19 September 2024
EMA/472934/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Menveo

Common name: Meningococcal group A, C, W135 and Y conjugate vaccine

Active substance:
Meningococcal group A oligosaccharide conjugated to *Corynebacterium diphtheriae* CRM197 protein,
Meningococcal group C oligosaccharide conjugated to *Corynebacterium diphtheriae* CRM197 protein,
Meningococcal group W-135 oligosaccharide conjugated to *Corynebacterium diphtheriae* CRM197 protein,
Meningococcal group Y oligosaccharide conjugated to *Corynebacterium diphtheriae* CRM197 protein

Procedure No. EMEA/H/C/001095/X/0119

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Ab	Antibody
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AS	Active Substance
CBG-MEB	College ter Beoordeling van Geneesmiddelen- Medicines Evaluation Board
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CPS	Capsular Polysaccharide
CRM197	Cross Reacting Material 197
ECDC	European Center of disease control
eCRF	Electronic Case Report Form
EEA	European Economic Area
EMA	European Medicines agency
EoS	End of Study
ETFE	Ethylene Tetrafluoroethylene
EU	European Union
FAS	Full Analysis Set
FP	Finished Product
FS	Free Saccharides
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufactering Practice
GMR	Geometric Mean ratio
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline Vaccines S.r.l.
hSBA	human Serum Bactericidal Assay
IAF	Informed Assent Form
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IMD	Invasive meningococcal disease
IRB	Institutional Review Board
IV	Intravenous
LL	Lower limit
LLOQ	Lower Limit Of Quantitation
LOD	Limit Of Detection
LoQ	List of Questions
LSAF	Life Science Analytic Framework
LSLV	Last Subject Last Visit

mAb	Monoclonal Antibody
MenA	Meningitis A
MenACWY vaccine	Meningococcal serogroups A, C, W, and Y vaccine
MenC	Meningitis c
MenW	Meningitis W
MenY	Meningitis Y
Menveo_Liq24	Menveo liquid naturally aged to 24 months
Menveo_Liq30	Menveo liquid naturally aged to 30 months
MO	Major Objection
N. meningitidis	*Neisseria meningitidis*
NI	Non-inferiority
O-AC	O-acetyl group
OC	Other Concern
PCD	Primary Completion Date
PCS	Product Control Strategy
PIP	Paediatric Investigational Plan
PO	Per os, i.e. orally
PPQ	Process Performance Qualification
PPS	Per-Protocol Set
PT	Preferred Term
QbD	Quality by Design
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	Randomization System on Internet
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
TSE	Transmissible Spongiform Encephalopathies
US	United States
WFI	Water for Injection
YoA	Years of Age

1. Background information on the procedure

1.1. Submission of the dossier

GSK Vaccines S.r.l submitted on 25 May 2023 an extension of the marketing authorisation to introduce a new pharmaceutical form (solution for injection). The RMP (version 11.1) is updated in accordance.

The MAH applied for an addition of a new pharmaceutical form.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (d) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0116/2023 on the granting of a product-specific waiver.

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 MAH 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 MAH received Scientific advice from the CHMP on 21 April 2017 (EMEA/H/SA/809/2/2017/III). The Scientific advice pertained to quality, clinical aspects.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Patrick Vrijlandt

The application was received by the EMA on	25 May 2023
The procedure started on	15 June 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 September 2023

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	4 September 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	12 October 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	21 May 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	26 June 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	25 July 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	14 August 2024
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	3 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 Menveo solution for injection on	19 September 2024

2. Scientific discussion

2.1. Problem statement

The claimed therapeutic indication for Menveo liquid is:

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

This is the same the indication currently issued for Menveo. The posology is likewise identical between Menveo liquid and Menveo.

Menveo was approved on 15 March 2010 based on an Article 8.3 (full) application. In the current procedure, GlaxoSmithKline Vaccines S.r.l. (GSK) seeks a line extension to register a new formulation of MenACWY vaccine (Menveo)- solution for injection which will be presented in a single vial, removing the need for reconstitution and simplifying vaccine administration, preventing administration errors. The investigational product is henceforth referred to as Menveo liquid.

2.1.1. Disease or condition

The gram-negative diplococci bacterium *Neisseria meningitidis* causes meningococcal disease, primarily meningitis and septicaemia. Multiple serogroups, including groups A, B, C, X, Y, Z, 29-E and W-135, are known to cause invasive meningococcal disease (IMD). Each serogroup is defined by chemically and immunologically distinctive polysaccharides.

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 populations (highest in adolescents and closed groups). However, only a small percentage of colonized persons develop invasive meningococcal disease (IMD), a serious bacterial infection caused by *Neisseria meningitidis* (ECDC). The bacteria can spread rapidly through contact with saliva or nasal secretions.

2.1.2. Epidemiology

The vast majority of cases of meningococcal disease worldwide are caused by 5 serogroups (A, B, C, Y and W-135). In Europe, serogroups B and C are the most common causes of IMD, however there has been an increase of IMD due to serogroup W. In the EU, an overall notification rate of 0.6 cases per 100 000 population was reported for IMD in 2018 from 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 by 30.4% from 2008 to 2018 (0.14/100 000 in 2008 to 0.10/100 000 in 2018) 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. The increase was driven by an hypervirulent serogroup W strain belonging to clonal complex 11(cc11) (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, with 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).

2.1.3. Clinical presentation, diagnosis 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. Symptoms can rapidly progress and within a few hours otherwise healthy individuals can be permanently disabled or die of the disease. Despite the availability of medical treatment and effective antibiotics, the mortality rate of IMD in 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

Prompt recognition of disease and administration of antibiotics, usually beta-lactam, are vital to improve the outcome in IMD. Upon a confirmed case of IMD, contact management and prophylactic antibiotic regimens and/or vaccination for close contacts is available, however implementation strategies may differ according to national/regional guidance.

There is evidence that fully liquid versions of vaccines are less prone to administration errors. Samad (2021) reported Menveo as one of the 14 2-component vaccines for which a high number of reconstitution errors were reported in the two passive surveillance systems, Institute for Safe Medication Practices (ISMP) National Vaccine Errors Reporting Program (VERP) (n=44), and US Food and Drug Administration (FDA) Vaccine Adverse Event Reporting System (VAERS) (n=477). After these reports were signalled, changes were made to the Menveo labelling after which the number of reconstitution errors declined. When a similar product needing reconstitution prior to administration, Menjugate (Meningococcal C vaccine), was changed to a fully liquid version, the reported product preparation errors and issues was reduced.

Prevention

There are numerous vaccines available for the prevention of IMD. Prevention of IMD relies mainly on vaccination. There are currently three quadrivalent vaccines available in the European union (Nimenrix [≥6 weeks of age], Menveo [≥2 years of age], MenQuadfi (≥12 months), which are indicated in children as young as ≥6 weeks. The majority, but not all of countries within the EU incorporate meningococcal vaccination for at least one serogroup in their program.

The Menveo liquid vaccine represents a fully liquid formulation of the currently licenced Menveo vaccine.

2.2. About the product

The investigational Menveo liquid vaccine represents a fully liquid formulation of the currently licenced Menveo vaccine.

The currently licenced Menveo (referred to throughout the document as Menveo) is a quadrivalent conjugate meningococcal vaccine, which contains oligosaccharides of serogroups A, C, W, and Y, conjugated to a non-toxic mutant of Corynebacterium diphtheriae toxin, termed "Cross Reacting Material 197" (CRM197). Immunisation with Menveo is intended to induce generation of bactericidal antibodies. These are antibodies capable of triggering complement- mediated cell lysis of N. meningitidis bacteria in vivo.

The final formulation consists of 10 µg/dose of oligosaccharide A and 5 µg/dose each of oligosaccharides C, W, and Y. The MenA-CRM component is lyophilised to stabilise it against hydrolytic cleavage of the saccharide moiety, whereas the hydrolytically more stable MenC-CRM, MenW-CRM, and MenY-CRM components are in solution. The vaccine is prepared for injection by reconstituting the lyophilised component with the solution prior to use.

In the current line-extension, the MAH seeks approval for Menveo liquid with the same indication and posology as Menveo. The antigen concentrations of the Menveo liquid formulation and Menveo remain the same.

2.3. Type of Application and aspects on development

Legal basis

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC, as amended - complete application. This is a line-extension.

Development programme

The clinical development program for Menveo liquid clinical development plan consisted of three clinical studies which would be performed in parallel for the clinical development of Menveo liquid: two Phase 2b studies (V59_71 and V59_78) using a vaccine with less favourable conditions (i.e., using a vaccine that was either at the end of its natural intended shelf-life [study V59_78] or artificially aged to contain approximately 30% FS for serogroup A [study V59_71]) and a Phase 3 non-inferiority study (V59_76) in adolescents and young adults using a single fresh lot of Menveo liquid.

The phase 3 trial was not conducted as the MAH did not consider it to provide additional significant value to the vaccine development. In principle this was agreed in scientific advice by the medicines evaluation board (MEB, WAG 23306 case 958685), as the data from studies V59_71 and V59_78 and the integrated safety analysis from these two studies could be sufficient.

Compliance with CHMP guidance

The most relevant CHMP guidelines applied:

- EMEA/CHMP/VWP/164653/05: Guideline on clinical evaluation of vaccines
- WHO guidance "Guidelines on clinical evaluation of vaccines: regulatory expectations"
- EMA/189724/2018: Extrapolation of efficacy and safety in paediatric medicine development - Scientific guideline
- CPMP/ICH/363/96: Note for Guidance on "Statistical Principles for Clinical Trials"
- CPMP/EWP/2158/99: Note for Guidance on "Choice of a Non-Inferiority Margin"
- EMA/CHMP/295050/2013: EMA Guideline on adjustment for baseline covariates in clinical trial

Scientific advice

During the course of development, the sponsor sought regulatory and scientific advice from EMA's Committee for Medicinal Products for Human Use (CHMP, [EMEA/H/SA/809/2/2017/III]) and from the CBG-MEB (WAG 23306 case 958685).

A few main points of the CHMP scientific advice relating to the clinical development were as follows:

- It was in agreed that considering the fact that mainly MenA was expected to be impacted by the differing formulation, this serogroup would be the main focus of the studies.
- It was advised that in accordance with EMEA/CHMP/VWP 164693/2005 and the 2016 WHO guideline on the clinical development of vaccines the primary endpoint should be based on the percentages that achieve hSBA titres at least 1:8 at day 29 and not on a comparison of GMTs as proposed by the Applicant. A non-inferiority margin that did not exceed 5% was recommended.

- It was stated that if the Applicant conducts the study in a population that is later shown to have baseline seropositivity rates more than 5-10% then the primary analysis must be conducted in those who are seronegative.

- It was advised that boosterability should be investigated as a theoretical concern remained the MenA FS could cause hyporesponsiveness to further doses of conjugate vaccines and potentially lower protection against natural infection.

A few main points of the MEB scientific advice relating to the clinical development were as follows:

- The MAH had modified the clinical development plan in which only two Phase 2b studies (V59_71 and V59_78) were submitted. The planned phase 3 study had not been conducted. The MAH requested advice on the appropriateness of this elimination. The MEB stated that "In principle, the data from studies 205343 (V59_71) and 207467 (V59_78) and the integrated safety analysis from these two studies appear sufficient as they would allow assessment of Menveo liquid. The studies include worst-case assessment of Menveo liquid, considering they investigated artificially aged Menveo liquid and Menveo liquid at end of shelf life. However, whether the data as generated by the studies are sufficiently compelling to support registration is a matter of assessment during submission."

- The MAH asked if the clinical evidence generated from these two phase 2 clinical studies together with the data already included in the marketing authorization of Menveo, supported the indication in children from 2 years of age. The MEB stated: "Whether the data are sufficiently compelling to support an indication from 2 years of age is a matter of assessment. Any differences between the Menveoliquid and Menveo observed, e.g. in impurities, will need to be adequately justified and the clinical impact of these differences discussed." And "The Applicant should thoroughly justify extrapolation of the results obtained in these studies to the 2-10 year-old population, taking into considerations the reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018). Therefore, the analysis based on serostatus at baseline will be critical importance to in support of an approval for a minimum age of 2 years of age. In addition, a separate analysis of results in subjects aged 10-18 years in study V59_78 is expected. Finally, the lack of data in children 2-10 years of age should be addressed in the risk management plan.

The MAH deviated from the CHMP guidance on a number of issues, the most important being the choice of primary endpoint and non-inferiority margin. This is discussed in further sections.

A product specific waiver has been agreed with the PDCO.

2.4. Quality aspects

2.4.1. Introduction

Meningococcal (Groups A, C, W, and Y) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (MenACWY) is a tetravalent conjugate meningococcal vaccine, which contains oligosaccharides of *Neisseria meningitidis* serogroups A, C, W and Y conjugated to a non-toxic mutant of Corynebacterium diphtheriae toxin, termed "Cross Reacting Material 197" (CRM197).

MenACWY lyophilised/liquid (hereafter referred to as "MenACWY") is the currently registered presentation, which has the MenA component in lyophilized form in one vial and the MenCWY components in liquid form in another vial. The currently registered vaccine is intended for injection by

reconstituting the lyophilized content (MenA Conjugate component and excipients) with the solution (MenCWY Conjugate component and excipients) immediately prior to use.

With this extension application, the MAH sought approval for the new, single-vial, fully liquid formulation (referred throughout the document as "MenACWY Liquid") to simplify vaccine administration and prevent reconstitution errors.

The finished product, MenACWY Liquid, is presented as a solution for injection in vial containing 10-5-5-5 µg per oligosaccharide of *N. meningitidis* serogroups A, C, W, and Y respectively conjugated to CRM197.

Other ingredients are: sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, sodium chloride and water for injections.

The product is available in one dose (0.5 mL) vials as described in section 6.5 of the SmPC.

2.4.2. Active substance

The Active Substances (ASs) used in the MenACWY Liquid presentation are the same as those currently approved for MenACWY registered presentation (Menveo, EMEA/H/C/001095). No change to the ASs manufacturing processes and testing panel was introduced for the manufacture of MenACWY Liquid.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and Pharmaceutical development

Description and composition of the finished product

MenACWY Liquid is a ready-to-use liquid preparation for intramuscular injection.

It is a quadrivalent conjugate meningococcal vaccine, which contains oligosaccharides of *N. meningitidis* serogroups A, C, W, and Y, conjugated to a non-toxic mutant of *Corynebacterium diphtheriae* (*C. diphtheriae*) toxin, termed "Cross Reacting Material 197" (CRM197).

The vaccine is presented as a monodose vial (3 mL glass, uncoloured glass, Type I) with bromobutyl rubber closure coated with ethylene tetrafluoroethylene, and aluminium and propylene flip-off cap.

There are no overages in terms of content to account for loss or degradation.

The composition of the MenACWY Liquid per dose (0.50 mL) is presented in the Table below.

Table 1 Composition of MenACWY Liquid (vials)

Ingredients	Quantity (per 0.5 mL dose)	Function	Reference/ Monograph standard
Active substances			
Meningococcal group A oligosaccharides conjugated to *C. diphtheriae* CRM_{197} protein [1]	10 µg MenA 16.7 to 33.3 µg CRM_{197}	Antigen + carrier protein	*In-house*
Meningococcal group C oligosaccharides conjugated to *C. diphtheriae* CRM_{197} protein [1]	5 µg MenC 7.1 to 12.5 µg CRM_{197}	Antigen + carrier protein	*In-house*
Meningococcal group W oligosaccharides conjugated to *C. diphtheriae* CRM_{197} protein [1]	5 µg MenW 3.3 to 8.3 µg CRM_{197}	Antigen + carrier protein	*In-house*
Meningococcal group Y oligosaccharides conjugated to *C. diphtheriae* CRM_{197} protein [1]	5 µg MenY 5.6 to 10.0 µg CRM_{197}	Antigen + carrier protein	*In-house*

The active substances and their quantities per dose are identical to the ones contained in the EU registered MenACWY lyophilised/liquid presentation.

The excipients are well-known and of compendial quality. The MenACWY Liquid presentation does not contain sucrose and potassium dihydrogen phosphate, whilst the lyophilised/liquid presentation does. In addition, adjustments were made to the buffer solution to maintain the same final buffer concentration of 10 mM.

The manufacturing process of MenACWY Liquid was based on the manufacturing process design of the MenCWY liquid. The main difference pertains to the formulation step in which MenA is added to the current MenCWY composition. As a result, the MAH adapted the MenCWY manufacturing process to include the MenA component by introducing, in parallel, some process improvements.

Pharmaceutical development

MenACWY Liquid is considered a life-cycle change of the current MenACWY registered product.

Due to the similarity between the two presentations, in which only MenA pharmaceutical form is different, the pharmaceutical development of MenACWY Liquid was based on the considerable information and extensive knowledge gained from registered MenACWY, both in terms of product and process development. Adaptations were made to both the presentation, the excipients and the buffers.

As a result of the new MenACWY Liquid formulation, changes were made to the excipients in terms of removal of sucrose as a stabilizer and potassium dihydrogen phosphate as pH buffering agent used in the lyophilized formulation. Additionally, the concentration of the sodium phosphate buffer components has been slightly altered to target the finished product pH, while maintaining the same final buffer concentration (10 mM) as is being used in MenACWY. The compatibility between the active substances and the excipients is supported by the finished product batch analysis data at release and the satisfactory long-time stability data generated at the recommended storage temperature.

In addition, the manufacturing process, release and stability panels have been modified to account for the different product matrix (i.e. MenA-CRM, MenC-CRM, MenW-CRM, MenY-CRM Total and Free Saccharide) and introduce some product specific methods were developed.

The degradation of MenA-CRM is different from the other antigens MenC-CRM, MenW-CRM and MenY-CRM in aqueous solution. Hydrolytic cleavage of the phosphodiester linkage and the O-acetyl group (O-AC) occurs and is temperature dependent, i.e. more rapid at higher temperatures. This results in free saccharides (FS) and de-O-acetylation of the MenA component. It is known from publicly available scientific literature (Berry et al., Infection and immunity, July 2002, p. 3707–3713; Berti et al, Molecules 2018, 23, 1340) that the O-acetyl groups on the bacterial capsular polysaccharide (CPS) antigens of *N. meningitidis* serogroup A are essential for the immune response to MenA vaccines. The %MenA free saccharide and O-acetylation are critical quality attributes (CQA) evolving over time. Based on the collected stability data and the clinically validated results on the Phase 2b lots, the MAH has defined acceptance criteria for %MenA FS and %O-Acetylation at release and at end of shelf-life (EoSL) that ensures the efficacy of the MenACWY Liquid product throughout the proposed 24 months shelf-life.

Physico-chemical comparability of the MenCWY components in MenACWY Liquid and in MenACWY presentations was evaluated and supplemented for the MenA component by evidence generated by two MenACWY Liquid Phase 2b clinical studies (study 205343 [V59_71] and study 207467 [V59_78]). As per request (D120 MO), comparability data (release testing, characterisation study results and stability testing) were provided and comparability between the currently authorised Menveo lyo+solvent vaccine and the Menveo Liquid vaccine has been sufficiently demonstrated.

Based on the overall results, it can be concluded that the introduction of MenA in liquid solution does not have adverse effect on the other vaccine components' (MenC, MenW and MenY) quality profile and, for the relevant attributes, Menveo Liquid (Phase 2 and PPQ lots) is comparable to Menveo lyophilised-liquid. Therefore, the known quality profile of Menveo lyophilised-liquid is also applicable to Menveo Liquid for MenC, MenW and MenY antigens. Furthermore, Menveo Liquid Phase 2 lots are comparable to Process Performance Qualification lots and therefore Phase 2 material is expected to be representative of future commercial material.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured, QC tested and released by GSK Vaccines S.r.l. in Sovicille, Italy. The manufacturing process is straightforward and consists of the thawing and mixture of the four antigens with the excipients. It has generally been described in sufficient detail. Flow-charts with narratives have been provided together with an overview of the major changes in manufacturing process between Menveo lyo+solvent and MenACWY liquid.

Quality by Design (QbD) principles for MenACWY Liquid were applied to MenACWY Liquid finished product development to define the Product Control Strategy (PCS) including elements from MenACWY commercial vaccine supplemented with specific product and process knowledge collected on the full liquid formulation. However, no design spaces were claimed for the manufacturing process of the finished product.

Critical steps are controlled at the final bulk, final container and finished product stages. In-process controls have been adequately described. The main steps of the formulation of MenACWY liquid include preparation of the buffer, concentrated bulk and final bulk. For each of these 3 steps, targets and ranges for process parameters have been set. Further quality tests include tests for bioburden and sterility.

The maximum cumulative exposure time to room temperature was established for the formulation process.

A batch scale is proposed. Process Performance Qualification was successfully executed. All batches are within the acceptance criteria.

2.4.3.3. Product specification

Part of the specification is kept identical to the currently authorised specification for the lyo-solvent Menveo vaccine. These tests and their specifications are for final container release: identity of the MenA/C/W/Y components, the amount of MenA/C/W/Y-CRM total saccharide, the MenC/W/Y-CRM free saccharide, appearance, visible particles, osmolality, and sterility. Other tests required an adaptation for the liquid vaccine and these are (for final container release): MenA-CRM free saccharide, pH, endotoxins, and extractable volume.

In general, the acceptance criteria have been sufficiently justified. The MAH used an artificially aged batch to substantiate some acceptance criteria. This artificially aged batch was used in clinical phase 2b study V59-71. The end-of-shelf life specifications and release specifications are sufficiently supported by the outcome of the clinical phase 2b studies.

Analytical procedures

The analytical procedures have been described in sufficient detail. As per request, additional clarification was provided about some validation issues and these were satisfactorily resolved.

It is noted that the finished product is tested for endotoxin using animal derived material. The Applicant is working to replace this with animal free material for endotoxin control. Impurities are controlled at an earlier stage, which is the same for the MenACWY lyo+solvent vaccine already manufactured.

Batch analysis

Batch results are provided for PPQ batches, naturally aged clinical batch, artificially aged clinical batch, and commercial batch. Results met their pre-specified acceptance criteria.

Reference standards or materials

Sufficient details on MenA reference standards have been provided.

Characterisation of impurities

Impurities found in the active substances and in the process intermediates have been controlled at an earlier stage during manufacturing of the active substances. There are, therefore, no product-related impurities that are monitored at this stage of processing.

Process-related impurities associated with the formulation, fill and finish of the finished product are related to the aseptic nature of the processing and are monitored through endotoxin and sterility testing of the final bulk and filled finished product.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed for the current MenACWY lyophilised/liquid presentation considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report-Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk

was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary. With regards to the MenACWY Liquid presentation, in view of the changes proposed in this line extension it is considered that no additional risk assessment is needed.

Due to the implementation of ICH Q3D guideline on elemental impurities, compliance to ICH Q3D should be confirmed. Although vaccines are strictly taken, not within the scope of ICH Q3D, a risk assessment of the elemental impurity level in the finished product should be performed in order to keep the same level of safety assurance on elemental impurities, as requested according to Ph. Eur. general chapter 5.20. A summary of this risk assessment and a control strategy for elemental impurities in accordance with ICH Q3D should be provided (recommendation).

Container closure system

The finished product is presented in a 3 ml, type 1 colourless glass vial of compendial quality, closed with a bromobutyl rubber stopper coated with ethylene tetrafluoroethylene (ETFE), and finished with a coloured flip-off cap.

The requested information concerning the details of the sterilization process of the empty vials and the qualification/validation has been provided and generally in line with EMA guideline EMA/CHMP/CVMP/QWP/850374/2015.

Extractables & Leachables studies were performed on the stoppers that will be used for the MenACWY liquid vaccine.

2.4.3.4. Stability of the product

Stability studies were conducted at long term, accelerated and stress conditions.

As per Agency's request, the MAH has performed a photostability study in compliance with ICH Q1B to verify that no impact on the product key stability indicator attributes is observed due to the light exposure of the vials. The study results sufficiently support the Applicant's conclusion that MenACWY Liquid vaccine does not show to be light sensitive. However, the Company still recommends keeping the product protected from light as already reported in section 6.4 of SmPC: "vials are kept in the carton protected from light", which is considered acceptable.

The proposed finished product shelf-life is 2 years, stored in a refrigerator (2°C - 8°C). The product should not be frozen and the vials should be kept in the outer carton in order to protect from light. This is acceptable.

Upon request, the proposed additional guidance for vaccine users in case of limited temporary temperature excursion has been aligned with the EMA guideline and sufficiently supported by the available stability data (see section 6.4 of the SmPC).

2.4.3.5. Adventitious agents

All the materials involved in the manufacture of MenACWY Liquid are the same with respect to what is currently approved for MenACWY production. The MenACWY Liquid vaccine is initiated from bacterial seed stocks that are not subject to infection by mammalian cell viruses.

In the light of the current scientific knowledge and irrespective of the geographical origin, bovine milk is unlikely to present any risk of TSE contamination (EMA/410/01 rev.3, Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products).

Information about viral safety and other adventitious agents for the CRM197 and *Neisseria meningitidis* Seed Stocks is presented. As these seed stocks are the same for lyo-solvent and MenACWY Liquid, this information is acceptable.

2.4.4. Discussion on chemical, and pharmaceutical aspects

MenACWY liquid is an extension application of the currently authorised MENVEO vaccine. The Applicant proposes to add all antigens to the liquid presentation for MenACWY liquid, whereas for MENVEO, the MenA antigen is lyophilised and reconstituted immediately before use with the liquid containing the other antigens, i.e. MenC, MenW and MenY.

Analytical comparability between MenACWY liquid and currently EU registered Menveo has been sufficiently demonstrated for the MenC-CRM, MenW-CRM and Men Y-CRM antigens.

The MenA-CRM antigen in aqueous solution undergoes hydrolytic cleavage of the phosphodiester linkage and the O-acetyl group. This leads to increased free saccharides and de-O-acetylated MenA species in the finished product when compared to Menveo. It is known that that the O-acetyl groups on the bacterial capsular polysaccharide (CPS) antigens of *N. meningitidis* serogroup A are essential for the immune response to MenA vaccines. To resolve the major objection on comparability, raised at D120, the MAH has provided data on free saccharides for MenA-CRM and presented characterisation data to show that no migration of MenA O-Acetylation groups occurs during storage. Specification acceptance criteria to control these quality attributes can be considered sufficiently justified based on clinical study outcomes using aged vaccine lots.

In conclusion, the provided Quality documentation sufficiently assures that the MenACWY liquid formulation meets current quality standards.

The MAH has been requested to provide a summary of the risk assessment and a control strategy for elemental impurities in accordance with ICH Q3D (**recommendation**).

2.4.5. 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.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to provide a summary of the risk assessment and a control strategy for elemental impurities in accordance with ICH Q3D.

2.5. Non-clinical aspects

2.5.1. Discussion on non-clinical aspects

MenACWY vaccine is already used in existing marketed products and no significant increase in

environmental exposure is anticipated.

Therefore, MenACWY vaccine is not expected to pose a risk to the environment.

2.5.2. Conclusion on the non-clinical aspects

No non-clinical data have been submitted within this line extension.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The MAH stated that both clinical trials were approved by Ethics Committees, followed the International Council for Harmonisation-GCP guidelines, conformed to the Declaration of Helsinki and informed, written consent was obtained from all subjects or legal guardians as per GCP requirements. The principles of Good Clinical Practices were also followed for the archiving of essential documents. GCP inspections took place for both sV59_71 (28 March – 01 April 2022 and 29-31 March 2022) and V59_78 (16-20 May 2022)

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

- **Tabular overview of clinical studies**

Overview of clinical studies included in the Menveo liquid dossier is shown in Table 2.

Table 2 Overview of clinical studies included in the Menveo dossier

Study ID # study centres/ location	**Design**	**Posology and # of subjects by group**	**Study Population (Exposed)**	**Primary Objective(s)**
Pivotal study				

Study ID # study centres/ location	Design	Posology and # of subjects by group	Study Population (Exposed)	Primary Objective(s)
V59_71 30 centres in 5 countries: Australia, Belgium, Canada, Germany, Italy Completed	A phase 2b, randomised, controlled, observer-blind, multicentre, non-inferiority immunogenicity and safety study of two formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and Menveo) administered to healthy adults 18 to 40 years of age.	IM, single dose Randomisation ratio ACWY_liq : ACWY=1:1 ACWY_liq: Randomised: 493 Exposed: 490 ACWY: Randomised: 490 Exposed: 489	Adults 18 to 40 years of age. Gender: 365 M/ 614 F Median age: 31.8 years	To demonstrate non-inferiority of the investigational MenACWY liquid vaccine with approximately 30% Men A free saccharides (FS) to that of currently licensed Menveo, as measured by the hSBA GMTs directed against N. meningitidis serogroup A at Day 29 after a single dose vaccination. Criterion: LL of 2 sides 95% CI of the ratio of hSBA GMTs against serogroup A between the liquid formulation and the licensed formulation was greater than 0.5.
V59_78: 49 centres in 9 countries Brazil, Estonia, Finland, France, Mexico, Russia Federation, South Africa, Spain, Turkey Completed	A phase 2b, randomised, controlled, observer-blind, multi-centre study to evaluate safety and immunogenicity of different formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and Menveo) administered to healthy adolescents and young adults 10 to 40 years of age.	IM, single dose Randomisation ratio 1:1:1:1 Phase 1: ACWY_liq24 : ACWY1 = 1:1 Phase 2: ACWY_liq30 : ACWY2 = 1:1 ACWY_liq24 Randomised: 420 Exposed: 420 ACWY1 Randomised: 426 Exposed: 424 ACWY_liq30 Randomised: 430 Exposed: 427 ACWY_2 = 1:1 Randomised: 420 Exposed: 419	Children and Adults aged 10-40 years Phase 1: Gender: 370 M/ 474 F Median Age: 21.0 years Phase 2: Gender: 359 M/ 487 F Median Age: 20.0 years	To demonstrate non-inferiority of the investigational MenACWY liquid product aged for approximately 24 and 30 months to that of currently licensed MenACWY vaccine, as measured by the hSBA GMTs directed against *N. meningitidis* serogroup A at Day 29 after a single dose vaccination. Criterion: LL of 2 sides 95% CI of the ratio of hSBA GMTs against serogroup A between the liquid formulation and the licensed formulation was greater than 0.5.
ACWY_liq = MenACWY liquid vaccine with approximately 30% Men A free saccharides ACWY_liq24 = MenACWY liquid vaccine aged approximately 24 months ACWY_liq30 = MenACWY liquid vaccine aged approximately 30 months ACWY = Licensed Menveo hSBA = human serum bactericidal assay GMT = Geometric mean titer				

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

No pharmacokinetics studies have been conducted for the new liquid formulation of Menveo. Pharmacokinetics studies are generally not needed for vaccines, consistent with current the Guidelines on clinical evaluation of vaccines.

2.6.2.2. 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).

Mechanism of action

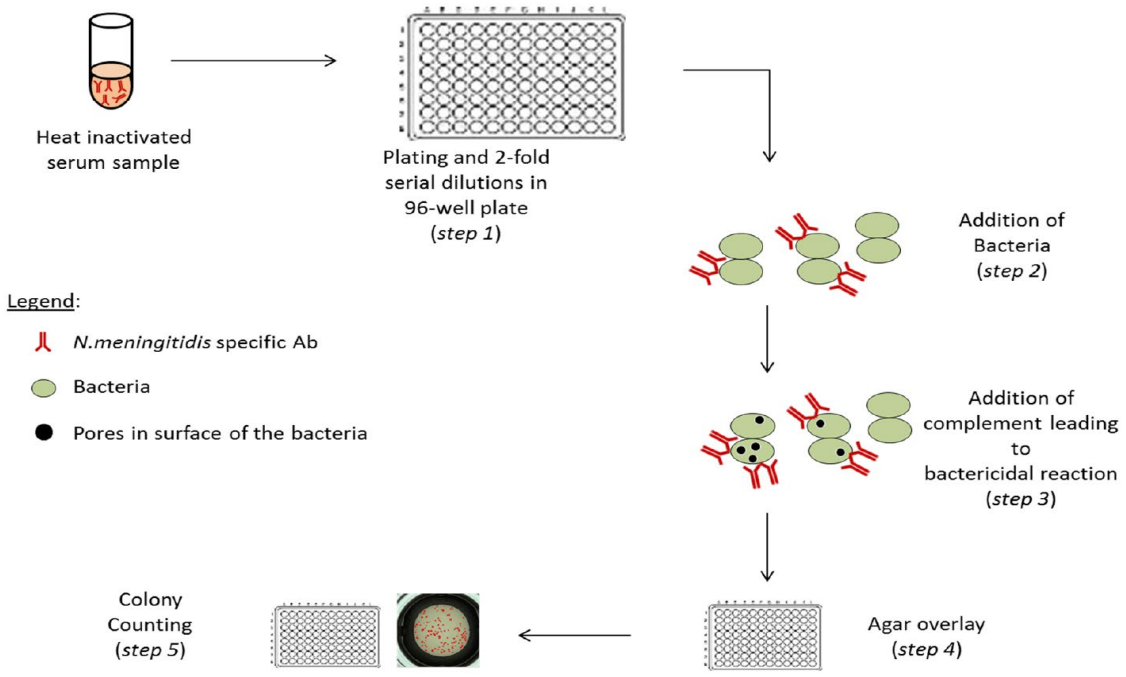
Vaccination with Menveo leads to the production of bactericidal antibodies directed against the capsular polysaccharides of the serogroups used in the vaccine.

In the MenveoLiq clinical program, hSBA titers were measured. The established correlate of protection is an hSBA titer ≥1:4.

Primary and Secondary pharmacology

The hSBA measures the bactericidal activity of human serum antibodies specific to N. meningitidis serogroup A, C, W or Y in the presence of human complement. The antibody titre following vaccination serves as a marker for the immunogenicity of the vaccine. The principle of the hSBA assay is presented in Figure 1.

Figure 1 General principle of the manual agar overlay hSBA method



Ab, antibody.

2.6.3. Discussion on clinical pharmacology

No human pharmacokinetic studies have been performed. This can be agreed as pharmacokinetic studies are not usually required for vaccines.

The MAH utilises 4 separate hSBA assays to determine the bactericidal activity of human serum antibodies specific to N. meningitidis serogroup A, C, W or Y in the presence of human complement. Qualification as well as validation reports were submitted.

The assay is considered fit for purpose.

2.6.4. Conclusions on clinical pharmacology

The assays used to determine immunogenicity results are considered fit for purpose.

2.6.5. Clinical efficacy

To support this line-extension, the MAH submitted immunogenicity data from two different phase 2b, randomised, controlled, observer-blind, multi-center, non-inferiority clinical trials (Table 1). During study V59_71 participants received either investigational Menveo liquid vaccine with approximately 30% Men A FS (referred to as artificially aged Menveo liquid) or Menveo and included adults aged 18-40 years. During study V59_78 participants received either the investigational Menveo liquid vaccine aged approximately 24 months (Phase 1) or 30 months (Phase 2) or Menveo.

2.6.5.1. Dose response studies

There were no dose-response studies performed. The dose used in this study was based on experience from previous preclinical and clinical studies that demonstrated acceptable toxicological, safety and immunogenicity profiles. The new formulation contains the same amount of MenA (10µg), MenC (5µg), MenW (5µg), and MenY (5µg) antigen as Menveo. The amount of CRM197 may differ by a small amount. The excipients also differ by amount and/or composition.

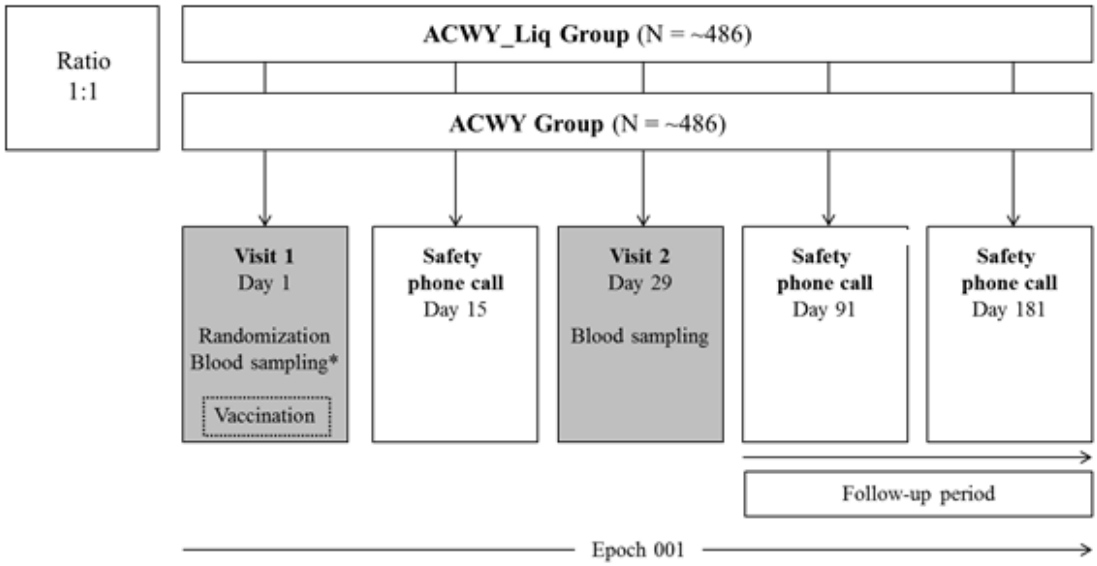
2.6.5.2. Main studies

Methods

Study V59_71

Study V59_71 is a phase 2b, randomised, controlled, observer-blind, multi-center, non-inferiority immunogenicity and safety study of two formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and Menveo) administered to healthy adults 18 to 40 years of age. Participants received either artificially aged Menveo liquid vaccine with approximately 30% Men A Free Saccharide (FS) or Menveo. The study design is presented in Figure 2Figure 1.

Figure 2 Overview of V59_71 study design

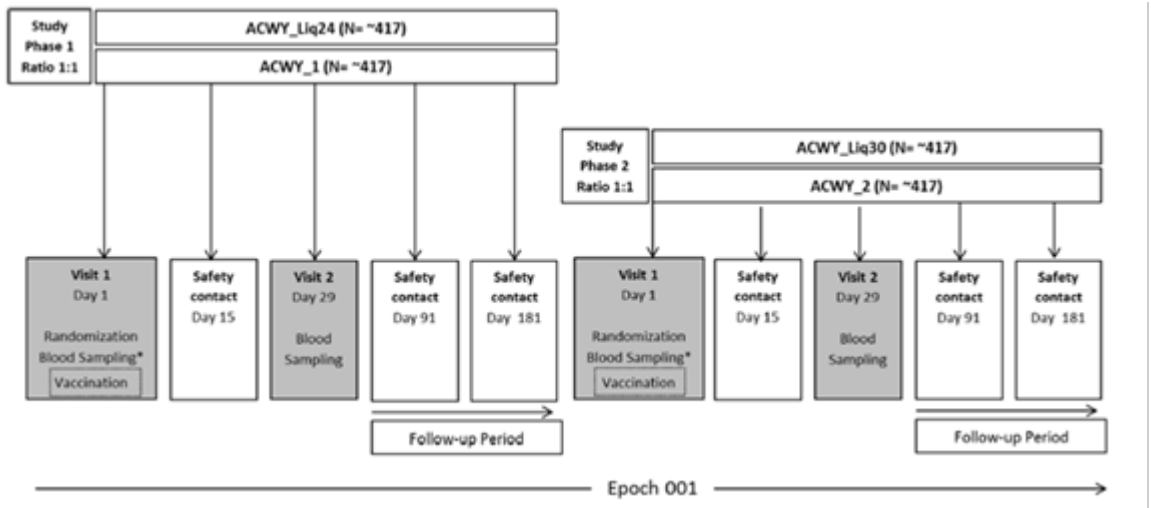


*At Visit 1, blood samples were taken pre-vaccination. ACWY_Liq = Subjects who received Menveo-Liquid; ACWY = Subjects who received Licensed Menveo

Study V59_78

Study V59_78 is a phase 2b, randomised, controlled, observer-blind, multi-center study to evaluate safety and immunogenicity of different formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and Menveo) administered to healthy adolescents and young adults 10 to 40 years of age. The study was divided into two "phases" into which participants were randomised on a 1:1 basis to either the investigational Menveo liquid vaccine aged approximately 24 or 30 months or Menveo. Study design is presented in Figure 3.

Figure 3: Overview of V59_71 study design



ACWY_Liq24/30 = Subjects who received Menveo-Liquid aged 24 or 30 months; ACWY_1/2 = Subjects who received Licensed Menveo Adjusted in either phase 1 or phase 2.

Study Participants

Both studies V59_71 and V59_78 enrolled healthy male or female (of nonchildbearing potential or who were using an effective birth control method) participants. Study V59_71 enrolled participants ≥18 to ≤40 years of age at the time of the vaccination. Study V59_78 enrolled participants aged ≥10 to ≤40 years of age at the time of vaccination.

The exclusion criteria between both studies differed in the acceptability of previous meningococcal vaccinations. In study V59_71 the exclusion criteria was worded as "history of any meningococcal vaccination." In study V59_78 the exclusion criteria were worded as "History of any meningococcal vaccination, with the exception of previous meningococcal C (conjugated or polysaccharide) vaccination, if the last dose of MenC was received at ≤24 months of age."

Treatments

In both studies participants received a single dose of 0.5 mL of the investigational liquid Menveo or the currently licensed Menveo.

In study V59_71 the investigational liquid Menveo was artificially aged, which included approximately 30% Men A FS.

In study V59_78 the investigational liquid Menveo was naturally aged for approximately 24 months in phase 1 and 30 months in phase 2.

Objectives

Study V59_71

Primary immunogenicity objective:

- To demonstrate non-inferiority of the investigational Menveo liquid vaccine with approximately 30% Men A FS to that of currently licensed Menveo vaccine, as measured by the human serum bactericidal assay **(hSBA) Geometric Mean Titers (GMTs) directed against *N. meningitidis* serogroup A** at Day 29 after a single dose vaccination.

Secondary immunogenicity objectives

- To compare the immunogenicity of the investigational Menveo liquid vaccine with approximately 30% Men A FS and the currently licensed Menveo vaccine, as measured by **hSBA GMTs directed against *N. meningitidis* serogroups C, W and Y** at Day 29.
- To compare the immunogenicity of the investigational Menveo liquid vaccine with approximately 30% Men A FS products to the currently licensed Menveo vaccine, as measured by the percentage of subjects with a **≥ 4-fold rise in post vaccination hSBA titer for *N. meningitidis* serogroups A, C, W and Y** at Day 29 compared to Day 1.
- To compare the immunogenicity of the investigational Menveo liquid vaccine with approximately 30% Men A FS to the currently licensed Menveo vaccine, as measured by the **percentage of subjects with hSBA titer ≥ 8 and ≥ LLOQ directed against *N. meningitidis* serogroups A, C, W and Y** at Day 29.
- To assess the **safety/reactogenicity** of the investigational Menveo liquid vaccine with approximately 30% Men A FS and the currently licensed Menveo vaccine.

Study V59_78

Primary immunogenicity objective:

- To demonstrate non-inferiority of the investigational Menveo liquid product aged for approximately 24 and 30 months to that of currently licensed Menveo vaccine, as measured by the **hSBA GMTs directed against *N. meningitidis* serogroup A** at Day 29 after a single dose vaccination.

Secondary immunogenicity objective:

- To compare the immunogenicity of the investigational Menveo Liquid products aged for approximately 24 or 30 months and the currently licensed Menveo vaccine, as measured by **hSBA GMTs directed against *N. meningitidis* serogroups C, W and Y**, at Day 29.
- To compare the immunogenicity of the investigational Menveo Liquid products aged for approximately 24 or 30 months and the currently licensed Menveo vaccine, as measured by **the percentage of subjects with a ≥ 4-fold rise in post vaccination hSBA titer for *N. meningitidis* serogroups A, C, W and Y** at Day 29 compared to Day 1.
- To compare the immunogenicity of the investigational Menveo Liquid products aged for approximately 24 or 30 months and the currently licensed Menveo vaccine, as measured by the **percentage of subjects with hSBA titer ≥ 8 and ≥ LLOQ directed against *N. meningitidis* serogroups A, C, W and Y** at Day 29.
- To assess the **safety/reactogenicity** of the investigational Menveo Liquid vaccine aged approximately 24 or 30 months and the currently licensed Menveo vaccine.

Outcomes/endpoints

The primary and secondary outcomes/endpoints for study V59_71 and Study V59_78 are similar.

Primary endpoints

- hSBA GMTs against *N. meningitidis* serogroup A at Day 29, for each vaccine group and between-group ratios (for study V59-71 between Menveo_Liq and Menveo and for study V59_78 between vaccine groups Menveo liquid aged to 24 months (Menveo_Liq24) and Menveo-1, and Menveo liquid aged to 30 months (Menveo_Liq30) and Menveo_2.

Secondary endpoints:

For study V59_71 comparison is between Menveo liquid and Menveo and for study V59_78 phase 1 comparison is between Menveo liquid aged to 24 months (Menveo_Liq24) and Menveo-1, and in phase 2 comparison is between Menveo liquid aged to 24 months (Menveo_Liq24) and Menveo2

- hSBA GMTs against *N. meningitidis* serogroup A (except Day 29), C, W, and Y at Day 1 and at Day 29, for each vaccine group and between-group ratios.
- Within-group ratios of hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1.
- Percentages of subjects with a ≥ 4-fold rise in post-vaccination hSBA titer for *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1, for each vaccine group and between-group differences.
  Note: A 4-fold rise is defined as: a) for individuals whose pre-vaccination titers are < the LOD, the post-vaccination titers must be ≥ 4-fold the LOD or ≥ the LLOQ whichever is greater; b) for individuals whose pre-vaccination titers are ≥ the LOD and ≤ the LLOQ, the post-vaccination

titers must be at least four times the LLOQ; c) for individuals whose pre-vaccination titers are > the LLOQ, the post-vaccination titers must be at least four times the pre-vaccination titer.

- Percentages of subjects with hSBA titer ≥8 and ≥LLOQ* against *N. meningitidis* serogroups A, C, W and Y at Day 1 and at Day 29, for each vaccine group and between-group differences. Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.

Non-inferiority was concluded by the MAH if the lower limit of the two-sided 95% confidence interval (CI) for the ratio of hSBA GMTs against serogroup A between the liquid formulation and the licensed formulation was greater than 0.5.

Sample size

Study V59_*71*

At least 972 subjects (486 subjects in each group) are needed to have a power of 90% to show non-inferiority for the ratio of the hSBA GMT of the Menveo liquid to the Menveo group for serogroup A with a NI margin of 0.5, an assumed ratio of 0.8 with a common standard deviation of 0.029 on logscale, a two-sided alpha level of 0.05, based on a t-test and with a 10% drop-out rate.

Study V59_78

At least 1668 subjects (417 subjects in each group Menveo_1, Menveo_2, Menveo_Liq24 and Menveo_Liq30) are needed to have an overall power of 81% to show for serogroup A, non-inferiority for the ratio of the hSBA GMT of Menveo_Liq24 group to the Menveo_1 group and for the ratio of hSBA-GMT of Menveo_Liq30 group to the Menveo_2 group with a NI margin of 0.5, an assumed ratio of 0.8 with a common standard deviation of 0.861 on logscale, a two-sided alpha level of 0.05, based on a t-test and with a 10% drop-out rate.

Randomisation and blinding (masking)

Both studies used for randomisation a Source DataBase for Internet Randomization system (SBIR) with randomisation ratio 1:1 and 1:1:1:1 for study V59-71 and V59-78, respectively and using a minimisation procedure accounting for centre. In study V59-78 the system's randomisation algorithm used a stratification by age stratum ((≥10 to <18 YoA versus ≥18 to ≤40 YoA) and within an age stratum the minimisation procedure. The minimisation procedure in studies V59-71 and V59-78 used a fixed percentage of randomness of 10%.

The studies were observer-blind. Treatment administration was performed by qualified study personnel (unblinded) who will not participate in the study.

Statistical methods

Analysis sets

Study V59_71 and Study V59_78

For both studies the primary immunogenicity analysis was based on the PPS population. All immunogenicity analyses were also performed on the FAS population.

All Enrolled Set: All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a subject ID.

All Exposed set: All enrolled subjects who received a study vaccination.

Full Analysis Set (FAS): All randomised subjects who received a study vaccination, and had an evaluable serum sample at Day 29. Subjects were analysed as randomised.

Per Protocol Set (PPS): All subjects in the FAS (Day 29) who received the randomised vaccine, have no protocol deviations leading to exclusion as defined prior to unblinding.

Primary immunogenicity endpoint and primary immunogenicity analysis

Study V59_71 and Study V59_78

The primary immunogenicity endpoint(s) is the between treatment group ratio of hSBA GMTs against *N. meningitidis* serogroup A at Day 29 for the vaccine groups Menveo_Liq versus Menveo in Study V59_71 and Menveo_Liq24 vs Menveo_1 in Phase 1 Study V59_78 and Menveo_Liq30 vs Menve_2 in Phase 2 Study V59_78.

For both studies, the primary immunogenicity analysis of the hSBA titers for serogroup A at Day 29 was based on an ANCOVA model performed in the log10-scale with vaccine group and country as fixed factors and the pre-vaccination titre at baseline as covariate. The between group ratio of GMTs was calculated, with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs.

Given the high likelihood of having centres with few subjects enrolled in the study, country will be used as a factor in the ANCOVA/ANOVA analyses instead of centre.

- A seronegative subject is a subject whose titer is below the LOD.
- Values below the limit of detection will be set to half that limit.

Missing data

Missing or non-evaluable measurements were not imputed.

Sensitivity/supportive analyses

For both studies:

- A permutation test was performed
- The primary immunogenicity analysis was performed for the FAS population

V59-78: The same analysis as for the primary immunogenicity analyses was performed, but also adjusted for age stratum.

Secondary immunogenicity analyses

The same analysis method (ANCOVA) as described for the primary immunogenicity endpoint was used for the secondary immunogenicity endpoints on GMTs.

The analysis of secondary immunogenicity endpoints related to percentage of subjects are performed on the PPS and FAS populations. Per group and serogroups A, C, W and Y the percentage and the corresponding two-sided 95% Clopper-Pearson CIs were computed. Differences in percentages and associated 95% CIs between study groups were calculated using the Miettinen and Nurminen score method.

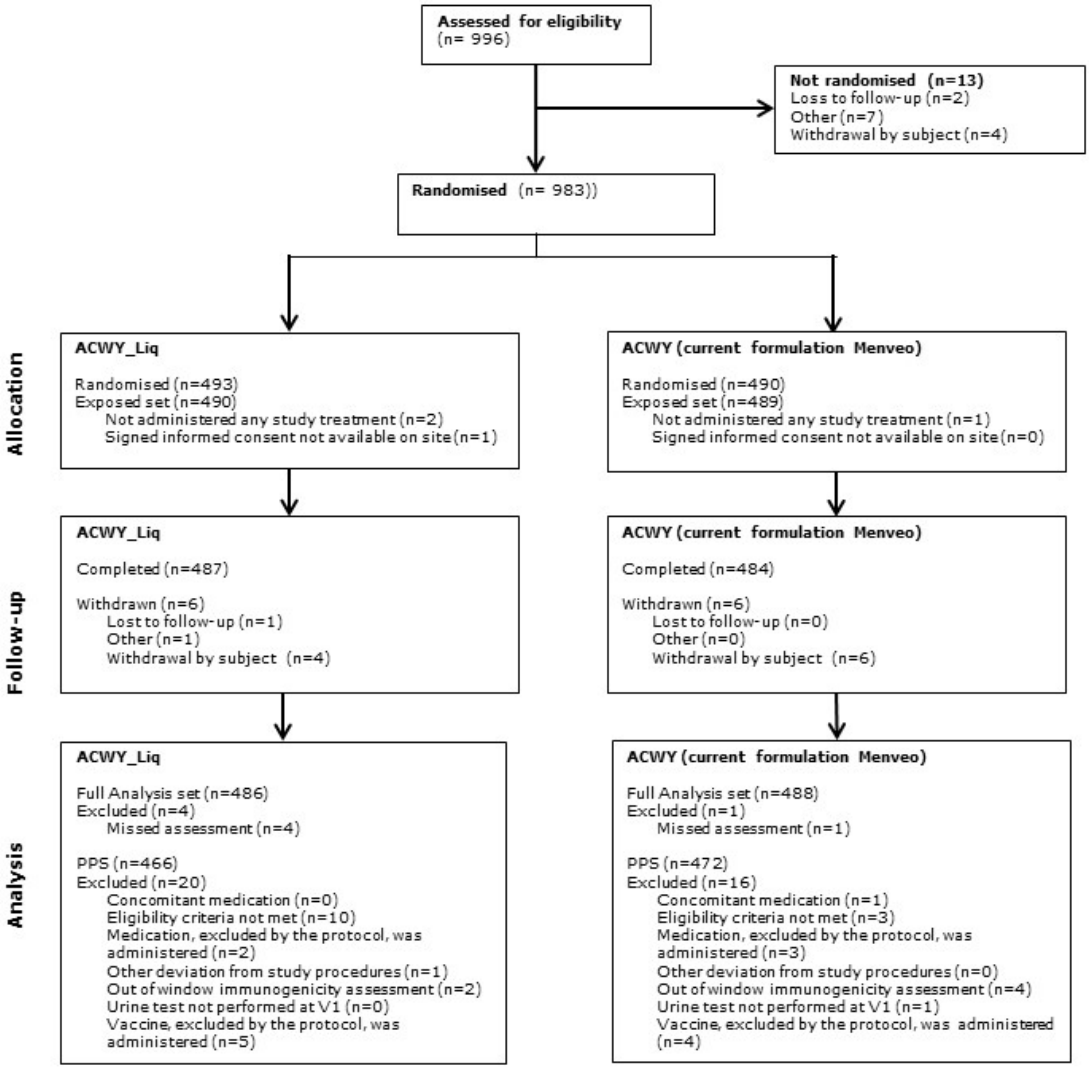
Results

Participant flow

Study V59_71

Subject disposition flowchart for study V59_71 is shown in **Error! Reference source not found.**. A total of 979 participants were exposed (Menveo liquid vs Menveo; 490 vs 489), of which 971 subjects (Menveo liquid vs Menveo; 487 vs 484) completed the study. A total of 25 subjects (6 in the Menveo liquid group and 6 in the Menveo group, 13 subjects were not randomised) were prematurely withdrawn from the study.

Figure 4 Study V59_71. Participant flow



ACWY_Liq = Subjects who received Menveo liquid

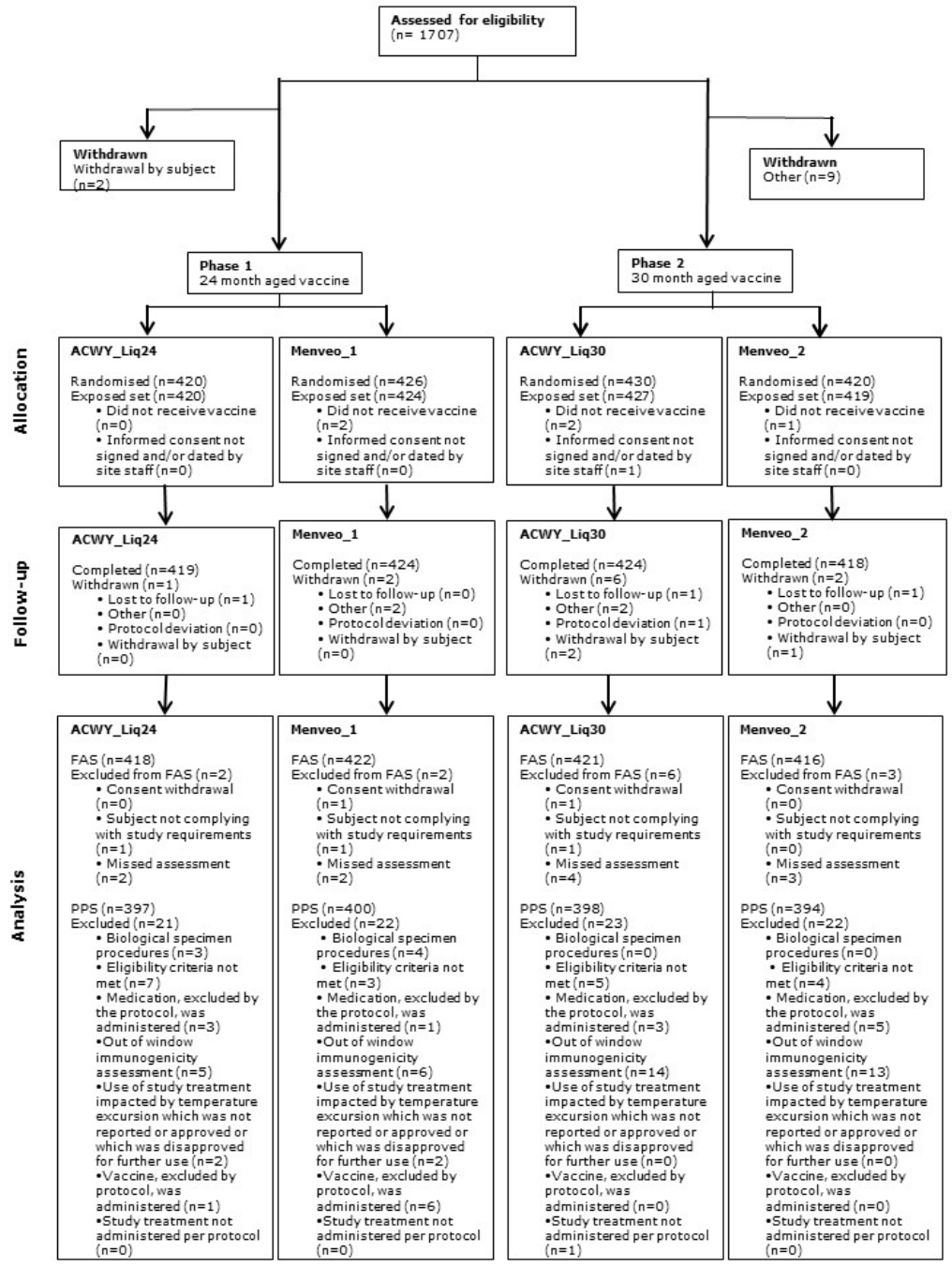
ACWY = Subjects who received Licensed MenACWY (i.e. Menveo)

Study V59_78

Subject disposition flowchart for study V59_78 is shown in below.

A total of 1707 subjects were enrolled (screened). In phase 1 of the study, a total of 844 participants were exposed (Menveo liquid vs Menveo; 420 vs 424), of which 843 subjects (Menveo liquid vs Menveo; 419 vs 424) completed the study. A total of 3 subjects (1 in the Menveo liquid group and 2 in the Menveo group) were prematurely withdrawn from the study. In phase 2 of the study, 846 participants were exposed (Menveo liquid vs Menveo; 427 vs 419), of which 842 subjects Menveo liquid vs Menveo; 424 vs 418) completed the study. A total of 8 subjects (6 in the Menveo liquid group and 2 in the Menveo group) were prematurely withdrawn from the study.

Figure 5 Study V59_78 subject disposition flow chart



ACWY-Liq24 = Subjects who received Menveo liquid vaccine aged 24 months; ACWY_1 = Subjects who received Licensed Menveo. ACWY-Liq30 = Subjects who received Menveo liquid vaccine aged 30 months, ACWY_2 = Subjects who received Licensed Menveo

Recruitment

Study V59_71 commenced on 7 September 2018 and was completed on 11 June 2019. Data lock point was 6 October 2020.

Study V59_78 commenced on 30 August 2018 and was completed on 17 December. Data lock point was 18 November 2020.

For both studies, for each subject enrolled, the duration of the study was to be approximately 6 months, starting at Visit 1 (Day 1) and ending at last safety contact (Day 181). The primary completion date (PCD) was visit 2 (Day 29).

Conduct of the study

Study V59_71

Protocol amendments

The initial protocol (dated 25 September 2017) was amended 3 times, all of which were implemented prior to database lock and were not expected to impact subject well-being, study conduct or outcome of the study. More information on the amendments is presented in the clinical assessment report.

Protocol deviations:

Protocol deviations are shown in Table 3. A total of 49 (5.0%) subjects had important protocol deviations: 29 (5.9%) in the Menveo liquid group and 20 (4.1%) in Menveo group. The most common reason for deviating from the protocol was "eligibility criteria not met" reported by a total of 26 (2.6%) subjects, followed by "assessment or timepoint completion" reported by a total of 19 (1.9%) of participants.

Table 3 V59_71. Summary of important protocol deviations leading to elimination from any analyses – All enrolled set

	Menveo_Liq N=493			Menveo N=490			Not Randomised N=13			Total N=996		
	occ	n	%	occ	n	%	occ	n	%	occ	n	%
At least one important protocol deviation	32	29	5.9	21	20	4.1	30	13	100.0	83	62	6.2
Assessment Or Time Point Completion	8	8	1.6	5	5	1.0	6	6	46.2	19	19	1.9
Eligibility Criteria Not Met	11	11	2.2	5	5	1.0	11	10	76.9	27	26	2.6
Excluded Medication, Vaccine Or Device	8	8	1.6	7	7	1.4	0	0	0.0	15	15	1.5
Failure To Report Safety Events Per Protocol	2	2	0.4	2	2	0.4	0	0	0.0	4	4	0.4
Informed Consent	1	1	0.2	0	0	0.0	0	0	0.0	1	1	0.1
Study Procedures	0	0	0.0	1	1	0.2	0	0	0.0	1	1	0.1
Wrong Study Treatment/Administration/Dose	2	2	0.4	1	1	0.2	13	13	100.0	16	16	1.6

n/% = number/percentage of subjects in a given category; Occ = number of occurrences = number of important protocol deviations; N = total number of subjects for each study group; As randomised, i.e. according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received; Menveo_Liq = Subjects who received Menveo-Liquid; Menveo = Subjects who received Licensed Menveo

Study V59_79

Protocol amendments

The initial protocol (dated 25 September 2017) was amended 3 times, all of which were implemented prior to database lock and were not expected to impact subject well-being, study conduct or outcome of the study. More information on the amendments is presented in the clinical assessment report.

Protocol deviations:

Phase 1

Protocol deviations are shown in Table 4. A total of 53 (6.5%) subjects had protocol deviations leading to elimination from at least one analysis: 25 (6.0%) in the Menveo liquid 24 month group and 28 (6.6%) in Menveo_1 group. Overall, "assessment or time point completion" and "eligibility criteria not met" were the 2 most common reasons for deviating from the protocol, reported respectively by a total of 18 (2.1%) and 16 (1.9%) subjects involved in part 1 of the study.

Phase 2

Protocol deviations are shown in Table 4. A total of 58 (6.8%) subjects had protocol deviations leading to elimination from at least one analysis: 32 (7.4%) in the Menveo liquid 30 month group and 26 (6.2%) in Menveo_2 group. The most common reason for deviating from the protocol in subjects participating in part 2 of the study was "assessment or time point completion" reported by a total of 41 (4.8%) subjects. For 1 subject in the Menveo liquid 30 month group, the ICF was not signed and dated by the sub investigator. The subject was then excluded from all analytical immunogenicity and safety sets.

Table 4 V59_78. Phase 1 and Phase 2. Summary of important protocol deviations leading to elimination from any analyses - All enrolled set

Phase 1	**Menveo-Liq24 N=420**			**Menveo_1 N=426**			**Not Randomised N=2**			**Total N=848**		
	occ	**n**	**%**	**occ**	**n**	**%**	**occ**	**n**	**%**	**occ**	**n**	**%**
At least one important protocol deviation	25	25	6.0	31	28	6.6	4	2	100.0	60	55	6.5
Assessment or time point completion	7	7	1.7	9	9	2.1	2	2	100.0	18	18	2.1
Eligibility Criteria Not Met	7	7	1.7	9	9	2.1	0	0	0.0	16	16	1.9
Excluded medication, vaccine or device	4	4	1.0	3	3	0.7	0	0	0.0	7	7	0.8
Failure to report safety events per protocol	2	2	0.5	2	2	0.5	0	0	0.0	4	4	0.5
Study Procedures	3	3	0.7	4	4	0.9	0	0	0.0	7	7	0.8
Wrong study treatment/administration/dose	2	2	0.5	4	4	0.9	2	2	100.0	8	8	0.9
Phase 2	**Menveo-Liq30 N=430**			**Menveo_2 N=420**			**Not Randomised N=9**			**Total N=859**		
	occ	**n**	**%**	**occ**	**n**	**%**	**occ**	**n**	**%**	**occ**	**n**	**%**
At least one important protocol deviation	37	32	7.4	27	26	6.2	20	9	100.0	84	67	7.8
Assessment or time point completion	22	22	5.1	17	17	4.0	2	2	22.2	41	41	4.8
Eligibility Criteria Not Met	6	6	1.4	4	4	1.0	9	9	100.0	19	19	2.2
Excluded medication, vaccine or device	3	3	0.7	5	5	1.2	0	0	0.0	8	8	0.9
Failure to report safety events per protocol	2	2	0.5	0	0	0.0	0	0	0.0	2	2	0.2

Study Procedures	1	1	0.2	0	0	0.0	0	0	0.0	1	1	0.1
Wrong study treatment/administration/dose	3	3	0.7	1	1	0.2	9	9	100.0	13	13	1.5

n/% = number/percentage of subjects in a given category; Occ = number of occurrences = number of important protocol deviations; N = total number of subjects for each study group; As randomised, i.e. according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received; Menveo_Liq24/30 = Subjects who received Menveo-Liquid aged 24 months or aged 30 months. Menveo_1 and Menveo_2 = Subjects who received Licensed Menveo in phase 1 or phase 2.

Baseline data

Study V59_71

Demographic and other baseline characteristics were generally balanced in the 2 vaccine groups and is shown in Table 5.

Table 5 Study V59_71. Baseline demographics of the All exposed set (modified by Assessor)

	Menveo_Liq N=490		**Menveo N=489**		**Total N=979**	
	Value or n	**%**	**Value or n**	**%**	**Value or n**	**%**
Age in years at First Vaccination (Mean, (SD))						
	31.7(5.8)		31.9(5.8)		31.8 (5.8)	
Country						
Australia	86	*17.6*	87	*17.8*	173	*17.7*
Belgium	88	*18.0*	87	*17.8*	175	*17.9*
Canada	141	*28.8*	139	*28.4*	280	*28.6*
Germany	100	*20.4*	100	*20.4*	200	*20.4*
Italy	75	*15.3*	76	*15.5*	151	*15.4*
Sex						
Male	181	*36.9*	184	*37.6*	365	*37.3*
Female	309	*63.1*	305	*62.4*	614	*62.7*
Race						
American Indian Or Alaska Native	4	*0.8*	0	*0.0*	4	*0.4*
Asian	40	*8.2*	27	*5.5*	67	*6.8*
Black Or African American	4	*0.8*	8	*1.6*	12	*1.2*
Native Hawaiian Or Other Pacific Islander	2	*0.4*	2	*0.4*	4	*0.4*
Other	13	*2.7*	13	*2.7*	26	*2.7*
White	427	*87.1*	439	*89.8*	866	*88.5*
Ethnicity						
Not Hispanic or latino	484	*98.8*	475	*97.1*	959	*98.0*
Height (cm, mean(SD))	170.0 (10)		171.1 (9.3)		170.5 (9.7)	
Weight (kg, mean)	76.2 (18.7)		77.2 (19.9)		76.7 (19.3)	

Menveo_Liq = Subjects who received Menveo liquid; Menveo = Subjects who received Licensed Menveo; N = total number of subjects for each study group n/% = number / percentage of subjects in a given category Value = value of the considered parameter.

Study V59_78

Phase 1

Demographic and other baseline characteristics were generally balanced between the 2 vaccine groups and is shown in Table 6.

Table 6 V59_78, Phase 1. Baseline demographics of the All exposed set (modified by Assessor)

	Menveo-Liq24 N=420		**Menveo_1 N=424**		**Total Phase 1 N=844**	
	Value or n	**%**	**Value or n**	**%**	**Value**	**%**
Age in years at First Vaccination (Mean, (SD))						
	22.0 (9.4)		22.2 (9.6)		22.3 (9.5)	
Age group						
Children and adolescents (10-17 years)	169	*40.2*	173	*40.8*	342	*40.5*
Adults (18-40 years)	251	*59.8*	251	*59.2*	502	*59.5*

Age group [EudraCT]						
Children	57	*13.6*	65	*15.3*	122	*14.5*
Adolescents (12-17 years)	112	*26.7*	108	*25.5*	220	*26.1*
Adults (18-64 years)	251	*59.8*	251	*59.2*	502	*59.5*
Sex						
Male	188	*44.8*	182	*42.9*	370	*43.8*
Female	232	*55.2*	242	*57.1*	474	*56.2*
Country						
Brazil*	0		0		0	*0*
Estonia	50	*11.9*	51	*12.0*	101	*12*
Finland	48	*11.4*	52	*12.3*	100	*11.8*
France	41	*9.8*	39	*9.2*	80	*9.5*
Mexico	33	*7.9*	32	*7.5*	65	*7.7*
Russian Federation	91	*21.7*	91	*21.5*	182	*21.6*
South Africa	36	*8.6*	39	*9.2*	75	*8.9*
Spain	84	*20.0*	82	*19.3*	166	*19.7*
Turkey	37	*8.8*	38	*9.0*	75	*8.9*
Race						
American Indian Or Alaska Native	0	*0.0*	1	*0.2*	1	*0.1*
Asian	4	*1.0*	4	*0.9*	8	*0.9*
Black Or African American	26	*6.2*	22	*5.2*	48	*5.7*
Other	58	*13.8*	54	*12.7*	112	*13.3*
White	332	*79.0*	343	*80.9*	675	*80*
Ethnicity						
Not Hispanic or Latino	375	*89.3*	391	*92.2*	766	*90.8*
Height (cm, mean (SD))	164.1 (12.6)		165.0 (12.5)		164.6 (12.60	
Weight (kg, mean (SD))	63.9		64.3		64.1	

Menveo_Liq24 = Subjects who received Menveo-Liquid aged 24 months; Menveo_1 = Subjects who received Licensed Menveo; N = total number of subjects for each study group n/% = number / percentage of subjects in a given category Value = value of the considered parameter
*Due to the longer ethical approval process in Brazil, it was planned that Brazilian participants would only be enrolled in Phase 2 of study V59_78.

Phase 2

Demographic and other baseline characteristics were generally balanced in the 2 vaccine groups and is shown in Table 7.

Table 7 V59_78. Phase 2. Baseline demographics of the All exposed set (modified by Assessor)

	Menveo-Liq30 N=427		**Menveo_2 N=419**		**Total Phase 2 N=846**	
	Value or n	**%**	**Value or n**	**%**	**Value or n**	**%**
Age in years at First Vaccination (Mean, (SD))						
	22.3 (9.8)		22.0 (9.3)		22.2 (9.6)	
Age group						
Children and adolescents (10-17 years)	173	*40.5*	168	*40.1*	341	*40.3*
Adults (18-40 years)	254	*59.5*	251	*59.9*	505	*59.7*
Age group [EudraCT]						
Children (2-11 years)	78	*18.3*	70	*16.7*	148	*17.5*
Adolescents (12-17 years)	95	*22.2*	98	*23.4*	193	*22.8*
Adults (18-64 years)	254	*59.5*	251	*59.9*	505	*59.7*
Sex						
Male	168	*39.3*	191	*45.6*	359	*42.4*
Female	259	*60.7*	228	*54.4*	487	*57.6*
Country						
Brazil*	104	*24.4*	105	*25.1*	209	*24.7*
Estonia	38	*8.9*	37	*8.8*	75	*8.9*
Finland	51	*11.9*	49	*11.7*	100	*11.8*
France	38	*8.9*	37	*8.8*	75	*8.9*
Mexico	35	*8.2*	35	*8.4*	70	*8.3*
Russian Federation	41	*9.6*	44	*10.5*	85	*10.0*
South Africa	22	*5.2*	20	*4.8*	42	*5.0*
Spain	70	*16.4*	67	*16.0*	137	*16.2*
Turkey	28	*6.6*	25	*6.0*	53	*6.3*
Race						
American Indian Or Alaska Native	1	*0.2*	2	*0.5*	3	*0.4*

Asian	2	*0.5*	3	*0.7*	5	*0.6*
Black Or African American	30	*7.0*	26	*6.2*	56	*6.6*
Other	83	*19.4*	84	*20.0*	167	*19.7*
White	311	*72.8*	304	*72.6*	615	*72.7*
Ethnicity						
Not Hispanic or Latino	375	*89.3*	391	*92.2*	766	*71.3*
Height (cm, mean (SD))	163.4 (12.2)		164.2 (12.9)		263.8 (12.5)	
Weight (kg, mean (SD))	63.5 (20.1)		64.2 (19.7)		63.8 (19.9)	

Menveo_Liq30 = Subjects who received Menveo-Liquid aged 30 months; Menveo_2 = Subjects who received Licensed Menveo; N = total number of subjects for each study group n/% = number / percentage of subjects in a given category Value = value of the considered parameter
*Due to the longer ethical approval process in Brazil, it was planned that Brazilian participants would only be enrolled in Phase 2 of study V59_78.

Numbers analysed

Study V59_71

The size of the analysis sets is provided in Table 8. Primary immunogenicity analyses were conducted using the per protocol set (PPS). The number of participants included in the FAS but not in the PPS was 20 versus 16 (Menveo liquid versus Menveo group). For the Menveo liquid group, the main reason for not being included in the PPS was "eligibility criteria not met," occurring in 10/20 subjects whereas this occurred in 3/16 subjects in the Menveo group. No AE's lead to withdrawal.

Table 8 Study V59_71. Subject disposition in analysis subsets.

	Enrolled	**Exposed** N (%)	**Full analysis set** N (%)	**Per protocol set** N (%)
Group Menveo liquid	493	490 (100)	486 (99.1)	466 (95.1)
Menveo	490	489 (100)	488 (99.8)	472 (96.5)
Total	996	979 (100)	974 (99.5)	938 (95.8)

% =Percent of the exposed group; Menveo_Liq = Subjects who received Menveo Liquid;

Study V_78

The size of the study groups analysed is provided in Table 9 for study V59_78.

Phase 1

Primary immunogenicity analyses were conducted using the PPS. The number of participants included in the FAS but not in the PPS was 21 versus 22 (Menveo_liq24 versus Menveo_1 group). For the Menveo liquid 24 month group, the main reason for not being included in the PPS was "eligibility criteria not met," occurring in 7/21 subjects whereas this occurred in 3/2 subjects in the Menveo_1 group. No AE's led to withdrawal.

Phase 2

Primary immunogenicity analyses were conducted using the PPS. The number of participants included in the FAS but not in the PPS was 23 (5.5%) versus 22 (5.3%) (Menveo liquid 30 month group versus Menveo_2 group). For the Menveo_liq30 group, the main reason for not being included in the PPS was "out of window assessment for immunogenicity," occurring in 14/23 subjects whereas this occurred in 13/22 subjects in the Menveo_2 group. No AE's lead to withdrawal.

Table 9 Study V59_78, Phase 1 and phase 2. Subject disposition in analysis subsets.

Phase 1	**Enrolled**	**Exposed** N (%)	**Full analysis set** N (%)	**Per protocol set** N (%)
Menveo_liq24	420	420 (100)	418 (99.5)	397 (94.5)

Menveo_1	426	424 (100)	422 (99.5)	400 (94.3)
Total	848	844 (100)	840	797
Phase 2				
Menveo_liq30	430	427 (100)	421 (98.6)	398 (93.2)
Menveo_2	420	419 (100)	416 (99.2)	394 (94.0)
Total	859	846 (100)	837 (98.9)	792 (93.6)

% =Percent of the exposed group
Menveo-Liq24/30 = Subjects who received Menveo liquid vaccine aged 24/30 months, Menveo_1/2 = Subjects who received Licensed Menveo vaccine in either phase 1 or phase 2.

Outcomes and estimation

Primary immunogenicity analysis

Study V59_71

At Day 29, the lower limit of the 2-sided 95% CI for the between group ratio of GMTs against serogroup A was 0.64. Results are shown in Table 10.

Table 10 Study V59_71. Primary endpoint: Adjusted hSBA geometric mean titers against N. meningitidis serogroup A and between group ratios at Day 29 – PPS

Serogroup	Time point		Menveo_Liq	Menveo	Menveo_Liq vs Menveo
Meningitis A 3125 Ab	Day 29	N	386	404	
		GMT	185.16	211.33	0.88
		95% CI (LL;UL)	(147.90; 231.81)	(169.61; 263.32)	(0.64; 1.20)

Menveo_Liq = Subjects who received Menveo-Liquid; Menveo = Subjects who received Licensed Menveo Adjusted GMT = geometric mean antibody titer adjusted for pre-vaccination titer. N = Number of subjects with pre and post-vaccination results available 95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit Statistical model used: ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors.

The permutation test of the primary endpoint showed an adjusted GMT ratio at Day 29 of 0.88 (95% CI: 0.64 – 1.20; p= 0.0004). The FAS analysis of the primary endpoint resulted in an adjusted GMT ratio at Day 29 of 0.88 with 95% CI (0.65, 1.20).

Study V59_78

Phase 1 and Phase 2:

Results for the primary endpoint in both phases of the study are shown in

*Table **11***. At Day 29, the lower limit of the two-sided 95% CI for the between group ratio of GMTs against serogroup A was 0.94 for the 24 month aged vaccine versus Menveo_1 and 0.87 for the 30 month aged vaccine versus Menveo_2.

Table 11 Study V59_78, Phase 1 and phase 2. Primary endpoint: Adjusted hSBA geometric mean titers against N. meningitidis serogroup A and between group ratios at Day 29 - PPS

Serogroup		Menveo-Liq24	Menveo_1	Menveo-Liq24 vs Menveo_1
Meningitis A 3125 Ab	N	363	373	
	GMT	386.66	318.34	1.21
	95% CI	(319.47; 467.97)	(264.14; 383.67)	(0.94; 1.57)
		Menveo-Liq30	**Menveo_2**	**Menveo-Liq30 vs Menveo_2**
	N	356	349	
	GMT	387.06	348.89	1.11
	95% CI	(322.72; 464.24)	(290.09; 419.61)	(0.87; 1.42)

Menveo-Liq24/30 = Subjects who received Menveo liquid vaccine aged 24/30 months, Menveo_1/2 = Subjects who received Licensed Menveo vaccine. Adjusted GMT = geometric mean antibody titer adjusted for pre-vaccination titer N = Number of subjects with pre and post vaccination results available. 95% CI = 95% confidence interval for the adjusted GMT Statistical model used: ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors. Age group was not used as a factor in the analysis

The permutation test of the primary endpoint showed an adjusted GMT ratio at Day 29 of 1.21 (95% CI: 0.94 – 1.56; p= 0.0001) for phase 1 and 1.11 (95% CI: 0.86 – 1.41; p= 0.0001) for phase 2. The FAS analysis of the primary endpoint resulted in an adjusted GMT ratio at Day 29 of 1.19 with 95% CI (0.93, 1.53) for phase 1 and 1.14 with 95% CI (0.89, 1.44) for phase 2.

Sensitivity analyses:

For both phases, a sensitivity analysis was performed including the age group as an additional factor in the same ANCOVA model with pre-vaccination titer as a covariate and vaccine group and country as factors. Results were similar to the results without age as a factor (Table 12).

Table 12 Study V59_78, Phase 1 and Phase 2. Sensitivity analysis. Adjusted hSBA geometric mean titers against N. meningitidis serogroup A and between group ratios at Day 29 - PPS (Day 29), age group adjusted

Serogroup		Menveo-Liq24	Menveo_1	Menveo-Liq24 vs Menveo_1
Meningitis A 3125 Ab	N	363	373	
	GMT	401.26	331.46	1.21
	95% CI	(331.23; 486.11)	(274.65; 400.03)	(0.94; 1.56)
		Menveo-Liq30	**Menveo_2**	**Menveo-Liq30 vs Menveo_2**
	N	356	349	
	GMT	396.15	360.53	1.10
	95% CI	(330.14; 475.36)	(299.32; 434.24)	(0.86; 1.41)

Menveo-Liq24/30 = Subjects who received Menveo liquid vaccine aged 24/30 months, Menveo_1 = Subjects who received Licensed Menveo vaccine. Adjusted GMT = geometric mean antibody titer adjusted for pre-vaccination titer N = Number of subjects with pre and post vaccination results available. 95% CI = 95% confidence interval for the adjusted GMT Statistical model used: ANCOVA model with pre-vaccination titer as covariate, vaccine group, age group, and country as factors.

Preferred immunogenicity analyses:

Percentage of subjects with hSBA titer ≥ 8 directed against N. meningitidis serogroups A, C, W and Y on day 29.

Study V59_71

By Day 29, the percentage of subjects with hSBA titers ≥ 8 increased in the 2 vaccine groups compared to Day 1 (baseline) and ranged from 73.3% (serogroup W) to 82.8% (serogroup A) in Menveo liquid group and from 73.1% (serogroup W) to 86.4% (serogroup A) in Menveo group, respectively. Group differences with 95%CI is shown in Table 13. The FAS analysis was similar to the PPS analysis.

Table 13 Study V59_71. Number and percentage of subjects with a hSBA titer equal or above 8 against N. meningitidis serogroups A, C, W and Y on day 1 and day 29, PPS.

Sero-group	Time point	Menveo_Liq					Menveo					Menveo_Liq vs Menveo		
					95%CI					95%CI			95% CI	
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
MenA	Day 1	446	39	8.7	6.3	11.8	446	50	11.2	8.4	14.5	-2.47	-6.47	1.49
	Day 29	406	336	**82.8**	78.7	86.3	428	370	**86.4**	82.8	89.5	-3.69	**-8.65**	1.21
MenC	Day 1	459	247	53.8	49.1	58.4	467	254	54.4	49.7	59.0	-0.58	-6.99	5.83
	Day 29	443	330	**74.5**	70.2	78.5	446	334	**74.9**	70.6	78.8	-0.40	**-6.12**	5.33
MenW	Day 1	455	181	39.8	35.3	44.4	457	209	45.7	41.1	50.4	-5.95	-12.33	0.47
	Day 29	454	333	**73.3**	69.0	77.4	457	334	**73.1**	68.8	77.1	0.26	**-5.49**	6.02
MenY	Day 1	458	104	22.7	18.9	26.8	463	118	25.5	21.6	29.7	-2.78	-8.30	2.76
	Day 29	460	355	**77.2**	73.1	80.9	463	352	**76.0**	71.9	79.8	1.15	**-4.33**	6.62

Menveo_Liq = Subjects who received Menveo-Liquid; Menveo = Subjects who received Licensed Menveo; N = Number of available results n/% = number/percentage of subjects with titer within the specified criterion 95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit

Study V59_78

Phase 1

By Day 29, the percentage of subjects with hSBA titers ≥ 8 increased in the 2 vaccine groups compared to Day 1 (baseline) and ranged from 73.3% (serogroup W) to 82.8% (serogroup A) in Menveo liquid group and from 73.1% (serogroup W) to 86.4% (serogroup A) in Menveo group, respectively. Group differences with 95%CI is shown in Table 14. The FAS analysis was similar to the PPS analysis.

Table 14 Study V59_78, Phase 1. Number and percentage of subjects with a hSBA titer equal or above 8 against N. meningitidis serogroups A, C, W and Y, and group differences at day 29. PPS

Sero-group	Time point	Menveo_Liq24					Menveo_1					Menveo_Liq24 vs Menveo		
					95% CI					95% CI			95%CI	
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
MenA	Day 1	381	46	12.07	8.98	15.77	389	40	10.28	7.45	13.74	1.79	-2.69	6.32
	Day 29	378	354	**93.65**	90.70	95.89	384	354	**92.19**	89.03	94.67	1.46	**-2.24**	5.22
MenC	Day 1	394	191	48.48	43.44	53.53	395	164	41.52	36.61	46.55	6.96	0.01	13.84
	Day 29	388	301	**77.58**	73.10	81.63	382	298	**78.01**	73.52	82.06	-0.43	**-6.32**	5.46
MenW	Day 1	379	120	31.66	27.01	36.61	396	113	28.54	24.14	33.26	3.13	-3.33	9.58
	Day 29	389	309	**79.43**	75.07	83.34	392	317	**80.87**	76.62	84.64	-1.43	**-7.05**	4.18
MenY	Day 1	390	89	22.82	18.75	27.31	398	87	21.86	17.90	26.25	0.96	-4.86	6.80
	Day 29	384	336	**87.50**	83.77	90.64	392	335	**85.46**	81.57	88.80	2.04	**-2.81**	6.90

Sero-group	Time point	Menveo_Liq24			95% CI		Menveo_1			95% CI		Menveo_Liq24 vs Menveo	95%CI	
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL

Menveo_Liq24 = Subjects who received Menveo liquid vaccine aged 24 months, Menveo_1 = Subjects who received. Licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit

Phase 2

At Day 29, the percentages of subjects with hSBA titer ≥ 8 increased in the 2 vaccine groups compared to Day 1 (baseline) and ranged from 84.17% (serogroup C) to 93.37% (serogroup A) in the Menveo liquid 30 month group and from 81.77% (serogroup W) to 94.01% (serogroup A) in the Menveo_2 group. Group differences with 95%CI is shown in *Table 15*. The FAS analysis was similar to the PPS analysis.

Table 15 Study V59_78, Phase 2. Number and percentage of subjects with a hSBA titer equal or above 8 against N. meningitidis serogroups A, C, W and Y, and group differences at day 29. PPS

Sero-group	Time point	Menveo_Liq30			95% CI		Menveo_2			95% CI		Menveo_Liq30 vs Menveo_2	95%CI	
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
MenA	Day 1	377	51	13.53	10.24	17.40	374	45	12.03	8.91	15.77	1.50	-3.32	6.33
	Day 29	377	352	**93.37**	90.37	95.66	367	345	**94.01**	91.06	96.21	-0.64	**-4.24**	2.96
MenC	Day 1	395	200	50.63	45.59	55.67	392	197	50.26	45.19	55.31	0.38	-6.60	7.35
	Day 29	379	319	**84.17**	80.10	87.70	379	314	**82.85**	78.67	86.51	1.32	**-3.99**	6.64
MenW	Day 1	382	110	28.80	24.30	33.62	376	113	30.05	25.46	34.96	-1.26	-7.75	5.23
	Day 29	389	334	**85.86**	82.00	89.17	384	314	**81.77**	77.54	85.50	4.09	**-1.11**	9.33
MenY	Day 1	391	84	21.48	17.51	25.89	385	86	22.34	18.27	26.83	-0.85	-6.69	4.98
	Day 29	393	346	**88.04**	84.42	91.08	386	338	**87.56**	83.85	90.69	0.48	**-4.16**	5.13

Menveo-Liq30 = Subjects who received Menveo liquid vaccine aged 30 months, Menveo_2 = Subjects who received. Licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit

Study V59_71:

Results for the number and percentage of subjects with a hSBA titer equal or above 8 against *N. meningitidis* serogroups A, C, W and Y and between group differences at Day 1 and Day 29 by baseline serostatus is shown in Table 16. The FAS analysis results were similar for both seronegative and seropositive subjects.

Table 16 Study V59_71. Number and percentage of subjects with a hSBA titer equal or above 8 against N. meningitidis serogroups A, C, W and Y and group differences at day 1 and day 29 by baseline serostatus – PPS

Sero-group	Time point	Menveo_Liq			95% CI		Menveo			95% CI		Menveo_Liq vs Menveo	95%CI	
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
Seronegative														
MenA	Day 1	398	0	0.0	0.0	0.9	384	0	0.0	0.0	1.0	0.00	-0.99	0.96
	Day 29	344	276	**80.2**	75.6	84.3	351	297	**84.6**	80.4	88.2	**-4.38**	**-10.09**	**1.29**
MenC	Day 1	162	0	0.0	0.0	2.3	151	0	0.0	0.0	2.4	0.00	-2.49	2.32
	Day 29	153	77	**50.3**	42.1	58.5	138	68	**49.3**	40.7	57.9	**1.05**	**-10.41**	**12.49**
MenW	Day 1	251	0	0.0	0.0	1.5	228	0	0.0	0.0	1.6	0.00	-1.66	1.51
	Day 29	245	132	**53.9**	47.4	60.2	221	110	**49.8**	43.0	56.6	**4.10**	**-4.98**	**13.12**
MenY	Day 1	334	0	0.0	0.0	1.1	328	0	0.0	0.0	1.1	0.00	-1.16	1.14
	Day 29	331	231	**69.8**	64.5	74.7	321	219	**68.2**	62.8	73.3	**1.56**	**-5.53**	**8.66**
Seropositive														
MenA	Day 1	48	39	81.3	67.4	91.1	62	50	80.6	68.6	89.6	0.60	-15.05	15.27
	Day 29	42	40	**95.2**	83.8	99.4	53	50	**94.3**	84.3	98.8	**0.90**	**-10.90**	**11.46**
MenC	Day 1	297	247	83.2	78.4	87.2	316	254	80.4	75.6	84.6	2.79	-3.38	8.91
	Day 29	284	248	**87.3**	82.9	91.0	303	262	**86.5**	82.1	90.1	**0.86**	**-4.70**	**6.36**
MenW	Day 1	204	181	88.7	83.6	92.7	229	209	91.3	86.8	94.6	-2.54	-8.49	3.15
	Day 29	200	193	**96.5**	92.9	98.6	222	213	**95.9**	92.4	98.1	**0.55**	**-3.48**	**4.50**

Sero-group	Time point	Menveo_Liq			95% CI		Menveo			95% CI		Menveo_Liq vs Menveo 95%CI		
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
MenY	Day 1	124	104	83.9	76.2	89.9	135	118	87.4	80.6	92.5	-3.54	-12.42	5.09
	Day 29	121	116	**95.9**	90.6	98.6	134	127	**94.8**	89.5	97.9	**1.09**	**-4.74**	**6.85**

Menveo_Liq = Subjects who received Menveo liquid artificially aged, Menveo = Subjects who received. Licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit; Subjects with missing value at baseline were excluded from the by baseline serostatus analysis 95% CI = 95% confidence interval

Study V59_78

Phase 1:

Results for number and percentage of subjects with a hSBA titer equal or above 8 against *N. meningitidis* serogroups A, C, W and Y and between group differences at Day 1 and Day 29 by baseline serostatus is shown in Table 17. The FAS analysis results were similar for both seronegative and seropositive subjects.

Table 17 Study V59_78, Phase 1. Number and percentage of subjects with a hSBA titer equal or above 8 against N. meningitidis serogroups A, C, W and Y and group differences at day 1 and day 29 by baseline serostatus – PPS

Sero-group	Time point	Menveo_Liq24			95% CI		Menveo_1			95% CI		Menveo_Liq24 vs Menveo_1 95%CI		
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
Seronegative														
MenA	Day 1	332	0	0.00	0.00	1.10	344	0	0.00	0.00	1.07	0.00	-1.11	1.15
	Day 29	317	295	**93.06**	89.68	95.60	329	302	**91.79**	88.28	94.52	**1.27**	**-2.91**	**5.47**
MenC	Day 1	158	0	0.00	0.00	2.31	179	0	0.00	0.00	2.04	0.00	-2.11	2.38
	Day 29	156	96	**61.54**	53.42	69.21	166	108	**65.06**	57.29	72.29	**-3.52**	**-14.01**	**7.00**
MenW	Day 1	251	0	0.00	0.00	1.46	278	0	0.00	0.00	1.32	0.00	-1.37	1.51
	Day 29	244	169	**69.26**	63.06	74.99	270	197	**72.96**	67.25	78.17	**-3.70**	**-11.57**	**4.13**
MenY	Day 1	290	0	0.00	0.00	1.26	304	0	0.00	0.00	1.21	0.00	-1.25	1.31
	Day 29	282	234	**82.98**	78.07	87.18	299	246	**82.27**	77.46	86.43	**0.70**	**-5.53**	**6.89**
Seropositive														
MenA	Day 1	49	46	93.88	83.13	98.72	45	40	88.89	75.95	96.29	4.99	-7.21	18.37
	Day 29	46	45	**97.83**	88.47	99.94	44	41	**93.18**	81.34	98.57	**4.64**	**-5.43**	**16.45**
MenC	Day 1	236	191	80.93	75.33	85.74	216	164	75.93	69.66	81.47	5.01	-2.58	12.67
	Day 29	229	203	**88.65**	83.81	92.45	211	186	**88.15**	83.01	92.18	**0.49**	**-5.56**	**6.67**
MenW	Day 1	128	120	93.75	88.06	97.26	118	113	95.76	90.39	98.61	-2.01	-8.21	4.09
	Day 29	128	124	**96.88**	92.19	99.14	118	116	**98.31**	94.01	99.79	**-1.43**	**-6.30**	**3.21**
MenY	Day 1	100	89	89.00	81.17	94.38	94	87	92.55	85.26	96.95	-3.55	-12.24	5.02
	Day 29	97	97	**100.00**	96.27	100.00	91	88	**96.70**	90.67	99.31	**3.30**	**-0.60**	**9.27**

Note: Subjects with missing value at baseline were excluded from the by baseline serostatus analysis
Menveo_Liq = Subjects who received Menveo liquid aged 24 months, Menveo_1 = Subjects who received licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit

Phase 2:

Results for number and percentage of subjects with a hSBA titer equal or above 8 against *N. meningitidis* serogroups A, C, W and Y and between group differences at Day 1 and Day 29 by baseline serostatus is shown in Table 18. The FAS analysis results were similar for both seronegative and seropositive subjects.

Table 18 V59_78, phase 2. Number and percentage of subjects with a hSBA titer equal or above 8 against N. meningitidis serogroups A, C, W and Y and group differences at day 1 and day 29 by baseline serostatus – PPS

Sero-group	Time point	Menveo_Liq30			95% CI		Menveo_2			95% CI		Menveo_Liq30 vs Menveo_2	95%CI	
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
Seronegative														
MenA	Day 1	316	0	0.00	0.00	1.16	320	0	0.00	0.00	1.15	0.00	-1.19	1.20
	Day 29	297	273	**91.92**	88.21	94.75	295	275	**93.22**	89.72	95.81	**-1.30**	**-5.68**	**3.02**
MenC	Day 1	137	0	0.00	0.00	2.66	152	0	0.00	0.00	2.40	0.00	-2.47	2.74
	Day 29	129	90	**69.77**	61.06	77.54	145	99	**68.28**	60.04	75.75	**1.49**	**-9.54**	**12.37**
MenW	Day 1	258	0	0.00	0.00	1.42	259	0	0.00	0.00	1.41	0.00	-1.46	1.47
	Day 29	251	199	**79.28**	73.74	84.12	251	184	**73.31**	67.38	78.67	**5.98**	**-1.48**	**13.41**
MenY	Day 1	303	0	0.00	0.00	1.21	293	0	0.00	0.00	1.25	0.00	-1.30	1.25
	Day 29	299	254	**84.95**	80.38	88.81	289	245	**84.78**	80.11	88.71	**0.17**	**-5.66**	**6.04**
Seropositive														
MenA	Day 1	61	51	83.61	71.91	91.85	54	45	83.33	70.71	92.08	0.27	-13.57	14.61
	Day 29	59	59	**100.00**	93.94	100.00	54	52	**96.30**	87.25	99.55	**3.70**	**-2.58**	**12.59**
MenC	Day 1	258	200	77.52	71.93	82.46	240	197	82.08	76.64	86.72	-4.56	-11.61	2.54
	Day 29	247	228	**92.31**	88.25	95.31	232	214	**92.24**	88.02	95.34	**0.07**	**-4.85**	**5.06**
MenW	Day 1	124	110	88.71	81.78	93.69	117	113	96.58	91.48	99.06	-7.87	-15.12	-1.35
	Day 29	123	121	**98.37**	94.25	99.80	115	113	**98.26**	93.86	99.79	**0.11**	**-4.21**	**4.68**
MenY	Day 1	88	84	95.45	88.77	98.75	92	86	93.48	86.34	97.57	1.98	-5.48	9.62
	Day 29	87	85	**97.70**	91.94	99.72	88	86	**97.73**	92.03	99.72	**-0.03**	**-6.02**	**5.91**

Note: Subjects with missing value at baseline were excluded from the by baseline serostatus analysis
Menveo_Liq30 = Subjects who received Menveo liquid aged 30 months, Menveo_2 = Subjects who received licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit

Adjusted hSBA titers geometric mean titers against N. meningitidis serogroups A, C, W and Y; by baseline serostatus

Study V59_71:

Adjusted hSBA geometric mean titers and ratio's against *N. meningitidis* serogroups A, C, W and Y and between group ratios at Day 29 by baseline serostatus is shown in Table 19. The FAS analysis results were similar for both seronegative and seropositive subjects.

Table 19 Study V59_71. Adjusted hSBA geometric mean titers against N. meningitidis serogroups A, C, W and Y and between group ratios at Day 29 by baseline serostatus – PPS

Sero-group	Time point		Menveo_Liq		95% CI		Menveo		95% CI		Menveo_Liq vs Menveo	95%CI	
			N	value	LL	UL	N	value	LL	UL	Ratio	LL	UL
Seronegative													
MenA	Day 1	GMT	398	2.00	2.00	2.00	384	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	344	149.23	116.75	190.75	351	182.78	143.36	233.02	0.82	**0.58**	1.15
	Day29/1	GMR	344	74.62	58.38	95.37	351	91.39	71.68	116.51	0.82	0.58	1.15
MenC	Day 1	GMT	162	2.00	2.00	2.00	151	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	153	36.55	22.58	59.17	138	29.90	17.96	49.76	1.22	**0.63**	2.38
	Day29/1	GMR	153	18.28	11.29	29.59	138	14.95	8.98	24.88	1.22	0.63	2.38
MenW	Day 1	GMT	251	2.00	2.00	2.00	228	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	245	18.26	13.82	24.13	221	13.98	10.42	18.74	1.31	**0.88**	1.94
	Day29/1	GMR	245	9.13	6.91	12.07	221	6.99	5.21	9.37	1.31	0.88	1.94
MenY	Day 1	GMT	334	2.00	2.00	2.00	328	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	331	41.30	32.25	52.89	321	32.77	25.50	42.11	1.26	**0.89**	1.79
	Day29/1	GMR	331	20.65	16.12	26.44	321	16.38	12.75	21.06	1.26	0.89	1.79
Seropositive													
MenA	Day 1	GMT	48	51.00	33.31	78.07	62	35.32	24.48	50.97	1.44	0.83	2.51
	Day 29	GMT	42	962.52	522.09	1774.48	53	620.01	362.33	1060.94	1.55	**0.69**	3.50
	Day29/1	GMR	42	20.45	11.89	35.17	53	17.42	10.82	28.05	1.17	0.57	2.41
MenC	Day 1	GMT	297	28.56	24.42	33.40	316	27.20	23.36	31.68	1.05	0.85	1.30
	Day 29	GMT	284	323.68	229.24	457.02	303	268.58	192.14	375.42	1.21	**0.75**	1.93
	Day29/1	GMR	284	11.04	8.28	14.72	303	9.62	7.28	12.72	1.15	0.77	1.70
MenW	Day 1	GMT	204	63.06	52.76	75.37	229	56.53	47.75	66.93	1.12	0.88	1.42
	Day 29	GMT	200	253.07	195.01	328.42	222	203.65	158.92	260.97	1.24	**0.88**	1.76
	Day29/1	GMR	200	3.87	3.07	4.87	222	3.41	2.74	4.24	1.14	0.83	1.55
MenY	Day 1	GMT	124	27.44	22.13	34.03	135	38.49	31.46	47.10	0.71	0.53	0.95
	Day 29	GMT	121	167.41	116.84	239.87	134	195.02	139.89	271.88	0.86	**0.53**	1.39

Sero-group	Time point		Menveo_Liq		95% CI		Menveo		95% CI		Menveo_Liq vs Menveo	95%CI	
			N	value	LL	UL	N	value	LL	UL	Ratio	LL	UL
	Day29/1	GMR	121	5.96	4.14	8.58	134	5.05	3.61	7.07	1.18	0.73	1.92

Note: Subjects with missing value at baseline were excluded from the by baseline serostatus analysis
Menveo_Liq = Subjects who received Menveo liquid artificially aged, Menveo = Subjects who received licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit; GMT/R = geometric mean titer/ratio.
Statistical model used: ANOVA model with vaccine group and country as factors

Study V59_78

Phase 1:

Results for adjusted hSBA geometric mean titers against *N. meningitidis* serogroup A, C, W, and Y and between group ratios by baseline serostatus is shown in Table 20. The FAS analysis results were similar for both seronegative and seropositive subjects.

Table 20 Study V59_78, phase 1. hSBA geometric mean titers against N. meningitidis serogroups A, C, W and Y, geometric mean ratios and between group ratios at day 1 and day 29 by baseline serostatus. PPS

Sero-group	Time point		Menveo_Liq24		95% CI		Menveo_1		95% CI		Menveo_Liq24 vs Menveo_1	95%CI	
			N	value	LL	UL	N	value	LL	UL	Ratio	LL	UL
Seronegative													
MenA	Day 1	GMT	332	2.00	2.00	2.00	344	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	317	340.25	276.63	418.50	329	303.19	247.97	370.69	1.12	**0.85**	1.48
	Day29/1	GMR	317	170.12	138.32	209.25	329	151.59	123.99	185.35	1.12	0.85	1.48
MenC	Day 1	GMT	158	2.00	2.00	2.00	179	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	156	67.16	42.83	105.31	166	100.90	64.41	158.05	0.67	**0.36**	1.21
	Day29/1	GMR	156	33.58	21.41	52.65	166	50.45	32.21	79.02	0.67	0.36	1.21
MenW	Day 1	GMT	251	2.00	2.00	2.00	278	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	244	32.44	24.67	42.65	270	37.29	28.68	48.49	0.87	**0.60**	1.25
	Day29/1	GMR	244	16.22	12.34	21.32	270	18.64	14.34	24.24	0.87	0.60	1.25
MenY	Day 1	GMT	290	2.00	2.00	2.00	304	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	282	85.05	66.71	108.44	299	81.65	64.33	103.63	1.04	**0.75**	1.45
	Day29/1	GMR	282	42.53	33.35	54.22	299	40.83	32.17	51.81	1.04	0.75	1.45
Seropositive													
MenA	Day 1	GMT	49	37.17	26.91	51.35	45	39.68	28.11	56.01	0.94	0.60	1.46
	Day 29	GMT	46	861.08	494.31	1499.96	44	427.80	241.31	758.41	2.01	**0.98**	4.14
	Day29/1	GMR	46	23.54	13.21	41.96	44	10.25	5.65	18.61	2.30	1.08	4.87
MenC	Day 1	GMT	236	22.51	19.09	26.55	216	19.47	16.41	23.09	1.16	0.93	1.44
	Day 29	GMT	229	244.92	173.26	346.22	211	235.00	163.51	337.75	1.04	**0.65**	1.66
	Day29/1	GMR	229	11.08	7.97	15.41	211	11.97	8.47	16.91	0.93	0.59	1.44
MenW	Day 1	GMT	128	60.91	48.33	76.75	118	73.58	58.39	92.72	0.83	0.62	1.10
	Day 29	GMT	128	241.43	172.72	337.48	118	247.72	177.24	346.23	0.97	**0.64**	1.47
	Day29/1	GMR	128	3.96	2.93	5.36	118	3.37	2.49	4.55	1.18	0.81	1.71
MenY	Day 1	GMT	100	46.15	35.71	59.65	94	48.78	37.54	63.37	0.95	0.69	1.31
	Day 29	GMT	97	325.40	215.04	492.40	91	290.06	190.03	442.76	1.12	**0.67**	1.89
	Day29/1	GMR	97	6.98	4.50	10.83	91	5.89	3.76	9.22	1.19	0.68	2.06

Note: Subjects with missing value at baseline were excluded from the by baseline serostatus analysis
Menveo_Liq24 = Subjects who received Menveo liquid aged 24 months, Menveo_1 = Subjects who received licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit; GMT/R = geometric mean titer/ratio.
Statistical model used: ANOVA model with vaccine group and country as factors

Phase 2:

Results for adjusted hSBA geometric mean titers against *N. meningitidis* serogroup A, C, W, and Y and between group ratios by baseline serostatus is shown in Table 21. The FAS analysis results were similar for both seronegative and seropositive subjects.

Table 21 Study V59_78, phase 2. hSBA geometric mean titers against N. meningitidis serogroups A, C, W and Y, geometric mean ratios and between group ratios at day 1 and day 29 by baseline serostatus - PPS.

Sero-group	Time point		Menveo_Liq30				Menveo_2				Menveo_Liq30 vs Menveo_2		
					95% CI				95% CI			95%CI	
			N	value	LL	UL	N	value	LL	UL	Ratio	LL	UL
Seronegative													
MenA	Day 1	GMT	316	2.00	2.00	2.00	320	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	297	321.03	260.78	395.21	295	290.52	235.29	358.71	1.11	**0.84**	1.46
	Day29/1	GMR	297	160.52	130.39	197.61	295	145.26	117.64	179.35	1.11	0.84	1.46
MenC	Day 1	GMT	137	2.00	2.00	2.00	152	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	129	94.85	56.90	158.11	145	94.10	57.20	154.78	1.01	**0.51**	1.99
	Day29/1	GMR	129	47.43	28.45	79.06	145	47.05	28.60	77.39	1.01	0.51	1.99
MenW	Day 1	GMT	258	2.00	2.00	2.00	259	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	251	49.59	38.39	64.05	251	39.29	30.26	51.01	1.26	**0.89**	1.79
	Day29/1	GMR	251	24.79	19.19	32.03	251	19.64	15.13	25.51	1.26	0.89	1.79
MenY	Day 1	GMT	303	2.00	2.00	2.00	293	2.00	2.00	2.00	1.00	.	.
	Day 29	GMT	299	90.98	71.69	115.45	289	94.41	73.98	120.48	0.96	**0.70**	1.33
	Day29/1	GMR	299	45.49	35.85	57.73	289	47.20	36.99	60.24	0.96	0.70	1.33
Seropositive													
MenA	Day 1	GMT	61	50.96	35.31	73.53	54	45.83	30.93	67.90	1.11	0.68	1.82
	Day 29	GMT	59	1065.08	713.00	1591.02	54	930.05	606.31	1426.66	1.15	**0.67**	1.97
	Day29/1	GMR	59	19.91	12.80	30.96	54	20.71	12.93	33.17	0.96	0.53	1.74
MenC	Day 1	GMT	258	21.27	18.21	24.84	240	22.71	19.31	26.72	0.94	0.76	1.15
	Day 29	GMT	247	418.35	295.36	592.54	232	353.68	245.69	509.14	1.18	**0.74**	1.89
	Day29/1	GMR	247	19.61	14.16	27.16	232	15.61	11.10	21.96	1.26	0.81	1.95
MenW	Day 1	GMT	124	56.50	44.84	71.19	117	63.99	50.39	81.25	0.88	0.65	1.19
	Day 29	GMT	123	241.26	171.13	340.15	115	302.01	211.61	431.03	0.80	**0.51**	1.25
	Day29/1	GMR	123	4.16	2.97	5.83	115	4.67	3.29	6.61	0.89	0.57	1.38
MenY	Day 1	GMT	88	48.78	38.11	62.43	92	42.74	33.44	54.64	1.14	0.82	1.59
	Day 29	GMT	87	242.29	159.05	369.12	88	288.01	188.58	439.86	0.84	**0.48**	1.48
	Day29/1	GMR	87	4.94	3.18	7.69	88	6.65	4.26	10.37	0.74	0.41	1.35

Note: Subjects with missing value at baseline were excluded from the by baseline serostatus analysis
Menveo_Liq30 = Subjects who received Menveo liquid aged 30 months, Menveo_2 = Subjects who received licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit; GMT/R = geometric mean titer/ratio.
Statistical model used: ANOVA model with vaccine group and country as factors

Secondary immunogenicity endpoint: Adjusted hSBA GMTs against serogroups C, W, Y

Study V59_71

At Day 29 adjusted hSBA GMTs against serogroups C, W and Y are shown in Table 22 and were similar between the 2 vaccine groups and ranged between 62.83 (serogroup Y) and 161.54 (serogroup C) in Menveo liquid group, and between 51.57 (serogroup W) and 135.78 (serogroup C) in Menveo group. Point estimates for the between group ratios of GMTs were above 1 for all 3 serogroups (1.19 for serogroups C and Y, 1.23 for serogroup W). Non-inferiority criteria for serogroups C, W and Y were not defined in the study protocol. The FAS analysis of Geometric Mean Titers against *N. meningitidis* serogroup C, W, Y resulted in an adjusted GMT ratio at Day 29 with 95% CI of 1.16 (0.82 – 1.63) for Men C, 1.24 (0.96 -1.58) for Men W, and 1.21 (0.92 – 1.60) for MenY.

Table 22 Study V59_71. Adjusted hSBA Geometric mean titers against N. Meningitidis serogroup A, C, W, Y and group ratio's at day 29 – PPS

Serogroup	Time point		Menveo_Liq	Menveo	Menveo_Liq vs Menveo
Meningitis C C11 Ab	Day 29	N	437	441	
		GMT	161.54	135.78	1.19
		95% CI (LL;UL)	(126.34; 206.55)	(106.39; 173.29)	(0.84; 1.68)
Meningitis W 240070 Ab	Day 29	N	445	443	
		GMT	63.40	51.57	1.23
		95% CI (LL;UL)	(52.97; 75.88)	(43.07; 61.74)	(0.96; 1.58)
	Day 29	N	452	455	

Meningitis Y 860800 Ab	GMT	62.83	52.59	1.19
	95% CI (LL;UL)	(51.39; 76.81)	(43.05; 64.25)	(0.90; 1.58)

Menveo_Liq = Subjects who received Menveo-Liquid; Menveo = Subjects who received licensed Menveo; Adjusted GMT = geometric mean antibody titer adjusted for pre-vaccination titer. N = Number of subjects with pre and post-vaccination results available 95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit; Statistical model used: ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors.

Study V59_78

Phase 1

At Day 29, adjusted hSBA GMTs against serogroups C, W and Y are shown in Table 23 were similar between the Menveo liquid vaccine (aged 24 months) and the licensed Menveo vaccine group. The adjusted hSBA GMTs ranged from 62.63 (serogroup W) to 143.48 (serogroup C) in Menveo-Liq24 group, and 66.37 (serogroup W) to 171.74 (serogroup C) in the Menveo_1 group. The between group ratios of GMTs were 0.84, 0.94 and 1.09 for serogroups C, W and Y respectively. The results of the FAS were similar to the PPS analysis.

Table 23 Study V59_78, Phase 1. Adjusted hSBA GMT's against serogroups C,W, and Y and between group ratios at Day 29. PPS

Serogroup	Time point		Menveo_Liq24	Menveo_1	Menveo_Liq24 vs Menveo_1
Meningitis C C11 Ab	Day 29	N	372	388	
		GMT	62.63	66.37	0.84
		95% CI (LL;UL)	(50.99; 76.92)	(54.26; 81.18)	(0.58; 1.19)
Meningitis W 240070 Ab	Day 29	N	379	390	
		GMT	115.66	106.47	0.94
		95% CI (LL;UL)	(94.13; 142.13)	(86.93; 130.42)	(0.72; 1.24)
Meningitis Y 860800 Ab	Day 29	N	385	377	
		GMT	143.48	171.74	1.09
		95% CI (LL;UL)	(110.49; 186.30)	(131.74; 223.87)	(0.82; 1.44)

Menveo_Liq24 = Subjects who received Menveo-Liquid aged 24 months; Menveo_1 = Subjects who received licensed Menveo; Adjusted GMT = geometric mean antibody titer adjusted for pre-vaccination titer; N = Number of subjects with pre and post-vaccination results available 95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit; Statistical model used: ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors.

Phase 2:

At Day 29 adjusted hSBA GMTs against serogroups C, W and Y are shown in Table 24 and ranged between 83.23 (serogroup W) and 256.70 (serogroup C) in Menveo liquid 30 month group, and between 75.42 (serogroup W) and 226.09 (serogroup C) in Menveo_2 group. The between group ratios of GMTs were above 1 for serogroups C and W (1.14 and 1.10, respectively). The results of the FAS were similar to the PPS analysis.

Table 24 Study V59_78, Phase 2. Adjusted hSBA GMT's against serogroups C,W, and Y and between group ratios at Day 29. PPS

Serogroup	Time point		Menveo_Liq30	Menveo_2	Menveo_Liq30 vs Menveo_2
Meningitis C C11 Ab	Day 29	N	374	366	
		GMT	83.23	75.42	1.14
		95% CI (LL;UL)	(68.19; 101.60)	(61.56; 92.41)	(0.79; 1.64)
Meningitis W 240070 Ab	Day 29	N	386	377	
		GMT	112.38	117.56	1.10
		95% CI (LL;UL)	(91.56; 137.92)	(95.39; 144.89)	(0.84; 1.45)
	Day 29	N	376	377	

Meningitis Y 860800 Ab	GMT 95% CI (LL;UL)	256.70 (195.29; 337.41)	226.09 (171.62; 297.85)	0.96 (0.72; 1.26)

Menveo_Liq30 = Subjects who received Menveo-Liquid aged 30 months; Menveo_2 = Subjects who received licensed Menveo; Adjusted GMT = geometric mean antibody titer adjusted for pre-vaccination titer; N = Number of subjects with pre and post-vaccination results available 95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit; Statistical model used: ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors.

Secondary immunogenicity endpoint: Percentages of subjects achieving a 4-fold rise in the post-vaccination hSBA

Study V59_71

At Day 29, the percentages of subjects achieving a 4-fold rise in post-vaccination hSBA titers ranged from 44.7% (serogroup W) to 79.8% (serogroup A) in Menveo liquid group and from 40.2% (serogroup W) to 83.7% (serogroup A) in Menveo group, respectively.

Table 25 Study V59_71. Number and percentage of subjects with a 4-fold rise or more in post-vaccination hSBA titer against N. meningitidis Day 29 by serogroup – PPS

Sero-group	Category	Menveo_Liq			95%CI		Menveo			95%CI		Menveo_Liq vs Menveo 95% CI		
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
MenA	Pre-vacc titer < LOD, post-vacc titer >= max (4*LOD, LLOQ)	344	275	79.9	75.3	84.0	351	297	84.6	80.4	88.2	-4.67	-10.39	1.01
	Total seroresponse	386	308	**79.8**	75.4	83.7	404	338	**83.7**	79.7	87.1	-3.87	**-9.30**	1.52
MenC	Pre-vacc titer < LOD, post-vacc titer >= max (4*LOD, LLOQ)	153	74	48.4	40.2	56.6	138	67	48.6	40.0	57.2	-0.18	-11.63	11.26
	Total seroresponse	437	246	**56.3**	51.5	61.0	441	240	**54.4**	49.6	59.1	1.87	**-4.70**	8.43
MenW	Pre-vacc titer < LOD, post-vacc titer >= max (4*LOD, LLOQ)	245	129	52.7	46.2	59.0	221	107	48.4	41.7	55.2	4.24	-4.85	13.26
	Total seroresponse	445	199	**44.7**	40.0	49.5	443	178	**40.2**	35.6	44.9	4.54	**-1.97**	11.01
MenY	Pre-vacc titer < LOD, post-vacc titer >= max (4*LOD, LLOQ)	331	220	66.5	61.1	71.5	321	203	63.2	57.7	68.5	3.23	-4.10	10.53
	Total seroresponse	452	286	**63.3**	58.6	67.7	455	264	**58.0**	53.3	62.6	5.25	**-1.11**	11.57

Menveo_Liq = Subjects who received Menveo-Liquid; Menveo = Subjects who received Licensed Menveo; N = Number of available results n/% = number/percentage of subjects with 4-fold rise meeting the specified criterion 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit

Study V59_78

Phase 1

At Day 29, the percentages of subjects achieving a 4-fold rise in the post vaccination hSBA titers is shown in Table 26. The FAS analysis of number and percentage of subjects with a 4-fold rise or more in post-vaccination hSBA titer against *N. meningitidis* serogroups A, C, W and Y resulted in a group differences and 95% CI similar to the PPS for all serogroups.

Table 26 Study V59_78. Phase 1. Number and percentage of subjects with a 4-fold rise or more in post-vaccination hSBA titer against N. meningitidis Day 29 by serogroup- PPS

Sero-group	Category	Menveo_Liq24			95%CI		Menveo_1			95%CI		Menveo_Liq24 vs Menveo_1	95% CI	
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
MenA	Pre-vacc titer < LOD, post-vacc titer >= max (4*LOD, LLOQ)	317	295	93.06	89.68	95.60	329	302	91.79	88.28	94.52	1.27	-2.91	5.47
	Total seroresponse	363	335	**92.29**	89.04	94.81	373	336	**90.08**	86.59	92.92	2.21	**-1.94**	6.40
MenC	Pre-vacc titer < LOD, post-vacc titer >= max (4*LOD, LLOQ)	156	93	59.62	51.47	67.39	166	106	63.86	56.05	71.16	-4.24	-14.79	6.37
	Total seroresponse	385	240	**62.34**	57.29	67.20	377	243	**64.46**	59.39	69.29	-2.12	**-8.94**	4.72
MenW	Pre-vacc titer < LOD, post-vacc titer >= max (4*LOD, LLOQ)	244	166	68.03	61.78	73.84	270	193	71.48	65.69	76.79	-3.45	-11.41	4.49
	Total seroresponse	372	221	**59.41**	54.23	64.44	388	235	**60.57**	55.51	65.46	-1.16	**-8.11**	5.80
MenY	Pre-vacc titer < LOD, post-vacc titer >= max (4*LOD, LLOQ)	282	221	78.37	73.10	83.03	299	240	80.27	75.30	84.63	-1.90	-8.54	4.70
	Total seroresponse	379	272	**71.77**	66.95	76.25	390	286	**73.33**	68.65	77.66	-1.57	**-7.88**	4.74

Menveo_Liq24 = Subjects who received Menveo-Liquid aged 24 months; Menveo_1 = Subjects who received Licensed Menveo; N = Number of available results n/% = number/percentage of subjects with 4-fold rise meeting the specified criterion 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit

Phase 2

At Day 29, the percentages of subjects achieving a 4-fold rise in hSBA titers is shown in Table 27. The FAS analysis of number and percentage of subjects with a 4-fold rise or more in post-vaccination hSBA titer against *N. meningitidis* serogroups A, C, W and Y resulted in a group differences and 95% CI similar to the PPS for all serogroups.

Table 27 Study V59_78, phase 2. Number and percentage of subjects with a 4-fold rise or more in post-vaccination hSBA titer against N. meningitidis Day 29.

Sero-group	Category	Menveo_Liq30			95%CI		Menveo_2			95%CI		Menveo_Liq30 vs Menveo_2	95% CI	
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
MenA	Pre-vacc titer < LOD, post-vacc titer >= max (4*LOD, LLOQ)	297	273	91.92	88.21	94.75	295	274	92.88	89.32	95.54	-0.96	-5.38	3.41
	Total seroresponse	356	326	**91.57**	88.19	94.24	349	320	**91.69**	88.28	94.36	-0.12	**-4.29**	4.07
MenC	Pre-vacc titer < LOD, post-vacc titer >= max (4*LOD, LLOQ)	129	88	68.22	59.44	76.13	145	96	66.21	57.89	73.85	2.01	-9.18	13.05
	Total seroresponse	376	273	**72.61**	67.80	77.05	377	263	**69.76**	64.85	74.36	2.85	**-3.63**	9.30
MenW	Pre-vacc titer < LOD, post-vacc titer >= max (4*LOD, LLOQ)	251	198	78.88	73.31	83.76	251	179	71.31	65.29	76.83	7.57	0.00	15.10
	Total seroresponse	374	249	**66.58**	61.55	71.34	366	229	**62.57**	57.39	67.54	4.01	**-2.89**	10.88
MenY	Pre-vacc titer < LOD, post-vacc titer >=	299	247	82.61	77.83	86.73	289	241	83.39	78.59	87.49	-0.78	-6.89	5.35

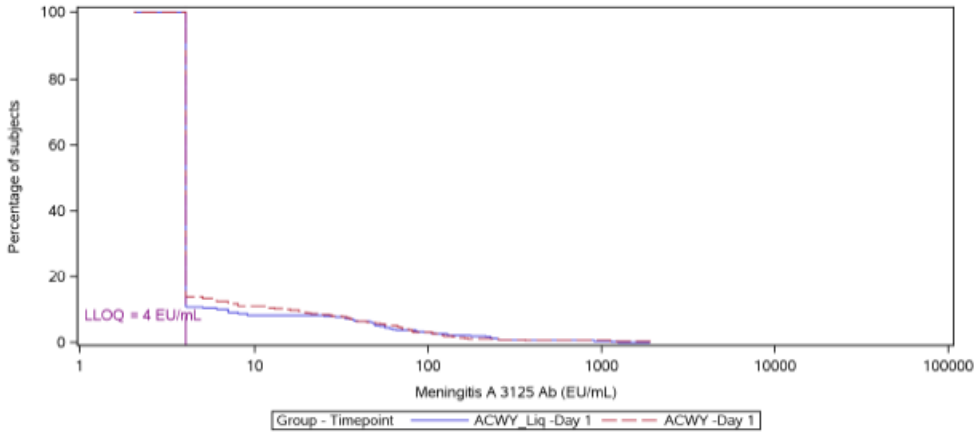
Sero-group	Category	Menveo_Liq30			95%CI		Menveo_2			95%CI		Menveo_Liq30 vs Menveo_2	95% CI	
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
	max (4*LOD, LLOQ)													
	Total seroresponse	386	287	**74.35**	69.69	78.64	377	291	**77.19**	72.62	81.33	-2.84	**-8.91**	3.26

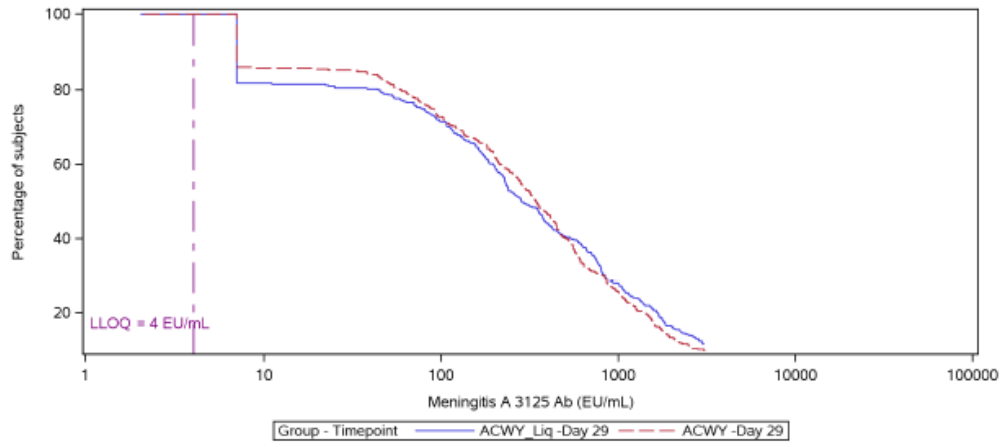
Menveo_Liq24 = Subjects who received Menveo-Liquid aged 30 months; Menveo_2 = Subjects who received Licensed Menveo; N = Number of available results n/% = number/percentage of subjects with 4-fold rise meeting the specified criterion 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit

Reverse cumulative distributions curves unpooled data

The MAH provided reverse cumulative distribution curves at day 1 and day 29 for all *N. meningitis* serogroups for both study V59_71 and V59_78. Only the reverse cumulative distribution curve for Meningitis A in study V59_71 is presented here, as it was originally the serotype of concern, and the clinical results for V59_71 are important for the quality specifications.

Figure 6 Reverse cumulative distribution curves of hSBA titers against N. meningitidis serogroups A, C, W and Y at Day 1 and Day 29, Study V59_71.





Post-hoc pooled analyses:

The MAH provided, in response to the first round of assessment, pooled analyses on the GMT ratio endpoint, percentage of subjects with a hSBA titre equal or above 8 against *N. meningitidis* serogroups A, C, W, and Y. Two different poolings were made,

1) a pooled analyses of V59_78 (Phase 1 and Phase 2).

2) a pooled analysis of study V59_71 and V59_78 (Phase 1 and Phase 2)

The MAH examined the immunogenicity endpoints in the overall pooled population, stratified by serostatus ((seronegative [hSBA titer < 4] and seropositive [hSBA titer ≥ 4]) and stratified by age groups (10-17 YO and ≥18 year old).

Geometric mean ratios

Overall, the LL of the 95% CI was above 0.67 for the ratio of GMTs for all comparisons and serogroups, except for serogroup C in subjects seronegative at baseline and subjects 10-17 years of age for the V59_71 and Phase 1 and Phase 2 pool Table 28. Results were similar when only phase 1 and phase 2 of V59_78 were combined (*Table 28*).

Table 28 Between group ratios at Day 29 of adjusted hSBA geometric mean titres against N. meningitidis serogroups A, C, W, and Y, Pooled studies V59_71 and V59_78 (Phase 1 and Phase 2) - Per Protocol Set (Day 29) overall, by baseline serostatus, and by age group.

		Overall*			Seronegative†			Seropositive†			10-17 years old‡			>=18 years old‡		
		MenACWY_Liq vs MenACWY														
			95% CI			95% CI			95% CI			95% CI			95% CI	
Serogroup	**Timepoint**	**Ratio**	**LL**	**UL**	**Ratio**	**LL**	**UL**	**Ratio**	**LL**	**UL**	**Ratio**	**LL**	**UL**	**Ratio**	**LL**	**UL**
Meningitis A 3125 Ab	Day 29	1.05	**0.89**	1.23	1.00	**0.84**	1.19	1.50	**1.01**	2.22	1.04	**0.81**	1.33	1.05	**0.86**	1.28
N		1105			958			147			305			800		
Meningitis C C11 Ab	Day 29	1.03	**0.84**	1.27	0.92	0.64	1.34	1.15	**0.87**	1.51	0.80	0.54	1.17	1.12	**0.88**	1.42
N		1198			438			760			316			882		
Meningitis W 240070 Ab	Day 29	1.08	**0.93**	1.26	1.12	**0.91**	1.39	1.04	**0.82**	1.31	0.99	**0.74**	1.32	1.14	**0.95**	1.37
N		1191			740			451			301			890		
Meningitis Y 860800 Ab	Day 29	1.07	**0.91**	1.26	1.09	**0.90**	1.32	0.93	**0.69**	1.25	1.14	**0.85**	1.53	1.07	**0.89**	1.30
N		1217			912			305			312			905		

95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit
*Statistical model used: ANCOVA model with pre-vaccination titre as covariate, vaccine group, country and study as factors where the variable country is nested within study. The two phases of V59_78 study are considered as two different studies for this analysis
†Statistical model used: ANOVA model with vaccine group, country and study as factors where the variable country is nested within study. The two phases of V59_78 study are considered as two different studies for this analysis,
‡Statistical model used: ANCOVA model with pre-vaccination titre as covariate, vaccine group, country and study as factors where the variable country is nested within study. The two phases of V59_78 study are considered as two different studies for this analysis
N=number of participants for whom GMR was able to be calculated

Table 29 Between group ratios at Day 29 of adjusted hSBA geometric mean titres against N. Meningitidis serogroups A, C, W, and Y, Pooled study V59_78 (Phase 1 and Phase 2) – Per Protocol Set (Day 29) overall, by baseline serostatus, and by age group

		Overall*			**Seronegative†**			**Seropositive†**			**10-17 years old‡**			**>=18 years old‡**		
		MenACWY_Liq vs MenACWY														
			95% CI			**95% CI**			**95% CI**			**95% CI**			**95% CI**	
Serogroup	**Time point**	**Ratio**	**LL**	**UL**	**Ratio**	**LL**	**UL**	**Ratio**	**LL**	**UL**	**Ratio**	**LL**	**UL**	**Ratio**	**LL**	**UL**
Meningitis A 3125 Ab	Day 29	1.16	**0.97**	1.39	1.11	**0.91**	1.35	1.55	**1.01**	2.39	1.03	**0.81**	1.32	1.25	**0.98**	1.61
N		719			614			105			305			414		
Meningitis C C11 Ab	Day 29	0.97	**0.75**	1.25	0.80	0.51	1.25	1.12	**0.80**	1.55	0.80	0.55	1.18	1.10	**0.79**	1.52
N		761			285			476			316			445		
Meningitis W 240070	Day 29	1.02	**0.84**	1.23	1.04	**0.81**	1.33	0.88	0.65	1.19	0.97	**0.73**	1.30	1.07	**0.83**	1.39
N		746			495			251			301			445		
Meningitis Y 860800 Ab	Day 29	1.02	**0.84**	1.24	0.99	**0.79**	1.25	0.99	**0.68**	1.44	1.11	**0.83**	1.50	0.98	**0.75**	1.27
N		765			581			184			312			453		

MenACWY_Liq = Subjects who received ACWY_Liq24 or ACWY_Liq30 vaccine in study V59_78; MenACWY = Subjects who received ACWY_1 or ACWY_2 vaccine in study V59_78
N = Number of subjects with pre and post-vaccination results available; Value = value of the considered parameter
95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit
*Statistical model used: ANCOVA model with pre-vaccination titre as covariate, vaccine group, country and study phase as factors
†Statistical model used: ANOVA model with vaccine group, country and study phase as factors,
‡ Statistical model used: ANCOVA model with pre-vaccination titre as covariate, vaccine group, country and study phase as factors
N=number of participants for whom GMR was able to be calculated

Percentages of subjects with titres above or equal 8

Percentages of subjects with titres above or equal 8

Overall, the LL of the 95% CI was ≥-5% for all serogroups at Day 29 post-vaccination. For subjects who were seronegative at baseline, the 95% CI was ≥-5% for serogroup A, W, and Y (Table 30). Results were similar when only phase 1 and phase 2 of V59_78 were combined (Table 31).

Table 30 Group differences at Day 1 and Day 29 of percentage of subjects with a hSBA titre equal or above 8 against N. meningitidis serogroups A, C, W, and Y, Pooled study V59_78 (Phase 1 and Phase 2) – Per Protocol Set (Day 29) overall, by baseline serostatus, and by age group

		Overall*			**Seronegative†**			**Seropositive†**			**10-17 years old‡**			**>=18 years old‡**		
		MenACWY_Liq vs MenACWY														
			95% CI			**95% CI**			**95% CI**			**95% CI**			**95% CI**	
Serogroup	**Time point**	**Group difference**	**LL**	**UL**	**Group difference**	**LL**	**UL**	**Group difference**	**LL**	**UL**	**Group difference**	**LL**	**UL**	**Group difference**	**LL**	**UL**
Meningitis A 3125 Ab	Day 1	1.66	-1.62	4.95	0.00	-0.58	0.59	2.32	-6.95	11.95	6.26	2.33	10.50	-1.37	-6.11	3.38
	Day 29	0.43	**-2.12**	3.00	0.04	**-2.94**	3.02	4.15	**-0.70**	10.58	-0.49	**-3.97**	2.99	0.99	**-2.66**	4.66
N(Menveo liquid; Menveo)		755;751			614;624			105;98			312;301			443;450		
Meningitis C C11 Ab	Day 1	3.69	-1.25	8.60	0.00	-1.15	1.29	-0.02	-5.18	5.19	3.71	-3.97	11.34	3.74	-2.66	10.11
	Day 29	0.41	**-3.56**	4.39	-1.30	-8.92	6.30	0.25	**-3.58**	4.14	1.30	**-4.75**	7.38	-0.22	-5.49	5.04
N(Menveo liquid; Menveo)		767;761			285;311			476;443			316;310			451;451		
Meningitis W 240070	Day 1	0.95	-3.63	5.53	0.00	-0.71	0.75	-4.90	-9.49	-0.59	4.58	-1.24	10.43	-1.34	-7.64	4.99
	Day 29	1.33	**-2.50**	5.17	1.21	**-4.21**	6.62	-0.67	**-3.63**	2.23	3.57	**-2.47**	9.62	-0.18	-5.14	4.79
N(Menveo liquid; Menveo)		778;776			495;521			251;233			314;313			464;463		
Meningitis Y 860800	Day 1	0.06	-4.06	4.18	0.00	-0.64	0.64	-0.99	-6.60	4.57	4.46	-1.36	10.31	-2.96	-8.58	2.68
	Day 29	1.27	**-2.07**	4.62	0.49	**-3.76**	4.74	1.71	**-1.42**	5.42	3.37	**-1.70**	8.51	-0.18	**-4.63**	4.27
N(Menveo liquid; Menveo)		777;778			581;588			184;179			317;312			460;403		

95% CI = 95% confidence interval; LL = lower limit; UL = upper limit
N=number of subjects with available results at day 29

Table 31 Group differences at Day 1 and Day 29 of percentage of subjects with hSBA titre equal or above 8 against N. meningitidis serogroups A, C, W, and Y, Pooled studies V59_71 and V59_78 (Phase 1 and Phase 2) - Per Protocol Set (Day 29) overall, by baseline serostatus, and by age group

		Overall*			**Seronegative†**			**Seropositive†**			**10-17 years old‡**			**>=18 years old‡**		
		MenACWY_Liq vs MenACWY														
			95% CI			**95% CI**			**95% CI**			**95% CI**			**95% CI**	
Serogroup	**Time point**	**Group difference**	**LL**	**UL**	**Group difference**	**LL**	**UL**	**Group difference**	**LL**	**UL**	**Group difference**	**LL**	**UL**	**Group difference**	**LL**	**UL**
Meningitis A 3125 Ab	Day 1	0.13	-2.40	2.66	0.00	-0.37	0.37	2.23	-5.75	10.21	6.26	2.33	10.50	-1.95	-5.05	1.14
	Day 29	-0.92	**-3.35**	1.50	-1.54	**-4.37**	1.27	3.26	**-1.21**	8.34	-0.49	**-3.97**	2.99	-1.20	**-4.26**	1.83
N(Menveo liquid; Menveo)		1161;1179			958;975			147;151			312;301			849;878		
Meningitis C C11 Ab	Day 1	2.08	-1.84	5.99	0.00	-0.79	0.83	0.99	-2.96	4.96	3.71	-3.97	11.34	1.59	-2.95	6.11
	Day 29	0.14	**-3.15**	3.42	-1.20	-7.62	5.22	0.60	**-2.57**	3.79	1.30	**-4.75**	7.38	-0.30	**-4.19**	3.59
N(Menveo liquid; Menveo)		1210;1207			438;449			760;746			316;310			894;897		
Meningitis W 240070	Day 1	-1.60	-5.36	2.18	0.00	-0.50	0.50	-3.62	-7.25	-0.10	4.58	-1.24	10.43	-3.63	-8.12	0.89
	Day 29	0.96	**-2.28**	4.19	1.40	**-3.40**	6.18	-0.03	**-2.34**	2.28	3.57	**-2.47**	9.62	0.06	**-3.75**	3.87
N(Menveo liquid; Menveo)		1232;1233			740;742			451;455			314;313			918;920		
Meningitis Y 860800	Day 1	-1.00	-4.30	2.31	0.00	-0.41	0.41	-1.87	-6.73	2.91	4.46	-1.36	10.31	-2.87	-6.81	1.08
	Day 29	1.24	**-1.71**	4.19	0.73	**-3.05**	4.51	1.54	**-1.30**	4.57	3.37	**-1.70**	8.51	0.47	**-3.08**	4.01
N(Menveo liquid; Menveo)		1237;1241			912;909			305;313			317;312			920;929		

95% CI = 95% confidence interval; LL = lower limit; UL = upper limit
N=number of subjects with available results at day 29

Reverse cumulative distribution curves by baseline status

Only the reverse cumulative distribution curves at day 29 for the pooled phase I and phase II analyses are shown for MenA (Figure 7) and MenC (*Figure 8*), Men W (Figure 9) or MenY (Figure 10). In general, there was no evidence of a differing pattern of Menveo and Menveo liquid in the seronegative or seropositive populations.

Figure 7 Reverse cumulative distribution curves of hSBA titers against N. meningitidis serogroups A, 29 Pooled study V59_78 (Phase I and Phase II), seronegative and seropositive

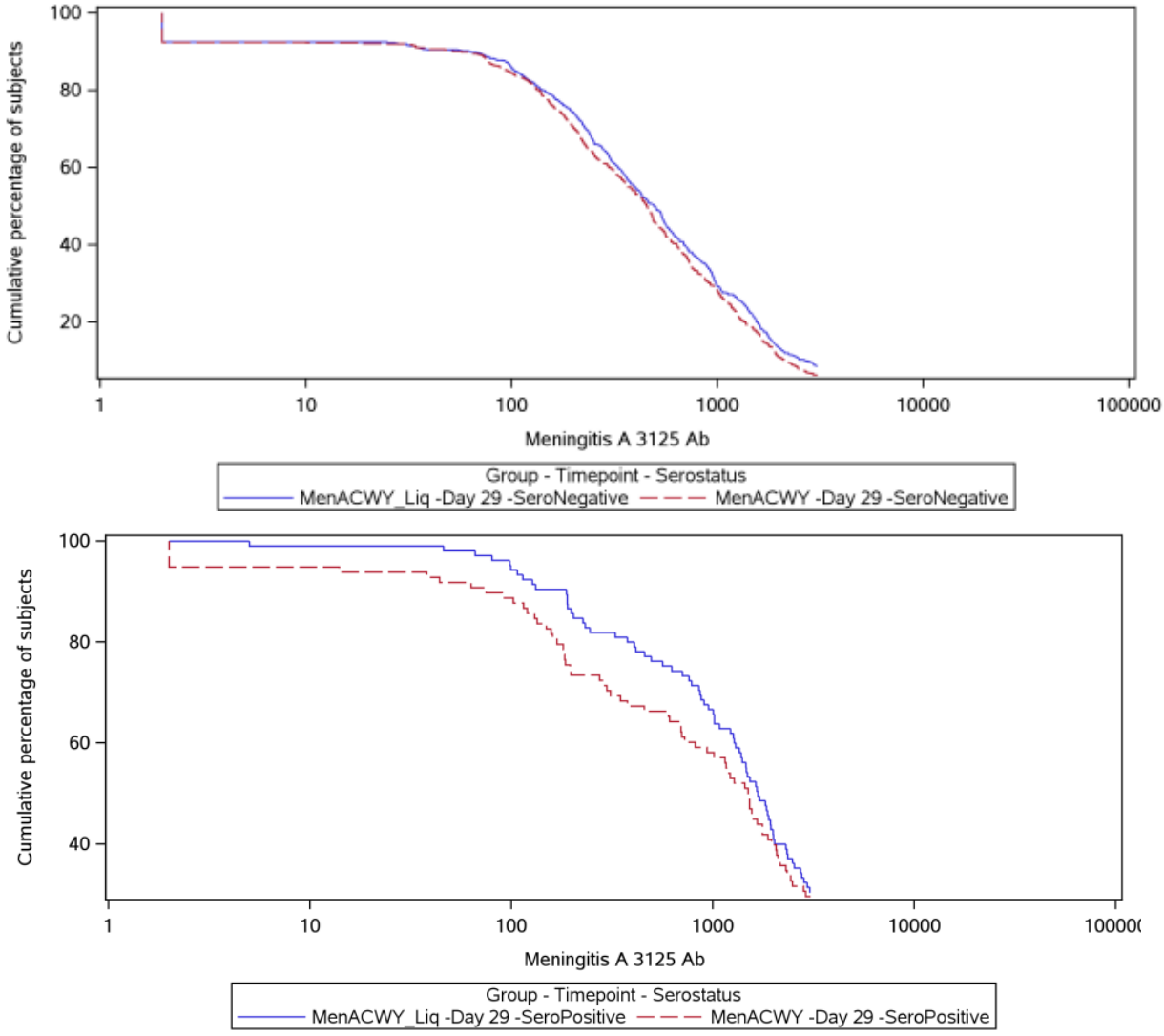


Figure 8 Reverse cumulative distribution curves of hSBA titers against N. meningitidis serogroups C, 29 Pooled study V59_78 (Phase I and Phase II), seronegative and seropositive

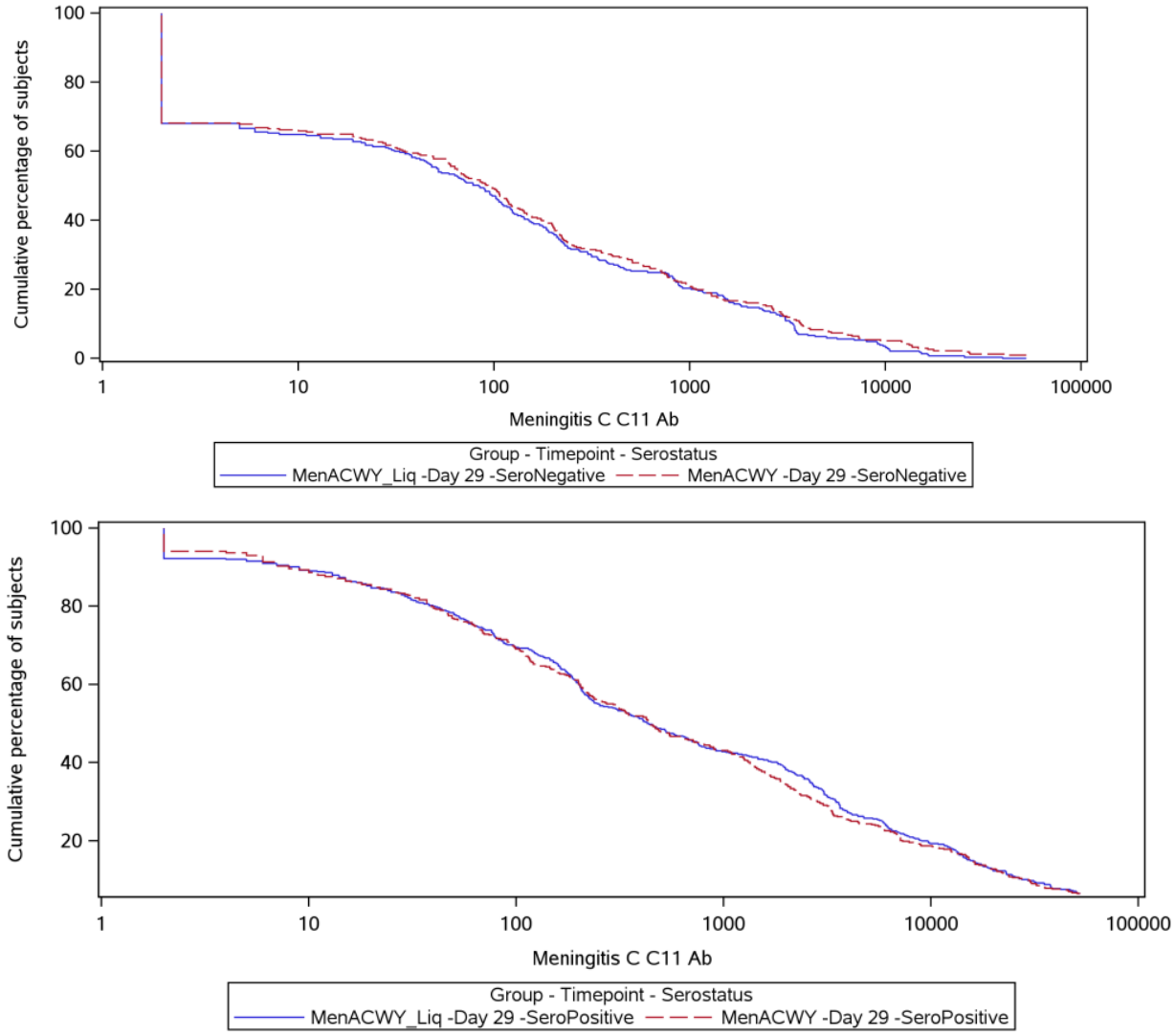
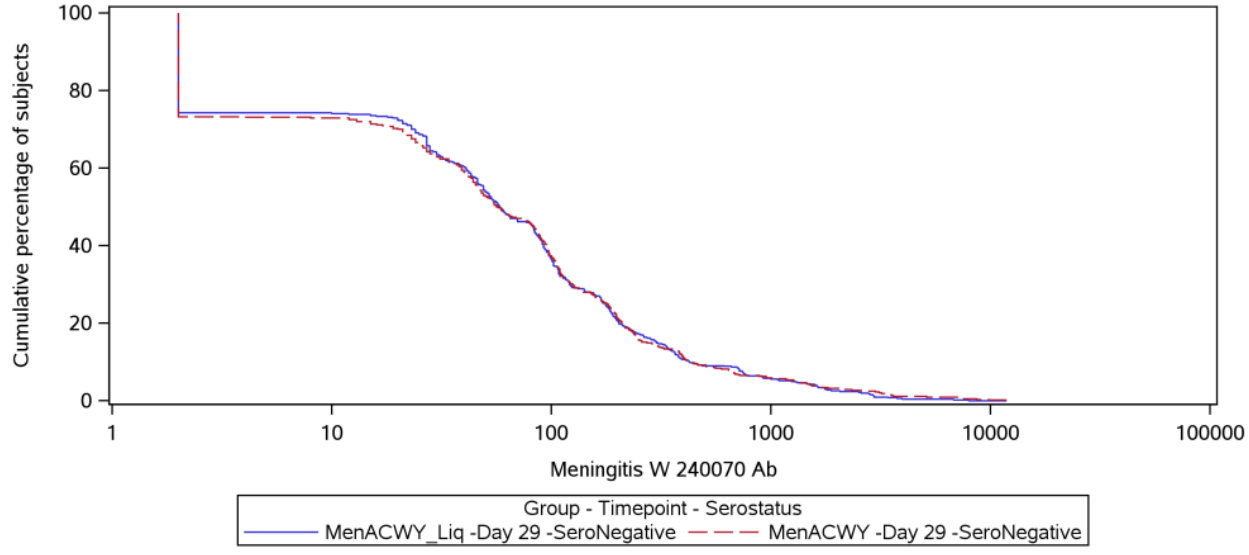


Figure 9 Reverse cumulative distribution curves of hSBA titers against N. meningitidis serogroups W, 29 Pooled study V59_78 (Phase I and Phase II), seronegative and seropositive



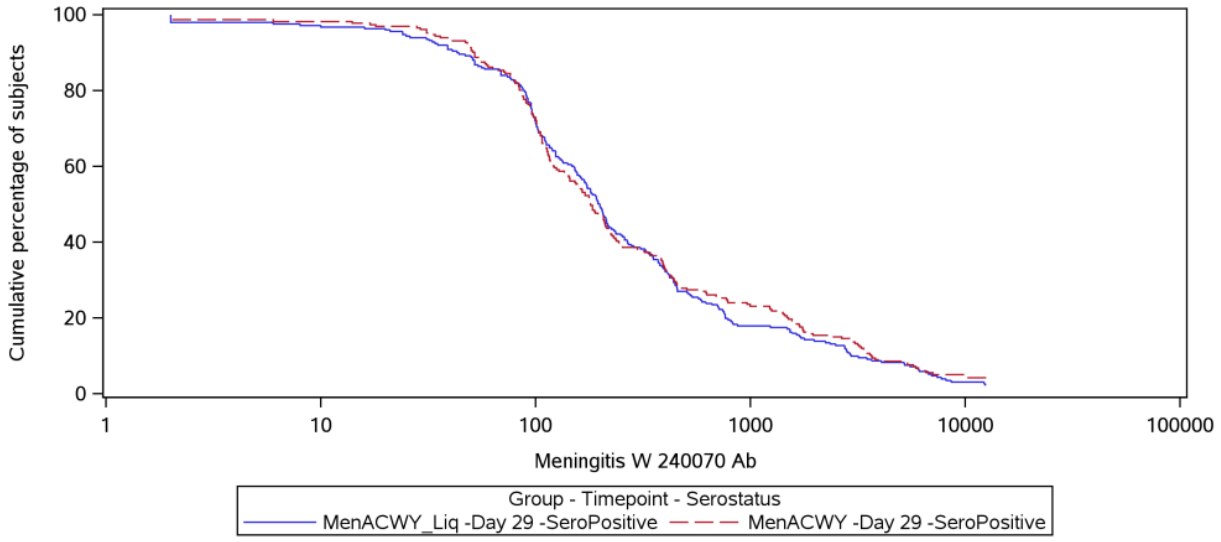
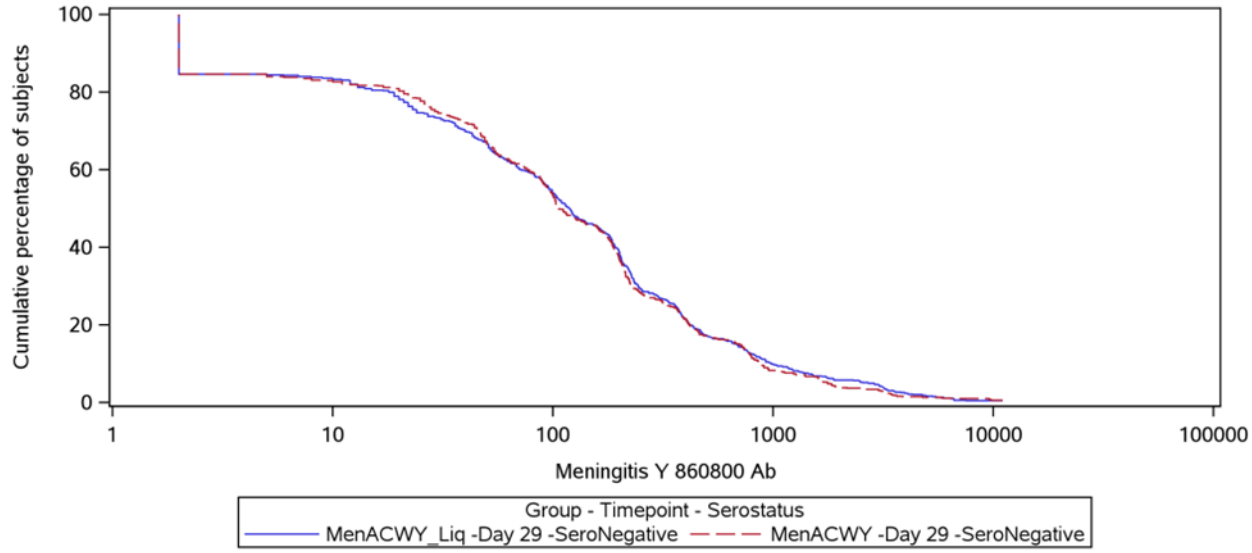
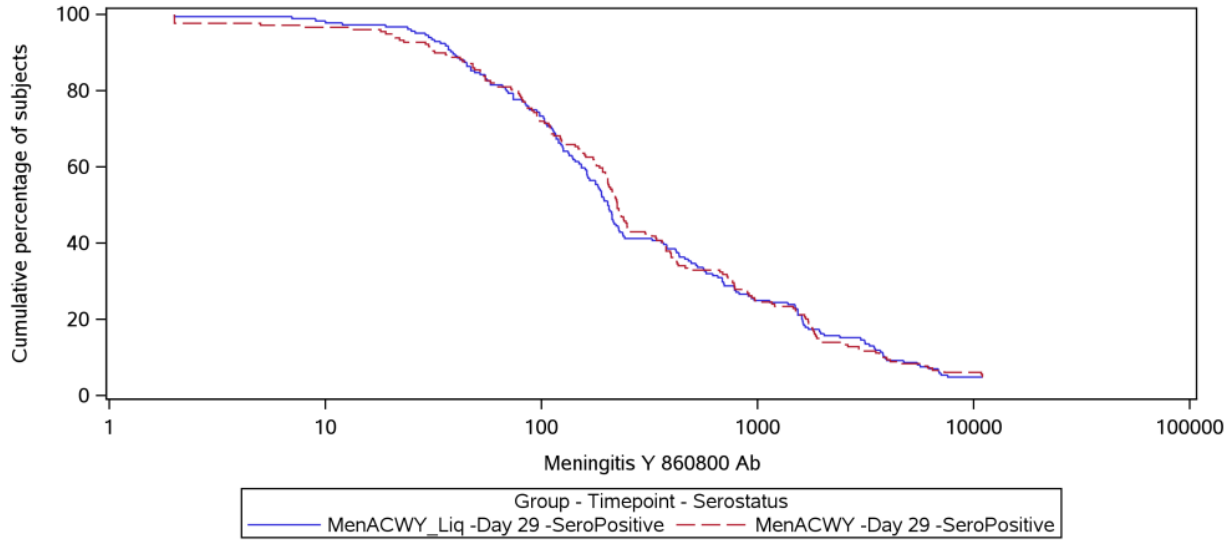


Figure 10 Reverse cumulative distribution curves of hSBA titers against N. meningitidis serogroups Y, 29 Pooled study V59_78 (Phase I and Phase II), seronegative and seropositive





Percentage of subjects achieving a 4-fold rise

The percentages of subjects achieving a 4-fold rise in hSBA titre were similar between the 2 vaccine groups across serogroups. The results for MenC are shown below, due to the MenC seronegative population not reaching the preferred endpoint in the pooled GMT analyses above (Table 32).

Table 32 Percentages of subjects with 4-fold rise in hBSA titres against Men C at Day 29 and 95% CI – Pooled analysis Phase 1 and Phase 2 from study V59_78 and pooled analysis from both studies V59_71 and V59_78.

	Pooled Phase 1 and Phase 2 V59_78		**Pooled V59_71 and V59_78**	
	MenACWY_Liq	**Menveo**	**MenACWY_Liq**	**Menveo**
Pre-vacc titre < LOD, post-vacc titre >= max (4 LOD, LLOQ)	63.5 (57.6-69.1) N=285	65.0 (59.4-70.3) N=311	58.2 (53.4-62.9) N=438	59.9 (55.2-64.5) N=449
Pre-vacc titre ≥ LOD but ≤ LLOQ, post-vacc titre ≥ 4 LLOQ	74.7 (63.3-84.0) N=75	68.9 (55.7-80.1) N=61	67.6 (57.8-76.4) N=105	57.5 (47.6-67.1) N=106
Pre-vacc titre > LLOQ, post-vacc titre ≥ 4 pre-vacc titre	68.8 (64.0-73.3) N=401	68.6 (63.7-73.2) N=382	66.1 (62.3-69.7) N=655	65.0 (61.2-68.7) N=640
Total seroresponse[§]	67.4 (64.0-70.7) N=761	67.1 (63.6-70.5) N=754	63.4 (60.6-66.1) N=1198	62.4 (59.6-65.2) N=1195

LOD = Lower limit of detection, LLOQ = Lower limit of quantitation

[§] Seroresponse is referred to a 4-fold rise in the submitted dossier and it is defined as: a) for individuals whose pre-vaccination titres were < the limit of detection (LOD), the post vaccination titres were to be ≥ 4-fold the LOD or ≥ the LLOQ whichever was greater; b) for individuals whose pre-vaccination titres were ≥ the LOD and ≤ the LLOQ, the post vaccination titres were to be at least 4 times the LLOQ; and c) for individuals whose pre-vaccination titres were > the LLOQ, the post vaccination titres were to be at least 4 times the pre-vaccination titre.

2.6.5.3. Ancillary analyses

In both studies, subgroup analyses for hSBA GMTs, percentage of subjects with hSBA titer ≥ against serogroups A, C, W and Y were performed by baseline serostatus (seronegative and seropositive). This is presented in the clinical AR under 'Preferred immunogenicity analyses of clinical relevance.'

In both studies, all primary and secondary endpoints were assessed by sex, race, country (including also an additional analysis "pooled Canadian sites versus pooled non Canadian sites" for study V59_71) for both PPS and FAS populations. In study V59_78 an additional subgroup analysis by age group (≥ 10 to < 18 YoA and ≥ 18 to ≤ 40 YoA) was performed.

Subgroup: Sex:

Study V59_71:

The primary endpoint analysis in males was 1.14 (0.68 – 1.92) in females was 0.76 (0.51 – 1.12).

Study V59_78:

Phase 1 The primary endpoint analysis in males was 0.86 (0.59 – 1.24) in females was 1.33 (0.95 – 1.86).

Phase 2: The primary endpoint analysis in males was 1.34 (0.90 – 1.99) in females was 1.12 (0.80 – 1.56).

Subgroup: Race:

Study V59_71:

Race was categorized into American Indian or Alaskan native (n=4), Asian (n=67), Black or African American (n=12), Native Hawaiian or other Pacific Islander (n=4), Other (n=26), and White (n=866). The subgroup White had a primary endpoint analysis (adjusted hSBA Geometric Mean Titer ratio against *N. meningitidis* serogroup A) with 95% CI of 0.89 (0.65-1.24).

Study V59_78:

Race was categorized into American Indian or Alaskan native, Asian, Black or African American, other, and white. The distribution differed according to study phase and was as follows (phase 1, phase 2):

American Indian or Alaskan native (1, 3), Asian (8, 5), Black or African American (48, 56), Other (112, 167), and White (675, 615).

Phase 1: The primary endpoint analysis with 95% CI was 0.58 (0.29 – 1.17) for the subgroup Other, and 1.31 (0.99 – 1.74) for the subgroup White.

Phase 2: The primary endpoint analysis with 95% CI was 0.53 (0.23 – 0.98) for the subgroup Other, and 1.28 (0.98 – 1.69) for the subgroup White.

Subgroup: Country

Study V59_71:

All countries contributed a substantial amount of subjects for the study: Australia (173), Belgium (175), Canada (280), Germany (200), and Italy (151). The primary endpoint analysis (adjusted hSBA Geometric Mean Titer ratio against *N. meningitidis* serogroup A) per country with 95% CI was 1.42 (0.66-3.06) for Australia, 1.18 (0.64 – 2.15) for Belgium, 0.77 (0.40 – 1.15) for Canada, 0.55 (0.29 – 1.04) for Germany, and 0.80 (0.34-1.92) for Italy. For non-Canadian sites combined, the difference was 0.92 (0.65 – 1.31).

Study V59_78:

Countries contributed differing amount of subjects for the study with the numbers reported as follows (Phase 1, Phase 2): Brazil (0,209), Estonia (101,75), Finland (100,100), France (80,75), Mexico (65,70), Russian Federation (182, 85), South Africa (75,42), Spain (166,137), Turkey (75,53)

Phase 1: The primary endpoint analysis (adjusted hSBA Geometric Mean Titer ratio against *N. meningitidis serogroup* A) per country with 95% CI was as follows: Brazil (no subjects); Estonia (2.32 (1.08 – 4.96)); Finland (0.87 (0.34 – 2.24)), France (1.04 (0.55 – 1.98)); Mexico (0.50 (0.25 – 0.99), Russian Federation (1.73 (1.09- 2.76), South Africa (1.04 (0.33 – 3.30), Spain (0.77 (0.46-1.29), Turkey (1.92 (0.65 – 5.63)).

Phase 2: The primary endpoint analysis (adjusted hSBA Geometric Mean Titer ratio against *N. meningitidis* serogroup A) per country with 95% CI was as follows: Brazil (0.78 (0.47-1.30); Estonia (1.35 (0.60 – 3.06)); Finland (3.38 (1.55 – 7.35), France (0.57 (0.29 – 1.14); Mexico (1.04 (0.52 – 2.27), Russian Federation (0.91 (0.47 – 1.75), South Africa (0.89 (0.13 – 5.88)), Spain (1.23 (0.61 – 2.47), Turkey (1.06 (0.57 – 1.97))

Subgroup: Age group (≥ 10 to < 18 YoA and ≥ 18 to ≤ 40 YoA):

Study V59_71:

Not performed. All subjects were ≥18 YoA.

Study V59_78

For the 2 age groups, the between group ratios of adjusted hSBA GMTs and the percentage of participants achieving hSBA titers ≥8 will be presented by study phase. During phase 1 of the study approximately 342 subjects were aged 10-17 years and 502 subjects were aged 10-40 years. During phase 2, approximately 341 subjects were aged 10-17 years and 505 were aged 10-40 years.

Adjusted hSBA geometric mean titers against *N. meningitidis* serogroups A, C, W and Y and between group ratios at Day 29 by age group for phase 1 is shown in tables below.

Table 33 Study V59_78, phase 1. Adjusted hSBA geometric mean titers against N. meningitidis serogroups A, C, W and Y and between group ratios at Day 29 by age group (children and adolescents (10-17 years) and adults (18 – 40 years)).

Sero-group	Time point	Menveo_Liq24				Menveo_1				Menveo_Liq24 vs Menveo_1		
				95% CI				95% CI			95%CI	
		N	value	LL	UL	N	value	LL	UL	Ratio	LL	UL
Age Group: Children and adolescents (10 – 17 years)												
MenA	Day 29	154	441.33	338.41	575.54	153	422.96	325.99	548.77	1.04	0.74	1.47
MenC	Day 29	159	201.13	137.19	294.88	155	243.20	165.65	357.06	0.83	0.51	1.35
MenW	Day 29	150	40.72	29.84	55.55	158	51.38	38.14	69.21	0.79	0.53	1.18
MenY	Day 29	157	109.92	80.31	150.46	157	112.85	82.99	153.44	0.97	0.65	1.46
Age Group: Adults (18 – 40 years)												
MenA	Day 29	209	362.33	276.85	474.18	220	268.44	206.90	348.30	1.35	0.94	1.94
MenC	Day 29	226	106.05	75.27	149.43	222	125.38	88.51	177.61	0.85	0.53	1.36
MenW	Day 29	222	85.60	64.97	112.79	230	77.66	59.13	102.00	1.10	0.76	1.61
MenY	Day 29	222	124.26	94.11	164.08	233	103.99	79.17	136.58	1.19	0.82	1.75

Menveo_Liq24 = Subjects who received Menveo liquid aged 24 months, Menveo_1 = Subjects who received licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit; GMT = geometric mean titer adjusted for pre-vaccination titer; Statistical model used: ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors.

Table 34 Study V59_78, phase 2. Adjusted hSBA geometric mean titers against N. meningitidis serogroups A, C, W and Y and between group ratios at Day 29 by age group (children and adolescents (10-17 years) and adults (18 – 40 years)) – PPS

Sero-group	Time point	Menveo_Liq30				Menveo_2				Menveo_Liq30 vs Menveo_2		
				95% CI				95% CI			95%CI	
		N	value	LL	UL	N	value	LL	UL	Ratio	LL	UL
Age Group: Children and adolescents (10 – 17 years)												
MenA	Day 29	151	397.32	303.93	519.41	138	382.73	288.50	507.73	1.04	0.73	1.48
MenC	Day 29	157	286.66	181.94	451.65	153	366.56	230.68	582.47	0.78	0.44	1.40
MenW	Day 29	151	71.12	50.98	99.23	146	57.61	40.85	81.24	1.23	0.81	1.88
MenY	Day 29	155	123.01	87.98	171.98	154	92.01	65.47	129.30	1.34	0.87	2.06
Age Group: Adults (18 – 40 years)												
MenA	Day 29	205	352.92	273.22	455.86	211	307.22	238.98	394.94	1.15	0.82	1.61
MenC	Day 29	219	221.98	157.63	312.60	224	156.43	110.92	220.63	1.42	0.90	2.23
MenW	Day 29	223	93.09	71.32	121.52	220	89.60	68.42	117.33	1.04	0.73	1.48
MenY	Day 29	231	106.38	81.03	139.65	223	134.99	102.20	178.30	0.79	0.55	1.13

Menveo_Liq24 = Subjects who received Menveo liquid aged 24 months, Menveo_1 = Subjects who received licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval for the adjusted GMT; LL = lower limit; UL = upper limit; GMT = geometric mean titer adjusted for pre-vaccination titer; Statistical model used: ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors.

Number and percentage of subjects with a hSBA titer equal or above 8 against *N. meningitidis* serogroups A, C, W and Y and group differences at day 1 and day 29 by age group are shown in Table 35 for children and adolescents (10-17 years) and adults (18-40 years) for phase 1 and in Table 36 for phase 2.

Table 35 Study V59_78, phase 1 Number and percentage of subjects with a hSBA titer equal or above 8 against N. meningitidis serogroups A, C, W and Y and group differences at day 1 and day 29 for children and adolescents (10-17 years). PPS

Sero-group	Time point	Menveo_Liq24					Menveo_1					Menveo_Liq24 vs Menveo_1		
					95% CI					95% CI			95%CI	
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
Age Group: Children and adolescents (10 - 17 years)														
MenA	Day 1	159	16	10.06	5.86	15.83	159	6	3.77	1.40	8.03	6.29	0.76	12.42
	Day 29	157	150	95.54	91.03	98.19	156	149	95.51	90.97	98.18	0.03	-5.02	5.10
MenC	Day 1	162	69	42.59	34.87	50.59	160	57	35.63	28.22	43.57	6.97	-3.71	17.49
	Day 29	159	129	81.13	74.17	86.89	157	124	78.98	71.77	85.07	2.15	-6.73	11.05
MenW	Day 1	154	31	20.13	14.11	27.34	159	20	12.58	7.86	18.76	7.55	-0.66	15.90
	Day 29	158	127	80.38	73.32	86.26	161	130	80.75	73.80	86.53	-0.37	-9.15	8.39
MenY	Day 1	160	31	19.38	13.56	26.36	162	25	15.43	10.24	21.93	3.94	-4.41	12.34
	Day 29	159	143	89.94	84.17	94.14	157	139	88.54	82.49	93.06	1.40	-5.61	8.50
Age Group: Adults (18 - 40 years)														
MenA	Day 1	222	30	13.51	9.31	18.73	230	34	14.78	10.46	20.04	-1.27	-7.77	5.26
	Day 29	221	204	92.31	87.97	95.46	228	205	89.91	85.25	93.50	2.40	-2.99	7.85
MenC	Day 1	232	122	52.59	45.95	59.16	235	107	45.53	39.04	52.13	7.05	-2.02	16.01
	Day 29	229	172	75.11	68.99	80.57	225	174	77.33	71.30	82.63	-2.22	-10.06	5.64
MenW	Day 1	225	89	39.56	33.12	46.27	237	93	39.24	32.98	45.77	0.32	-8.57	9.22
	Day 29	231	182	78.79	72.95	83.88	231	187	80.95	75.29	85.81	-2.16	-9.52	5.19
MenY	Day 1	230	58	25.22	19.74	31.35	236	62	26.27	20.77	32.37	-1.05	-8.99	6.91
	Day 29	225	193	85.78	80.52	90.06	235	196	83.40	78.02	87.92	2.37	-4.31	9.03

Note: Subjects with missing value at baseline were excluded from the by baseline serostatus analysis
Menveo_Liq24 = Subjects who received Menveo liquid aged 24 months, Menveo_1 = Subjects who received licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit

Table 36 Study V59_78, phase 2. Number and percentage of subjects with a hSBA titer equal or above 8 against N. meningitidis serogroups A, C, W and Y and group differences at day 1 and day 29 for children and adolescents (10-17 years). PPS

Sero-group	Time point	Menveo_Liq30					Menveo_2					Menveo_Liq30 vs Menveo_2		
					95% CI					95% CI			95%CI	
		N	n	%	LL	UL	N	n	%	LL	UL	Group Δ	LL	UL
Age Group: Children and adolescents (10 - 17 years)														
MenA	Day 1	156	16	10.26	5.98	16.12	149	6	4.03	1.49	8.56	6.23	0.45	12.50
	Day 29	155	147	94.84	90.08	97.75	145	139	95.86	91.21	98.47	-1.02	-6.28	4.22
MenC	Day 1	160	75	46.88	38.95	54.92	157	73	46.50	38.51	54.62	0.38	-10.56	11.31
	Day 29	157	132	84.08	77.40	89.42	153	128	83.66	76.83	89.14	0.42	-7.88	8.76
MenW	Day 1	155	26	16.77	11.26	23.60	151	23	15.23	9.91	21.97	1.54	-6.81	9.88
	Day 29	156	136	87.18	80.90	91.99	152	121	79.61	72.32	85.70	7.57	-0.76	16.03
MenY	Day 1	157	29	18.47	12.73	25.44	156	21	13.46	8.53	19.84	5.01	-3.18	13.26
	Day 29	158	142	89.87	84.08	94.10	155	131	84.52	77.84	89.82	5.36	-2.11	13.01
Age Group: Adults (18 - 40 years)														
MenA	Day 1	221	35	15.84	11.29	21.33	225	39	17.33	12.63	22.92	-1.50	-8.47	5.48
	Day 29	222	205	92.34	88.02	95.48	222	206	92.79	88.56	95.82	-0.45	-5.54	4.61
MenC	Day 1	235	125	53.19	46.59	59.71	235	124	52.77	46.17	59.29	0.43	-8.58	9.42
	Day 29	222	187	84.23	78.76	88.77	226	186	82.30	76.69	87.04	1.93	-5.05	8.91
MenW	Day 1	227	84	37.00	30.71	43.64	225	90	40.00	33.55	46.72	-3.00	-11.92	5.97
	Day 29	233	198	84.98	79.73	89.31	232	193	83.19	77.74	87.76	1.79	-4.92	8.52
MenY	Day 1	234	55	23.50	18.22	29.47	229	65	28.38	22.64	34.70	-4.88	-12.86	3.12
	Day 29	235	204	86.81	81.80	90.86	231	207	89.61	84.94	93.23	-2.80	-8.79	3.13

Note: Subjects with missing value at baseline were excluded from the by baseline serostatus analysis
Menveo_Liq30 = Subjects who received Menveo liquid aged 30 months, Menveo_2 = Subjects who received licensed Menveo vaccine. N = number of subjects with available results. n/% = number/percentage of subjects with titer within the specified criterion. 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. Study V59_71 is shown in Table 37 and study V59_78 is shown in Table 38. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37 Summary of efficacy for trial V59_71

Title: A phase 2b, randomised, controlled, observer-blind, multicenter, non-inferiority immunogenicity and safety study of two formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and Menveo) administered to healthy adults 18 to 40 years of age.			
Study identifier	Study number: 205343 (MENACWY CONJ-032 [V59_71]) EudraCT number: 2017-003692-61 IND number: 11278		
Design	A phase 2b, randomised, controlled, observer-blind, multi-center study conducted 30 centres in 5 countries: 8 centres in Australia, 2 centres in Belgium, 10 centres in Canada, 6 centres in Germany, and 4 centres in Italy.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		approximately 6 months, starting at Visit 1 (Day 1) and ending at last safety contact (Day 181). The primary completion date (PCD) was visit 2 (Day 29). not applicable not applicable
Hypothesis	Non-inferiority; lower limit (LL) of the two-sided 95% confidence interval (CI) for the ratio of hSBA geometric mean titers (GMTs) against serogroup A between the liquid formulation and the licensed formulation is greater than 0.5. The testing strategy only includes the primary endpoint.		
Treatments groups	Menveo_Liq		A single dose of artificially aged investigational Menveo liquid vaccine (GSK3536820A) with approximately 30% Men A free saccharides N= 493 randomised N= 490 exposed
	Menveo		A single dose of currently licensed GSK' Menveo vaccine N= 490 randomised N= 489 exposed
Endpoints and definitions	Primary endpoint	Ratio of hSBA GMTs against serogroup A for the artificially aged Menveo_Liquid vaccine versus Menveo	LL of the two-sided 95% CI for the ratio of hSBA GMTs against serogroup A > 0.5.
	Secondary endpoint	Ratio of hSBA GMTs against serogroups C, W and Y for the Menveo_Liq vaccine versus Menveo	Ratio of hSBA GMTs.
	Secondary endpoint	The difference in percentage of subjects with hSBA titers ≥ 8 increased on day 29 compared to Day 1 for the artificially aged Menveo_Liquid vaccine compared to Menveo.	Immunogenicity measured by the percentage of subjects with a ≥ 4-fold rise in post vaccination hSBA titer for serogroups A, C, W and Y at Day 29 a) for individuals whose pre-vaccination titers are < the LOD, the post-vaccination titers must be ≥ 4-fold the LOD or ≥ the LLOQ whichever is greater;

			b) for individuals whose pre-vaccination titers are ≥ the LOD and ≤ the LLOQ, the post-vaccination titers must be at least four times the LLOQ; c) for individuals whose pre-vaccination titers are > the LLOQ, the post-vaccination titers must be at least four times the pre-vaccination titer.
	Secondary endpoint	The difference in percentage of subjects with hSBA titer ≥ 8 directed against *N. meningitidis* serogroups A, C, W and Y at Day 29 for the artificially aged Menveo_Liquid vaccine compared to Menveo.	Percentages of subjects with hSBA titer ≥8 against *N. meningitidis* serogroups A, C, W and Y at Day 1 and at Day 29, for each vaccine group and between-group differences.
Database lock	6 October 2020		

Results and Analysis

Analysis description	**Primary Analysis:** ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors for the ratio of hSBA GMTs against serogroup A for the artificially aged Menveo_liquid vaccine versus Menveo.		
Analysis population and time point description	Per protocol set Day 29		
Descriptive statistics and estimate variability	Treatment group	Menveo_Liq	Menveo
	Number of subject	386	404
	MenA GMT	185.16	211.33
	95% CI	(147.90; 231.81)	(169.61 ; 263.32)
Effect estimate per comparison	Comparison group	Menveo_Liq versus Menveo	
		Between group ratio GMT for serogroup A	0.88
		Confidence interval	(0.64; 1.20)
		ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors.	
Notes	For serogroup A, the LL of the 95% CI is above the MAH pre-defined non-inferiority criterion of 0.5 and below the CHMP recommended non-inferiority criterion of 0.67.		
Analysis description	**Secondary analysis:** ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors for hSBA GMTs against serogroups C, W, and Y for the Menveo_liquid vaccine versus Menveo		
Analysis population and time point description	Per protocol set Day 29		
Descriptive statistics and estimate variability	Treatment group	Menveo_Liq	Menveo
	Number of subjects, MenC	437	441
	MenC GMT	161.54	135.78
	95% CI	(126.34;206.55)	(106.39;173.29)
	Number of subjects, MenW	445	443
	MenW GMT	63.40	51.57
	95% CI	(52.97;75.88)	(43.07;61.74)
	Number of subjects, Men Y	452	455
	MenY GMT	62.83	52.59
	95% CI	(51.39; 76.81)	(43.05; 64.25)
Effect estimate	Comparison group	Menveo_Liq versus Menveo	
		Between group MenC GMT ratio	1.19
		95% Confidence interval	0.84;1.68

per comparison		Between group MenW GMT ratio	1.23
		95% Confidence interval	0.96;1.58
		Between group MenY GMT ratio	1.19
		95% Confidence interval	0.90;1.58
Analysis description	**Secondary analysis:** Miettinen and Nurminen score method was used to calculate the 95% CI for the between study group difference in the percentage of subjects with hSBA titers ≥ 8 increased on day 29 compared to Day 1		
Analysis population and time point description	Per protocol set Day 29		
Descriptive statistics and estimate variability	Treatment group	Menveo_Liq	Menveo
	Number of subjects, MenA	336	370
	% MenA hSBA titer ≥ 8	82.8	86.4
	95% CI	78.7;86.3	82.8;89.5
	Number of subjects, MenC	330	334
	% MenC hSBA titer ≥ 8	74.5	74.9
	95% CI	70.2;78.5	70.6;78.8
	Number of subjects, MenW	333	334
	% MenW hSBA titer ≥ 8	73.3	73.1
	95% CI	69.0;77.4	68.8;77.1
	Number of subjects, Men Y	355	352
	% MenY hSBA titer ≥ 8	77.2	76.0
	95% CI	73.1;80.9	71.9;79.8
Effect estimate per comparison	Comparison group	Phase 1: Menveo_Liq versus Menveo	
		Group difference for serogroup A	-3.69
		95% Confidence interval	(-8.65;1.21)
		Group difference for serogroup C	-0.4
		95% Confidence interval	-6.12;5.33
		Group difference for serogroup W	0.26
		95% Confidence interval	(-5.49;6.02)
		Group difference for serogroup Y	1.15
		95% Confidence interval	(-4.33; 6.62)
Notes	For the secondary endpoint percent of subjects achieving a 4-fold rise in hSBA titers (not shown in the summary table), refer to section "outcomes and estimation." In general, results were similar to the results for the secondary endpoint "percent of participants achieving an hSBA titer ≥8."		
Menveo_Liq = Subjects who received Menveo-Liquid; Menveo = Subjects who received Licensed Menveo Adjusted GMT = geometric mean antibody titer adjusted for pre-vaccination titer. N = Number of subjects with pre and post-vaccination results available 95% CI = 95% confidence interval for the adjusted GMT; hSBA = human serum bactericidal assay			

Table 38 Summary of efficacy for trial V59_78

Title: A phase 2b, randomised, controlled, observer-blind, multi-center study to evaluate safety and immunogenicity of different formulations of GSK Biologicals' Meningococcal Menveo conjugate vaccine (GSK3536820A and Menveo) administered to healthy adolescents and young adults 10 to 40 years of age.		
Study identifier	Study number: 207467 (MENACWY CONJ-069 [V59_78]) EudraCT number: 2017-003456-23 IND number: 11278	
Design	A phase 2b, randomised, controlled, observer-blind, multi-center study conducted at 49 centers in 9 countries: 5 centers in Brazil, 4 centers in Estonia, 6 centres in Finland, 5 centres in France, 2 centres in Mexico, 10 centres in Russia Federation, 2 centres in South Africa, 13 centres in Spain and 2 centres in Turkey.	
	Duration of main phase:	approximately 6 months, starting at Visit 1 (Day 1) and ending at last safety contact (Day 181). The primary completion date (PCD) was visit 2 (Day 29). not applicable

	Duration of Run-in phase: Duration of Extension phase:		not applicable
Hypothesis	Non-inferiority; lower limit (LL) the two-sided 95% confidence interval (CI) for the ratio of hSBA geometric mean titers (GMTs) against serogroup A between the liquid formulation and the licensed formulation is greater than 0.5. The testing strategy only includes the primary endpoint.		
Treatments groups	Menveo_Liq24 (phase 1) Menveo_1 (phase 1) = Menveo Menveo_Liq30 (phase 2)		A single dose of investigational Menveo liquid vaccine (GSK3536820A) aged 24 months by storage at 2-8 ℃. N= 420 randomised N= 420 exposed A single dose of currently licensed GSK' Menveo vaccine N= 430 randomised N= 427 exposed A single dose of investigational Menveo liquid vaccine (GSK3536820A) aged 30 months by storage at 2-8 ℃. N= 426 randomised N= 424 exposed
	Menveo_2 (phase 2) = Menveo Menveo_Liq24 (phase 1) Menveo_1 (phase 1) = Menveo		A single dose of currently licensed GSK' Menveo vaccine N= 420 randomised N= 419 exposed A single dose of investigational Menveo liquid vaccine (GSK3536820A) aged 24 months by storage at 2-8 ℃. N= 420 randomised N= 420 exposed A single dose of currently licensed GSK' Menveo vaccine N= 430 randomised N= 427 exposed
	Menveo_Liq30 (phase 2) Menveo_2 (phase 2) = Menveo Menveo_Liq24 (phase 1)		A single dose of investigational Menveo liquid vaccine (GSK3536820A) aged 30 months by storage at 2-8 ℃. N= 426 randomised N= 424 exposed A single dose of currently licensed GSK' Menveo vaccine N= 420 randomised N= 419 exposed A single dose of investigational Menveo liquid vaccine (GSK3536820A) aged 24 months by storage at 2-8 ℃. N= 420 randomised N= 420 exposed
	Menveo_1 (phase 1) = Menveo Menveo_Liq30 (phase 2) Menveo_2 (phase 2) = Menveo		A single dose of currently licensed GSK' Menveo vaccine N= 430 randomised N= 427 exposed A single dose of investigational Menveo liquid vaccine (GSK3536820A) aged 30 months by storage at 2-8 ℃. N= 426 randomised N= 424 exposed A single dose of currently licensed GSK' Menveo vaccine N= 420 randomised N= 419 exposed
	Primary endpoint	Ratio of hSBA GMTs against serogroup A for the	Non-inferiority of the Menveo_Liquid vaccines (aged 24 or 30 months) for the serogroup A;

Endpoints and definitions		Menveo_Liquid vaccines (aged 24 or 30 months) versus Menveo.	testing conducted sequentially for subsequent phases. LL of the two-sided 95% CI for the ratio of hSBA GMTs against serogroup A > 0.5.
	Secondary endpoint	Ratio of hSBA GMTs against serogroups C, W, and Y for the Menveo_Liquid vaccines (aged 24 or 30 months) versus Menveo	Immunogenicity of the Menveo_Liquid vaccines (aged 24 or 30 months) for serogroups C,W, and Y measured by ratio of hSBA GMT's.
	Secondary endpoint	The difference in percentage of subjects with a ≥ 4-fold rise in post vaccination hSBA titer at Day 29 for the Menveo_Liquid vaccines (aged 24 or 30 months) compared to Menveo	Immunogenicity measured by the percentage of subjects with a ≥ 4-fold rise in post vaccination hSBA titer for serogroups A, C, W and Y a) for individuals whose pre-vaccination titers are < the LOD, the post-vaccination titers must be ≥4-fold the LOD or ≥ the LLOQ whichever is greater; b) for individuals whose pre-vaccination titers are ≥ the LOD and ≤ the LLOQ, the post-vaccination titers must be at least four times the LLOQ; c) for individuals whose pre-vaccination titers are > the LLOQ, the post-vaccination titers must be at least four times the pre-vaccination titer.
	Secondary endpoint	The difference in percentage of subjects with hSBA titer ≥ 8 directed against N. meningitidis serogroups A, C, W and Y at Day 29 for the Menveo_Liquid vaccines (aged 24 or 30 months) compared to Menveo.	Percentages of subjects with hSBA titer ≥8 against *N. meningitidis* serogroups A, C, W and Y at Day 1 and at Day 29, for each vaccine group and between-group differences.
Database lock	18-nov-20		

Results and Analysis

Analysis description	**Primary Analysis:** ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors for the ratio of hSBA GMTs against serogroup A for the Menveo_Liquid vaccines (aged 24 or 30 months) versus Menveo..				
Analysis population and time point description	Per protocol set Day 29				
Descriptive statistics and estimate variability	Treatment group	Menveo_Liq24 (phase 1)	Menveo_1 (phase 1)	Menveo_Liq30 (phase 2)	Menveo_2 (phase 2)
	Number of subject	363	373	356	349
	Men AGMT	386.66	318.34	387.06	348.89
	95% CI	(319.47; 467.97)	(264.14; 383.67)	(322.72; 464.24)	(0.87 ; 1.42)
Effect estimate per comparison	Comparison group	Phase 1: Menveo_Liq24 versus Menveo_1			
		Between group MenA GMT ratio			1.21
		95% CI			(0.94; 1.57)
	Comparison group	Phase 2: Menveo_Liq30 versus Menveo_2			
		Between group MenA GMT ratio			1.11
		95% CI			(0.87;1.42)

Notes	For serogroup A, both Menveo_Liq24 and Menveo_Liq 30 the LL above the MAH pre-defined non-inferiority criterion of 0.5 and above the CHMP recommended non-inferiority criterion of 0.67.				
Analysis description	**Secondary analysis:** ANCOVA model with pre-vaccination titer as covariate, vaccine group and country as factors for hSBA GMTs against serogroups C, W, and Y for the Menveo_Liquid vaccines (aged 24 or 30 months) versus Menveo.				
Analysis population and time point description	Per protocol set Day 29				
Descriptive statistics and estimate variability	Treatment group	Menveo_Liq24 (phase 1)	Menveo_1 (phase 1)	Menveo_Liq30 (phase 2)	Menveo_2 (phase 2)
	# of subjects, MenC	385	377	376	377
	Men C GMT	143.48	318.34	256.70	266.09
	95% CI	(110.49;186.30)	(171.74; 223.87)	(195.29; 337.41)	(171.62; 297.85)
	# of subjects, MenW	372	388	374	366
	Men W GMT	62.63	66.37	387.06	75.42
	95% CI	(50.99; 76.92)	(54.26;81.18)	(322.72; 464.24)	(61.56; 92.41)
	# of subjects, Men Y	379	390	386	377
	Men Y GMT	115.66	106.47	112.38	117.56
	95% CI	(94.13;142.13)	(86.93;130.42)	(91.56; 137.92)	(95.39 ; 144.89)
Effect estimate per comparison	Comparison group	Phase 1: Menveo_Liq24 versus Menveo_1			
		Between group MenC GMT ratio	0.84		
		95% CI	(0.58; 1.19)		
		Between group MenW GMT ratio	0.94		
		95% CI	(0.72; 1.24)		
		Between group Men Y GMT ratio	1.09		
		95% CI	(0.82;1.44)		
	Comparison group	Phase 2: Menveo_Liq30 versus Menveo_2			
		Between group MenC GMT ratio	1.14		
		95% CI	(0.79; 1.64)		
		Between group MenW GMT ratio	1.10		
		95% CI	(0.84; 1.45)		
		Between group Men Y GMT ratio	0.96		
		95% CI	(0.72; 1.26)		
Analysis description	**Secondary analysis:** Miettinen and Nurminen score method was used to calculate 95% CI for the between study group difference in the percentage of subjects with hSBA titers ≥ 8 increased on day 29 compared to Day 1				
Analysis population and time point description	Per protocol set Day 29				
Descriptive statistics and estimate variability	Treatment group	Menveo_Liq24 (phase 1)	Menveo_1	Menveo_Liq30 (phase 2)	Menveo_2 (phase 2)
	# of subjects, MenA	354	354	352	345
	% MenA hSBA titer ≥ 8	93.70	92.19	93.37	94.01
	95% CI	(90.70; 95.89)	(89.03; 94.67)	(90.37; 95.66)	(91.06; 96.21)
	# of subjects, MenC	301	298	319	314

	% MenC hSBA titer ≥ 8	77.58	78.01	84.17	82.85
	95% CI	(73.10; 81.63)	(73.52; 82.06)	(80.10; 87.70)	(78.67; 86.51)
	# of subjects, MenW	309	317	334	314
	% MenW hSBA titer ≥ 8	79.43	80.87	85.86	81.77
	95% CI	(75.07; 83.34)	(76.62; 84.64)	(82.00; 89.17)	(77.54; 85.50:
	# of subjects, Men Y	336	335	346	338
	% MenY hSBA titer ≥ 8	87.50	85.46	88.04	87.56
	95% CI	(83.77; 90.64)	(81.57; 88.80)	(84.42; 91.06)	(83.85; 90.69)
Effect estimate per comparison	Comparison group	*Phase 1: Menveo_Liq24 versus Menveo_1*			
		Between group MenA	1.46		
		95% CI	(-2.24; 5.22)		
		Between group MenC	-0.43		
		95% CI	(-6.32; 5.46)		
		Between group Men W	-1.43		
		95% CI	(-7.05; 4.18)		
		Between group MenY	2.04		
		95% CI	(-2.81; 6.90)		
	Comparison group	*Phase 2: Menveo_Liq30 versus Menveo_2*			
		Between group MenA	-0.64		
		95% CI	(-4.24; 2.95)		
		Between group Men C	1.32		
		95% CI	(-3.99; 6.64)		
		Between group MenW	4.09		
		95% CI	(-1.11; 9.33)		
		Between group MenY	0.48		
		95% CI	(-4.16; 5.13)		
Notes	Secondary endpoint not shown in the table (percent of subjects achieving a 4-fold rise in hSBA titers, refer to section "outcomes and estimation." In general, results were similar to the results for the secondary endpoint "percent of participants achieving an hSBA titer ≥8. Subgroup analyses for country show divergent results for differing countries, even when comparing countries with similar vaccination schedule and baseline risk. Subgroup analyses for age group and baseline hSBA titer ≥8 show divergent results for majority of endpoints.				

Menveo_Liq24/30 = Subjects who received Menveo liquid aged 24 or 30 months; Menveo_1/2 = Subjects who received Licensed Menveo Adjusted in either phase 1 or phase 2. GMT = geometric mean antibody titer adjusted for pre-vaccination titer. N = Number of subjects with pre and post-vaccination results available 95% CI = 95% confidence interval for the adjusted GMT; hSBA = human serum bactericidal assay

2.6.5.4. Clinical studies in special populations

None of the studies included older adults (> 40 years of age).

Study V59_71 only included participants ages 18-40 years. In study V59_78, 683 children and adolescents aged 10-17 years were exposed.

2.6.5.5. In vitro biomarker test for patient selection for efficacy

Not applicable

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

There were pre-specified pooled analyses performed for immunogenicity. Any pooled analyses for immunogenicity were performed after the first assessment round.

2.6.6. Discussion on clinical efficacy

This submission concerns a line extension to register a fully liquid formulation of the MenACWY vaccine, Menveo (referred to here as the Menveo liquid). To support this line-extension, the MAH submitted immunogenicity data from two different phase 2b, randomised, controlled, observer-blind, multi-center, non-inferiority clinical trials.

The sought indication for the investigational Menveo liquid is "the 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. The use of this vaccine should be in accordance with official recommendations." This indication is identical to the indication currently approved for Menveo. The proposed posology is likewise identical to the approved posology for Menveo.

The currently licensed Menveo is a quadrivalent conjugate meningococcal vaccine, with the final formulation presented in two vials (one powder and one solution) intended to be combined prior to administration. In the current line-extension, the MAH presents a fully liquid formulation of Menveo which it claims will simplify the vaccine administration, prevent occurrence of administration errors and optimize vaccine shipment and storage. For the currently licenced Menveo, reconstitution errors occur at a reporting rate of 3.66 cases per 100 000 doses distributed. Based on experience with Meningococcal C vaccine, there is evidence to support the claim that a fully liquid version will result in fewer administration errors.

Design and conduct of clinical studies

The clinical development of the Menveo liquid formulation has been previously discussed with CHMP in scientific advice. In the CHMP Scientific Advice provided in 2017 (EMEA/H/SA/809/2/2017/III), it was stated that the primary endpoint should be based on the percentages of participants that achieve hSBA titres of at least 1:8 at day 29 and not on a comparison of GMTs as proposed by the Applicant, as the percentage of participants expected to be adequately protected best informs on clinical benefit. For this endpoint it was recommended that the MAH considers a non-inferiority lower limit (LL) margin of -5%. For the comparison of GMTs (advised to be used as a secondary outcome), the lower bound of the 95% confidence interval around the GMT ratio should be at least 0.67 and not 0.5 as proposed by the Applicant. These key advice were not followed. The margins used in the studies presented here should not be used as a precedent for future studies.

It was agreed with the MAH that the MenA component, which had previously shown instability in solution, is the main concern of the study. However, the responses to the other serogroups are nevertheless considered important for confirmation. From a quality perspective, it has been sufficiently demonstrated that the introduction of MenA in liquid solution does not have an adverse effect on the other vaccine components' (MenC, MenW and MenY) quality profile.

In response to the two major objections in the first round of assessment concerning 1) the demonstration of non-inferiority of Menveo liquid and 2) the extrapolation to the 2-9 year old population, the MAH provided post-hoc analyses, in which the studies were pooled and GMT ratio's and the percent of participants with a hSBA titer ≥1:8 were calculated for both the overall population and subgroups based on serostatus. One pool with V59_71 and both phase 1 and phase 2 of V59_78, and

one pool with only phase 1 and phase 2 of study V59_78. The design, inclusion criteria, and population of the studies were considered sufficiently similar to warrant pooling. Furthermore, the effect estimates in the unpooled data did not point to large differences between the two formulations, however, the individual studies were insufficiently precise to confidently establish non-inferioirty of Menveo liquid. Due to the post-hoc nature of these analyses, these are considered as descriptive, supportive evidence to be viewed alongside the original primary analyses as contributing to the totality of evidence.

Design of the study

The study design of V59_71 and V59_78 were comparable. The active comparator in both studies is the licensed formulation of Menveo produced 12-38 months prior to administration. This is considered appropriate.

Selection of study population

In both studies, no formal stratification was used in the randomisation procedure, instead a minimisation procedure was used accounting for factor centre. The percentage of randomness for both studies V59-71 and V59_78, namely 10%, which is considered very low. The used randomisation method with only 10% of randomness might affect the balance of unknown confounders and this issue may be relevant for the interpretation of subgroup analyses. However, this issue was not further pursued.

The enrolled study population of otherwise healthy individuals represents the population generally targeted for vaccine administration via national vaccination programs. The age range of the study population, ≥10 to ≤40 years, is different compared to the proposed indication which also includes individuals ≥2 years to <10 years of age.

Study V59_78, but not study V59_71 could include participants with previous monovalent meningitis C vaccination. As details of the previous MenC vaccinations were not collected, it was not possible to describe different immune responses in those previous vaccinated versus not vaccinated.

Efficacy data and additional analyses

With regards to the primary endpoint, although not the preferred PE as it cannot be directly translated into expected clinical protection rates, GMT ratio is considered a relevant endpoint to compare different formulations and as it is a continuous outcome likely more sensitive to small differences than the dichotomized responder analysis (% with hSBA >1:8). For clinical relevance, the percentage of subjects with hSBA titres ≥8 was included as a secondary analysis and these results are therefore preferred for clinical interpretation.

For the analysis of the primary endpoint (MenA GMT ratios), the MAHs pre-specified NI margin of the LL of the 95% CI of 0.5 compared to Menveo was met for the artificially aged (0.88, 95%CI: 0.64-1.20), the 24-month aged (1.21, 95%CI: -0.94-1.57) and the 30 month aged product (1.11, 95%CI : 0.87-1.42). Therefore, the studies were formally successful according to the MAHs prespecified NI margin and type I error controlled non-inferiority of the Menveo liquid to Menveo can be claimed. However, the stricter NI margins preferred by CHMP were not met for the GMT and % with hSBA >1:8%. Therefore, there was uncertainty if the claimed non-inferiority based on the wider margin indeed translated into no clinically relevant difference in immunogenicity elicited by the liquid formulation compared to the commercially available Menveo. This resulted in an MO in the first assessment round.

Upon pooling of the data, the LL of the 95% CI was above both -5% and 0.67 for the population including both seronegatives and seropositives. The pooled analyses were not pre-specified but provide sufficient reassurance that the point estimates for the GMT ratios are all close to one and the confidence intervals become narrower upon pooling. Although predefined narrower non-inferiority margins would have led to more compelling evidence, this supports the MAH's argument that the Menveo liquid and Menveo formulations have a similar immunogenicity profile and the two formulations are indeed non-inferior as concluded in the original analyses.

Focus on Meningitis A serogroup:

It was agreed in previous scientific advice that the MenA component, which had previously shown instability in liquid, would be the main concern of the study. The observed MenA GMT of the artificially aged liquid Menveo is lower than for commercial Menveo (GMT ratio 0.88, 95%CI: 0.64-1.20), although with a wide confidence interval. As the reverse cumulative distributions curves of the unpooled data for MenA do not point to a different pattern in immune response induced by the artificially aged Menveo and the Menveo liquid, this is unlikely to be a clinically relevant difference. Based on these results, it can be concluded that the immune response to the artificially aged Menveo liquid formulation and the commercial Menveo formulation are indeed comparable.

Extrapolation to younger ages

Safety and immunogenicity of the 2–9-year-old population has been investigated for the lyophilized formulation of Menveo. The Menveo liquid formulation has been investigated in individuals 10 years of age and older in the two studies presented in this submission. As the percentage of seropositive participants in both studies were >10%, the analysis based on seronegative subjects will be considered important with regards to extrapolation to 2–9-year-olds included in the indication, but not in the studies (V59_71 enrolled adults ≥18-≤40 YoA and V59_78 enrolled participants ≥10-≤40 YoA). For the currently authorized Menveo, the safety and immunogenicity has however been investigated and established in 2–9-year-olds.

In the population seronegative at baseline, the effect estimates of the % of participants achieving a hSBA titer ≥1:8 did not indicate a large difference between Menveo liquid and Menveo, however the confidence intervals were too broad to demonstrate non-inferiority based on the CHMP preferred NI margin of -5% with enough certainty for extrapolation. Although wider confidence intervals may be expected for subgroups, these results were insufficient to claim similarity between the two formulations in the seronegative population. Similar results were seen when looking at the between group GMT ratios for the seronegative population.

The pooling of the phase 1 and phase 2 from study V59_78 allows more insight in the comparative immune response between the two formulations in the seronegative subgroup. In seronegative individuals, for both the percent of individuals attaining a hSBA titer of ≥8 and for the comparison of GMT ratio's, the more stringent non-inferiority margins preferred by CHMP were met with the exception of the MenC component. Individuals seronegative for MenC formed the smallest seronegative subgroup. Importantly, the RCDCs do not indicate divergent responses for seronegative and seropositive individuals to the different vaccine formulations as the curves for both groups overlap. Moreover, the MAH has also demonstrated that the percentages of subjects with 4-fold rise in hSBA titres against MenC were high and comparable between the Menveo liquid formulation and the licensed Menveo formulation. In conclusion, there is no indication of a different immune response to the two formulations in seronegative and seropositive individuals, supporting the extrapolation to 2–9-year-old individuals.

2.6.7. Conclusions on the clinical efficacy

The totality of evidence, including pre-defined analyses in which type I controlled non-inferiority of Menveo liquid to Menveo was claimed, supported by post-hoc pooled analyses, the RCDCs and secondary immunogenicity endpoints, is sufficiently compelling to conclude that the immune response to the Menveo liquid is indeed non-inferior to the response induced by Menveo.

Moreover, in the subgroup of persons seronegative at baseline it can be concluded that there is a comparable response to the Menveo liquid and Menveo formulations for all serogroups, supporting extrapolation of the findings to younger age groups (2 to 9 years).

2.6.8. Clinical safety

Standard safety data collection methods, in-line with those adopted throughout the Menveo clinical development program, were used for studies V59_71 and V59_78 and consisted of the assessment of reactogenicity (solicited local and systemic AEs), and evaluation of unsolicited AEs, including medically attended AEs, AEs leading to withdrawal from the study and SAEs.

In both studies solicited local (induration/erythema/pain at injection site) and systemic AEs (chills, nausea, myalgia, arthralgia, headache, fatigue, loss of appetite, fever (temperature ≥38.0ºC) within 30 minutes after vaccination were collected at the site and recorded in the eCRF and from 30 minutes through Day 7 post-vaccination were recorded by the subjects on patient electronic diary cards (this includes solicited AEs collected from 30 minutes until 6 hours after vaccination).

2.6.8.1. Patient exposure

Overall, 1337 subjects received Menveo Liquid and 1332 subjects received Menveo. The numbers in the different safety sets are presented below in Table 39.

Table 39 Summary of the number of subjects evaluated for safety

	V59_71		V59_78				Pooled analysis		
	Menveo Liq	Menveo	Meveo Liq24	Menveo 1	Menveo Liq30	Menveo 2	Menveo Liquid	Menveo	Total
	n	n	n	n	n	n	n	n	n
All enrolled set	493	490	420	426	430	420			
All exposed set	490	489	420	424	427	419	1337	1332	2669
Solicited safety set (30 mins)	490	489	420	424	427	419	1337	1332	2669
Solicited safety set (30 minutes – Day 7)	489	487	418	422	425	419	1332	1328	2660
Unsolicited safety set	489	489	420	424	427	419	1336	1332	2668

Menveo-Liq24 = Subjects who received Menveo Liquid vaccine aged 24 months, Menveo_1 = Subjects who received Licensed Menveo vaccine
Menveo-Liq30 = Subjects who received Menveo Liquid vaccine aged 30 months, Menveo_2 = Subjects who received Licensed Menveo vaccine

2.6.8.2. Adverse events

Solicited adverse events (local and systemic)

First 30 minutes

In **study V59_78** the frequency of solicited adverse events (local and systemic) reported within the first 30 minutes were comparable (71.5% and 71.6% of subjects in the Menveo-Liq24 group and Menveo_1 group, 73.2% and 70.6% of subjects in the Menveo-Liq30 group and Menveo_2 group, respectively).

The **pooled analysis** of solicited AEs (local and systemic) reported within the first 30 minutes after vaccination shows that the percentages of subjects experiencing at least one solicited AE appear comparable between treatment groups for the local adverse events (4.9% (95% CI 3.8 -6.2) in the Menveo Liquid group and 3.5% (95%CI 2.5 -4.6) in the Menveo group).

Table 40 A Percentage of subjects with solicited local and systemic AEs reported within 30-min (Day 1, 30 mins) post-vaccination period, Phase 1 and Phase 2 (study V59_78)

	Menveo-Liq24				**Menveo_1**				**Menveo-Liq30**				**Menveo_2**			
			95% CI				**95% CI**				**95% CI**				**95% CI**	
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
N	420				424				427				419			
Any adverse event	15	3.6	2.0	5.8	11	2.6	1.3	4.6	30	7.0	4.8	9.9	29	6.9	4.7	9.8
Local adverse event	14	3.3	1.8	5.5	8	1.9	0.8	3.7	26	6.1	4.0	8.8	23	5.5	3.5	8.1
Systemic adverse event	1	0.2	0.0	1.3	3	0.7	0.1	2.1	7	1.6	0.7	3.3	6	1.4	0.5	3.1

Menveo-Liq24 = Subjects who received Menveo Liquid vaccine aged 24 months
Menveo_1 = Subjects who received Licensed Menveo vaccine
Menveo-Liq30 = Subjects who received Menveo Liquid vaccine aged 30 months,
Menveo_2 = Subjects who received Licensed Menveo vaccine,
AE = Adverse Event

Table 41 Percentage of subjects with solicited local and systemic adverse events reported within 30-min (Day 1, 30 mins) post-vaccination period; Solicited Safety Set (30 min)

	Menveo-Liq				**Menveo**			
			95% CI				**95% CI**	
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
N	1337				1332			
Any adverse event	73	5.5	4.3	6.8	58	4.4	3.3	5.6
Local adverse event	65	4.9	3.8	6.2	46	3.5	2.5	4.6
Systemic adverse event	13	1.0	0.5	1.7	14	1.1	0.6	1.8

Menveo Liquid = Subjects who received Menveo_Liq vaccine in study V59_71 (205343) pooled with subjects who received Menveo_Liq24 or Menveo_Liq30 vaccine in study V59_78 (207467)
Menveo = Subjects who received Menveo vaccine in study V59_71 (205343) pooled with subjects who received Menveo_1 or Menveo_2 vaccine in study V59_78 (207467)
N = number of subjects
n/% = number/percentage of subjects presenting at least one type of adverse event
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

30 minutes till day 7

In study **V59_78** the percentages of subjects experiencing at least one solicited AE (local and systemic) from 30 minutes through Day 7 following vaccination were more or less similar: 71.5% in the Menveo-Liq24 group; 71.6% in the Menveo_1 group; 73.2% in the Menveo-Liq30 group and 70.6% in the Menveo_2 group, see Table *42*. The **pooled analysis** of this time period further supports

this observation (69.2% and 68.2% of subjects in the Menveo Liquid group and Menveo group, respectively), see Table *43*.

Table 42 Percentage of subjects with solicited local and systemic AEs reported during 7-Day post-vaccination period - Solicited Safety Set (30 minutes - Day 7)

	Menveo-Liq24				**Menveo_1**				**Menveo-Liq30**				**Menveo_2**			
			95% CI				**95% CI**				**95% CI**				**95% CI**	
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
N	418				422				425				419			
Any AE	299	**71.5**	66.9	75.8	302	**71.6**	67.0	75.8	311	**73.2**	68.7	77.3	296	**70.6**	66.0	75.0
Local AE	198	**47.4**	42.5	52.3	193	**45.7**	40.9	50.6	211	**49.6**	44.8	54.5	199	**47.5**	42.6	52.4
Systemic AE	253	**60.5**	55.7	65.2	244	**57.8**	52.9	62.6	245	**57.6**	52.8	62.4	232	**55.4**	50.5	60.2

Menveo-Liq24 = Subjects who received Menveo Liquid vaccine aged 24 months, Menveo_1 = Subjects who received Licensed Menveo vaccine; Menveo-Liq30 = Subjects who received Menveo Liquid vaccine aged 30 months, Menveo_2 = Subjects who received Licensed Menveo vaccine N = number of subjects
n/% = number/percentage of subjects presenting at least one type of adverse event
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit, AE = Adverse Event

Table 43 Pooled analysis: Percentage of subjects with solicited local and systemic adverse events reported during the 7-day (30 minutes after vaccination to Day 7) post-vaccination period - Solicited Safety Set (30 minutes - Day 7)

	Menveo Liquid				**Menveo**			
			95% CI				**95% CI**	
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
N	1332				1328			
Any adverse event	922	**69.2**	66.7	71.7	906	**68.2**	65.6	70.7
Local adverse event	613	**46.0**	43.3	48.7	578	**43.5**	40.8	46.2
Systemic adverse event	735	**55.2**	52.5	57.9	719	**54.1**	51.4	56.8

Menveo Liquid = Subjects who received Menveo_Liq vaccine in study V59_71 (205343) pooled with subjects who received Menveo_Liq24 or Menveo_Liq30 vaccine in study V59_78 (207467)
Menveo = Subjects who received Menveo vaccine in study V59_71 (205343) pooled with subjects who received Menveo_1 or Menveo_2 vaccine in study V59_78 (207467)
N = number of subjects
n/% = number/percentage of subjects presenting at least one type of adverse event
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

During **study V59_78**, pain at the injection site was the most frequently reported **solicited local AE** in both vaccine groups in both phases (Table 44). Most local reactions were mild or moderate in severity. In the **pooled analysis** a similar pattern was observed.). Most local reactions had an onset between 30 minutes to Day 3 post vaccination and resolved within 7 days after vaccination

In **study V59_78** the most frequently reported **solicited systemic AE** were fatigue and headache. The intensity of fatigue and headache was mostly mild. In the **pooled analysis** a similar pattern was observed. Fever occurred in similar frequencies across treatment groups and phases: it was reported in 3.6% of subjects in the Menveo-Liq24 group, 4.3% of subjects in the Menveo_1 group, 3.5% of subjects in the Menveo-Liq30 group, and 2.9% of subjects in the Menveo_2 group. The majority of solicited systemic AEs resolved within 7 days after vaccination.

Table 44 Study V59_78 phase 2: Percentage of subjects with at least one solicited local and systemic adverse event (any and severe) reported during the 7-day post-vaccination period.

		Menveo Liq24				**Menveo_1**				**Menveo Liq30**				**Menveo_2**			
				95% CI				**95% CI**				**95% CI**				**95% CI**	
Solicited local adverse events																	
		n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Erythema	N	418				422				425				419			
	Any	48	**11.5**	8.6	14.9	51	**12.1**	9.1	15.6	58	**13.6**	10.5	17.3	40	**9.5**	6.9	12.8
	>100 mm	7	**1.7**	0.7	3.4	6	**1.4**	0.5	3.1	12	**2.8**	1.5	4.9	5	**1.2**	0.4	2.8

Induration	N	418				422				425				419			
	Any	50	**12.0**	9.0	15.5	51	**12.1**	9.1	15.6	54	**12.7**	9.7	16.3	39	**9.3**	6.7	12.5
	>100 mm	6	**1.4**	0.5	3.1	7	**1.7**	0.7	3.4	9	**2.1**	1.0	4.0	4	**1.0**	0.3	2.4
Pain	N	418				422				425				419			
	Any	189	**45.2**	40.4	50.1	181	**42.9**	38.1	47.8	202	**47.5**	42.7	52.4	192	**45.8**	41.0	50.7
	Severe	7	**1.7**	0.7	3.4	5	**1.2**	0.4	2.7	5	**1.2**	0.4	2.7	3	**0.7**	0.1	2.1
Solicited systemic adverse events																	
fatigue	N	418				422				425				419			
	Any	174	**41.6**	36.9	46.5	175	**41.5**	36.7	46.3	149	**35.1**	30.5	39.8	147	**35.1**	30.5	39.9
	Severe	6	**1.4**	0.5	3.1	8	**1.9**	0.8	3.7	9	**2.1**	1.0	4.0	6	**1.4**	0.5	3.1
headache	N	418				422				425				419			
	Any	164	**39.2**	34.5	44.1	151	**35.8**	31.2	40.6	189	**39.8**	35.1	44.6	157	**37.5**	32.8	42.3
	Severe	4	**1.0**	0.3	2.4	6	**1.4**	0.5	3.1	7	**1.6**	0.7	3.4	3	**0.7**	0.1	2.1
Arthralgia	N	418				422				425				419			
	Any	45	**10.8**	8.0	14.1	50	**11.8**	8.9	15.3	49	**11.5**	8.7	15.0	40	**9.5**	6.9	12.8
	Severe	4	**1.0**	0.3	2.4	1	**0.2**	0.0	1.3	2	**0.5**	0.1	1.7	2	**0.5**	0.1	1.7
Chills	N	418				422				425				419			
	Any	75	**17.9**	14.4	22.0	79	**18.7**	15.1	22.8	78	**18.4**	14.8	22.4	56	**13.4**	10.3	17.0
	Severe	2	**0.5**	0.1	1.7	1	**0.2**	0.0	1.3	2	**0.5**	0.1	1.7	0	**0**		
Fever	N	418				422				425				419			
	Yes	15	**3.6**	2.0	5.8	18	**4.3**	2.5	6.7	15	**3.5**	2.0	5.8	12	**2.9**	1.5	4.9
	No	403	**96.4**	94.2	98.0	404	**95.7**	93.3	97.5	410	**96.5**	94.2	98.0	407 5	**97.1**	95.1	98.5
Loss of Appetite	N	418				422				425				419			
	Any	53	**12.7**	9.6	16.3	54	**12.8**	9.8	16.4	63	**14.8**	11.6	18.6	34	**8.1**	5.7	11.2
	Severe	1	**0.2**	0.0	1.3	0	**0**			4	**0.9**	0.3	2.4	2	**0.5**	0.1	1.7
Myalgia	N	418				422				425				419			
	Any	60	**14.4**	11.1	18.1	59	**14.0**	10.8	17.7	58	**13.6**	10.5	17.3	65	**15.5**	12.2	19.3
	Severe	5	**1.2**	0.4	2.8	2	**0.5**	0.1	1.7	4	**0.9**	0.3	2.4	1	**0.2**	0.0	1.3
Nausea	N	418				422				425				419			
	Any	54	**12.9**	9.9	16.5	48	**11.4**	8.5	14.8	42	**9.9**	7.2	13.1	46	**11.0**	8.2	14.4
	Severe	2	**0.5**	0.1	1.7	2	**0.5**	0.1	1.7	2	**0.5**	0.1	1.7	2	**0.5**	0.1	1.7

Menveo Liq24/30 = Subjects who received Menveo_Liquid vaccine aged 24/30 months; Menveo_1/2 = Subjects who received Menveo vaccine; N = number of subjects; n/% = number/percentage of subjects presenting at least one type of adverse event; 95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Table 45 Pooled analysis: Percentage of subjects with at least one solicited local and systemic adverse event (any and severe) reported during the 7-day (30 minutes after vaccination to Day 7) post-vaccination period - Solicited Safety Set (30 minutes - Day 7)

		Menveo Liquid				**Menveo**			
				95% CI				**95% CI**	
		n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
solicited systemic adverse event									
Erythema	N	1332				1328			
	Any	134	**10.1**	8.5	11.8	119	**9.0**	7.5	10.6
	>100 mm	22	**1.7**	1.0	2.5	17	**1.3**	0.7	2.0
Induration	N	1332				1328			
	Any	129	**9.7**	8.1	11.4	114	**8.6**	7.1	10.2
	>100 mm	17	**1.3**	0.7	2.0	15	**1.1**	0.6	1.9
Pain	N	1332				1328			
	Any	591	**44.4**	41.7	47.1	555	**41.8**	39.1	44.5
	Severe	14	**1.1**	0.6	1.8	10	**0.8**	0.4	1.4
solicited systemic adverse event									
Arthralgia	N	1332				1328			
	Any	137	**10.3**	8.7	12.0	136	**10.2**	8.7	12.0
	Severe	7	**0.5**	0.2	1.1	7	**0.5**	0.2	1.1
Chills	N	1332				1328			
	Any	195	**14.6**	12.8	16.7	175	**13.2**	11.4	15.1
	Severe	4	**0.3**	0.1	0.8	3	**0.2**	0.0	0.7
Fatigue	N	1332				1328			
	Any	482	**36.2**	33.6	38.8	481	**36.2**	33.6	38.9
	Severe	25	**1.9**	1.2	2.8	20	**1.5**	0.9	2.3
Fever	N	1332				1328			
	>= 38° C	37	**2.8**	2.0	3.8	40	**3.0**	2.2	4.1
	>= 40° C	1	**0.1**	0.0	0.4	1	**0.1**	0.0	0.4
Headache	N	1332				1328			
	Any	491	**36.9**	34.3	39.5	473	**35.6**	33.0	38.3
	Severe	15	**1.1**	0.6	1.9	16	**1.2**	0.7	1.9
Loss of Appetite	N	1332				1328			
	Any	147	**11.0**	9.4	12.8	128	**9.6**	8.1	11.4
	Severe	9	**0.7**	0.3	1.3	6	**0.5**	0.2	1.0

Myalgia	N	1332				1328			
	Any	176	**13.2**	11.4	15.2	182	**13.7**	11.9	15.7
	Severe	11	**0.8**	0.4	1.5	8	**0.6**	0.3	1.2
Nausea	N	1332				1328			
	Any	145	**10.9**	9.3	12.7	144	**10.8**	9.2	12.6
	Severe	6	**0.5**	0.2	1.0	8	**0.6**	0.3	1.2

Menveo Liquid = Subjects who received Menveo_Liq vaccine in study V59_71 (205343) pooled with subjects who received Menveo_Liq24 or Menveo_Liq30 vaccine in study V59_78 (207467)
Menveo = Subjects who received Menveo vaccine in study V59_71 (205343) pooled with subjects who received Menveo_1 or Menveo_2 vaccine in study V59_78 (207467)
N = number of subjects; fever = body temperature ≥ 38.0°C
n/% = number/percentage of subjects presenting at least one type of adverse event
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Unsolicited adverse event till day 29

In **study V59_78** comparable percentages of subjects in both vaccine groups experienced at least one unsolicited AEs between Day 1 and Day 29 (Menveo-Liq24: 18.3%, Menveo_1: 21.5%: Menveo-Liq30: 23.7%, Menveo_2: 23.2%). The most frequently reported **unsolicited AEs** between Day 1 and Day 29 after vaccine administration by PT during phase 1 were headache, nasopharyngitis, and upper respiratory tract infection. In phase 2 the most frequently reported unsolicited AEs were headache, injection site pain and injection site erythema (Table 46).
In the **pooled analysis** at least one unsolicited AE was reported in 22.1% and 22.4% of subjects in the Menveo Liquid group and Menveo group, respectively. Both in the Menveo Liquid and Menveo groups the most frequently reported **unsolicited AEs** were: headache, nasopharyngitis, upper respiratory tract infection, and injection site pain (Table 47). Overall, 13 (1.0%) and 6 subjects (0.5%) reported severe unsolicited AEs in the Menveo Liquid group and Menveo group, respectively. In both vaccine groups each of the severe unsolicited AEs by PT was only reported by 1 subject (0.1%).

Table 46 Summary of subjects with at least one unsolicited AE (>1%) classified by MedDRA Primary System Organ Class and Preferred Term during the 29-day (Days 1-29) post-vaccination period Phase 1 and 2; Unsolicited Safety Set

	Menveo-Liq24				**Menveo_1**				**Menveo-Liq30**				**Menveo_2**			
	N=420				**N=424**				**N=427**				**N=419**			
Primary SOC Preferred Term			**95% CI**				**95% CI**				**95% CI**				**95% CI**	
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Any Adverse Event	77	**18.3**	14.7	22.4	91	**21.5**	17.6	25.7	101	**23.7**	19.7	28.0	97	**23.2**	19.2	27.5
Abdominal pain	4	**1.0**	0.3	2.4	4	**0.9**	0.3	2.4								
Pyrexia	6	**1.4**	0.5	3.1	2	**0.5**	0.1	1.7								
Nasopharyngitis	7	**1.7**	0.7	3.4	15	**3.5**	2.0	5.8	6	**1.4**	0.5	3.0	6	**1.4**	0.5	3.1
Upper respiratory tract infection	8	**1.9**	0.8	3.7	8	**1.9**	0.8	3.7	7	**1.6**	0.7	3.3	4	**1.0**	0.3	2.4
Arthralgia	6	**1.4**	0.5	3.1	3	**0.7**	0.1	2.1	6	**1.4**	0.5	3.0	1	**0.2**	0.0	1.3
Headache	13	**3.1**	1.7	5.2	13	**3.1**	1.6	5.2	26	**6.1**	4.0	8.8	24	**5.7**	3.7	8.4
Diarrhoea									6	**1.4**	0.5	3.0	5	**1.2**	0.4	2.8
Fatigue									8	**1.9**	0.8	3.7	3	**0.7**	0.1	2.1
Injection site erythema									10	**2.3**	1.1	4.3	7	**1.7**	0.7	3.4
Injection site induration									8	**1.9**	0.8	3.7	4	**1.0**	0.3	2.4
Injection site pain									12	**2.8**	1.5	4.9	9	**2.1**	1.0	4.0
Rhinitis									5	**1.2**	0.4	2.7	7	**1.7**	0.7	3.4
Back pain									5	**1.2**	0.4	2.7	4	**1.0**	0.3	2.4

n/% = number/percentage of subjects reporting the adverse event at least once
N = number of subjects included in the considered analysis set in each group
At least one adverse event = at least one adverse event experienced (regardless of the MedDRA Preferred Term), MedDRA version 23.0
Menveo-Liq24 = Subjects who received Menveo Liquid vaccine aged 24 months, Menveo_1 = Subjects who received Licensed Menveo vaccine
95% CI = Exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
SOC = System Organ Class

Table 47 Summary of subjects with unsolicited adverse (>0.5%) events classified by MedDRA preferred term with onset during the 29-day (Days 1-29) post-vaccination period sorted by overall frequency. Unsolicited Safety Set

	Menveo Liquid; N=1336				**Menveo; N=1332**			
			95% CI				**95% CI**	
Primary System Organ Class Preferred Term	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Any Adverse Event								
Headache	48	3.6	2.7	4.7	51	3.8	2.9	5.0
Nasopharyngitis	24	1.8	1.2	2.7	31	2.3	1.6	3.3
Upper respiratory tract infection	25	1.9	1.2	2.8	18	1.4	0.8	2.1
Injection site pain	19	1.4	0.9	2.2	13	1.0	0.5	1.7
Injection site erythema	16	1.2	0.7	1.9	12	0.9	0.5	1.6
Rhinitis	9	0.7	0.3	1.3	17	1.3	0.7	2.0
Abdominal pain	10	0.7	0.4	1.4	11	0.8	0.4	1.5
Arthralgia	13	1.0	0.5	1.7	6	0.5	0.2	1.0
Fatigue	11	0.8	0.4	1.5	8	0.6	0.3	1.2
Diarrhoea	11	0.8	0.4	1.5	7	0.5	0.2	1.1
Injection site induration	13	1.0	0.5	1.7	5	0.4	0.1	0.9
Pyrexia	13	1.0	0.5	1.7	4	0.3	0.1	0.8
Myalgia	8	0.6	0.3	1.2	6	0.5	0.2	1.0
Oropharyngeal pain	10	0.7	0.4	1.4	4	0.3	0.1	0.8

95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
n/% = number/percentage of subjects presenting at least one type of adverse event
* Adverse events reported by a subject classified by the same Primary System Organ Class are counted once
N = number of subjects included in the considered analysis set in each group
Menveo = Subjects who received Menveo vaccine in study V59_71 (205343) pooled with subjects who received Menveo_1 or Menveo_2 vaccine in study V59_78 (207467)
Menveo Liquid = Subjects who received Menveo_Liq vaccine in study V59_71 (205343) pooled with subjects who received Menveo_Liq24 or Menveo_Liq30 vaccine in study
V59_78 (207467)

Unsolicited related adverse events

In **study V59_78** comparable percentages of subjects in both vaccine groups experienced at least one related unsolicited AEs between Day 1 and Day 29 (5.2% in the Menveo_Liq24 vs 4.7% in the Menveo_1 group and 7.3% in the Menveo_Liq30 group vs 5.3% in the Menveo_2 group), Table 48.

The most frequently reported unsolicited AEs by PT considered by the investigator to be related to study vaccines in phase 1 was headache. Few subjects experienced severe unsolicited AEs in both vaccine groups (Menveo-Liq24: 1.2%, Menveo_1: 0.2%), 6 of which were considered by the investigator to be related to the study vaccines (Menveo- Liq24: 5 and Menveo_1: 1), injection site erythema, injection site induration, injection site oedema, injection site pain, and pyrexia in the Menveo-Liq24 group and injection site oedema in the Menveo_1 group.

The most frequently reported unsolicited AEs by PT considered by the investigator to be related to study vaccines were: injection site pain, injection site erythema, injection site induration, and headache. Few subjects (0.5% of subjects) experienced severe unsolicited AEs in both vaccines, respectively 4 of which were considered by the investigator to be related to the study vaccines

(MenveoLiq30: 2 and Menveo_2: 2), facial pain and fatigue in the Menveo-Liq30 and injection site erythema and injection site pain in the Menveo_2 group.

Table 48 Summary of subjects with at least one unsolicited AE (>0.5%) classified by MedDRA Primary System Organ Class and Preferred Term related to vaccination during the 29-day (Days 1-29) post-vaccination period Phase 1 and 2; Unsolicited Safety Set

	Menveo-Liq				**Menveo**			
			95% CI				**95% CI**	
Primary System Organ Class **Preferred Term**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Phase 1: Menveo_Liq24 vs Menveo_1								
Number of participants in safety set	420				424			
Any Adverse Event	22	5.2	3.3	7.8	20	4.7	2.9	7.2
Abdominal pain	3	0.7	0.1	2.1	1	0.2	0.0	1.3
Chills	1	0.2	0.0	1.3	2	0.5	0.1	1.7
Fatigue	0	0.0			2	0.5	0.1	1.7
Injection site erythema	3	0.7	0.1	2.1	1	0.2	0.0	1.3
Injection site induration	2	0.5	0.1	1.7	0	0.0		
Injection site pain	3	0.7	0.1	2.1	2	0.5	0.1	1.7
Injection site pruritus	2	0.5	0.1	1.7	3	0.7	0.1	2.1
Pyrexia	3	0.7	0.1	2.1	0	0.0		
Decreased appetite	1	0.2	0.0	1.3	2	0.5	0.1	1.7
Headache	5	1.2	0.4	2.8	5	1.2	0.4	2.7
Phase 2: Menveo_Liq30 vs Menveo_2								
Number of participants in safety set	427				419			
Any Adverse Event	31	7.3	5.0	10.1	22	5.3	3.3	7.8
Nausea	2	0.5	0.1	1.7	0	0.0		
Fatigue	3	0.7	0.1	2.0	3	0.7	0.1	2.1
Injection site erythema	10	2.3	1.1	4.3	7	1.7	0.7	3.4
Injection site induration	8	1.9	0.8	3.7	4	1.0	0.3	2.4
Injection site pain	12	2.8	1.5	4.9	9	2.1	1.0	4.0
Injection site pruritus	2	0.5	0.1	1.7	2	0.5	0.1	1.7
Pyrexia	2	0.5	0.1	1.7	0	0.0		
Arthralgia	4	0.9	0.3	2.4	1	0.2	0.0	1.3
Myalgia	2	0.5	0.1	1.7	2	0.5	0.1	1.7
Headache	7	1.6	0.7	3.3	7	1.7	0.7	3.4

95% CI = Exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
n/% = number/percentage of subjects reporting the adverse event at least once
N = number of subjects included in the considered analysis set in each group
At least one adverse event = at least one adverse event experienced (regardless of the MedDRA Preferred Term), MedDRA version 23.0
Menveo-Liq24/30 = Subjects who received Menveo Liquid vaccine aged 24/30 months, Menveo_1/2 = Subjects who received Licensed Menveo vaccine

In the **pooled analysis**, at least one related unsolicited AE was reported in 6.2% and 5.0% of subjects in the Menveo Liquid group and Menveo group, respectively. The most frequently reported related unsolicited AEs by PT were: injection site pain, headache, and injection site erythema (Table 49).

Overall, 5 subjects (0.4%) and 3 subjects (0.2%) reported severe related unsolicited AEs in the Menveo Liquid group and Menveo group, respectively. The AEs reported were facial pain, fatigue, injection site erythema, injection site induration, injection site oedema, injection site pain, and pyrexia in the Menveo Liquid group and injection site erythema, injection site oedema and injection site pain in the Menveo group.

Table 49 Summary of subjects with unsolicited adverse events (>0.5%) classified by MedDRA preferred term related to vaccination with onset during the 29-day (Days 1-29) post-vaccination period sorted by overall frequency Unsolicited Safety Set

	Menveo Liquid; N=1336				Menveo; N=1332			
			95% CI				95% CI	
Preferred Term	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Injection site pain	19	1.4	0.9	2.2	13	1.0	0.5	1.7
Headache	15	1.1	0.6	1.8	16	1.2	0.7	1.9
Injection site erythema	16	1.2	0.7	1.9	12	0.9	0.5	1.6
Injection site induration	12	0.9	0.5	1.6	5	0.4	0.1	0.9
Fatigue	5	0.4	0.1	0.9	5	0.4	0.1	0.9
Injection site pruritus	5	0.4	0.1	0.9	5	0.4	0.1	0.9
Pyrexia	7	0.5	0.2	1.1	0	0		

Menveo Liquid = Subjects who received Menveo_Liq vaccine in study V59_71 (205343) pooled with subjects who received Menveo_Liq24 or Menveo_Liq30 vaccine in study
V59_78 (207467) 95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
n/% = number/percentage of subjects presenting at least one type of adverse event
* Adverse events reported by a subject classified by the same Primary System Organ Class are counted once
N = number of subjects included in the considered analysis set in each group

2.6.8.3. Serious adverse event/deaths/other significant events

SAE's

During the entire study period (Day 1 to Day 181) within study **V59_78**, in total 13 participants experienced an SAE: 4 SAEs were reported by 4 subjects (1%) in the Menveo-Liq24 group (tooth abscess, soft tissue injury, appendicitis noninfective, and ovarian cyst ruptured) and 1 SAE was reported by 1 subject (0.2%) in the Menveo_1 group (malignant melanoma), 4 SAEs were reported by 4 subjects (0.9%) in the Menveo-Liq30 group (post procedural haemorrhage, tibia fracture, abortion spontaneous, and depression) and 4 SAEs were reported by 4 subjects (1.0%) in the Menveo_2 group (phimosis, otitis externa, tension headache, and adnexa uteri pain). None of the SAEs was considered by the investigator to be related to the study vaccines.

Pooled data: During the entire safety follow-up period (Day 1 to Day 181) in the 2 studies, 14 subjects (1.0%) in the Menveo Liquid group and 14 subjects (1.1%) in the Menveo group reported SAEs. In the Menveo Liquid group, the most frequently reported SAEs were abortion spontaneous by 2 (0.1%) subjects and ovarian cyst ruptured by 2 (0.1%) subjects. Other SAEs did not occur more than once in each group. None of the SAEs was considered by the investigator to be related to the study vaccines.

Death

No deaths were reported.

Adverse events resulting in medically attended visits

During the entire safety follow-up period (Day 1 to Day 181) similar percentages of **medically attended AEs** were reported in the 2 vaccine groups (18.6% and 17.3% in the Menveo Liquid group and Menveo group, respectively). The most frequently reported medically attended AEs by PT were pharyngitis (1.2%), upper respiratory tract infection (1.1%), gastroenteritis (1.0%), influenza (1.0%),

nasopharyngitis (1.0%) and viral infection (0.9%) in the Menveo Liquid group; nasopharyngitis (1.0%) and bronchitis and pharyngitis (reported by 0.8% of subjects each PT) in the Menveo group.

Medically attended AEs considered as related to study vaccination were reported in the 2 vaccine groups (1.0% and 0.8% in the Menveo Liquid group and Menveo group, respectively). The most frequently reported medically attended AEs considered as related by PT were injection site erythema (0.4%), injection site induration (0.4%), injection site pain (0.4%) and headache (0.3%) in the Menveo Liquid group; injection site erythema (0.4%), injection site pain (0.3%), injection site induration (0.2%), fatigue (0.2%) and headache (0.2%) in the Menveo group.

Special patient populations

In these sub-group analysis only the pooled date are presented.

Age and Sex

Age

The analysis based on age revealed higher percentages of subjects ≥ 10 to <18 years of age reporting solicited AEs than subjects ≥18 years of age during first 7 day after vaccination. This observation was seen in both the Menveo Liquid and Menveo.

From 30 minutes through Day 7, in both age groups pain at the injection site was the most frequently reported solicited local AE. Erythema and induration at the injection site were reported more frequently in subjects ≥ 10 to <18 years of age than in subjects ≥ 18 years of age.

From 30 minutes through Day 7, most solicited systemic AEs were reported more frequently in subjects ≥ 10 to <18 years of age than in subjects ≥ 18 years of age. In subjects ≥10 to <18 years of age the most frequently reported solicited systemic AE was headache. In subjects ≥ 18 years of age the most frequently reported solicited systemic AE was fatigue.

The safety profile in general was comparable for both age subgroups.

Table 50 Pooled analysis: Summary of subjects by unsolicited adverse event category during the 29-day (Days 1-29) post-vaccination period by age group - Unsolicited Safety Set

	Menveo_Liquid				Menveo				Total			
			95% CI				95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Age Group: Children And Adolescents (10-17 years)												
N	342				341				683			
At least one unsolicited AE	77	**22.5**	18.2	27.3	73	**21.4**	17.2	26.1	150	**22**	18.9	25.3
At least one related unsolicited AE	25	**7.3**	4.8	10.6	17	**5.0**	2.9	7.9	42	**6.1**	4.5	8.2
At least one SAE	0	**0**			0	**0**			0	**0**		
At least one related SEA	0	**0**			0	**0**			0	**0**		
At least one MAAE	28	**8.2**	5.5	11.6	32	**9.4**	6.5	13.0	60	**8.8**	6.8	11.2
At least one related MAAE	9	**2.6**	1.2	4.9	9	**2.6**	1.2	5.0	18	**2.6**	1.6	4.1
At least one AE leading to withdrawal	0	**0**			0	**0**			0	**0**		
At least one fatal AE	0	**0**			0	**0**			0	**0**		
Age Group: Adults (18-40 years)*												
N												
At least one unsolicited AE	218	**21.9**	19.4	24.6	226	**22.8**	20.2	25.5	444	**22.4**	20.6	24.3
At least one related unsolicited AE	58	**5.8**	4.5	7.5	50	**5.0**	3.8	6.6	108	**5.4**	4.5	6.5
At least one SAE	4	**0.4**	0.1	1.0	3	**0.3**	0.1	0.9	7	**0.4**	0.1	0.7
At least one related SEA	0	**0**			0	**0**			0	**0**		
At least one MAAE	62	**6.2**	4.8	7.9	60	**6.1**	4.7	7.7	122	**6.1**	5.1	7.3
At least one related MAAE	5	**0.5**	0.2	1.2	2	**0.2**	0.0	0.7	7	**0.4**	0.1	0.7
At least one AE leading to withdrawal	0	**0**			0	**0**			0	**0**		
At least one fatal AE	0	**0**			0	**0**			0	**0**		

Menveo Liquid = Subjects who received Menveo_Liq vaccine in study V59_71 (205343) pooled with subjects who received Menveo_Liq24 or Menveo_Liq30 vaccine in study V59_78 (207467)
Menveo = Subjects who received Menveo vaccine in study V59_71 (205343) pooled with subjects who received Menveo_1 or Menveo_2 vaccine in study V59_78 (207467)
N = number of subjects included in the considered analysis set in each group
* Adverse events reported by a subject classified by the same Primary System Organ Class are counted once
n/% = number/percentage of subjects presenting at least one type of adverse event
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
*One subject 44 years of age was exposed to Menveo Liquid and included in the safety analysis
AE: adverse event; MAAE: medically attended adverse event; SAE: serious adverse event.

Sex

The analyses per sex were not predefined but provided upon request. In general, females reported a higher proportion of adverse events, both solicited and unsolicited, than males, with no difference across subjects receiving Menveo liquid vs subjects receiving Menveo (*Table 51*).

Table 51 Summary of subjects by unsolicited adverse event category during the 29-day (Days 1-29) by sex – unsolicited safety set

Male	Menveo Liquid N=537				Menveo N=557				Total N=1094			
	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one unsolicited AE	93	17.3	14.2	20.8	108	19.4	16.2	22.9	201	18.4	16.1	20.8
At least one related unsolicited AE	26	4.8	3.2	7.0	23	4.1	2.6	6.1	49	4.5	3.3	5.9
At least one serious unsolicited AE	0	0.0			0	0.0			0	0.0		
At least one related serious unsolicited AE	0	0.0			0	0.0			0	0.0		
At least one medically attended unsolicited AE	29	5.4	3.6	7.7	37	6.6	4.7	9.0	66	6.0	4.7	7.6
At least one related medically attended unsolicited AE	5	0.9	0.3	2.2	7	1.3	0.5	2.6	12	1.1	0.6	1.9
At least one leading to withdrawal unsolicited AE	0	0			0	0			0	0		
At least one leading to withdrawal unsolicited AE	0	0			0	0			0	0		

Female	Menveo Liquid N=799				Menveo N=775				Total N=1574			
	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one unsolicited AE	202	**25.3**	22.3	28.4	191	**24.6**	21.6	27.8	**393**	25.0	22.8	27.2
At least one related unsolicited AE	57	**7.1**	5.4	9.1	44	**5.7**	4.2	7.5	**101**	6.4	5.3	7.7
At least one serious unsolicited AE	4	**0.5**	0.1	1.3	3	**0.4**	0.1	1.1	**7**	0.4	0.2	0.9
At least one related serious unsolicited AE	0	**0.0**			0	**0.0**			**0**	0.0		
At least one medically attended unsolicited AE	61	**7.6**	5.9	9.7	55	**7.1**	5.4	9.1	**116**	7.4	6.1	8.8
At least one related medically attended unsolicited AE	9	**1.1**	0.5	2.1	4	**0.5**	0.1	1.3	**13**	0.8	0.4	1.4
At least one leading to withdrawal unsolicited AE	0	**0.0**			0	**0.0**			**0**	0.0		
At least one leading to withdrawal unsolicited AE	0	**0.0**			0	**0.0**			**0**	0.0		

n/% = number/percentage of subjects presenting at least one type of adverse event
* Adverse events reported by a subject classified by the same Primary System Organ Class are counted once
N = number of subjects included in the considered analysis set in each group
MenACWY = Subjects who received ACWY vaccine in study V59_71 pooled with subjects who received ACWY_1 or ACWY_2 vaccine in study V59_78
MenACWY Liquid = Subjects who received ACWY_Liq vaccine in study V59_71 pooled with subjects who received ACWY_Liq24 or ACWY_Liq30 vaccine in study V59_78

2.6.8.4. Laboratory findings

Not applicable

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Immunological events

Discussed in the efficacy part

2.6.8.7. Safety related to drug-drug interactions and other interactions

No information submitted

2.6.8.8. Discontinuation due to adverse events

None of the patients discontinued due to adverse events

2.6.8.9. Post marketing experience

Menveo Liquid is a new formulation, recently approved in the US and Brazil; therefore, there are no post-marketing data on Menveo Liquid in the safety database.

2.6.9. Discussion on clinical safety

The safety profile of the currently licensed Menveo is well known and has been studied extensively. The clinical safety of Menveo liquid was evaluated in 2 clinical trials, V59_71 and V59_78, in which participants ≥ 10 years of age received either artificially or naturally aged Menveo liquid formulation and, in the control group, Menveo.

Standard safety data collection methods, in-line with those adopted throughout the *Menveo* clinical development program, were used for both studies, V59_71 and V59_78, and consisted of the assessment of reactogenicity events (solicited local and systemic AEs), and evaluation of unsolicited AEs, including medically attended AEs, AEs leading to withdrawal from the study and SAEs.

In both studies solicited local (induration/erythema/pain at injection site) and systemic AEs (chills, nausea, myalgia, arthralgia, headache, fatigue, loss of appetite, fever [temperature ≥38.0ºC]) within 30 minutes after vaccination were collected at the site and recorded in the eCRF and from 30 minutes through Day 7 post-vaccination were recorded by the subjects on patient electronic diary cards (this includes solicited AEs collected from 30 minutes until 6 hours after vaccination).

An integrated safety analysis was performed.

Exposure

In total, 1337 subjects were exposed to a single dose of the new formulation, Menveo liquid. Slightly more females were included (59.8%) and most subjects were of white race (80.0%). The size and composition of the safety database is considered sufficient to evaluate uncommon (0.1% to 1%) and commonly (1% - 10%) occurring adverse events. Within the context of the proposed changes in formulation and the well-known safety profile of Menveo, the overall safety database is considered acceptable. However, the safety information for children and adolescents is considered limited as only 324 subjects were exposed to Menveo Liquid (24 and 30 months maturation combined) in study V59_78.

Solicited adverse events (local and systemic)

Within 30 minutes after vaccination in study V59_78, <10% of participants experienced any solicited AE (3.6% of subjects in the Menveo liquid 24 month, 2.6% in the Menveo_1 group, 7.0% in the Menveo liquid 30-month group and 6.9% of in the Menveo_2 group). The percentage of participants experiencing a solicited AE was slightly higher in the Menveo liquid group. This was confirmed in the pooled analysis, with any solicited adverse event being reported by 5.5% (95% CI 4.3-6.8) of participants in the Menveo liquid group and 4.4% (95%CI 3.3 -5.6) in the Menveo group.

Observations about reactogenicity events occurring between 30 minutes and 7 days after vaccination were consistent across studies, with the majority of participants (>68%) experiencing 1 or more solicited AEs within 7 days.

During study V59_78, solicited local adverse events were comparable between the Menveo Liquid group versus the Menveo group (47.4% of participants in the Menveo liquid 24 month group vs 45.7% in the Menveo_1 group and 49.6% in the Menveo liquid 30 month group vs 47.5% in the Menveo_2 group). Pain at the injection site was the most frequently reported solicited local AE in both vaccine groups in both phases. The majority of cases were mild and severe pain was reported by <2% of participants. Most of the solicited local AEs following vaccination in both treatment arms were mild to moderate in intensity, had an onset between 30 minutes to Day 3 post vaccination and resolved within 7 days after vaccination. Differences observed between the Menveo liquid and Menveo arms do not indicate a clinical relevant difference.

Solicited systemic events were experienced by the majority of participants from 30 minutes after vaccination until 7 days after vaccination, (60.5% in the Menveo liquid 24-month group vs 57.8% in the Menveo_1 group and 57.6% in the Menveo liquid 30-month group vs 55.4% in the Menveo_2 group). The most frequently reported systemic AEs were fatigue and headache in both vaccine groups and both phases. The intensity of fatigue and headache was mostly mild. Severe fatigue was reported by <2.5% of participants and severe headache by <2% in both treatment groups and phases. Fever occurred in similar frequencies across treatment groups and phases: 3.6% of subjects in the Menveo liquid 24-month group, 4.3% of subjects in the Menveo_1 group, 3.5% of subjects in the Menveo liquid 30 month group, and 2.9% of subjects in the Menveo_2 group. The majority of solicited systemic AEs resolved within 7 days after vaccination.

The pooled analysis showed similar results. The majority of participants experienced at least 1 solicited systemic or local AE (69.2% in the Menveo liquid group vs 68.2% in the Menveo group). The most frequently reported solicited AEs were pain at the injection site, headache and fatigue. The vast majority of solicited AEs were mild to moderate in intensity and resolved within 7 days after vaccination. Although the frequency of most solicited AE's is slightly higher for the liquid formulation, this difference was not considered clinically relevant.

The observed reactogenicity profile is in general in line with what is known for Menveo.

Unsolicited adverse events

In study V59_78 comparable percentages of subjects in both vaccine groups experienced at least one unsolicited AE between Day 1 and Day 29 (Menveo liquid 24 month: 18.3%, Menveo_1: 21.5%: Menveo liquid 30 month: 23.7%, Menveo_2: 23.2%). The most frequently reported unsolicited AEs between Day 1 and Day 29 after vaccine administration in both groups and both phases were in the SOC infections and infestations, general disorders and administration site conditions and nervous system disorders. The reported adverse events were similar (i.e. not considered clinically relevant different) in presentation and frequency between treatment groups.

In the pooled analysis at least one unsolicited AE was reported in 22.1% and 22.4% of subjects in the Menveo liquid group and Menveo group, respectively. In line with study V59_78, the most frequently reported unsolicited AEs were in the SOC general disorder and administration site conditions and infections and infestations. Overall, 13 (1.0%) and 6 subjects (0.5%) reported severe unsolicited AEs in the Menveo Liquid group and Menveo group, respectively. In both vaccine groups each of the severe unsolicited AEs was only reported by 1 subject (0.1%).

The proportion of participants experiencing vaccine-related AEs were similar between groups: (5.2% in the Menveo liquid 24-month vs 4.7% in the Menveo_1 group and 7.3% in the Menveo liquid 30 month group vs 5.3% in the Menveo_2 group). The most frequently reported unsolicited AEs in study V59_78 considered by the investigator to be related to study vaccines were considered solicited AEs during the first 7 days after vaccination: headache in phase 1 reported by 5 subjects (1.2%) in both treatment arms and injection site pain (2.8% vs 2.1%), injection site erythema (2.3% vs 1.7%), injection site induration (1.9% vs 1.0), and headache (1.6%) in the Menveo liquid 30 month group and Menveo_2 group respectively. Few subjects (<1% of subjects) experienced severe unsolicited AEs related to the vaccine in both treatment groups and phases of the study. None were reported by more than 1 participant.

In the pooled analysis, at least one related unsolicited AE was reported in 6.2% and 5.0% of subjects in the Menveo liquid group and Menveo group, respectively. The most frequently reported related unsolicited AEs were: injection site pain (reported in 1.4% and 1.0% of subjects in the Menveo Liquid and Menveo groups, respectively), headache (reported in 1.1% and 1.2% of subjects in the Menveo

liquid and Menveo groups, respectively), and injection site erythema (reported in 1.2% and 0.9% of subjects in the Menveo liquid and Menveo groups, respectively).

Of note, the SmPC currently provides three different ADR tables (i.e. one for children 2-10 years, one for individuals 11-65 years, and one with post-marketing ADRs). According to the SmPC guidance, separate tables are acceptable in exceptional cases where the adverse reaction profiles markedly differ depending on the use of the product. Slightly different ADR profiles based on age do not constitute such exceptional circumstances. The MAH cited multiple reasons for not updating section 4.8 of the SmPC, including the desire to keep the information in 4.8 between Menveo liquid and Menveo lyophilized similar, as these come from the same data sources. The MAH has committed to submit a variation within the next 6 months. This variation should update the Menveo lyophilized SmPC to QRD format (thereby aligning it with Menveo liquid), update section 4.8 of the SmPC for both Menveo lyophilized and Menveo liquid in which a single ADR table is provided for all age groups and post-marketing data, and should re-evaluates (using both clinical and post-marketing data) whether the frequencies of some post-marketing ADR's are still "unknown."

A number of hypersensitivity reactions are reported via the ADR "rash", including one patient presenting with urticaria judged related to vaccination. This is a clear hypersensitivity event for which inclusion in the labelling could be relevant to prescribers. In the next PSUR, the MAH has committed to provide a cumulative review of all evidence concerning urticaria.

No deaths were reported.

During the entire safety follow-up period (Day 1 to Day 181) in the 2 studies, 14 subjects (1.0%) in the Menveo Liquid group and 14 subjects (1.1%) in the Menveo group reported SAEs. None of the SAEs were considered related.

Frequencies of medically attended AEs were largely comparable between the two treatment groups. MAAEs considered related to the vaccine occurred in ≤1% of participants in both treatment groups and were mostly related to solicited AEs.

Special patient populations

In this sub-group analysis only the pooled data are presented and discussed.

An analysis based on sex was submitted upon request. As expected, females showed higher reactogenicity than males, however the differences are not great enough to warrant different prescribing practices and therefore do not need to be incorporated into the SmPC.

The analysis based on age revealed that, as expected, higher percentages of subjects ≥ 10 to <18 years of age reported solicited AEs than subjects ≥18 years of age during the first 30 minutes and in the period 30 minutes to 7 days. This observation was seen in both the Menveo Liquid and Menveo. Overall, the profile of solicited AEs was similar between the two age groups, with pain at the injection site being the most frequently reported solicited AE, followed by headache and fatigue. Considering the small differences in frequencies and the fact that the vast majority of solicited AEs are mild to moderate in intensity and of short duration, these differences are not considered clinically relevant.

Extrapolation to children between 2 and 10 years of age

No safety information for children aged 2-9 years was submitted although the Applicant does include this population in the requested indication and the currently licensed Menveo is indicated for this population. In case the formulations can be considered similar, extrapolation of the safety data from the currently licensed Menveo to the liquid formulation would be acceptable.

2.6.10. Conclusions on the clinical safety

The safety profile of Menveo liquid appears to be similar to the safety profile of the currently licensed formulation. It is a moderately reactogenic vaccine, with the majority of participants reporting 1 or more AEs; however, these were mostly mild or moderate in intensity and of short duration (≤3 days). The most frequently reported AEs by PT were solicited AEs. As expected, reactogenicity decreased with age. No SAEs or deaths occurred that were considered possibly related to Menveo liquid. No new safety signals were observed. Menveo liquid is well tolerated in children ≥10 years, adolescents and adults. No new safety signals were observed.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP v11.1:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.7.1.1. Discussion on safety specification

The concerns regarding the extrapolation to children 2-9 years of age are considered resolved. Therefore, it is acceptable that there are no safety concerns.

2.7.1.2. Conclusions on the safety specification

Having considered the data in the safety specification the rapporteur agrees the empty summary of safety concerns is appropriate.

2.7.2. Pharmacovigilance plan

No pharmacovigilance activities beyond routine pharmacovigilance activities have been proposed. This is acceptable.

2.7.3. Risk minimisation measures

No additional risk minimisation measures have been proposed. This is considered acceptable.

2.7.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 11.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: since the package leaflets of Menveo Liquid and the currently licensed Menveo formulation are almost identical, the results of the Menjugate package leaflet user testing are also considered applicable to the Menveo Liquid package leaflet and no additional user testing is deemed necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed therapeutic indication for the Menveo liquid is identical to the indication currently included for the Menveo vaccine:

"The 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. The use of this vaccine should be in accordance with official recommendations". *Neisseria meningitidis* forms a leading cause of bacterial meningitis and sepsis in both industrialised and developing countries worldwide. Invasive meningococcal disease (IMD) develops rapidly and has a case-fatality ratio of 8-16%, even when promptly diagnosed and treated. The numerous serotypes of meningococcus are characterized by differences in the polysaccharide capsule. Five serogroups (A, B, C, Y and W-135) are responsible for the vast majority of cases of meningococcal disease worldwide. In Europe, serogroups B and C are

the most common causes of IMD, however there has been an increase of IMD due to serogroup W. (ECDC)

3.1.2. Available therapies and unmet medical need

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.

Prevention

There are various vaccines available for the prevention of IMD. There are currently three quadrivalent vaccines available in the European union. The majority, but not all of countries within the EU incorporate meningococcal vaccination for at least one serogroup in their program.

The currently licensed Menveo is a quadrivalent conjugate meningococcal vaccine, with the final formulation available in a two vial presentation to be combined prior to administration.

Unmet medical need

In the current line-extension, the MAH presents a fully liquid form which it claims will simplify the vaccine administration, prevent occurrence of administration errors and to optimise vaccine shipment and storage.

3.1.3. Main clinical studies

The evidence presented for the use of the Menveo liquid vaccine in this line-extension is presented in the form of safety and immunogenicity data from two different phase 2b, randomised, controlled, observer-blind, multi-center, non-inferiority clinical trials.

In study V59_71 healthy participants aged 18 to 40 years of age were randomised to either the investigational artificially aged Menveo liquid vaccine, which includes approximately 30% Men A free saccharides (FS), (n=493) or the currently licensed Menveo vaccine (n=490, Menveo).

In study V59_78 otherwise healthy participants aged 10-40 years of age were randomised to either the investigational naturally aged Menveo liquid vaccine, aged approximately 24 months (n=420, Phase 1) or 30 months (n=426, Phase 2), or the currently licensed Menveo vaccine (n=430 in phase 1 and 420 in phase 2).

3.2. Favourable effects

- **Non-inferiority**: For V59_71 and both phase 1 and phase 2 of V59_78, the primary outcome (GMT ratio) with the non-inferiority criteria for which the study was powered (LL of the 95% CI ≥0.5) was attained. Therefore the studies were formally successful.
- **Supportive evidence:** The immunogenicity results of the pooled studies (for both seroprotection and seroresponse) further support the conclusion that there are no clinically

relevant differences between the two formulations. Upon pooling the studies, the LL of the 95% CI for GMT's was ≥-5% for the percentage of participants achieving seroprotection (hSBA titer ≥1:8) and ≥0.67 for the percentage of participants with a seroresponse (GMT ratio) for all N. meningitis serogroups.

- **Immunogenicity results in seronegative individuals**, consisting of GMT ratio's, hSBA titers, 4-fold rise, and reverse cumulative distribution curves do not indicate a different immunogenicity profile of Menveo and Menveo liquid in seropositive and seronegative individuals.

3.3. Uncertainties and limitations about favourable effects

- **Extrapolation to younger population**: There were no subjects included who were 2-9 years of age, whereas the age range of ≥2 years is included in the indication. Acceptance of this age range in the indication is based on extrapolation of the results in children aged 10 and older. The currently approved Menveo was however investigated in 2-9 year olds.
- **Use of minimisation**: In both studies a minimisation procedure was used for randomisation with for both studies V59-71 and V59-78 a percentage of randomness of 10% was used. No justification of the chosen randomness was provided. A randomness of 10% is considered very low and it is not clear whether such a low level of randomness would be sufficient to balance out unknown confounders. Therefore, subgroup analyses should be interpreted with care.

3.4. Unfavourable effects

The clinical safety profile of the liquid formulation was derived from the pooled data obtained in 2 clinical studies V59_78 and V59_71.

- **Comparable and consistent:** The safety profile for Menveo liquid and Menveo were overall comparable. A consistent reactogenicity profile was observed in the different studies. The majority of participants, >70% experienced at least 1 solicited AEs between 30 minutes and 7 days after vaccination. Injection-site pain was the most frequently reported solicited AE, followed by headache, and fatigue. Most of the reported solicited local AEs following vaccination with either vaccine were mild to moderate and resolved within 7 days.
- **Age**: The analysis based on age revealed higher percentages of subjects ≥ 10 to <18 years of age reported solicited AEs than subjects ≥18 years of age during the 7 days after vaccination. This observation was seen in both the Menveo Liquid and Menveo.
- **No new safety signals** were found in the submitted data for Menveo. None of the patients discontinued due to adverse events. No deaths or related SAEs were reported.

3.5. Uncertainties and limitations about unfavourable effects

- **Missing information:** It is not expected that the comparative safety between the two formulations is different in children aged 2-9 than observed in children aged 10 years and

older. Although the commercially authorized Menveo did investigate safety in this age group, no safety information for children aged 2-9 years was submitted for Menveo liquid.

3.6. Effects Table

There is no clinical efficacy data available in the dossier. Immunogenicity results are used to infer efficacy.

Table 52 Effects Table for Menveo liquid (unpooled data)

Effect	Short Description	Unit	Menveo Liquid	Menveo	Between group ratio/Δ	Uncertainties/ Strength of evidence
Favourable Effects						
GMTs for serogroup A						
	V59-71 Artificially aged vaccine	GMT	185.16	211.33	0.88 (0.64; 1.20)	**Primary endpoint** Primary endpoint as defined in protocol attained.
	V59-78, phase 1 24 mo aged vaccine	GMT	386.66	318.34	1.21 (0.94; 1.57)	
	V59-78, phase 2 30 mo aged vaccine	GMT	386.66	318.34	1.11 (0.87; 1.42)	
	Pooled 24 & 30 month data	GMT	393.62	297.58	1.16 (0.97-1.39)	Post-hoc analysis
% participants with hSBA titer ≥1:8 All serogroups	V59-71 Artificially aged vaccine	% MenA MenC MenW MenY	82.8 74.5 73.3 77.2	86.4 74.9 73.1 76.0	-3.69 (-8.64; 1.21) -0.40 (-6.12; 5.33) 0.26 (-5.49; 6.02) 1.15 (-4.33; 6.62)	**Secondary endpoint**
	V59-78, phase 1 24 mo aged vaccine	% MenA MenC MenW MenY	93.65 77.58 79.43 87.50	92.19 78.01 80.87 85.46	1.46 (-2.24; 5.52) -0.43 (-6.32; 5.46) -1.43 (-7.05; 4.18) 2.04 (-2.81; 6.90)	
	V59-78, phase 2 30 mo aged vaccine	% MenA MenC MenW MenY	93.37 84.17 85.86 88.04	94.01 82.85 81.77 87.56	-0.64 (-4.24; 2.96) 1.32 (-3.99; 6.64) 4.09 (-1.11; 9.33) 0.48 (-4.16; 5.13)	
	Pooled 24 & 30 month data	% MenA MenC MenW MenY		93.08 80.42 81.31 86.50	0.43 (-2.12; 3.00) 0.41 (-3.56; 4.39) 1.33 (-2.50; 5.17) 1.27 (-2.07; 4.62)	Post-hoc analysis
Unfavourable Effects						
Local solicited AE [1]	Injection-site pain	%	46	44		Source: V59_78 phase 1 and 2 SoE: These were the most commonly reported AEs in participants in both phases of study V59-78, supportive study V59_71 and the pooled analysis (ISS)
Systemic solicited AE[1]	Fatigue	%	38	38		
	Headache	%	42	37		

Abbreviations: GMT = Geometric Mean Titer; AE = adverse event; SoE = strength of evidence; FAS = full analysis set

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

This submission concerns a line extension to register a fully liquid formulation of the MenACWY vaccine, Menveo. There are currently three quadrivalent vaccines available in the European union (Nimenrix [≥6 weeks of age], Menveo [≥2 years of age], MenQuadfi (≥12 months)). The advantage of this new formulation relates to the ease of administration associated with a theoretically lower occurrence of administration errors when the need for reconstitution is no longer present.

In the MAH submitted studies, the primary objectives were met. Therefore, the studies were formally successful and type I error controlled non-inferiority of the Menveo liquid to Menveo can be claimed. However, as the studies were not planned using the CHMP preferred primary endpoint nor the more stringent CHMP recommended NI margins, there was some uncertainty whether the claimed non-inferiority indeed translates in no clinically relevant difference in immunogenicity between the Menveo Liquid and currently licensed Menveo formulation. Evidence from pooled analyses submitted after the first assessment round support the absence of clinically relevant differences in the response to the two formulations; the point estimates for the GMT ratios remained close to 1 and the difference in percentage responders (hSBA>1:8) close to 0, whilst confidence intervals became narrower. Further, the reverse cumulative distribution curves further suggest an overall similar response to both formulations across serogroups.

Furthermore, as these pooled analyses suggest that the Menveo liquid and Menveo behave similarly in seronegative persons, it is agreed that the results may be extrapolated to the broader indication currently approved for Menveo.

The documented safety exposure is sufficient for an adequate assessment of the safety profile of Menveo Liquid, also in light of the well-established safety profile of the currently licensed Menveo. The safety profile of Menveo Liquid was comparable to the safety profile of Menveo. In the 2 studies submitted in the dossier, no new safety signals were observed for Menveo liquid compared to Menveo.

3.7.2. Balance of benefits and risks

Based on the available data, the totality of evidence is sufficiently compelling to conclude that Menveo liquid is indeed similarly immunogenic as the currently authorised (lyophilized) formulation of Menveo and that the liquid formulation will not result in reduced efficacy. Furthermore, as the pooled analyses suggest that the Menveo liquid also behaves similarly as Menveo in seronegative persons, and there is no rationale to expect a differential response between the Menveo liquid and Menveo in younger children, it is agreed that the results may be extrapolated to the broader age indication currently approved for Menveo.

The overall benefit/risk balance of Menveo liquid is positive.

3.8. Conclusions

The overall benefit/risk balance of Menveo is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Menveo new pharmaceutical form, solution for injection is favourable in the following indication:

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.

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

The CHMP therefore recommends the extension of the marketing authorisation for Menveo 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.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

- **Risk Management Plan (RMP)**

The 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.