACWY-naïve and ACWY-experienced the estimated percentage of seroresponders (defined as those with at least a 4-fold rise in hSBA titre from baseline) for all four serogroups after two doses of MenABCWY vaccine was >93%. This was non-inferior (using a non-inferiority margin of 10%) 1 month after the second vaccination compared with one month after a single dose of Menveo administered concomitantly with Trumenba. In addition, also a single dose of MenABCWY (estimated seroresponse in ACWY-naïve >62% and ACWY-experienced >93% for all serogroups) was non-inferior to a single dose of Menveo, one month after administration.
    - Also for the four primary MenB strains the percentage of seroresponders showed non-inferiority one month after two doses of MenABCWY vaccine (estimated proportion of seroresponders >68% for all four primary strains) compared with Trumenba, with the first dose administered concomitantly with Menveo (estimated proportion of seroresponders >57% for all four primary strains). In addition, the percentage of participants achieving a hSBA titre ≥ LLOQ for all four primary MenB combined (composite response) at one month after the second vaccination showed noninferiority for MenABCWY (78.3%) compared with Trumenba (68.7%). Findings were consistent across different analysis sets and in line with conclusions of supportive study B1971057.
- **Proportion of participants above LLOQ**
    - The accepted CoP is hSBA titre ≥1:4, seroprotection is defined here based on the LLOQ for the hSBA. Some individual participants in either group who did not achieve titres ≥ LLOQ may still have achieved titres above the accepted CoP, but this could not be reliably quantified based on the limits of the assay.
    - The estimated proportions of MenABCWY recipients achieving a seroprotective hSBA titre (hSBA titre ≥ LLOQ) at 1 month after Vaccination 2 compared to those of Trumenba + Menveo recipients were similar (PMB80 (A22) and PMB2001 (A56), estimated seroprotection >88%) or higher (PMB2948 (B24) (83.4% vs 74.0%) and PMB2707 (B44) (94.3% vs 87.4%)).
- **Immune persistence**
    - For serogroups A, C, W and Y at 48 months post-vaccination 2, both in the ACWY-naïve and ACWY-experienced groups estimated proportions of participants with titres ≥1:8 were comparable (overlapping 95%CI) between those who received two doses of MenABCWY vaccine or a single dose of Menveo, administered concomitantly with Trumenba.
    - The estimated proportion of recipients with protective MenB hSBA titres ≥ LLOQ were similar between the arm receiving two doses of MenABCWY and the arm receiving two doses of bivalent rLP2086, administered concomitantly with Menveo at the first dose, up to 48 months after vaccination 2.

- **Anamnestic response after four years**
    - In both the ACWY-naïve and ACWY-experienced groups 100% of participants achieved protective hSBA titres ≥1:8 for serogroups A, C, W, and Y at 1 month after the booster dose administered 48 months after vaccination 2 in the MenABCWY arms as well as the bivalent rLP2086 + Menveo arms.
    - At 1 month after the booster dose, the estimated proportions of MenABCWY recipients and bivalent rLP2086 + Menveo recipients achieving hSBA titres ≥LLOQ for the 4 primary MenB test strains were comparable between both vaccine groups (>93.8% for all four primary strains).

3.3. Uncertainties and limitations about favourable effects

- **Reduced response for MenACWY with increasing number of doses:** Among ACWY-experienced participants vaccinated with two doses of MenABCWY vaccine, the GMTs for A, C, W and Y were lower 1 month post vaccination 2 compared with 1 month post vaccination 1. Also after a booster dose administered four years later, lower GMTs were observed in the group who have previously received two doses of vaccine with A, C, W, Y components compared with those primed with a single dose of Menveo. The clinical relevance of these observations is unknown, as no impact on the percentage of participants achieving seroresponse was observed.
- **Immunological endpoints:** Clinical efficacy data are not available. The determination of favourable effects for pentavalent MenABCWY vaccine is based on functional antibody data from hSBA assays. An hSBA titre ≥ 1:4 is generally assumed to be protective against meningococcal disease and has been applied to all meningococcal groups as a correlate of protection.
- **Uncertainties regarding obtained estimates:** The applicant used Menveo and Trumenba as the active comparator, while the candidate vaccine contains Nimenrix and Trumenba. Although both Menveo and Nimenrix carry MenACWY antigens, the vaccines are not identical as they have different conjugates, which hampers interpretability of some findings with regard to serogroups A, C, W and Y. Lower responses for MenB strains were observed in the active comparator arm compared with the MenABCWY arm, with no clear rationale provided.

  Lack of separate arms assessing MenACWY and MenB respectively in the pivotal trial adds uncertainty to the interpretation of the immunological results since data relating to the potential for immune interference, or discussion of this aspect, was not included in the dossier.

  There are no data on immunogenicity in MenB-experienced individuals since only MenB-naïve were eligible for inclusion to the clinical studies.
- **Booster response:** There are only limited, supportive data regarding booster vaccination. The timing interval from primary vaccination to booster vaccination is 48 months in Study B1971057, however, no justification has been provided. The SmPC states no data available indicate the need and timing of a booster dose.

  The booster response was lower in experienced participants receiving the pentavalent vaccine compared to experienced participants receiving Bivalent rLP2086 + MenACWY-CRM. The clinical relevance of this finding is unknown.

3.4. Unfavourable effects

The clinical safety profile was mainly derived from data derived from the pivotal study C3511001, which represents a major part of the overall exposure to the pentavalent MenABCWY vaccine (1763 of in total 2306 participants).

- **Reactogenicity:** In study C3511001, the vast majority of participants experienced at least 1 solicited AE. Injection-site pain was the most frequently reported solicited AE (reported by 94% of participants in the MenABCWY group vs 90% in the Trumenba + Menveo group), followed by fatigue (64% of participants in both groups), and headache (58% of participants in both groups). Most of the reported solicited AEs were mild to moderate in intensity and resolved within 3 days. The reactogenicity profile is comparable between studies.
- **Unsolicited AEs.** At least one unsolicited AE was reported in 21% and 20% of subjects in the MenABCWY group and Trumenba+Menveo, respectively. Related unsolicited adverse events were experienced by a low percentage of participants in study C3511001, 0.6% for both the MenABCWY and Trumenba+Menveo group. Most related AEs were reactogenicity events in the SOC of general disorders and administration site conditions.
- **SAEs.** The proportion of participants with SAEs in the 3 studies was below 2% in all studies In the studies investigating the 0-, and 6-month schedule (including booster vaccination), the percentage of participants experiencing an SAE was comparable between the MenABCWY and Trumenba+Menveo groups. The most frequently reported SAEs were in the SOC psychiatric disorders, which is not unexpected given the age of the population investigated. None of the SAEs was considered by the investigator to be related to the study vaccines.

3.5. Uncertainties and limitations about unfavourable effects

- **Size of the safety database**: The size of the safety database, 2600, is below the size recommended in the guideline on clinical evaluation of vaccines (3,000), limiting the detection of more rare adverse events. Information on rare but serious AEs should be systematically collected post-licensure. The applicant is asked to commit to follow-up rare adverse events in future PSURs
- **Lack of direct comparison to Nimenrix:** The lack of a direct head-to-head comparison to Nimenrix limits the benefit/risk discussion on the value of a single dose of pentavalent vaccine in protection against MenA, C, W, and Y compared to Nimenrix.
- **Restless leg syndrome:** A single case of restless leg syndrome possibly related to the MenABCWY vaccine was observed in study C3511004. As this is a single case, there is insufficient information available to determine the clinical impact of this observation. Further follow-up post-licensure is warranted to gain more insight in the potential relation between MenABCWY vaccine and restless legs syndrome. The applicant has committed to follow-up restless legs in PSURS.
- **Lack of collection of predefined AESIs:** In the three clinical studies supporting this MAA no AESIs based on a predefined list of PTs were collected and analysis of AESIs/AEs of clinical interest were conducted posthoc based on -in part- unclear definitions.

3.6. Effects Table

Table 42. Effects Table for Penbraya for active immunisation of individuals 10 years of age and older to prevent invasive disease caused by Neisseria meningitidis groups A, B, C, W, and Y

Effect	Short Description	Unit	MenABCWY	Trumenba + Menveo	Uncertainties/ Strength of evidence	References
	Favourable Effects					
Percentage of seroresponders (≥ 4-fold increase from baseline)	Non-inferior (NI margin 10%) proportion of participants with sero-responses for A, C, W and Y one month after two doses of MenABCWY compared with one month after a single dose of Menveo	n sero-responders/ N participants	**ACWY-naive**		*SOE*: Conclusions consistent in other analysis populations as well as with supportive study B1971057.	Study C3511001
			A 437/447 C 421/451 W 427/439 Y 421/446	242/254 132/252 178/244 175/248		
			ACWY-experienced			
			A 361/385 C 362/386 W 365/376 Y 360/387	220/227 214/226 214/222 209/223		
		Difference (%) between groups (95%CI)	**ACWY-naïve** A 2.5 (-0.2, 6.0) C 41.0 (34.4, 47.5) W 24.3 (18.8, 30.4) Y 23.8 (18.0, 30.1)			
			ACWY-experienced A -3.2 (-6.5, 0.5) C -0.9 (-4.6, 3.3) W 0.7 (-2.2, 4.3) Y -0.7 (-4.6, 3.8)			
	Non-inferior (NI margin 10%) proportion of participants with sero- responses for 4 primary MenB strains one month after two doses of MenABCWY compared with two doses of Trumenba	n sero-responders/N participants	A22 646/778 A56 774/807 B24 567/833 B44 731/845	313/396 378/400 239/418 322/419		
		Difference (%) between groups (95%CI)	A22 4.0 (-0.7, 8.9) A56 1.4 (-1.0, 4.3) B24 10.9 (5.2, 16.6) B44 7.3 (2.9, 11.9)			
Composite hSBA response (>LLOQ for all four primary MenB strains)	Non-inferior (NI margin 10%) proportion of participants with sero-responses for 4 primary MenB strains one month after two doses of MenABCWY compared with two doses of Trumenba	n sero-responders/N participants	591/755	263/383		
		Difference (%) between groups (95%CI)	9.6 (4.2, 15.2)			
	Unfavourable Effects					
Local solicited AE	Injection-site pain	% of individuals	94	90	*SOE*: reactogenicity profile comparable across studies and to known profile of Trumenba	
Systemic solicited AE	Fatigue	% of individuals	64	64		
	Headache	% of individuals	58	58		

Abbreviations: SOE: strength of evidence

Notes: Seroresponse is defined as: a) for participants with a baseline hSBA titre below the LOD (or an hSBA titre of <1:4), a 4-fold response is defined as an hSBA titre of ≥1:16. b) For participants with a baseline hSBA titre of ≥ LOD (i.e., hSBA titre of ≥1:4) and < LLOQ (i.e., hSBA titre of 1:8), a 4-fold response is defined as an hSBA titre of ≥4 times LLOQ. c) For participants with a baseline hSBA titre of ≥ LLOQ, a 4-fold response is defined as an hSBA titre of ≥4 times the baseline titre

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

N meningitidis is a human pathogen that colonizes the upper respiratory tract, which, in some individuals, can cause serious, life-threatening invasive meningococcal disease (IMD). IMD clinically presents as septicaemia, meningitis, or both. *N meningitidis* groups A, B, C, W, and Y are the 5 most common of the 6 meningococcal serogroups that cause the vast majority of meningococcal disease globally. Incidence of meningococcal disease is highest in infants and children younger than 5 years of age, adolescents and young adults, and older adults (≥65 years). Several prophylactic vaccines are currently available: monovalent meningococcal B and C vaccines, as well as quadrivalent A, C, W and Y vaccines. Currently a pentavalent vaccine including serogroups A, B, C, W and Y is not approved. The MenABCWY vaccine in this application is a combination of two approved vaccines Trumenba (MenB) and Nimenrix (MenACWY).

The indication is active immunisation against all five meningococcal groups. The proposed posology includes two doses administered 6 to 12 months apart. The current posology of the Nimenrix component is a single dose, (MenACWY), while for the Trumenba component (MenB)- two doses should be administered 6 months apart. Therefore, also for the pentavalent vaccine, the 2 dose posology is acceptable.

The established correlate of protection for meningococcal disease is an hSBA titre ≥1:4. The primary immunogenicity endpoints in the studies submitted focussed the proportion of subjects with at least a four-fold increase in titres compared with baseline (seroresponse). Given the definition of seroresponse and the LLoQ of the assays used in the submitted studies, all participants who are scored as seroresponders can be considered protected. Therefore, the primary endpoint is considered clinically relevant.

Two doses of MenABCWY vaccine generated a proportion of seroresponders non-inferior to two doses of Trumenba for four primary MenB strains, as well as for a composite response (all 4 strains > LLOQ). It is noteworthy that the estimated response in the comparator arm was lower compared to the MenABCWY arm (estimated difference >7%) for 2 out of 4 MenB test strains, as well as for the composite response (>9% estimated difference). This is unexpected, especially since this was not observed in study B1971057, where the estimated proportion of participants achieving hSBA titres ≥LLOQ were similar for all serogroups with overlapping 95% CIs.

The estimated percentage of seroresponders for MenA, C, W and Y after two doses of MenABCWY vaccine was >93%. This response was non-inferior (using a non-inferiority margin of 10%) compared to the response seen after a single dose of Menveo administered concomitantly with Trumenba. In addition also a single dose of MenABCWY vaccine showed non-inferior immune responses compared with a single dose of Menveo. The clinical benefit of a second dose of MenABCWY vaccine for A, C, W and Y components is limited to MenC in ACWY-naïve participants. However the second dose of MenABCWY does not seem to negatively impact the seroprotection rates for other serogroups and/or in the ACWY-experienced population.

The NI margin used by the applicant was not sufficiently justified, and its clinical relevance not explained. In the context of a severe and potentially deadly disease as invasive meningococcal disease, a more stringent margin would have been more appropriate.

Data regarding booster vaccination is limited and only considered supportive. The time interval (48 months) prior to boosting used in the clinical study lacks justification and there is no specified time interval for a booster dose in the SmPC. In addition, the benefit of a booster dose for individuals who

have previously received primary vaccination against MenACWY is questioned as long-lasting immune responses are shown for MenACWY vaccines.

The documented safety exposure is sufficient for an adequate assessment of the safety profile of pentavalent vaccine, also in light of the well-established safety profile of the currently licensed Trumenba and Nimenrix which constitute the pentavalent vaccine. The safety profile of the pentavalent vaccine was comparable to the safety profile of currently licensed Trumenba. The pentavalent vaccine is a reactogenic vaccine with ~94% of participants in clinical studies reporting local and ~81% reporting systemic reactogenicity after primary vaccination. The most frequently reported AEs were injection-site pain, followed by fatigue, and headache. Reactogenicity reactions were mostly mild to moderate, transient and self-limited. SAEs were infrequent in both the MenABCWY arm and Trumenba + Menveo arm. However, a single case of restless leg syndrome in the Trumenba + Menveo arm was observed which was possibly related to the vaccines administered was observed. As this is a single case, there is insufficient information available to determine the clinical impact of this observation. Further follow-up post-licensure is warranted to gain more insight. No Adverse events of special interest based on a predefined list of PTs were collected in the three clinical studies. In addition to the PSUR safety topics Severe cutaneous adverse reactions (SCARs) and Autoimmune and neuroinflammatory conditions (HLGT Autoimmune disorder), Aseptic meningitis and related terms should be closely monitored in the PSUR follow up.

Based on the PIP, Study C3511002, evaluating MenABCWY in infants (2 months & 6 months of age), was terminated due to cases of fever requiring invasive investigations in infants 2 months. As a result, the applicant included a warning in section 4.2 of the SmPC for MenABCWY concerning the use of MenABCWY in children 2 to 6 months of age, as agreed within Trumenba SmPC under procedure EMEA/H/C/004051/II/0052.

3.7.2. Balance of benefits and risks

No pentavalent vaccine against invasive meningococcal disease is currently approved. Vaccination using a pentavalent vaccine could provide broad immunogenicity against all 5 antigens (A, B, C, W-135 and Y) and potentially simplify vaccination programmes in those 10 years and older.

The primary immunogenicity endpoints are met. The potential benefit for a second dose of A, C, W and Y components as used in the proposed posology seems limited to ACWY-naïve participants for serogroup C only. For the other serogroups and among ACWY-experienced participants the seroprotection rates seem not negatively influenced by an additional dose of A, C, W, and Y.

The safety profile observed is acceptable.

3.8. Conclusions

The overall benefit/risk balance of Penbraya is positive, subject to the conditions stated in section 'Recommendations'.

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 Penbraya is favourable in the following indication(s):

Penbraya is indicated for active immunisation of individuals 10 years of age and older to

prevent invasive disease caused by Neisseria meningitidis groups A, B, C, W, and Y.

The use of this vaccine should be in accordance with 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0055/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.