EMADOC-1700519818-2678750
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMA/VR/0000295915

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:
Hexacima	diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rdna), poliomyelitis (inact.) and haemophilus type b conjugate vaccine (adsorbed)
Hexyon	diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rdna), poliomyelitis (inact.) and haemophilus type b conjugate vaccine (adsorbed)

Marketing authorisation holder (MAH): Sanofi Winthrop Industrie

This application is in the area of: (Non-)Clinical

eCTD sequences related to the procedure: 0355, 0364

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Submission deadline	21 Nov 2025	21 Nov 2025
☐	Validation	7 Dec 2025	28 Nov 2025
☐	Start date	8 Dec 2025	8 Dec 2025
☐	CHMP Rapporteur AR	12 Jan 2026	12 Jan 2026
☐	CHMP Comments	26 Jan 2026	N/A
☐	Updated CHMP Rapporteur AR	29 Jan 2026	N/A
☐	Start of CHMP written procedure	3 Feb 2026	3 Feb 2026
☐	CHMP Outcome-RSI	5 Feb 2026	5 Feb 2026
☐	Submission of responses – Timeline changed	24 Apr 2026	24 Apr 2026
☐	Restart	27 Apr 2026	27 Apr 2026
☐	CHMP Rapporteur AR	01 Jun 2026	01 Jun 2026
☐	CHMP Comments	15 Jun 2026	15 Jun 2026
☐	Updated CHMP Rapporteur AR	18 Jun 2026	18 Jun 2026
☒	CHMP Outcome	25 Jun 2026	25 Jun 2026

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 18 November 2025 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of section 4.5 of the SmPC in order to update information regarding the co-administration of Hexaxim with meningococcal B conjugate vaccine based on results from study A3L00057 (NCT2019-002585-12). This is a Phase 4, randomised, open-label, controlled, two-arm, multi-centre study conducted in Italy and Finland, in 397 healthy infants who received a 2+1 dose regimen (at 3, 5, and 12 months of age [MoA]) with the Hexavalent vaccine administered concomitantly with PCV13, and concomitantly (at 3, 5, and 12 MoA in Group 1) or sequentially (at 4, 6, and 13 MoA in Group 2) with the 4CMenB vaccine according to a 1:1 ratio.

The requested variation(s) proposed amendments to the Summary of Product Characteristics

2. Overall conclusion and impact on the benefit/risk balance

This variation concerns an update of section 4.5 of the SmPC in order to update information regarding the co-administration of Hexacima/Hexyon with meningococcal B conjugate vaccine based on results from study A3L00057.

A3L00057 was a Phase 4, randomised, open-label, controlled, two-arm, multi-centre study conducted in Italy and Finland, in 397 healthy infants who received a 2+1 dose regimen (at 3, 5, and 12 MoA) with the Hexavalent vaccine administered concomitantly with PCV13, and concomitantly (at 3, 5, and 12 MoA in Group 1) or sequentially (at 4, 6, and 13 MoA in Group 2) with the 4CMenB.

Almost 400 participants have been included in the study, adequately distributed into Groups 1 (co-administration) and 2 (sequential administration). Participation between Finland (98 participants) and Italy (299 participants) was imbalanced.

Conduct of the study was impaired by the COVID-19 pandemic, resulting in a long recruitment-period (January 2021-January 2023), and expansion to an additional country (Finland).

The T3L90 batch used in Italy had an initial expiry date of May 2022 based on the 36-month shelf-life which was extended to May 2023 following approval by the European Medicines Agency [EMA] of the variation for a 48-month shelf-life. Potential impact of the original and extended expiry date has been evaluated regarding immunogenicity. The compiled data still suggest a cautious interpretation due to the small respective subgroup. One might perceive an increased immunological response by decrease of batch-age with exception of the anti-PRP-percentages ≥1µg/ml. The clinical relevance is not known but does not raise concerns.

The Primary Objective was to demonstrate the NI of the co-administration of the Hexavalent vaccine with the 4CMenB vaccine (Group 1) compared to the sequential administration of the same vaccines (Group 2) in terms of seroprotection rates for anti-HBsAg (≥ 10 mIU/mL) and anti-PRP antibodies (≥ 1

µg/ml). Primary Objective (Immunogenicity) was not achieved. For Hepatitis B seroprotection rates at one month after the 3rd dose non-inferiority of co-administration vs sequential dosing was demonstrated. However, for *Haemophilus influenzae* B (seroprotection rate against PRP, i.e. percentage of participants with antibody concentration ≥1 µg/mL) non-inferiority was not demonstrated.

In terms of the Secondary Objectives, descriptive analyses for each antigen have been presented. Established Correlates of Protection have been analysed. For Diphtheria, Tetanus, Polio (3 serotypes), and Hepatitis B results were adequate. For Pertussis, 4-fold increases were low, but still acceptable.

For *Haemophilus influenzae* the MAH added several analyses. All these results support adequate short-term- and long-term-rates for both Groups. Slightly lower numbers for the co-admin-Group (Group 1) compared with the sequential Group (Group 2) are known from similar settings. Adequate protection in both groups is acknowledged despite the failure of non-inferiority testing.

Surrogates of protection (including fHbp) for the MenB vaccination have been presented and are considered to be acceptable. All presented values are close to 100%. Although GMT-values for Group 1 participants are slightly lower than for participants in Group 2, these values are close to 100% and therefore considered to be acceptable.

Vaccine seroresponse rates regarding PCV13 against the 13 serotypes ranged from 98.3% to 100% in Group 1 and Group 2, except for serotype 3, with 92.3% in Group 1 and 95.7% in Group 2.
In the FAS, the GMCs were similar between Group 1 and Group 2 for each serotype, except serotypes 1 and 19F, for which GMCs were higher in Group 1.

Post-hoc analysis by country elucidates differences which are partly explained by differences in vaccination schedules. Some findings could not be explained, e.g. the low seroresponse rate for anti-PRP in Group 1 in Finland. The considerably lower number of participants in the Finnish cohort, use of a different batch, and other country-specific reasons might be causative. However, vaccine responses, irrespective of the administration schedule, are considered to be robust despite the noted differences.

Safety of the study vaccines was assessed for all participants as secondary objective by collecting solicited reactions (from Day 0 to Day 7 after each vaccination), unsolicited non-serious AEs (from Day 0 to Day 30 after each vaccination), and SAEs and AESIs (throughout the study A3L00057).

The Safety overview-table showed concentration on solicited local and systemic reactions as in similar settings. Serious adverse events were rare, deaths and serious adverse reactions were zero.

Reactogenicity (solicited adverse events) of the 3 evaluated vaccines is close together with a trend to more severe reactions after MenB vaccination. Further, numbers of severe reactions (Grade 3) are considerably higher in the Coadmin Group compared with the Sequential Group. However, this finding is as expected. Profile of the reported solicited reactions concurs with the profile in the SmPC.

Fever was reported in 73.7% of participants in Group 1 and 56.0% in Group 2. Fever of Grade 3 intensity was reported in ≤1.1% of participants in both groups. Due to an increased risk of fever when Hexacima/Hexyon was co-administered with MenB vaccine, the SmPC advises that separate vaccinations can be considered when possible.

All documented SAEs were not related with the vaccinations and represent a spectrum of infectious diseases of the respective childhood age-group with the exception of an aortic valve stenosis, presumably a connatal cardiac disease.

Overall, the safety profile of Hexacima/Hexyon as documented with concomitant administration of MenB vaccine is consistent with the known safety profile as reflected in the SmPC. Higher rates of reactogenicity are within acceptable limits, and mirror expected values.

The benefit-risk balance of Hexacima/Hexyon remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		Type
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of section 4.5 of the SmPC in order to update information regarding the co-administration of Hexaxim with meningococcal B conjugate vaccine based on results from study A3L00057 (NCT2019-002585-12). This is a Phase 4, randomised, open-label, controlled, two-arm, multi-centre study conducted in Italy and Finland, in 397 healthy infants who received a 2+1 dose regimen (at 3, 5, and 12 months of age [MoA]) with the Hexavalent vaccine administered concomitantly with pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) and concomitantly (at 3, 5, and 12 MoA in Group 1) or sequentially (at 4, 6, and 13 MoA in Group 2) with the meningococcal group B Vaccine (rDNA, component, adsorbed) vaccine.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I are recommended.

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion Hexyon/Hexacima-VR-0000295915

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

DTaP-IPV-HB-Hib[1], hexavalent vaccine (Hexaxim, Hexacima, or Hexyon depending on countries, and referred to as Hexaxim in the rest of this document) is a diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed) (Anatomical Therapeutic Chemical [ATC] code: J07CA) presented as a fully liquid ready-to-use suspension for injection (0.5 mL).

Hexaxim is indicated for primary and booster vaccination of infants and toddlers from 6 weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive diseases caused by *Haemophilus influenzae* type b. The use of this vaccine should be in accordance with official recommendations.

Hexaxim was first approved in December 2012 in Peru, was approved for use in the European Union (EU) in April 2013. Hexaxim is now approved in over 110 countries worldwide. The vial presentation is pre-qualified by the World Health Organization (WHO) since December 2014. An extensive program of clinical trials supports its use in a diverse range of primary series and booster schedules, including co-administration with other routine pediatric vaccines.

Bexsero is a meningococcal group B vaccine (rDNA, component, adsorbed) indicated for active immunization of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B.

Several European countries recommend co-administration of hexavalent vaccines and 4CMenB vaccine as part of their National Immunization Program. Co-administration of vaccines decrease the number of medical visits and can increase the overall vaccination coverage. The clinical data on immunogenicity and safety of such co-administration is useful to provide further information regarding Hexaxim.

The purpose of this application is to provide the results of study **A3L00057** (NCT2019-002585-12), evaluating the co-administration of Hexaxim with 4CMenB vaccine. The objective of this clinical variation, which provides data for co-administration of Hexaxim with meningococcal B conjugate vaccine, is to support revision of the information provided in Section 4.5 of the SmPC.

Background Information on Study A3L00057

A3L00057 (NCT2019-002585-12), was a Phase 4, randomised, open-label, controlled, two-arm, multi-centre study conducted in Italy and Finland, in 397 healthy infants who received a 2+1 dose regimen (at 3, 5, and 12 months of age [MoA]) with the Hexavalent vaccine administered concomitantly with PCV13, and concomitantly (at 3, 5, and 12 MoA in Group 1) or sequentially (at 4, 6, and 13 MoA in Group 2) with the 4CMenB according to a 1:1 ratio.

Immunogenicity was assessed for the Hexavalent vaccine, the 4CMenB vaccine, and the PCV13 vaccine.

Safety was assessed for all participants after each vaccination.

The study used as a basis for clinical data presented in this dossier was conducted in compliance with Good Clinical Practice (GCP), as required by the ICH E6 Guideline for Good Clinical Practice. The study also meets the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the Sponsor, applicable national laws and regulations

Of note, the study was initially planned to be conducted in 1 country (Italy). The 1st participant was enrolled in January 2021. However, due to the coronavirus disease 2019 (COVID-19) pandemic

[1] diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed)

situation, the enrolment was slower than anticipated. Therefore, to limit the duration of the study, one additional country (Finland) where the study vaccines licensed was added. Enrolment in Finland started on September 2022. For this purpose, another batch of Hexaxim was used in Finland.

6. Clinical Pharmacology aspects

6.1. Methods – analysis of data submitted

For A3L00057, all immunological assays (except Meningococcal serogroup B) were performed at the Sanofi Inc., Global Clinical Immunology (GCI) Platform, in Swiftwater, Pennsylvania, USA. Immunological characterization for 4CMenB vaccination was performed at United Kingdom Health Security Agency working under the Sponsor's responsibilities.

The following serological assays were used to generate the immunogenicity results:

- Diphtheria, Tetanus, and Pertussis-Electrochemiluminescence Assay (DTP-ECL)
- Poliovirus Micrometabolic Inhibition Test using Wild Type virus and Vero cells (MIT-WT)
- VITROS ECi Hepatitis B Surface Antigen (HBsAg) Assay
- *Haemophilus influenzae* type b (Hib) Polyribosylribitol Phosphate (PRP) Radioimmunoassay (RIA)
- *Neisseria meningitidis* serogroup B Serum Bactericidal Antibody Assay using human complement (hSBA)
- Multiplexed Electrochemiluminescent Method for the Detection of human immunoglobulin G (IgG) Antibodies to Pneumococcal Polysaccharide Antigens in Human Sera Samples (PnPS-ECL)

A description of the principle, justification, background, and procedure for each serological assay is provided in Module 5 of the submission. Included in the description of the assay procedure is a description of critical materials, references (reference standard for determining concentration or reference serum for ensuring assay validity), quality controls, calculation methods, and assay validity criteria. This document contains an overview of the validation studies available for each assay and the descriptions of the validation characteristics that were studied. In addition, it summarizes the validation study data presented in the report.

6.2. Discussion and Conclusion

Validation information for the serological assays demonstrates that the assays were appropriate and suitable for the intended use in the evaluation of clinical samples.

7. Clinical Efficacy aspects

A3L00057 was a Phase 4, randomised, open-label, controlled, two-arm, multi-centre study conducted in Italy and Finland, in 397 healthy infants who received a 2+1 dose regimen (at 3, 5, and 12 MoA) with the Hexavalent vaccine administered concomitantly with PCV13, and concomitantly (at 3, 5, and 12 MoA in Group 1) or sequentially (at 4, 6, and 13 MoA in Group 2) with the 4CMenB.

396 Healthy infants were planned to be randomised to Group 1 (co-administration) or Group 2 (sequential administration) according to a 1:1 ratio.

Immunogenicity was assessed for the Hexavalent vaccine, the 4CMenB vaccine, and the PCV13 vaccine. Immunogenicity was assessed pre dose 1 and 1-month post-Dose 3 for the hexavalent vaccine and 4CMenB vaccine; and, 1-month post-Dose 3 for the PCV13 vaccine.

Bexsero can be given concomitantly with any of the following vaccine antigens, either as monovalent or as combination vaccines: diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, heptavalent pneumococcal conjugate, measles, mumps, rubella, varicella, and meningococcal groups A, C, W, Y conjugate. Co-administration of the MenB vaccine (Bexsero) with a hexavalent vaccine (Infanrix hexa) has been assessed in 1 clinical study showing no interference in the immune response to any antigen.

Hexaxim has been used in co-administration with PCV7 or PCV13 in several clinical studies; Hexaxim has been co-administered with PCV13 in European studies, showing no interference in the immune response to any antigens contained in Hexaxim or PCV13 vaccines. The current study aimed to assess the co-administration of Hexaxim with the 4CMenB vaccine (Bexsero), comparing a co-administration group to a sequential administration group, thus allowing identification of potential interference between both vaccines.

This was an open-label study as the number of vaccines administered in each group was different at each visit. The assessment of primary endpoints (immunogenicity of the hexavalent vaccine) and secondary endpoints (immunogenicity of the study vaccines) was performed by laboratory staff blinded to study group.

Overall, 398 participants were enrolled, and 397 participants were randomised in the study (2021-2023). Among these randomised participants, 201 and 196 participants were randomised in Group 1 (co-administration) and Group 2 (sequential administration), respectively.

Among the 397 participants randomised in the study:

- In Italy, 299 participants (75.3%) were randomised in 5 centres: 151 in Group 1 and 148 in Group 2.
- In Finland, 98 participants (24.7%) were randomised in 6 centres: 50 in Group 1 and 48 in Group 2.

Group 1 (co-administration) – 201 participants

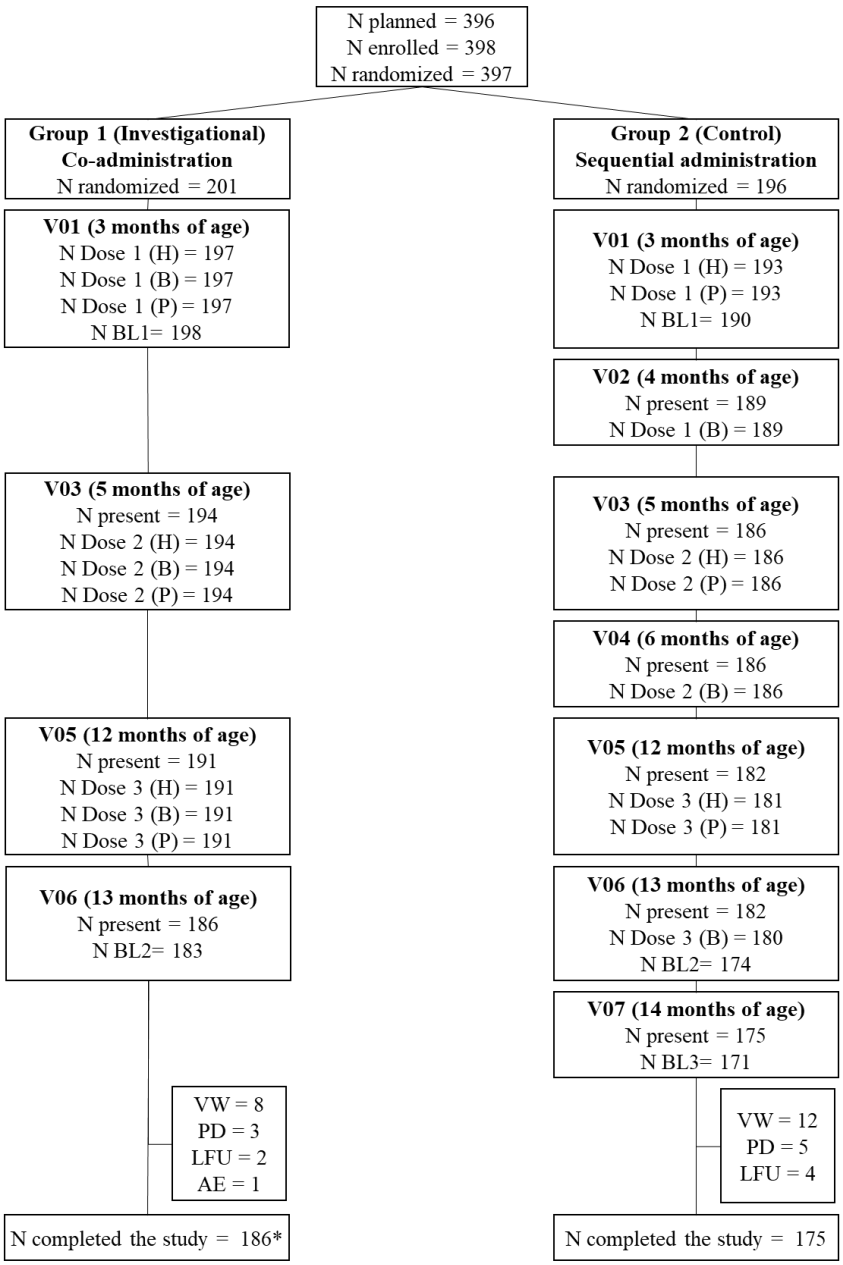
- 197 participants (98.0%) in Group 1 received the 1st dose of the Hexavalent vaccine, 4CMenB vaccine, and PCV13 vaccine at 3 MoA
- 194 participants (96.5%) in Group 1 received the 2nd dose of the Hexavalent vaccine, 4CMenB vaccine, and PCV13 vaccine at 5 MoA
- 191 participants (95.0%) in Group 1 received the 3rd of the Hexavalent vaccine, 4CMenB vaccine, and PCV13 vaccine at 12 MoA
- 186 participants (92.5%) completed the study in Group 1.

Group 2 (sequential administration) 196 participants

- 193 participants (98.5%) received the 1st dose of the Hexavalent vaccine and PCV13 vaccine at 3 MoA
- 189 participants (96.4%) received the 1st dose of the 4CMenB vaccine at 4 MoA
- 186 participants (94.9%) received the 2nd dose of the Hexavalent vaccine and PCV13 vaccine at 5 MoA
- 186 participants (94.9%) received the 2nd dose of the 4CMenB vaccine at 6 MoA
- 181 participants (92.3%) received the 3rd dose of the Hexavalent vaccine and PCV13 vaccine at 12 MoA

- 180 participants (91.8%) received the 3rd dose of the 4CMenB vaccine at 13 MoA
- 175 participants (89.3%) completed the study in Group 2.

Figure 1: participant disposition Flow-chart



Abbreviations: AE, adverse event; B, Bexsero, BL, blood sample; H, Hexaxim; LFU, lost to follow-up; P, Prevenar 13; PD, protocol deviation; VW, voluntary withdrawal by parent(s)/legally acceptable representative(s)

* One participant in Group 1 was randomised, vaccinated for Dose 1, 2 and 3 but did not attend last study visit (post-Dose 3 visit); this participant was erroneously reported as completed in the eCRF and has been removed from the number of completed participants in statistical tables.
Source: Clinical Overview

Vaccinations and Blood samplings followed the schedule, below.

Table 1: Vaccinations and Blood samplings schedule

		Age of the participant (in months)						
		3	4	5	6	12	13	14
Group 1 (N=198) Co-administration	Vaccination schedule	H+P+B		H+P+B		H+P+B		
	Blood sampling schedule	BL1					BL2	
Group 2 (N=198) Sequential administration	Vaccination schedule	H+P	B	H+P	B	H+P	B	
	Blood sampling schedule	BL1					BL2	BL3

Abbreviations: BL: blood sample; H: Hexavalent vaccine administered intramuscularly (IM) into the right thigh; B: 4CMenB vaccine administered IM into the left thigh; P: PCV13 vaccine administered IM into the left thigh

Source: CSR p38/407

The time window for blood sample post-dose 3 for evaluation of immunogenicity of the Hexavalent vaccine was extended from 15-37 days to 15-51 days due to observed difficulties in adherence to protocol requirement at the time study was conducted (COVID-19 pandemic was still active).

Hexyon/Hexacima/Hexaxim, manufactured by Sanofi Winthrop Industrie (formerly Sanofi Pasteur), was supplied as a suspension for injection in pre-filled syringe. Batch numbers T3L90 (Italy) and U3P16 (Finland) were applied. The T3L90 batch used in Italy had an initial expiry date of May 2022 based on the 36-month shelf-life which was extended to May 2023 following approval by the European Medicines Agency [EMA] of the variation for a 48-month shelf-life.

The Primary Objective was to demonstrate the NI of the co-administration of the Hexavalent vaccine with the 4CMenB vaccine (Group 1) compared to the sequential administration of the same vaccines (Group 2) in terms of seroprotection rates for anti-HBsAg (≥ 10 mIU/mL) and anti-PRP antibodies (≥ 1 µg/ml).

The Secondary Immunogenicity Objectives were:

- To describe the immune responses against all antigens of the Hexavalent vaccine and the 3 antigens of the 4CMenB vaccine before the 1st dose and 1 month after the 3rd dose of each vaccine for each of the study groups
- To describe the immune responses against all antigens of the pneumococcal conjugate vaccine 13-valent vaccine after the 3rd dose for each of the study groups

7.1. Results

Results regarding the Primary Objective - to demonstrate the NI of the co-administration of the Hexavalent vaccine with the 4CMenB vaccine (Group 1) compared to the sequential administration of the same vaccines (Group 2) in terms of seroprotection rates for anti-HBsAg (≥ 10 mIU/mL) and anti-PRP antibodies (≥ 1 µg/ml) – are presented in the Table, below:

Table 2: Non-inferiority Analysis of post-Dose 3 Anti-PRP and Anti-HBsAg Seroprotection Rates – PPAS (per protocol analysis set)

			Results			Group Comparison				
			n/M	%	(95% CI)	Difference	95% CI (2-sided)	Delta (%)	Non inferiority*	Global hypothesis **
Anti-PRP (RIA - mcg/mL)	Seroprotection (>= 1 mcg/mL)	Group 1 (Co-administration)	129/149	86.6	(80.0; 91.6)					
		Group 2 (Sequential administration)	92/97	94.8	(88.4; 98.3)					
		Group 1 (Co-administration) vs Group 2 (Sequential administration)				-8.3	(-15.3; -0.4)	-10%	No	
Anti-HBsAg (VITROS ECi/ECiQ - mIU/mL)	Seroprotection (>= 10 mIU/mL)	Group 1 (Co-administration)	146/149	98.0	(94.2; 99.6)					
		Group 2 (Sequential administration)	93/97	95.9	(89.8; 98.9)					
		Group 1 (Co-administration) vs Group 2 (Sequential administration)				2.1	(-2.4; 8.3)	-10%	Yes	
										No

n: number of subjects fulfilling the item listed

M: number of subjects with available data for relevant endpoint.

*Non-inferiority concluded if the lower limit of 2-sided 95% CI of difference between groups is greater than -10%.

**The global hypothesis concluded if the difference in both Anti-PRP and Anti-HBsAg seroprotection rates between Group 1 and Group 2 is greater than -10%.

Source: Clinical Overview

Non-inferiority of post-dose 3 seroprotection rate for anti-PRP antibodies

At 1 month post-dose 3, the seroprotection rate against PRP (ie, percentage of participants with antibody concentration ≥ 1 µg/mL) was 86.6% (95% CI: 80.0; 91.6) in Group 1 and 94.8% (95% CI: 88.4; 98.3) in Group 2.

The difference between Group 1 and Group 2 in the seroprotection rates against PRP antigen was -8.3 (95% CI: -15.3; -0.4).

As the lower limit of the 95% CI of the difference in seroprotection rates was lower than -10% for PRP antigen, the NI of the co-administration (Group 1) versus sequential administration (Group 2) of the Hexavalent and 4CMenB vaccines was not demonstrated in the PPAS.

Non-inferiority of post-dose 3 seroprotection rate for anti-HBsAg antibodies

At 1 month post-dose 3, the seroprotection rate against HBsAg (ie, percentage of participants with antibody concentration ≥ 10 mIU/mL) was 98.0% (95% confidence interval: 94.2; 99.6) in Group 1 and 95.9% (95% CI: 89.8; 98.9) in Group 2.

The difference between Group 1 and Group 2 in the seroprotection rates against HBsAg antigen was 2.1 (95% CI: -2.4; 8.3).

As the lower limit of the 95% CI of the difference in seroprotection rates was greater than -10% for HBsAg, the NI of the co-administration (Group 1) versus sequential administration (Group 2) of the Hexavalent and 4CMenB vaccines was demonstrated in the PPAS.

Overall, the primary objective of the study was not met as the NI of the seroprotection rates was demonstrated for anti-HBsAg antibodies only.

Comparable results were observed in the Full Analysis Set (FAS).

Results regarding the Secondary Objectives – to

1. describe the immune responses against all antigens of the Hexavalent vaccine and the 3 antigens of the 4CMenB vaccine before the 1st dose and 1 month after the 3rd dose of each vaccine for each of the study groups – and
2. to describe the immune responses against all antigens of the pneumococcal conjugate vaccine 13-valent vaccine after the 3rd dose for each of the study groups

are presented, below.

Table 3: Summary of Immunogenicity criteria for the hexavalent vaccine antigens - pre-Dose 1 and post-Dose 3 - PPAS

			Group 1 Co-administration (N=149)			Group 2 Sequential administration (N=97)		
Antigen	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Anti-D (ECL - IU/mL)	Pre-Dose 1 (V01 (M3))	>= 0.01 IU/mL	139/149	93.3	(88.0; 96.7)	90/97	92.8	(85.7; 97.0)
		>= 0.1 IU/mL	83/149	55.7	(47.3; 63.8)	47/97	48.5	(38.2; 58.8)
		>= 1 IU/mL	6/149	4.0	(1.5; 8.6)	5/97	5.2	(1.7; 11.6)
	Post-Dose 3 (V06 (M13))	>= 0.01 IU/mL	149/149	100	(97.6; 100)	97/97	100	(96.3; 100)
		>= 0.1 IU/mL	149/149	**100**	(97.6; 100)	97/97	**100**	(96.3; 100)
		>= 1 IU/mL	138/149	92.6	(87.2; 96.3)	94/97	96.9	(91.2; 99.4)
Anti-T (ECL - IU/mL)	Pre-Dose 1 (V01 (M3))	>= 0.01 IU/mL	148/149	99.3	(96.3; 100)	96/96	100	(96.2; 100)
		>= 0.1 IU/mL	142/149	95.3	(90.6; 98.1)	89/96	92.7	(85.6; 97.0)
		>= 1 IU/mL	83/149	55.7	(47.3; 63.8)	45/96	46.9	(36.6; 57.3)
	Post-Dose 3 (V06 (M13))	>= 0.01 IU/mL	149/149	100	(97.6; 100)	97/97	100	(96.3; 100)
		>= 0.1 IU/mL	149/149	**100**	(97.6; 100)	97/97	**100**	(96.3; 100)
		>= 1 IU/mL	135/149	90.6	(84.7; 94.8)	93/97	95.9	(89.8; 98.9)
Anti-Polio 1 (MIT - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 8 1/dil	33/91	36.3	(26.4; 47.0)	25/60	41.7	(29.1; 55.1)
	Post-Dose 3 (V06 (M13))	>= 8 1/dil	128/128	**100**	(97.2; 100)	95/95	**100**	(96.2; 100)
Anti-Polio 2 (MIT - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 8 1/dil	69/107	64.5	(54.6; 73.5)	51/64	79.7	(67.8; 88.7)
	Post-Dose 3 (V06 (M13))	>= 8 1/dil	129/129	**100**	(97.2; 100)	96/96	**100**	(96.2; 100)
Anti-Polio 3 (MIT - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 8 1/dil	52/113	46.0	(36.6; 55.6)	31/70	44.3	(32.4; 56.7)
	Post-Dose 3 (V06 (M13))	>= 8 1/dil	131/131	**100**	(97.2; 100)	96/96	**100**	(96.2; 100)
Anti-PT (ECL - EU/mL)	Pre-Dose 1 (V01 (M3))	>= LLOQ	109/149	73.2	(65.3; 80.1)	63/96	65.6	(55.2; 75.0)
		>= 4 x LLOQ	72/149	48.3	(40.1; 56.6)	42/96	43.8	(33.6; 54.3)
	Post-Dose 3 (V06 (M13))	>= LLOQ	149/149	100	(97.6; 100)	97/97	100	(96.3; 100)
		>= 4 x LLOQ	149/149	**100**	(97.6; 100)	97/97	**100**	(96.3; 100)
	Post-Dose 3 (V06 (M13))/ pre-Dose 1 (V01 (M3))	Vaccine response*	145/149	**97.3**	(93.3; 99.3)	92/96	**95.8**	(89.7; 98.9)
		Seroconversion (>= 4-fold increase)	107/149	**71.8**	(63.9; 78.9)	75/96	**78.1**	(68.5; 85.9)
Anti-FHA (ECL - EU/mL)	Pre-Dose 1 (V01 (M3))	>= LLOQ	146/148	98.6	(95.2; 99.8)	86/94	91.5	(83.9; 96.3)
		>= 4 x LLOQ	126/148	85.1	(78.4; 90.4)	60/94	63.8	(53.3; 73.5)
	Post-Dose 3 (V06 (M13))	>= LLOQ	149/149	100	(97.6; 100)	97/97	100	(96.3; 100)

Antigen	Timepoint	Criteria	Group 1 Co-administration (N=149) n/M	%	(95% CI)	Group 2 Sequential administration (N=97) n/M	%	(95% CI)
		>= 4 x LLOQ	149/149	**100**	(97.6; 100)	97/97	**100**	(96.3; 100)
	Post-Dose 3 (V06 (M13))/ pre-Dose 1 (V01 (M3))	Vaccine response*	120/148	**81.1**	(73.8; 87.0)	72/94	**76.6**	(66.7; 84.7)
		Seroconversion (>= 4-fold increase)	71/148	**48.0**	(39.7; 56.3)	51/94	**54.3**	(43.7; 64.6)
Anti-PRP (RIA - mcg/mL)	Pre-Dose 1 (V01 (M3))	>= 0.15 mcg/mL	40/149	26.8	(19.9; 34.7)	26/97	26.8	(18.3; 36.8)
		>= 1 mcg/mL	4/149	2.7	(0.7; 6.7)	2/97	2.1	(0.3; 7.3)
	Post-Dose 3 (V06 (M13))	>= 0.15 mcg/mL	146/149	98.0	(94.2; 99.6)	96/97	99.0	(94.4; 100)
		>= 1 mcg/mL	129/149	**86.6**	(80.0; 91.6)	92/97	**94.8**	(88.4; 98.3)
Anti-HBsAg (VITROS ECi/ECiQ - mIU/mL)	Pre-Dose 1 (V01 (M3))	>= 10 mIU/mL	60/146	41.1	(33.0; 49.5)	30/95	31.6	(22.4; 41.9)
		>= 100 mIU/mL	24/146	16.4	(10.8; 23.5)	11/95	11.6	(5.9; 19.8)
	Post-Dose 3 (V06 (M13))	>= 10 mIU/mL	146/149	**98.0**	(94.2; 99.6)	93/97	**95.9**	(89.8; 98.9)
		>= 100 mIU/mL	135/149	90.6	(84.7; 94.8)	80/97	82.5	(73.4; 89.4)

n: number of subjects experiencing the endpoint listed in the first three columns
M: number of subjects with available data for the relevant endpoint
LLOQ: Anti-PT=2.00 EU/mL, Anti-FHA=2.00 EU/mL.
* Vaccine response is defined as:
If the pre-Dose 1 concentration is < 4 x LLOQ then post-Dose 3 vaccination concentration ≥ 4 x LLOQ
Source: Clinical Overview

At 1 month post-dose 3:

- 100% of the participants in Group 1 (Co-administration) and Group 2 (Sequential administration) were seroprotected against diphtheria (i.e., antibody concentrations ≥ 0.01 IU/mL and ≥ 0.1 IU/mL) and more than 92% of them achieved the threshold associated with long-term protection (i.e., antibody concentration ≥ 1.0 IU/mL).
- 100% of the participants in Group 1 and Group 2 were seroprotected against tetanus (i.e., antibody concentrations ≥ 0.01 IU/mL and ≥ 0.1 IU/mL) and more than 90% of them achieved the threshold associated with long-term protection (i.e., antibody concentration ≥ 1.0 IU/mL).
- 100% of the participants in Group 1 and Group 2 were seroprotected (i.e., reached antibody titres ≥ 8 (1/dil) against the 3 polio serotypes.
- 100% of the participants in Group 1 and Group 2 had anti-PT and anti-FHA antibody concentrations ≥ 8 EU/mL (i.e., ≥ 4 LLOQ).
- Vaccine response rates (if the pre-Dose 1 concentration is < 4 x LLOQ then post-Dose 3 vaccination concentration ≥ 4 x LLOQ) were 97.3% (95% CI: 93.3; 99.3) of the participants in Group 1 and 95.8% (95% CI: 89.7; 98.9) in Group 2 for anti-PT; for anti-FHA the rates were 81.1% (95% CI: 73.8; 87.0) of the participants in Group 1 and 76.6% (95% CI: 66.7; 84.7) in Group 2
- ≥ 4-fold increase in antibody concentration from pre-dose 1 to post-dose 3 was 71.8% (95% CI: 63.9; 78.9) of the participants in Group 1 and 78.1% (95% CI: 68.5; 85.9) in Group 2 for

anti-PT; for anti-FHA the percentages were 48.0% (95% CI: 39.7; 56.3) in Group 1 and 54.3% (95% CI: 43.7; 64.6) in Group 2.

- 98.0% (95% CI: 94.2; 99.6) of the participants in Group 1 and 99.0% (95% CI: 94.4; 100) in Group 2 were seroprotected (ie, antibody concentrations ≥ 0.15 µg/mL) against PRP. 86.6% (95% CI: 80.0; 91.6) of participants in Group 1 and 94.8% (95% CI: 88.4; 98.3) in Group 2 had anti-PRP ≥ 1.0 µg/mL.
- 98.0% (95% CI: 94.2; 99.6) of the participants in Group 1 and 95.9% (95% CI: 89.8; 98.9) in Group 2 were seroprotected against HBsAg (ie, antibody concentrations ≥ 10 mIU/mL).

At 1 month post-dose 3, the GMCs/GMTs were lower in Group 1 than in Group 2 for anti-polio 1 antibodies, tended to be lower in Group 1 than in Group 2 for anti-PRP antibodies and were similar in both groups for the other antigens.

For each antigen of the Hexavalent vaccine, comparable results were observed in the FAS.

Regarding immunogenicity of the MenB Vaccine seroresponse-rates and GMTs have been provided as presented in the Table, below.

Table 4 Summary of Immunogenicity criteria for the MenB vaccine antigens - pre-Dose 1 and post-Dose 3 - PPAS

			Group 1 Co-administration (N=149)			Group 2 Sequential administration (N=97)		
Antigen	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Anti-fHbp (44/76-SL - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 5 1/dil	5/123	4.1	(1.3; 9.2)	2/83	2.4	(0.3; 8.4)
	Post-Dose 3 (V06 (M13) or V07 (M14))*	>= 5 1/dil	125/127	**98.4**	(94.4; 99.8)	94/94	**100**	(96.2; 100)
Anti-NadA (5/99 - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 5 1/dil	1/123	0.8	(0; 4.4)	0/83	NC	(NC; NC)
	Post-Dose 3 (V06 (M13) or V07 (M14))*	>= 5 1/dil	127/127	**100**	(97.1; 100)	93/93	**100**	(96.1; 100)
Anti-PorA P1.4 (NZ 98/254 - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 5 1/dil	0/123	NC	(NC; NC)	0/83	NC	(NC; NC)
	Post-Dose 3 (V06 (M13) or V07 (M14))*	>= 5 1/dil	124/127	**97.6**	(93.3; 99.5)	93/94	**98.9**	(94.2; 100)

n: number of subjects experiencing the endpoint
M: number of subjects with available data for the relevant endpoint
* V06 (M13) for Group 1 and V07 (M14) for Group 2
Source: Clinical Overview

At 1 month post-dose 3, the seroresponse rates (i.e., the percentages of participants achieving hSBA antibody titres ≥ 5 [1/dil]) were high (ie, > 97%) for each antigen and similar between both groups:

- For anti-fHbp: 98.4% (95% CI: 94.4; 99.8) in Group 1 and 100% (95% CI: 96.2; 100) in Group 2
- For anti-NadA: 100% (95% CI: 97.1; 100) in Group 1 and 100% (95% CI: 96.1; 100) in Group 2
- For anti-PorA P1.4: 97.6% (95% CI: 93.3; 99.5) in Group 1 and 98.9% (95% CI: 94.2; 100) in Group 2

At 1 month post-dose 3, the GMTs were lower in Group 1 than in Group 2 for anti-fHbp and anti-PorA P1.4 antibodies. There was a trend to lower GMTs in Group 1 than in Group 2 for anti-NadA antibodies.

Comparable results were observed in the FAS.

Regarding immunogenicity of the PCV13 Vaccine, response-rates (ie, the percentages of participants achieving antibody titres ≥ 0.35 µg/mL) and GMCs have been provided (Secondary Objective #2).

At 1 month post-dose 3, the GMCs of anti-pneumococcal antibodies against each of the PCV13 serotypes were overall similar between groups, except for serotypes 1, 6A, 19A, and 19F for which GMCs were higher in Group 1 (co-administration) than in Group 2 (sequential administration).

At 1 month post-dose 3, overall, the vaccine seroresponse rates (ie, the percentages of participants achieving antibody titres ≥ 0.35 µg/mL) against the 13 serotypes ranged from 98.3% to 100% in Group 1 and Group 2, except for serotype 3, with 92.3% (95% CI: 85.9; 96.4) in Group 1 and 95.7% (95% CI: 89.5; 98.8) in Group 2.

In the FAS, the GMCs were similar between Group 1 and Group 2 for each serotype, except serotypes 1 and 19F, for which GMCs were higher in Group 1 than in Group 2; vaccine seroresponse rates were similar between Group 1 and Group 2 for each serotype.

Post-hoc-analyses by country (Italy – Finland)

Post-hoc analyses were conducted by group and by country to describe the immune responses against all antigens of the Hexavalent vaccine after the 3rd dose in Group 1 (co-administration) and Group 2 (sequential administration). Respective Results are presented below for Hexaxim and for MenB.

Table 5: *Summary of Immunogenicity criteria for the hexavalent vaccine antigens - pre-Dose 1 and post-Dose 3 by study groups and by country – PPAS*

			Group 1 Co-administration (N=149)						**Group 2 Sequential administration (N=97)**					
			Italy (N=112)			**Finland (N=37)**			**Italy (N=68)**			**Finland (N=29)**		
Antigen	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Anti-D (ECL - IU/mL)	Pre-Dose 1 (V01 (M3))	>= 0.01 IU/mL	104/112	92.9	(86.4 ; 96.9)	35/37	94.6	(81.8 ; 99.3)	62/68	91.2	(81.8 ; 96.7)	28/29	96.6	(82.2 ; 99.9)
		>= 0.1 IU/mL	66/112	58.9	(49.2 ; 68.1)	17/37	45.9	(29.5 ; 63.1)	38/68	55.9	(43.3 ; 67.9)	9/29	31.0	(15.3 ; 50.8)
		>= 1 IU/mL	6/112	5.4	(2.0 ; 11.3)	0/37	NC	(NC ; NC)	5/68	7.4	(2.4 ; 16.3)	0/29	NC	(NC ; NC)
	Post-Dose 3 (V06 (M13))	>= 0.01 IU/mL	112/112	100	(96.8 ; 100)	37/37	100	(90.5 ; 100)	68/68	100	(94.7 ; 100)	29/29	100	(88.1 ; 100)
		>= 0.1 IU/mL	112/112	**100**	(96.8 ; 100)	37/37	**100**	(90.5 ; 100)	68/68	**100**	(94.7 ; 100)	29/29	**100**	(88.1 ; 100)
		>= 1 IU/mL	103/112	92.0	(85.3 ; 96.3)	35/37	94.6	(81.8 ; 99.3)	66/68	97.1	(89.8 ; 99.6)	28/29	96.6	(82.2 ; 99.9)
Anti-T (ECL - IU/mL)	Pre-Dose 1 (V01 (M3))	>= 0.01 IU/mL	111/112	99.1	(95.1 ; 100)	37/37	100	(90.5 ; 100)	67/67	100	(94.6 ; 100)	29/29	100	(88.1 ; 100)
		>= 0.1 IU/mL	106/112	94.6	(88.7 ; 98.0)	36/37	97.3	(85.8 ; 99.9)	62/67	92.5	(83.4 ; 97.5)	27/29	93.1	(77.2 ; 99.2)
		>= 1 IU/mL	80/112	71.4	(62.1 ; 79.6)	3/37	8.1	(1.7 ; 21.9)	44/67	65.7	(53.1 ; 76.8)	1/29	3.4	(0.1 ; 17.8)
	Post-Dose 3 (V06 (M13))	>= 0.01 IU/mL	112/112	100	(96.8 ; 100)	37/37	100	(90.5 ; 100)	68/68	100	(94.7 ; 100)	29/29	100	(88.1 ; 100)
		>= 0.1 IU/mL	112/112	**100**	(96.8 ; 100)	37/37	**100**	(90.5 ; 100)	68/68	**100**	(94.7 ; 100)	29/29	**100**	(88.1 ; 100)
		>= 1 IU/mL	104/112	92.9	(86.4 ; 96.9)	31/37	83.8	(68.0 ; 93.8)	66/68	97.1	(89.8 ; 99.6)	27/29	93.1	(77.2 ; 99.2)
Anti-Polio 1 (MIT - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 8 1/dil	20/69	29.0	(18.7 ; 41.2)	13/22	59.1	(36.4 ; 79.3)	10/39	25.6	(13.0 ; 42.1)	15/21	71.4	(47.8 ; 88.7)
	Post-Dose 3 (V06 (M13))	>= 8 1/dil	92/92	**100**	(96.1 ; 100)	36/36	**100**	(90.3 ; 100)	66/66	**100**	(94.6 ; 100)	29/29	**100**	(88.1 ; 100)
Anti-Polio 2 (MIT - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 8 1/dil	40/73	54.8	(42.7 ; 66.5)	29/34	85.3	(68.9 ; 95.0)	27/39	69.2	(52.4 ; 83.0)	24/25	96.0	(79.6 ; 99.9)
	Post-Dose 3 (V06 (M13))	>= 8 1/dil	93/93	**100**	(96.1 ; 100)	36/36	**100**	(90.3 ; 100)	67/67	**100**	(94.6 ; 100)	29/29	**100**	(88.1 ; 100)
Anti-Polio 3 (MIT - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 8 1/dil	27/79	34.2	(23.9 ; 45.7)	25/34	73.5	(55.6 ; 87.1)	14/45	31.1	(18.2 ; 46.6)	17/25	68.0	(46.5 ; 85.1)

			Group 1 Co-administration (N=149)						Group 2 Sequential administration (N=97)					
			Italy (N=112)			Finland (N=37)			Italy (N=68)			Finland (N=29)		
Antigen	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
	Post-Dose 3 (V06 (M13))	>= 8 1/dil	95/95	**100**	(96.2 ; 100)	36/36	**100**	(90.3 ; 100)	67/67	**100**	(94.6 ; 100)	29/29	**100**	(88.1 ; 100)
Anti-PT (ECL - EU/mL)	Pre-Dose 1 (V01 (M3))	>= LLOQ	96/112	85.7	(77.8 ; 91.6)	13/37	35.1	(20.2 ; 52.5)	56/67	83.6	(72.5 ; 91.5)	7/29	24.1	(10.3 ; 43.5)
		>= 4 x LLOQ	66/112	58.9	(49.2 ; 68.1)	6/37	16.2	(6.2 ; 32.0)	41/67	61.2	(48.5 ; 72.9)	1/29	3.4	(0.1 ; 17.8)
	Post-Dose 3 (V06 (M13))	>= LLOQ	112/112	100	(96.8 ; 100)	37/37	100	(90.5 ; 100)	68/68	100	(94.7 ; 100)	29/29	100	(88.1 ; 100)
		>= 4 x LLOQ	112/112	**100**	(96.8 ; 100)	37/37	**100**	(90.5 ; 100)	68/68	**100**	(94.7 ; 100)	29/29	**100**	(88.1 ; 100)
	Post-Dose 3 (V06 (M13))/ pre-Dose 1 (V01 (M3))	Vaccine response*	108/112	**96.4**	(91.1 ; 99.0)	37/37	**100**	(90.5 ; 100)	63/67	**94.0**	(85.4 ; 98.3)	29/29	**100**	(88.1 ; 100)
		Seroconversion (>= 4-fold increase)	73/112	65.2	(55.6 ; 73.9)	34/37	91.9	(78.1 ; 98.3)	46/67	68.7	(56.2 ; 79.4)	29/29	100	(88.1 ; 100)
Anti-FHA (ECL - EU/mL)	Pre-Dose 1 (V01 (M3))	>= LLOQ	111/111	100	(96.7 ; 100)	35/37	94.6	(81.8 ; 99.3)	65/65	100	(94.5 ; 100)	21/29	72.4	(52.8 ; 87.3)
		>= 4 x LLOQ	105/111	94.6	(88.6 ; 98.0)	21/37	56.8	(39.5 ; 72.9)	55/65	84.6	(73.5 ; 92.4)	5/29	17.2	(5.8 ; 35.8)
	Post-Dose 3 (V06 (M13))	>= LLOQ	112/112	100	(96.8 ; 100)	37/37	100	(90.5 ; 100)	68/68	100	(94.7 ; 100)	29/29	100	(88.1 ; 100)
		>= 4 x LLOQ	112/112	**100**	(96.8 ; 100)	37/37	**100**	(90.5 ; 100)	68/68	**100**	(94.7 ; 100)	29/29	**100**	(88.1 ; 100)
	Post-Dose 3 (V06 (M13))/ pre-Dose 1 (V01 (M3))	Vaccine response*	83/111	**74.8**	(65.6 ; 82.5)	37/37	**100**	(90.5 ; 100)	43/65	**66.2**	(53.4 ; 77.4)	29/29	**100**	(88.1 ; 100)
		Seroconversion (>= 4-fold increase)	40/111	36.0	(27.1 ; 45.7)	31/37	83.8	(68.0 ; 93.8)	22/65	33.8	(22.6 ; 46.6)	29/29	100	(88.1 ; 100)
Anti-PRP (RIA - mcg/mL)	Pre-Dose 1 (V01 (M3))	>= 0.15 mcg/mL	24/112	21.4	(14.2 ; 30.2)	16/37	43.2	(27.1 ; 60.5)	15/68	22.1	(12.9 ; 33.8)	11/29	37.9	(20.7 ; 57.7)
		>= 1 mcg/mL	2/112	1.8	(0.2 ; 6.3)	2/37	5.4	(0.7 ; 18.2)	2/68	2.9	(0.4 ; 10.2)	0/29	NC	(NC ; NC)
	Post-Dose 3 (V06 (M13))	>= 0.15 mcg/mL	112/112	**100**	(96.8 ; 100)	34/37	**91.9**	(78.1 ; 98.3)	67/68	**98.5**	(92.1 ; 100)	29/29	**100**	(88.1 ; 100)
		>= 1 mcg/mL	100/112	**89.3**	(82.0 ; 94.3)	29/37	**78.4**	(61.8 ; 90.2)	65/68	**95.6**	(87.6 ; 99.1)	27/29	**93.1**	(77.2 ; 99.2)

			Group 1 Co-administration (N=149)						Group 2 Sequential administration (N=97)					
			Italy (N=112)			Finland (N=37)			Italy (N=68)			Finland (N=29)		
Antigen	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Anti-HBsAg (VITROS ECi/ECiQ - mIU/mL)	Pre-Dose 1 (V01 (M3))	>= 10 mIU/mL	46/109	42.2	(32.8 ; 52.0)	14/37	37.8	(22.5 ; 55.2)	19/67	28.4	(18.0 ; 40.7)	11/28	39.3	(21.5 ; 59.4)
		>= 100 mIU/mL	18/109	16.5	(10.1 ; 24.8)	6/37	16.2	(6.2 ; 32.0)	4/67	6.0	(1.7 ; 14.6)	7/28	25.0	(10.7 ; 44.9)
	Post-Dose 3 (V06 (M13))	>= 10 mIU/mL	111/112	**99.1**	(95.1 ; 100)	35/37	**94.6**	(81.8 ; 99.3)	65/68	**95.6**	(87.6 ; 99.1)	28/29	**96.6**	(82.2 ; 99.9)
		>= 100 mIU/mL	104/112	92.9	(86.4 ; 96.9)	31/37	83.8	(68.0 ; 93.8)	56/68	82.4	(71.2 ; 90.5)	24/29	82.8	(64.2 ; 94.2)

n: number of subjects experiencing the endpoint listed in the first three columns
M: number of subjects with available data for the relevant endpoint
LLOQ: Anti-PT=2.00 EU/mL, Anti-FHA=2.00 EU/mL.
* Vaccine response is defined as:
If the pre-Dose 1 concentration is < 4 x LLOQ then post-Dose 3 vaccination concentration >= 4 x LLOQ
If the pre-Dose 1 concentration >= 4 x LLOQ then post-Dose 3 vaccination concentration >= the pre-Dose 1 concentration
Source: Clinical Overview (CSR Appendix 15, Table 8.27a)

At 1 month post-dose 3, 100% of the participants in Group 1 and Group 2, in Italy and in Finland, were seroprotected against diphtheria, tetanus and the 3 polio serotypes.

Regarding response to the pertussis antigens:

- At 1 month post-dose 3, 100% of the participants in Group 1 and Group 2, in Italy and in Finland, had anti-PT and anti-FHA antibody concentrations ≥ 8 EU/mL (i.e. ≥ 4 LLOQ).
- In both groups, post-dose 3 anti-PT and anti-FHA seroconversion rates (≥4fold increase) were lower (i.e., non-overlapping CIs) in Italy than in Finland:
  - For anti-PT, post-dose 3 seroconversion rates were:
    - Group 1: 65.2% (95% CI: 55.6; 73.9) in Italy and 91.9% (95% CI: 78.1; 98.3) in Finland
    - Group 2: 68.7% (95% CI: 56.2; 79.4) in Italy and 100% (95% CI: 88.1; 100) in Finland
  - For anti-FHA, post-dose 3 seroconversion rates were:
    - Group 1: 36.0% (95% CI: 27.1; 45.7) in Italy and 83.8% (95% CI: 68.0; 93.8) in Finland
    - Group 2: 33.8% (95% CI: 22.6; 46.6) in Italy and 100% (95% CI: 88.1; 100) in Finland

In Italy, the high percentage of participants born to women who received a TdaP vaccination during pregnancy (about 64%; see CSR Section 4.4.2) resulted in higher pre-dose 1 antibody levels and thus, in lower seroconversion rates for both anti-PT and anti-FHA [see CSR Appendix 15, Table 8.43a and Table 8.45a].

- In both groups, post-dose 3 anti-PT vaccine response rates were similar in Italy and in Finland, and anti-FHA vaccine response rates were lower (i.e., non-overlapping CIs) in Italy than in Finland:
  - For anti-PT, post-dose 3 vaccine response rates were:
    - Group 1: 96.4% (95% CI: 91.1; 99.0) in Italy and 100% (95% CI: 90.5; 100) in Finland
    - Group 2: 94.0% (95% CI: 85.4; 98.3) in Italy and 100% (95% CI: 88.1; 100) in Finland
  - For anti-FHA, post-dose 3 vaccine response rates were:
    - Group 1: 74.8% (95% CI: 65.6; 82.5) in Italy and 100% (95% CI: 90.5; 100) in Finland
    - Group 2: 66.2% (95% CI: 53.4; 77.4) in Italy and 100% (95% CI: 88.1; 100) in Finland

Post-dose 3 anti-PRP seroprotection rates (ie, antibody concentrations ≥ 1 µg/mL) tended to be higher in Italy than in Finland in Group 1 and were comparable between both countries in Group 2:

- Group 1: 89.3% (95% CI: 82.0; 94.3) in Italy and 78.4% (95% CI: 61.8; 90.2) in Finland
- Group 2: 95.6% (95% CI: 87.6; 99.1) in Italy and 93.1 (95% CI: 77.2; 99.2) in Finland

It is to be noted that pre-dose 1 anti-PRP seroprotection rates (i.e., antibody concentrations ≥ 0.15 µg/mL) were numerically lower in Italy than in Finland in both groups:

- Group 1: 21.4% (95% CI: 14.2; 30.2) in Italy and 43.2% (95% CI: 27.1; 60.5) in Finland
- Group 2: 22.1% (95% CI: 12.9; 33.8) in Italy and 37.9% (95% CI: 20.7; 57.7) in Finland

In both groups, post-dose 3 anti-HBsAg seroprotection rates (i.e., antibody concentration ≥ 10 mIU/mL) were comparable between Italy and Finland:

- Group 1: 99.1% (95% CI: 95.1; 100) in Italy and 94.6% (95% CI: 81.8; 99.3) in Finland

- Group 2: 95.6% (95% CI: 87.6; 99.1) in Italy and 96.6% (95% CI: 82.2; 99.9) in Finland

Comparable results were observed in the FAS [CSR Appendix 15, Table 8.28a].

Geometric Means have been evaluated by country, in addition:

Table 6: Summary of geometric means for the hexavalent vaccine antigens - post-Dose 3 by study groups and by country

		Group 1 Co-administration (N=149)						Group 2 Sequential administration (N=97)					
		Italy (N=112)			Finland (N=37)			Italy (N=68)			Finland (N=29)		
Antigen	**Timepoint**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**
Anti-D (ECL - IU/mL)	Post-Dose 3 (V06 (M13))	112	**2.51**	(2.23; 2.82)	37	**2.27**	(1.89; 2.74)	68	**2.77**	(2.36; 3.25)	29	**2.64**	(2.06; 3.38)
Anti-T (ECL - IU/mL)	Post-Dose 3 (V06 (M13))	112	**4.01**	(3.39; 4.73)	37	**2.58**	(1.98; 3.36)	68	**5.05**	(4.02; 6.34)	29	**3.76**	(2.73; 5.19)
Anti-Polio 1 (MIT - 1/dil)	Post-Dose 3 (V06 (M13))	92	**1036**	(850; 1262)	36	**569**	(389; 833)	66	**1974**	(1514; 2574)	29	**1300**	(809; 2089)
Anti-Polio 2 (MIT - 1/dil)	Post-Dose 3 (V06 (M13))	93	**2629**	(2083; 3317)	36	**1625**	(1084; 2438)	67	**3435**	(2709; 4356)	29	**2896**	(2077; 4038)
Anti-Polio 3 (MIT - 1/dil)	Post-Dose 3 (V06 (M13))	95	**1569**	(1206; 2042)	36	**1367**	(906; 2063)	67	**1754**	(1244; 2473)	29	**2421**	(1461; 4012)
Anti-PT (ECL - EU/mL)	Post-Dose 3 (V06 (M13))	112	**97.3**	(86.5; 109)	37	**113**	(90.2; 142)	68	**83.7**	(71.4; 98.2)	29	**143**	(105; 196)
Anti-FHA (ECL - EU/mL)	Post-Dose 3 (V06 (M13))	112	**140**	(122; 160)	37	**178**	(145; 219)	68	**127**	(110; 148)	29	**228**	(185; 279)
Anti-PRP (RIA - mcg/mL)	Post-Dose 3 (V06 (M13))	112	**7.11**	(5.30; 9.53)	37	**4.68**	(2.45; 8.96)	68	**10.3**	(7.41; 14.3)	29	**9.33**	(5.29; 16.5)
Anti-HBsAg (VITROS ECi/ECiQ - mIU/mL)	Post-Dose 3 (V06 (M13))	112	**1430**	(1044; 1958)	37	**962**	(438; 2110)	68	**928**	(532; 1621)	29	**1345**	(582; 3106)

M: number of subjects with available data for the relevant endpoint
Source: Clinical Overview [CSR Appendix 15, Table 8.21a]

At 1 month post-dose 3, in both groups, GMCs/GMTs of antibodies against diphtheria were similar between Italy and Finland.

For anti-tetanus antibodies, GMCs (IU/mL) were higher (ie, non-overlapping CIs) in Italy than in Finland in Group 1 and tended to be higher in Italy than in Finland in Group 2, as shown below:

- Group 1: 4.01 (95% CI: 3.39; 4.73) in Italy and 2.58 (95% CI: 1.98; 3.36) in Finland
- Group 2: 5.05 (95% CI: 4.02; 6.34) in Italy and 3.76 (95% CI: 2.73; 5.19) in Finland

The same trend was observed for anti-polio 1 antibodies GMTs (1/dil), as shown below:

- Group 1: 1036 (95% CI: 850; 1262) in Italy and 569 (95% CI: 389; 833) in Finland
- Group 2: 1974 (95% CI: 1514; 2574) in Italy and 1300 (95% CI: 809; 2089) in Finland

In both groups, GMTs of antibodies against anti-polio 2 and anti-polio 3 were similar between Italy and Finland.

For anti-PT and anti-FHA antibodies, GMCs (EU/mL) were comparable between countries in Group 1 and were lower (i.e., non-overlapping CIs) in Italy than in Finland in Group 2, as shown below:

- For anti-PT, post-dose 3 GMCs were:
  - Group 1: 97.3 (95% CI: 86.5; 109) in Italy and 113 (95% CI: 90.2; 142) in Finland
  - Group 2: 83.7 (95% CI: 71.4; 98.2) in Italy and 143 (95% CI: 105; 196) in Finland
- For anti-FHA, post-dose 3 GMCs were:
  - Group 1: 140 (95% CI: 122; 160) in Italy and 178 (95% CI: 145; 219) in Finland
  - Group 2: 127 (95% CI: 110; 148) in Italy and 228 (95% CI: 185; 279) in Finland

For anti-PRP antibodies, GMCs (µg/mL) in Group 1 tended to be higher in Italy than in Finland and were similar between both countries in Group 2, as shown below:

- Group 1: 7.11 (95% CI: 5.30; 9.53) in Italy and 4.68 (95% CI: 2.45; 8.96) in Finland
- Group 2: 10.3 (95% CI: 7.41; 14.3) in Italy and 9.33 (95% CI: 5.29; 16.5) in Finland

In both groups, GMCs/GMTs of antibodies against HBsAg were similar between Italy and Finland.

Comparable results were observed in the FAS [CSR Appendix 15, Table 8.22a].

Post-hoc analyses were conducted by country to describe the immune responses against the 3 antigens of the 4CMenB vaccine after the 3rd dose in Group 1 (co-administration) and Group 2 (sequential administration).

The summary of seroresponse rates for the 4CMenB vaccine antigens by group and by country in the PPAS is presented in Table 6.

GMTs for the 4CMenB vaccine antigens by group and by country in the PPAS is presented in CSR.

Table 7: Summary of Immunogenicity criteria for the MenB vaccine antigens - pre-Dose 1 and post-Dose 3 by study groups and by country – PPAS

			Group 1 Co-administration (N=149)						Group 2 Sequential administration (N=97)					
			Italy (N=112)			Finland (N=37)			Italy (N=68)			Finland (N=29)		
Antigen	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Anti-fHbp (44/76-SL - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 5 1/dil	5/92	5.4	(1.8; 12.2)	0/31	NC	(NC; NC)	2/56	3.6	(0.4; 12.3)	0/27	NC	(NC; NC)
	Post-Dose 3 (V06 (M13) or V07 (M14))*	>= 5 1/dil	90/91	**98.9**	(94.0; 100)	35/36	**97.2**	(85.5; 99.9)	65/65	**100**	(94.5; 100)	29/29	**100**	(88.1; 100)
Anti-NadA (5/99 - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 5 1/dil	1/92	1.1	(0; 5.9)	0/31	NC	(NC; NC)	0/56	NC	(NC; NC)	0/27	NC	(NC; NC)
	Post-Dose 3 (V06 (M13) or V07 (M14))*	>= 5 1/dil	91/91	**100**	(96.0; 100)	36/36	**100**	(90.3; 100)	64/64	**100**	(94.4; 100)	29/29	**100**	(88.1; 100)
Anti-PorA P1.4 (NZ 98/254 - 1/dil)	Pre-Dose 1 (V01 (M3))	>= 5 1/dil	0/92	NC	(NC; NC)	0/31	NC	(NC; NC)	0/56	NC	(NC; NC)	0/27	NC	(NC; NC)
	Post-Dose 3 (V06 (M13) or V07 (M14))*	>= 5 1/dil	90/91	**98.9**	(94.0; 100)	34/36	**94.4**	(81.3; 99.3)	65/65	**100**	(94.5; 100)	28/29	**96.6**	(82.2; 99.9)

n: number of subjects experiencing the endpoint
M: number of subjects with available data for the relevant endpoint
* V06 (M13) for Group 1 and V07 (M14) for Group 2

Post-dose 3 seroresponse rates for the 3 antigens tested were comparable between Italy and Finland (> 94%).

Post-dose 3 GMTs tended to be higher in Italy than in Finland for anti-fHbp and anti PorA P1.4 antibodies both in Group 1 (co-administration) and Group 2 (sequential administration) and for anti-NadA antibodies in Group 1.

7.2. Discussion

The size of the study is considered to be adequate in the light of the longstanding experience with the Vaccine. Almost 400 participants have been included, overall, representing a relevant data-pool. Distribution into Groups 1 (co-administration) and 2 (sequential administration) is similar, whereas participation between Finland (98 participants) and Italy (299 participants) is imbalanced and might be causative for bias.

Conduct of the study was impaired by the pandemic. The enrolment into the study was affected by slow recruitment and expanding to an additional country (Finland). Enrolment span over a long period with recruitment (in Italy from January 2021 to July 2022 and in Finland from September 2022 to January 2023) together with country-specific differences may have led to more variability.

The T3L90 batch used in Italy had an initial expiry date of May 2022 based on the 36-month shelf-life which was extended to May 2023 following approval by the European Medicines Agency [EMA] of the variation for a 48-month shelf-life. For excluding any influence of the extension of the expiry date of the T3L90 Batch (Italy) on the study results, a respective analysis should be amended. Immunogenicity results for vaccinations before and after the extended expiry date in comparison with the results from Finland Have been evaluated.

Primary Objective was not achieved. For Hepatitis B (seroprotection rates for anti-HBsAg ≥ 10 mIU/mL) at one month after the 3rd dose non-inferiority of co-administration vs sequential dosing was demonstrated. However, for Haemophilus influenzae B (seroprotection rate against PRP, ie percentage of participants with antibody concentration ≥ 1 µg/mL) non-inferiority was not demonstrated.

In terms of the Secondary Objectives, descriptive analyses for each antigen have been presented. Established Correlates of Protection have been analysed. For diphtheria , 100% of participants reached short-term- and >92% long-term-protection at 1 month post dose 3. Similarly, 100% reached short-term-protection and >90% long-term-protection for tetanus. 100% of participants had titres ≥ 8 (1/dil) against the 3 polio serotypes.

Results for pertussis were 100% of participants having anti-PT and anti-FHA antibody concentrations ≥ 8 EU/mL (ie, ≥ 4 LLOQ). Percentages of 4-fold-increases for anti-PT from pre-dose 1 to post-dose 3 were 71.8% of Group 1, and 78.1% of Group 2, and for anti-FHA 48.0 % in Group 1 and 54.3% in Group 2. The latter values are considered to be low but acceptable.

For Haemophilus influenzae short-term seroprotection rates of 98 and 99% for Groups 1 and 2, respectively, have been reached. Further, long-term-rates of 86.6 and 94.4% for Groups 1 and 2 have been documented. These numbers are considered to be acceptable, although numbers for the coadmin-group (Group 1) are slightly lower than for the sequential group (Group 2). As this observation is known from similar settings, adequate protection in both groups is acknowledged despite the failure of non-inferiority testing.

For Hepatitis B (HBsAg concentrations ≥ 10 mIU/mL) seroprotection rates were 98% (Group 1) and 95.9 (Group 2). These values are considered to be high and acceptable.

Surrogates of protection (including fHbp) for the MenB vaccination have been presented as seroresponse rates with respect to an LLOQ of 4 (1/dil). All presented values are close to 100%. Although GMT-values for Group 1 participants are slightly lower than for participants in Group 2, these values are close to 100% and therefore considered to be acceptable.

Vaccine seroresponse rates regarding PCV13 against the 13 serotypes ranged from 98.3% to 100% in Group 1 and Group 2, except for serotype 3, with 92.3% in Group 1 and 95.7% in Group 2.
In the FAS, the GMCs were similar between Group 1 and Group 2 for each serotype, except serotypes 1 and 19F, for which GMCs were higher in Group 1.

Regarding MenB, seroresponse rates at 1 month after dose 3 were high (ie, > 97%) for each of the 3 antigens fHbp, NadA, and PorA P1.4) with only slightly lower results in Group 1 – which is acknowledged. Similarly, GMTs at 1 month post-dose 3, the GMTs were lower in Group 1 than in Group 2 for all 3 antigens.

Post-hoc analysis by country elucidates some cause of bias in this study: The MAH describes non-overlapping confidence-intervals for seroconversion rates (Pertussis: both, anti-PT and anti-FHA) together with very low seroconversion rates (≥4fold increase) of 36 and 33.8% for anti FHA in participants from Italy versus 83.8% and 100% (Group 1 and 2) in Finland. As a reason for this phenomenon a higher TdaP-vaccination rate of zero in Finland and 64.2% in Italy has been identified, which is supported by corresponding pre-dose values.

Of note, the pre-dose-values for anti-Polio 1, 2, and 3 similarly differ considerably between both countries while seroconversion is robust in all groups.

Regarding Haemophilus influenzae the results between Italy and Finland also differ: For Group 1 89 versus 78%, and for Group 2 96 versus 93% for anti-PRP seroprotection rates ≥ 0.15 µg/ml. However, the reciprocal pre-dose 1 values might explain this difference.

Seroprotection rates for Hepatitis B are more comparable between Italy and Finland.

Overall the evaluation by country shows differences. Some reasons have been elucidated by differences in vaccination schedules. Some findings could not be explained, e.g. the low seroresponse rate for anti-PRP in Group 1 in Finland. The considerably lower number of participants in the Finnish cohort, use of a different batch, and other country-specific reasons might be causative. Taking the results together, vaccine responses, irrespective of the administration schedule, are considered to be robust despite the noted differences.

7.3. Conclusions on immunogenicity

Almost 400 participants have been included in the study, adequately distributed into Groups 1 (co-administration) and 2 (sequential administration). Participation between Finland (98 participants) and Italy (299 participants) is imbalanced.

Conduct of the study was impaired by the COVID-19 pandemic, resulting in a long recruitment-period (January 2021-January 2023), and expansion to an additional country (Finland).

The T3L90 batch used in Italy had an initial expiry date of May 2022 based on the 36-month shelf-life which was extended to May 2023 following approval by the European Medicines Agency [EMA] of the variation for a 48-month shelf-life. Potential impact of the original und extended expiry date has been evaluated regarding immunogenicity. The compiled data still suggest a cautious interpretation due to the small respective subgroup. One might perceive an increased immunological response by decrease of batch-age with exception of the anti-PRP-percentages ≥1µg/ml. The clinical relevance is not known but does not raise concerns.

Primary Objective was not achieved. For Hepatitis B (seroprotection rates for anti-HBsAg ≥ 10 mIU/mL) at one month after the 3rd dose non-inferiority of co-administration vs sequential dosing was demonstrated. However, for Haemophilus influenzae B (seroprotection rate against PRP, ie percentage of participants with antibody concentration ≥ 1 µg/mL) non-inferiority was not demonstrated.

In terms of the Secondary Objectives, descriptive analyses for each antigen have been presented. Established Correlates of Protection have been analyzed. For Diphtheria, Tetanus, Polio (3 serotypes), and Hepatitis B results were adequate. For Pertussis, 4-fold increases were low, but still acceptable.

For Haemophilus influenzae the MAH added several analyses. All these results support adequate short-term- and long-term-rates for both Groups. Slightly lower numbers for the Coadmin-Group (Group 1) compared with the sequential Group (Group 2) are known from similar settings. Adequate protection in both groups is acknowledged despite the failure of non-inferiority testing.

Surrogates of protection (including fHbp) for the MenB vaccination have been presented and are considered to be acceptable.

Post-hoc analysis by country elucidates differences which are partly explained by differences in vaccination schedules. Some findings could not be explained, e.g. the low seroresponse rate for anti-PRP in Group 1 in Finland. The considerably lower number of participants in the Finnish cohort, use of a different batch, and other country-specific reasons might be causative. However, vaccine responses, irrespective of the administration schedule, are considered to be robust despite the noted differences.

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

Safety of study vaccines was assessed for all participants as secondary objective by collecting solicited reactions (from Day 0 to Day 7 after each vaccination), unsolicited non-serious AEs (from Day 0 to Day 30 after each vaccination), and SAEs and AESIs (throughout the study).

Based on the nature of the investigational vaccine (inactivated) and the previous clinical experience accumulated with this product, the study did not include an Early Safety Data Review. Safety data were collected and monitored on an ongoing basis.

8.2. Results

A tabular overview regarding any injection is presented, below:

Table 8: Safety overview after any injection – SafAS (Safety analysis set)

	Group 1 Co-administration (N=194)			**Group 2 Sequential administration (N=192)**		
Period/ Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 minutes after any vaccine injections						
Immediate unsolicited AE	1/194	0.5	(0; 2.8)	1/192	0.5	(0; 2.9)
Immediate unsolicited AR	1/194	0.5	(0; 2.8)	1/192	0.5	(0; 2.9)
Solicited reaction within 7 days after any vaccine injections	190/194	97.9	(94.8; 99.4)	188/191	98.4	(95.5; 99.7)

Period/ Participants experiencing at least one:	Group 1 Co-administration (N=194) n/M	%	(95% CI)	Group 2 Sequential administration (N=192) n/M	%	(95% CI)
Solicited injection site reaction	177/194	91.2	(86.3; 94.8)	176/191	92.1	(87.4; 95.5)
Hexavalent vaccine	164/194	84.5	(78.7; 89.3)	158/191	82.7	(76.6; 87.8)
MenB vaccine	172/194	88.7	(83.3; 92.8)	159/186	85.5	(79.6; 90.2)
PCV vaccine	167/194	86.1	(80.4; 90.6)	149/191	78.0	(71.5; 83.7)
Solicited systemic reaction	186/194	95.9	(92.0; 98.2)	186/191	97.4	(94.0; 99.1)
Hexavalent and PCV vaccines*				185/191	96.9	(93.3; 98.8)
MenB vaccine*				172/186	92.5	(87.7; 95.8)
Within 30 days after any vaccine injections						
Unsolicited AE	107/194	55.2	(47.9; 62.3)	134/192	69.8	(62.8; 76.2)
Unsolicited AR	23/194	11.9	(7.7; 17.3)	24/192	12.5	(8.2; 18.0)
AE leading to study discontinuation	1/194	0.5	(0; 2.8)	0/192	0	(0; 1.9)
SAE	3/194	1.5	(0.3; 4.5)	6/192	3.1	(1.2; 6.7)
SAE leading to study discontinuation	1/194	0.5	(0; 2.8)	0/192	0	(0; 1.9)
SAR	0/194	0	(0; 1.9)	0/192	0	(0; 1.9)
SAR leading to study discontinuation	0/194	0	(0; 1.9)	0/192	0	(0; 1.9)
Death	0/194	0	(0; 1.9)	0/192	0	(0; 1.9)
AESI	0/194	0	(0; 1.9)	0/192	0	(0; 1.9)
During the study						
AE leading to study discontinuation	1/194	0.5	(0; 2.8)	0/192	0	(0; 1.9)
SAE	10/194	5.2	(2.5; 9.3)	8/192	4.2	(1.8; 8.0)
SAE leading to study discontinuation	1/194	0.5	(0; 2.8)	0/192	0	(0; 1.9)
SAR	0/194	0	(0; 1.9)	0/192	0	(0; 1.9)
SAR leading to study discontinuation	0/194	0	(0; 1.9)	0/192	0	(0; 1.9)
Death	0/194	0	(0; 1.9)	0/192	0	(0; 1.9)
AESI	0/194	0	(0; 1.9)	1/192	0.5	(0; 2.9)

n: number of participants experiencing the endpoint listed in the first column
M: number of participants with available data for the relevant endpoint
AR: Reactions related to study vaccine
*Group 2 received MenB vaccine on different visit than Hexavalent and PCV vaccines due to sequential administration.
Study: A3L00057
Source: Clinical Overview

Immediate reactions: One participant in Group 1 (co-administration) and 1 participant in Group 2 (sequential administration) each experienced 1 immediate unsolicited AR within 30 minutes of any vaccination. The participant in Group 1 experienced redness of the cheeks and chin (preferred term: erythema) that occurred post-dose 2. The participant in Group 2 experienced redness on chest (preferred term: erythema) that occurred post-dose 1 of the 4CMenB vaccine.

The percentage of participants who experienced at least 1 solicited injection site reaction after any vaccination were 97.9% in Group 1 and 98.4% in Group 2.

Solicited reactions of Grade 3 intensity after any vaccination were reported in 46.4% of participants in Group 1 and 36.6% of participants in Group 2.

Solicited injection site reactions within 7 days after any vaccination were reported in 91.2% of participants in Group 1 and 92.1% of participants in Group 2.

The percentages of participants who experienced at least 1 solicited injection site reaction were:

- 84.5% in Group 1 and 82.7% in Group 2 for the Hexavalent vaccine
- 88.7% in Group 1 and 85.5% in Group 2 for the 4CMenB vaccine
- 86.1% in Group 1 and 78.0% in Group 2 for the PCV13 vaccine

Solicited injection site reactions of Grade 3 intensity after any vaccination were reported in 29.9% of participants in Group 1 and 24.6% of participants in Group 2.

The percentages of participants who experienced at least 1 solicited injection site reaction of Grade 3 intensity were:

- 21.6% in Group 1 and 11.5% in Group 2 for the Hexavalent vaccine
- 25.8% in Group 1 and 16.7% in Group 2 for the 4CMenB vaccine
- 23.7% in Group 1 and 11.0% in Group 2 for the PCV13 vaccine

Profile: After any dose of Hexaxim, the most frequently reported injection site reactions in Group 1 (co-administration) and Group 2 (sequential) were tenderness, followed by erythema and swelling:

- Tenderness was reported in 79.4% of participants in Group 1 and 67.5% in Group 2.
- Erythema was reported in 63.9% of participants in Group 1 and 55.5% in Group 2
- Swelling was reported in 53.6% of participants in Group 1 and 39.8% in Group 2

The percentages of participants who experienced at least 1 solicited systemic reaction within 7 days after any vaccination were 95.9% in Group 1 and 97.4% in Group 2.

In Group 2 (sequential administration), the percentages of participants who experienced at least 1 solicited systemic reaction after vaccination were 96.9% for the Hexavalent and PCV13 vaccines and 92.5% for the 4CMenB vaccine.

Solicited systemic reactions of Grade 3 intensity after any vaccination were reported in 35.6% of participants in Group 1 and 27.7% in Group 2.

In Group 2 (sequential administration), the percentages of participants who experienced at least 1 solicited systemic reaction of Grade 3 intensity were 18.3% for the Hexavalent and PCV13 vaccines and 20.4% for the 4CMenB vaccine.

Profile: Within 7 days after any vaccination, the most frequently reported solicited systemic reactions in Group 1 (co-administration) and Group 2 (sequential administration) were irritability, crying abnormal, and drowsiness, followed by fever, appetite lost, and vomiting:

- Irritability was reported in 91.2% of participants in Group 1 and 90.1% in Group 2.
- Crying abnormal was reported in 88.1% of participants in Group 1 and of participants in Group 2.
- Drowsiness was reported in 84.5% of participants in Group 1 and 85.9% in Group 2.
- Fever was reported in 73.7% of participants in Group 1 and 56.0% in Group 2. Fever of Grade 3 intensity was reported in ≤ 1.1% of participants in both groups.
- Appetite lost was reported in 68.6% of participants in Group 1 and 69.6% in Group 2.
- Vomiting was reported in 25.3% of participants in Group 1 and 30.9 in Group 2.

The percentages of participants who experienced at least 1 unsolicited AE within 30 days after any vaccination were 55.2% in Group 1 (co-administration) and 69.8% in Group 2 (sequential).

There were 11.9% of participants in Group 1 and 12.5% in Group 2 with at least 1 unsolicited related AE (AR) after any vaccination.

The percentages of participants who experienced at least 1 unsolicited injection site AR after any vaccination were 8.8% in Group 1 and 7.3% in Group 2.

The percentages of participants who experienced at least 1 unsolicited systemic AR after any vaccination were 4.6% in Group 1 and 6.8% in Group 2.

Grade 3 unsolicited AEs after any vaccination were reported in 3.6% of participants in Group 1 and 4.2% in Group 2.

No Grade 3 unsolicited ARs were reported in Group 1 and 1 was reported in Group 2 (gastroenteritis on the day of the 2nd vaccination with the 4CMenB vaccine)

One participant in Group 1 experienced an unrelated SAE (aortic valve stenosis of Grade 3 intensity that occurred 28 days post-dose 1, and lead to discontinuation from the study.

No AESIs were reported in Group 1, and one participant in Group 2 experienced an unrelated SAE considered as an AESI (hazelnut anaphylactic shock of Grade 2 intensity).

Serious adverse events and deaths

No deaths were reported in any group during the study.

During the study, 10 participants (5.2%) in Group 1 and 8 participants (4.2%) in Group 2 experienced at least 1 SAE. None of the SAEs were related to the study vaccines.

Within 30 days after any vaccination, 3 participants (1.5%) in Group 1 experienced 4 SAEs and 6 participants (3.1%) in Group 2 experienced 7 SAEs. Details of the SAEs (ref CSR p122/407) are presented, below.

Table 9: serious adverse events details

	Group 1 Co-administration (N=194)								Group 2 Sequential administration (N=192)							
	All SAEs				Related SAEs				All SAEs				Related SAEs			
Participants experiencing at least one:	n	%	(95% CI)	n SAEs	n	%	(95% CI)	n SAEs	n	%	(95% CI)	n SAEs	n	%	(95% CI)	n SAEs
SAE	3	1.5	(0.3; 4.5)	4	0	0	(0; 1.9)	0	6	3.1	(1.2; 6.7)	7	0	0	(0; 1.9)	0
Cardiac disorders	1	0.5	(0; 2.8)	1	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0
Aortic valve stenosis	1	0.5	(0; 2.8)	1	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0
Infections and infestations	2	1.0	(0.1; 3.7)	3	0	0	(0; 1.9)	0	6	3.1	(1.2; 6.7)	7	0	0	(0; 1.9)	0
Bronchiolitis	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0	3	1.6	(0.3; 4.5)	3	0	0	(0; 1.9)	0
COVID-19	1	0.5	(0; 2.8)	1	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0
Pneumonia	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0	2	1.0	(0.1; 3.7)	2	0	0	(0; 1.9)	0
Respiratory syncytial virus bronchiolitis	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0	1	0.5	(0; 2.9)	1	0	0	(0; 1.9)	0
Respiratory syncytial virus infection	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0	1	0.5	(0; 2.9)	1	0	0	(0; 1.9)	0
Rhinitis	1	0.5	(0; 2.8)	1	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0
Urinary tract infection	1	0.5	(0; 2.8)	1	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0	0	0	(0; 1.9)	0

n: number of participants experiencing the endpoint listed in the first column
n SAEs: number of SAEs
Related SAEs: causal relationship reported by an investigator as related to study vaccine. If the relationship is missing, the SAE will be considered as related to study vaccine
Study: A3L00057 Program: T08079.sas Datasets=ADSL ADAE Output: PRODOPS/PLC16002/A3L00057/CSR_01/REPORT/OUTPUT/T08079_i.rtf (07FEB2025 17:24)
Source: Section 8, Table 8.79

Post-marketing Surveillance: The review and analyses of spontaneous data extracted from the Sanofi global safety database from 01 June 2013 to 17 April 2023 identified 18 320 spontaneous AE reports worldwide following Hexaxim vaccination, with more than 180 million doses of Hexaxim having been distributed. The 10 most frequently reported events (non-serious and serious) were fever, injection site erythema, crying, injection site swelling, rash, irritability, injection site pain, diarrhea, vomiting, and decreased appetite, with a frequency ranging between 0.36 and 5.14 per 100 000 doses

distributed. Of the serious reported events, the 5 most frequent were fever, convulsion with or without fever, crying, HHE/hypotonia, and vomiting. These findings are consistent with the known safety profile of Hexaxim. The review and analyses of the same data up to a more recent time point (from 18 April 2022 to 17 April 2025) identified no new relevant safety information.

8.3. Discussion and Conclusion

Safety of the study vaccines was assessed for all participants as secondary objective by collecting solicited reactions (from Day 0 to Day 7 after each vaccination), unsolicited non-serious AEs (from Day 0 to Day 30 after each vaccination), and SAEs and AESIs (throughout the study **A3L00057**).

The Safety overview-table shows concentration on solicited local and systemic reactions as in similar settings. Serious adverse events are rare, deaths and SARs were zero.

Reactogenicity (Solicited Adverse Events) of the 3 evaluated vaccines is close together with a trend to more severe reactions after MenB vaccination. Further, numbers of severe reactions (Grade 3) are considerably higher in the Coadmin Group compared with the Sequential Group. However, this finding is as expected. Profile of the reported solicited reactions concurs with the profile in the SmPC.

All documented SAEs were not related with the vaccinations and represent a spectrum of infectious diseases of the respective childhood age-group with the exception of an aortic valve stenosis, presumably a connatal cardiac disease.

Overall, the safety profile of Hexaxim as documented with concomitant administration of MenB vaccine is consistent with the known safety profile as reflected in the SmPC. Higher rates of reactogenicity are within acceptable limits, and mirror expected values.

9. Changes to the Product Information

Update of section 4.5 of the SmPC in order to amend information regarding the co-administration of Hexaxim with meningococcal B conjugate vaccine based on results from study A3L00057 (NCT2019-002585-12) has been proposed by the MAH. The proposed wording is acknowledged.

No changes are proposed for the PL.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

10. Request for supplementary information

10.1. Other concerns

OC 1: The T3L90 batch used in Italy had an initial expiry date of May 2022 based on the 36-month shelf-life which was extended to May 2023 following approval by the European Medicines Agency [EMA] of the variation for a 48-month shelf-life.

For excluding any influence of the extension of the expiry date of the T3L90 Batch (Italy) on the study results, a respective analysis should be amended. Immunogenicity results for vaccinations before and after the extended expiry date in comparison with the results from Finland are requested.

11. Assessment of the responses to the request for supplementary information

11.1. Other concerns

Clinical aspects

Question 1
The T3L90 batch used in Italy had an initial expiry date of May 2022 based on the 36-month shelf-life which was extended to May 2023 following approval by the European Medicines Agency [EMA] of the variation for a 48-month shelf-life.

For excluding any influence of the extension of the expiry date of the T3L90 Batch (Italy) on the study results, a respective analysis should be amended. Immunogenicity results for vaccinations before and after the extended expiry date in comparison with the results from Finland are requested.

Summary of the MAH's response

Introductory comment

Minor errors were noted in the exploratory analysis of post-Dose 3 anti-PRP levels according to age of the batch (at the time of Dose 1) presented in the CSR Section 5.1.3 and Appendix 15. Due to a programming discrepancy during statistical analysis, few participants who received Hexaxim batch T3L90 (Italy) were misclassified and not included in the subgroup of participants who received 3 doses aged 37 to 48 months ('37-48 months'). Thus, in the FAS, the number of evaluable participants for the subgroup '37-48 months' is 16 and not 9 as initially reported.

Section 5.1.3 of the CSR and the Appendix 15 have been revised, accordingly. An "Erratum Summary" to the CSR including the revised Appendix 15 has been provided as part of the submission.

Responses

In A3L00057 study, Hexaxim was administered to infants as a 2+1 schedule given at 3, 5 and 12 months of age (i.e. booster dose given 9 months after the first dose). Two (2) batches of the Hexaxim vaccine were used: the T3L90 batch was used in Italy and the U3P16 batch was used in Finland.

The T3L90 batch used in Italy had an initial expiry date of May 2022 based on the 36-month shelf-life which was extended to May 2023 following EMA approval on 25 June 2020 of the Worksharing - EMEA/H/C/xxxx/WS/1821/G - Extension of Shelf Life of Finished Product from 36 months to 48 months.

In Italy, enrolment occurred from January 2021 to July 2022 meaning that infants recruited before end of May 2022 received a first dose of Hexaxim aged up to 36 months; only infants recruited in June and July 2022 received a first dose of Hexaxim aged 37 or 38 months.

Only infants recruited in June and July 2022 received a full 2+1 schedule of Hexaxim aged 37 to 48 months. The other infants who were recruited earlier received a 2+1 schedule with the first dose of Hexaxim aged 20 to 36 months and subsequent doses of Hexaxim aged up to 45 months.

The U3P16 batch used in Finland had an expiry date of March 2024 corresponding to a 48-month shelf-life. Enrolment occurred from September 2022 to January 2023, thus the age of Hexaxim batch at the time of Dose 1 ranged from 30 to 34 months. Subsequent doses of Hexaxim aged up to 43 months.

Following the Request for Supplementary Information received, complementary descriptive analyses were performed for participants who received Hexaxim Batch T3L90 (Italy). Post-dose 3 anti-PRP antibody responses were described for the subgroup of participants who received 3 doses aged 37 to 48 months and for the subgroup of remaining participants ('up to 36 months'), pooled data in the FAS.

Table 10 Post-dose 3 anti-PRP (RIA-mcg/mL) response according to batch age for Hexaxim batch T3L90 (Italy) - FAS

	Batch T3L90 (Italy) (N=298)	Batch T3L90 37-48 months (Italy)* (N=17)**	Batch T3L90 up to 36 months (Italy) (N=279)
M	271	16	255
Geometric Mean (GM)			
GM	7.77	6.42	7.86
(95% CI)	(6.50 ; 9.28)	(3.05 ; 13.5)	(6.53 ; 9.46)
>= 0.15 µg/mL			
n/M (%)	268/271 (98.9)	15/16 (93.8)	253/255 (99.2)
(95% CI)	(96.8 ; 99.8)	(69.8 ; 99.8)	(97.2 ; 99.9)
>= 1 µg/mL			
n/M (%)	246/271 (90.8)	15/16 (93.8)	231/255 (90.6)
(95% CI)	(86.7 ; 93.9)	(69.8 ; 99.8)	(86.3 ; 93.9)

(*) Subgroup of subjects vaccinated with batch T3L90 (Italy) and all doses aged 37 to 48 months.
(**) Among the 19 subjects vaccinated with doses of batch T3L90 aged 37 to 48 months, 2 subjects did not complete vaccination schedule.
M: number of subjects with available data for the relevant endpoint
n: number of subjects experiencing the endpoint listed in the first column
Study: A3L00057 Program: T15002A.sas Datasets=ADSL ADIS Output: PRODOPS/PLC16002/A3L00057/CSR_01/REPORT/OUTPUT/T15002A_x.pdf (08APR2026 4:57)

Source: Response Document

Table 11. Post-Dose 3 anti-PRP (RIA – mcg/mL) responses according to Hexaxim batch and for subjects who received 3 doses from batch aged 37 to 48 months - FAS

	Batch T3L90 (Italy) (N=298)	Batch T3L90 37-48 months (Italy)* (N= ~~9~~ 17)	Batch U3P16 (Finland) (N=92)
M	271	~~9~~ 16	81
Geometric Mean (GM)			
GM	7.77	~~4.67~~ 6.42	6.43
(95% CI)	(6.50 ; 9.28)	~~(1.21 ; 18.1)~~ (3.05 ; 13.5)	(4.34 ; 9.50)
>= 0.15 µg/mL			
n/M (%)	268/271 (98.9)	~~8/9 (88.9)~~ 15/16 (93.8)	77/81 (95.1)
(95% CI)	(96.8 ; 99.8)	~~(51.8 ; 99.7)~~ (69.8 ; 99.8)	(87.8 ; 98.6)
>= 1 µg/mL			
n/M (%)	246/271 (90.8)	~~8/9 (88.9)~~ 15/16 (93.8)	67/81 (82.7)
(95% CI)	(86.7 ; 93.9)	~~(51.8 ; 99.7)~~ (69.8 ; 99.8)	(72.7 ; 90.2)

(*) Subgroup of subjects vaccinated with batch T3L90 (Italy) and all doses aged 37 to 48 months.
M: number of subjects with available data for the relevant endpoint
n: number of subjects experiencing the endpoint listed in the first column
Study: A3L00057 Program: T15001to02.sas Datasets=ADSL ADIS Output: PRODOPS/PLC16002/A3L00057/CSR_01/REPORT/OUTPUT/T15002 ~~x.pdf (07FEB2025 16:42)~~ revised_x.pdf (31MAR2026 7:55)

Source: "Erratum Summary" in the updated CSR for Appendix 15

According to the updated CSR, the following numbers are reflected for the FAS:

Post-dose 3 anti-PRP seroprotection rates ≥ 0.15 µg/mL were:
- 98.9% (95% CI: 96.8; 99.8) for batch T3L90 (Italy)
- 95.1% (95% CI: 87.8; 98.6) for batch U3P16 (Finland)

Post-dose 3 anti-PRP seroprotection rates ≥ 1 µg/mL were:
- 90.8% (95% CI: 86.7; 93.9) for batch T3L90 (Italy)
- 82.7% (95% CI: 72.7; 90.2) for batch U3P16 (Finland)

Among the 9 participants who received 3 doses aged 37 to 48 months (batch T3L90 in Italy), 8 of them (88.9% [95% CI: 51.8; 99.7]) achieved anti-PRP seroprotection thresholds (≥ 0.15 µg/mL and ≥ 1 µg/mL).

In the FAS, post-dose 3 anti-PRP GMCs were:

- 7.77 (95% CI: 6.50; 9.28) for batch T3L90 (Italy)
- 6.43 (95% CI: 4.34; 9.50) for batch U3P16 (Finland)

For the 9 participants who received 3 doses aged 37 to 48 months (batch T3L90 in Italy), GMCs were 4.67 (95% CI: 1.21; 18.1).

According to the ema-responses, the following numbers are reflected for the FAS (batch T3L90, Italy):

- Post-dose 3 anti-PRP seroprotection rates ≥ 0.15 µg/mL were:
  98.9% (95% CI: 96.8; 99.8) for all participants
  99.2% (95% CI: 97.2; 99.9) for the subgroup 'up to 36 months'
  93.8% (95% CI: 69.8; 99.8) for the subgroup '37-48 months'
- Post-dose 3 anti-PRP seroprotection rates ≥ 1 µg/mL were:
  90.8% (95% CI: 86.7; 93.9) for all participants
  90.6% (95% CI: 86.3; 93.9) for the subgroup 'up to 36 months'
  93.8% (95% CI: 69.8; 99.8) for the subgroup '37-48 months'
- Post-dose 3 anti-PRP GMCs (µg/mL) were:
  7.77 (95% CI: 6.50; 9.28) for all participants
  7.86 (95% CI: 6.53; 9.46) for the subgroup 'up to 36 months'
  6.42 (95% CI: 3.05; 13.5) for the subgroup '37-48 months'

Assessment of the MAH's response

The MAH provided a Response-Document, an updated CSR with Erratum Summary for CSR and Appendix 15 and an updated Appendix 15.

Unfortunately, the requested data are not well-structured but had to be compiled by the Assessor from these sources. Further, it seems that the "Erratum Summary" describes the changes for Section 5.1.3 of the CSR, but this Section 5.1.3 remains still unchanged in the updated document. (OC). (The MAH is asked to review the submitted CSR-document and update Section 5.1.3, respectively).

Further, the provided numbers of relevant participants in the respective vaccination group, is misleading. According to the Cover letter, "in the FAS, the number of evaluable participants for the subgroup '37-48 months' is 16 and not 9 as reported in the CSR initially". According to the footnote to Table 3.2A a number of N=17 was commented by ** "Among the 19 subjects with doses of batch T3L90aged 37 to 48 months, 2 subjects did not complete vaccination schedule". In summary, 19 instead of 9 initially reported subjects are assumed to be concerned by the shelf-life extension.

The requested information can be compiled from amended Table 3.2 as updated in Appendix 15 combined with the partially provided information in Table 3.2A of the Response-Document.

Table 12 (updated Appendix 15) and Table 3.2A (Response-Document)

	T3L90 (Italy) N=298 (all)	T3L90 (Italy) N=19 (37-48mo)	T3L90 (Italy) N=279 (≤ 36mo)	U3P16 (Finland) N=98 (30-43mo)
M	271	16	255	81
Geometric Mean	7,77	6.42	7.86	6.43
Anti PRP ≥0.15µg/ml	268/271	15/16	253/255	77/81
%	98.9	93.8	99.2	95.1
Anti PRP ≥1µg/ml	246/271	15/16	231/255	67/81
%	90.8	93.8	90.6	82.7

The tabulated compiled data still suggest a cautious interpretation due to the small respective subgroup. One might perceive an increased immunological response by decrease of batch-age with exception of the anti-PRP-percentages ≥1µg/ml. The clinical relevance is not known but does not raise concerns.

Table 3.2A of the Response document is presented in a hardly readable size. Requested analysis has not been reflected in the updated CSR (**OC)**.

Conclusion

In summary, the amended analysis does not raise concerns regarding clinically relevant decrease of the immunogenicity by age of the batch. However, the raised formal points should be addressed, thoroughly.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

12. 2nd Request for supplementary information

12.1. Other concerns

OC 1: The "Erratum Summary" describes the changes for Section 5.1.3 of the CSR, but this Section 5.1.3 remains still unchanged in the updated document. The MAH is asked to review the submitted CSR-document and update Section 5.1.3, respectively.

OC 2: Table 3.2A of the Response document in the given context has not been reflected in the updated CSR. Summarized Table 3.2A/updated Table 3.2 according to the assessment should be amended in Section 5.3.1 of the CSR in a well-legible size, respectively.

13. Assessment of the responses to the 2nd Request for supplementary information

13.1. Other concerns

OC 1: The "Erratum Summary" describes the changes for Section 5.1.3 of the CSR, but this Section 5.1.3 remains still unchanged in the updated document. The MAH is asked to review the submitted CSR-document and update Section 5.1.3, respectively.

Summary of the MAH's response

The MAH replaced the "Erratum Summary" Section in the CSR by a "List of Changes from Clinical Study Report Version 1.0 Dated 09 Sep 2025 to Version 2.0 Dated 05 Jun 2026" and updated Section 5.1.3 in the CSR. Further, an updated CSR-body and an updated Appendix-15 have been submitted.

Assessment of the MAH's response

Requested updates have been submitted. Point is solved.

OC 2: Table 3.2A of the Response document in the given context has not been reflected in the updated CSR. Summarized Table 3.2A/updated Table 3.2 according to the assessment should be amended in Section 5.3.1 of the CSR in a well-legible size, respectively.

Summary of the MAH's response

Respective Table 3.2A of the Response document has been amended.

Assessment of the MAH's response

Table 3.2A has been amended. Point is solved.

Conclusion

In summary, the amended analysis does not raise concerns regarding clinically relevant decrease of the immunogenicity by age of the batch. However, the raised formal points have been addressed, adequately.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly