EMA/CHMP/471748/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Vaxelis

International non-proprietary name: diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inact.) and Haemophilus type b conjugate vaccine (adsorbed)

Procedure No. EMEA/H/C/003982/II/0088

Note

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

Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	13 Sep 2021	13 Sep 2021
☐	CHMP Rapporteur Assessment Report	18 Oct 2021	20 Oct 2021
☐	CHMP members comments	29 Oct 2021	N/A
☐	Updated CHMP Rapporteur Assessment Report	04 Nov 2021	N/A
☐	Start of written procedure	9 Nov 2021	N/A
☐	Request for supplementary information	11 Nov 2021	11 Nov 2021
☐	Start of procedure	29 Dec 2021	29 Dec 2021
☐	CHMP Rapporteur Assessment Report	12 Jan 2022	12 Jan 2022
☐	CHMP members comments	17 Jan 2022	17 Jan 2022
☐	Updated CHMP Rapporteur Assessment Report	20 Jan 2022	19 Jan 2022
☐	Start of written procedure	25 Jan 2022	N/A
☒	Opinion	27 Jan 2022	27 Jan 2022

Table of contents

1. Background information on the procedure 4

2. Overall conclusion and impact on the benefit/risk balance 4

3. Recommendations 5

4. EPAR changes 6

5. Introduction 8

5.1. Methods – analysis of data submitted 8

5.2. Results 13

5.3. Discussion 18

6. Changes to the Product Information 19

7. Request for supplementary information 21

7.1. Major objections 21

7.2. Other concerns 21

8. Assessment of the responses to the request for supplementary information 21

8.1. Major objections 21

8.2. Other concerns 21

9. Attachments 23

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, MCM Vaccine B.V. submitted to the European Medicines Agency on 20 August 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Update of section 5.1 of the SmPC in order to include information about long-term durability of the immune protection against HBV infection based on study V419-013 A Hepatitis B Vaccine Challenge Study to Demonstrate the Durability of Protection Against Hepatitis B Virus Infection in Healthy Children Vaccinated Approximately 9 Years Previously With a 2- or 3-Dose Infant Series and Toddler Dose of Vaxelis (study report P013V419). In addition, the MAH is updating sections 4.7 and 4.8 of the SmPC to implement EMA proposed wording and a typo error.
The MAH took the opportunity to update the list of local representatives in the PL and implement minor editorial changes in sections 4.8 and 6.6 of the SmPC and section 2 of the PL. Furthermore, the PI is brought in line with the latest QRD template version 10.2 rev. 1.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

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

Vaxelis is a hexavalent vaccine co-developed by Sanofi Pasteur and MSD and was approved in the EU in 2016.

Vaxelis is indicated for active immunization against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis (caused by poliovirus Types 1, 2, and 3), and invasive disease caused by Haemophilus influenzae type b in children from the age of 6 weeks. The vaccine is administered as a 0.5-mL intramuscular injection in a 2- or 3-dose infant vaccination series (with an interval of at least 1 month between doses) followed by a toddler dose (least 6 months after the last priming dose), depending on local recommendations.

This submission relates to a paediatric study (V419-013). The submission of the final study report is also in accordance with Article 46 of Regulation (EC) No 1901/2006 which sets out the obligation for MAHs to submit any MAH-sponsored studies involving the use of an authorised medicinal products in the paediatric population to the competent authority.

Study V419-013 is a stand-alone study and is not included in a paediatric investigation plan (PIP).

The data submitted concern the long-term durability of protection against HBV infection 8-9 years after vaccination with a 3 + 1 or 2 + 1 Vaxelis series (i.e., a 3 or 2 dose primary vaccination series followed by a single toddler dose) from the Hepatitis B Vaccine Challenge Study V419-013. The MAH, MCM Vaccine B.V., submitted this variation application to propose updates of the Summary of Product Characteristics (SmPC) section 5.1 Pharmacodynamic properties with information about long-term durability of the immune protection against HBV infection.

Study V419-013 is an open-label study conducted at 10 study-sites in Finland. The aim of the study was to evaluate long-term antibody persistence and immune memory 8-9 years after primary vaccination with Vaxelis. Participants 8 to 10 years of age who previously participated in either V419-007 or V419-008 and

received a 3 + 1 Vaxelis or 2 + 1 Vaxelis schedule, respectively, were enrolled. All participants were to receive one dose of the HBVAXPRO vaccine as hepatitis B surface antigen challenge. This vaccine is approved in the EU for active immunisation against hepatitis B virus infection in individuals from birth through 15 years of age considered at risk of exposure to hepatitis B virus.

An anti-HBs level ⩾10 mIU/mL is accepted as correlate of protection against HBV infection. It is known that when this level is achieved 1 to 3 months after receipt of a complete and adequately administered vaccination course, individuals are considered completely protected against both acute and chronic infection for decades. Reaching anti-HBs levels ⩾10 mIU/mL 30 days after a single dose challenge provides acceptable evidence to show persistent protection against HBV infection.

In this study, the proportion of participants with a protective anti-HBs level (≥10 mIU/mL) 30 days post-challenge is assessed and anti-HBs GMCs are evaluated pre- and post-challenge. Throughout the study, AEs resulting in discontinuation and SAEs were collected. The design, objectives, methods and endpoints of the study are endorsed.

Of the 207 participants enrolled, 205 received the HBVAXPRO challenge.

At 8-9 years after primary vaccination, protective anti-HBs levels ⩾10 mIU/mL were still present in 40.9% and 49.1% of the participants who previously received a 2 + 1 or 3 + 1 Vaxelis schedule, respectively. Thirty days after receiving the hepatitis B surface antigen challenge HBVAXPRO, nearly all participants (201 out of 202) had seroprotective anti-HBs antibody concentrations.

The mean GMC increased from 9.63 mIU/mL (95% CI: 7.88 - 11.76) pre-challenge, to 685.84 mIU/mL (95% CI: 605.67 - 776.63) 30 days after the challenge. Furthermore, 96.0% of the participants showed a ⩾4-fold rise in anti-HBs antibody titers, confirming the robust anamnestic response after Hepatitis B surface antigen challenge.

No significant differences were observed in the humoral immune response in participants who initially were administered a 3 + 1 or a 2 + 1 Vaxelis schedule, both pre- and post-challenge with HBVAXPRO.

These results suggest long-term persistence of protection against Hepatitis B infection up to at least 8-9 years after primary vaccination with Vaxelis.

No SAEs and no AEs resulting in discontinuation were reported after vaccination with the hepatitis B surface antigen challenge HBVAXPRO. The safety profile of Vaxelis remains unchanged.

Based on the data from V419-013, it is concluded that 8-9 years after having received a 3 + 1 or 2 + 1 Vaxelis schedule, anti-HBs levels remain above the seroprotection level of 10 mIU/mL in 40.9% and 49.1% of the individuals, respectively. In addition, administration of a hepatitis B surface antigen challenge with HBVAXPRO markedly increased anti-HBs antibody levels, reaching a seroprotective titer above 10 mIU/mL in nearly all subjects. This data demonstrates an anamnestic response and hence long-term persistence of immune memory.

These data are consistent with the literature on immune persistence hepatitis B vaccination.

The updates in the SmPC are considered in line with the data of study V419-013.

The benefit-risk balance of Vaxelis remains positive.

3. Recommendations

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

Variation approved		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Update of section 5.1 of the SmPC in order to include information about long-term durability of the immune protection against HBV infection based on study V419-013 A Hepatitis B Vaccine Challenge Study to Demonstrate the Durability of Protection Against Hepatitis B Virus Infection in Healthy Children Vaccinated Approximately 9 Years Previously With a 2- or 3-Dose Infant Series and Toddler Dose of Vaxelis (study report P013V419). In addition, the MAH is updating section 4.4 and sections 4.7 and 4.8 of the SmPC to implement CHMP recommended wording and amend a typographical error.
The MAH took the opportunity to update the list of local representatives in the PL and implement minor editorial changes in sections 4.8 and 6.6 of the SmPC and section 2 of the PL. Furthermore, the PI is brought in line with the latest QRD template version 10.2 rev. 1.

☒is recommended for approval.

Amendments to the marketing authorisation

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

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Based on data from V419-013, it was concluded that 8-9 years after having received a 3 + 1 or 2 + 1 Vaxelis schedule, anti-HBs levels remain above the seroprotection level of 10 mIU/mL in 40.9% and 49.1% of the individuals, respectively. In addition, administration of a hepatitis B surface antigen challenge with HBVAXPRO markedly increased anti-HBs antibody levels, reaching a seroprotective titer above 10 mIU/mL in nearly all subjects. These data demonstrate an anamnestic response and hence long-term persistence of immune memory. The SmPC was updated to adequately reflect the data from study V419-013.

For more information, please refer to the Summary of Product Characteristics.

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

5. Introduction

- **Background on the product:**

Vaxelis is a hexavalent vaccine (diphtheria, tetanus, pertussis [acellular, component], hepatitis B [rDNA], poliomyelitis [inactivated], and Haemophilus type b conjugate vaccine [adsorbed], [DTaP5- HB-IPV-Hib]) co-developed by Sanofi Pasteur and MSD.

Vaxelis is indicated for active immunization against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis (caused by poliovirus Types 1, 2, and 3), and invasive disease caused by Haemophilus influenzae type b in children from the age of 6 weeks. Vaxelis was approved in the EU in 2016 and in the US in 2018. The vaccine is administered as a 0.5-mL intramuscular injection in a 2- or 3-dose infant vaccination series (with an interval of at least 1 month between doses) followed by a toddler dose (least 6 months after the last priming dose), depending on local recommendations.

- **Purpose of the Variation and Proposed changes to the Product Information:**

This submission relates to a paediatric study (V419-013). The submission of the final study report is also in accordance with Article 46 of Regulation (EC) No 1901/2006 which sets out the obligation for MAHs to submit any MAH-sponsored studies involving the use of an authorised medicinal products in the paediatric population to the competent authority.

Study V419-013 is a stand-alone study and is not included in a paediatric investigation plan (PIP).

This variation concerns the long-term durability of protection against HBV infection approximately 9 years after vaccination with a 3 + 1 or 2 + 1 Vaxelis series (i.e., a 3 or 2 dose primary vaccination series followed by a single toddler dose) from the Hepatitis B Vaccine Challenge Study V419-013.

MCM Vaccine B.V. submitted this variation application to update the Summary of Product Characteristics (SmPC) section 5.1 Pharmacodynamic properties with information about long-term durability of the immune protection against HBV infection.

5.1. Methods – analysis of data submitted

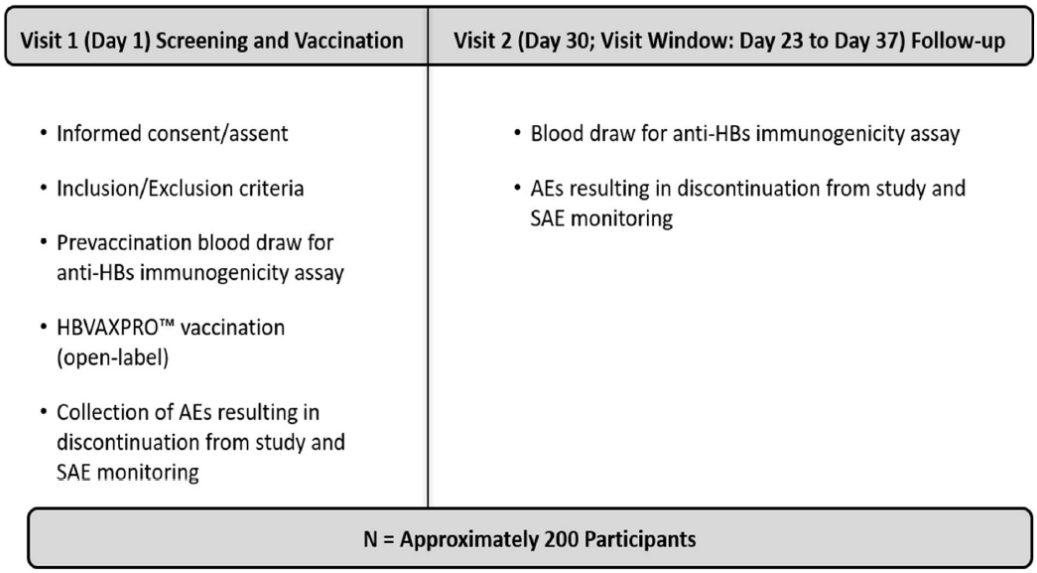
The study V419-013 was a single-group, open-label, single-dose, and multi-site study to evaluate the long-term durability of the immune protection against HBV infection approximately 9 years after receipt of a primary Vaxelis immunization series. Participants had previously participated in studies V419-007 or V419-008 and received Vaxelis according to a 3 + 1 (at 2, 3, 4 and 12 months of age) or a 2 + 1 (at 2, 4, and 11 to 12 months of age) schedule, respectively. They were 8 to 10 years of age at Protocol V419-013 enrolment.

Immune protection against HBV infection was demonstrated by administering a hepatitis B surface antigen challenge in the form of a hepatitis B vaccine (HBVAXPRO [5-µg dose], MSD) and measuring anti-HBs levels pre- and post-challenge. A post-challenge anti-HBs level of ≥10 mIU/mL was considered evidence of persistent protection against HBV infection.

- **<u>Design and objectives:</u>**

The study V419-013 was a single-group, open-label, single-dose, and multi-site study conducted in Finland in healthy participants 8 to 10 years of age who had previously participated in studies V419-007 or V419-008 and received Vaxelis according to a 3 + 1 or a 2 + 1 (infant + toddler) schedule, respectively (Figure 1). Study participants were challenged with HBVAXPRO vaccine. HBVAXPRO is a well-established hepatitis B vaccine that has been used worldwide since its initial licensure in 1986. The dose of 5 µg (0.5 mL) is approved for persons from birth through 15 years of age.

An overview of the primary and secondary objectives is provided in Table 1.



AE = adverse event
anti-HBs = hepatitis B surface antibody
SAE = serious adverse event

Figure 1. V419-013 Study Design

Table 1. Objectives and endpoints

Objectives	Endpoints
Primary	
• **Objective**: To evaluate the proportion of participants with a protective hepatitis B surface antibody (anti-HBs) level of ≥10 mIU/mL at 30 days post-challenge (Day 30) with HBVAXPRO™.	• Anti-HBs level
Secondary	
• **Objective**: To evaluate anti-HBs geometric mean concentrations (GMCs) pre-challenge on Day 1 and 30 days post-challenge with HBVAXPRO™.	• Anti-HBs level

Assessor's comment:

The paediatric study V419-013 is a single-group, open-label, single-dose study conducted at 10 study-sites in Finland. The aim of the study was to evaluate long-term antibody persistence and immune memory 8-9 years after primary vaccination with Vaxelis. Participants 8 to 10 years of age who previously participated in studies V419-007 or V419-008 and received Vaxelis according to, respectively, a 3 + 1 or a 2 + 1 (infant + toddler) schedule were enrolled. The level of protective Hepatitis B surface antibodies (anti-HBs) was analysed before and 30 days after a challenge with the HBVAXPRO vaccine.

The HBVAXPRO vaccine, used as hepatitis B surface antigen challenge, contains half of the amount of HBsAg compared to Vaxelis (5 µg vs. 10 µg) and a higher dose of aluminium hydroxyphosphate sulfate (0.25 mg vs. 0.15 mg). HBVAXPRO is approved in EU for active immunisation against hepatitis B virus infection in individuals from birth through 15 years of age considered at risk of exposure to hepatitis B virus. This vaccine is administered as a 3-dose (0, 1, 6 months) or 4-dose (0, 1, 2, 12 months) primary vaccination series.

The study primarily assesses the proportion of participants with a protective anti-HBs level (≥10 mIU/mL, discussed in section 'study endpoints') at 30 days post-challenge and secondarily, anti-HBs GMCs are evaluated pre- and post-challenge. As an exploratory objective, the proportion of participants with a ≥4-fold rise in the level anti-HBs antibodies by 30 days post-challenge is analysed as an indication of the robustness of the response. No separate analysis was done on the effect of the challenge in those subjects with HBs Ab >10 mIU/ml vs those with Ab <10 mIU/ml before the challenge. In addition, the proportion of subjects achieving HBs Ab titers above 100 mIU/ml after the challenge was also not investigated, while this analysis is recommended according to the WHO GL of 2010 'Recommendations to Assure the Quality, Safety and Efficacy of Recombinant Hepatitis B Vaccines'.

Throughout the study, AEs resulting in discontinuation and SAEs are collected.

The design and objectives are endorsed.

- **Methods used to evaluate immunogenicity**

Blood samples for immunogenicity assays were drawn immediately before vaccination at Visit 1 (Day 1) and at 30 days post-challenge at Visit 2 (Day 30). Anti-HBs concentration was measured by using the hepatitis B ECi assay.

Assessor's comment:

A Hepatitis B Enhanced chemiluminescence (ECi) assay was used to measure anti-HBs concentrations just before and 30 days after administration of the HBVAXPRO vaccine challenge. This assay is a solid phase sandwich enzyme-labelled immunoassay, with a LLOQ of 5 mIU/mL. The control samples used to monitor performance of the assay consist of (a) three internally prepared control serum pools (high-positive, low-positive and negative); (b) a positive and negative manufacturer supplied control; and (c) the WHO reference standard at 10 mIU/mL. Information on the manufacturer of the ECi assay and whether the assay is qualified or validated were not found. Upon request, applicant clarified that the ECi assay is a partially validated assay performed by Focus Diagnostics (now Q2 Vaccines). The ECi assay was the same for this study (V419-013) was the same as for the MAA Phase 3 pivotal clinical studies. **(RFI, Issue resolved).**

- **Study endpoints**

Study endpoints are depicted in Table 1.

The primary immunogenicity endpoint is the proportion of participants with a protective anti-HBs level of ≥10 mIU/mL at 30 days post-challenge with HBVAXPRO.

The secondary immunogenicity endpoint is the anti-HBs GMCs pre-challenge on Day 1 and 30 days post-challenge with HBVAXPRO.

The exploratory immunogenicity endpoint includes the proportion of participants with a ≥4-fold rise in anti-HBs level from pre-challenge on Day 1 to 30 days post-challenge with HBVAXPRO.

This study will monitor safety through the collection of AEs resulting in discontinuation from study and SAEs at Visit 1 and Visit 2 (Day 30).

The following changes in the planned analyses of the study were made:

- The proportion of participants with a protective anti-HBs level of ≥10 mIU/mL pre-challenge on Day 1 was reported by subgroup of prior Vaxelis schedule (i.e., 3 + 1 schedule in Protocol V419-007 and 2 + 1 schedule in Protocol V419-008).
- The point estimates of the proportions for both subgroups were calculated, and the corresponding 95% CIs were calculated.

Assessor's comment:

This study investigates if a hepatitis B surface antigen challenge with HBVAXPRO, 8-9 years after primary vaccination with Vaxelis, induces an anamnestic response by Day 30. It is known that despite reduction of anti-HBs antibodies over time, B cell central memory is generally prolonged and protective efficacy is generally maintained at a high level. The antibodies induced by antigenic stimulation of memory cells are used as a surrogate to assess immune memory..

An anti-HBs level ≥10 mIU/mL is accepted as correlate of protection against HBV infection. It is known that when this level is achieved 1 to 3 months after receipt of a complete and adequately administered vaccination course, individuals are considered completely protected against both acute and chronic infection for decades. Reaching anti-HBs levels ≥10 mIU/mL 30 days after a single dose challenge provides acceptable evidence to show persistent protection against HBV infection. It is known that for Hepatitis B, the peak anamnestic response is reached approximately 30 days after antigen challenge. In addition, as Hepatitis B infection has a long incubation period (30 to 180 days, with an average of 75 days), the analysis timepoint of 30 days post-challenge is considered appropriate and relevant.

As secondary endpoint, anti-HBs GMCs pre- and 30-days post-challenge will be assessed. As an exploratory endpoint, the proportion of subjects with at least a 4-fold increase in anti-HBs antibody concentrations at 30-days post-challenge will be assessed. A strong increase in anti-HBs levels after a challenge is indicative of an anamnestic response associated with persistent protection.

Although there is no endpoint based on anti-HBs levels 8-9 years after primary vaccination and before administering the hepatitis B surface antigen challenge, the proportion of participants with a protective baseline anti-HBs level was also calculated. As protection against infection can be maintained even if subsequently over time anti-HBs concentrations decline under 10 mIU/mL, it is difficult to interpret the clinical importance of these results.

Analysis of anti-HBs levels was also reported by prior Vaxelis schedule received (3 + 1 or 2 + 1 dose). In addition, it would have been interesting to see if there are difference in anamnestic response between baseline seronegative or seropositive individuals prior to the challenge, but this was not analysed.

Overall, the study endpoints are endorsed.

References Correlate of protection: WHO position paper Hepatitis B 2017; Plotkin CID 2008; Plotkin, S. A. 2010.

References long-term persistence: Steiner, M., et al 2010; Kosalaraksa, P., et al 2018; Van Der Meeren, O., et al 2014

- **Population evaluated**

Inclusion criteria

A participant was eligible for inclusion in the study if the participant:

1. Was healthy (based on a review of medical history and targeted physical examination) based on the clinical judgment of the investigator.

2. Had participated in Protocol V419-007 and received a 3 + 1 Vaxelis schedule or participated in Protocol V419-008 and received a 2 + 1 Vaxelis schedule.
3. Was male or female, 8 years to 10 years of age, at the time of signing the informed consent/assent.
4. The participant (or legally acceptable representative if applicable) provided written informed consent/assent for the study.

Exclusion criteria

Key criteria for exclusion of participants from the study included:

1. Had a history of diagnosis (clinical, serological, or microbiological) of HBV infection.
2. Had a known or suspected impairment of immunological function (eg, HIV, splenectomy).
3. Had a known hypersensitivity to any component of the study vaccine.
4. Had a known or suspected blood dyscrasias, leukemia, lymphomas of any type or other malignant neoplasms affecting the hematopoietic and lymphatic system.
5. Had a bleeding disorder contraindicating intramuscular vaccinations.
6. Had a recent febrile illness (defined as oral temperature ≥38.1° C [≥100.5° F]; axillary temperature ≥37.8° C [≥100.0° F]) occurring within 72 hours prior to receipt of study vaccine.
7. Had received any hepatitis B vaccine after participation in Protocol V419-007 or V419-008.
8. Was receiving immunosuppressive therapy.
9. Met one or more of protocol-defined systemic steroid exclusion criteria.
10. Had received any licensed, non-live vaccine within the 14 days before receipt of study vaccine or was scheduled to receive any licensed, non-live vaccine within 30 days following receipt of any study vaccine.
11. Had received any licensed live vaccine within 30 days before receipt of study vaccine or was scheduled to receive any live vaccine within 30 days following receipt of any study vaccine.
12. Had received a blood transfusion or blood products, including immunoglobulins within the 6 months before receipt of study vaccine or was scheduled to receive a blood transfusion or blood product within 30 days of receipt of study vaccine. Autologous blood transfusions were not considered an exclusion criterion.

Additional details are available in the study protocol.

Assessor's comment:

All study-participants in V419-013 previously participated in either V419-007 or V419-008 and received a 3 + 1 Vaxelis or 2 + 1 Vaxelis schedule, respectively. All participants were 8 to 10 years of age at time of enrolment. Individuals with a history of HBV infection, as well as subjects who received a hepatitis B vaccine after the previous study, were excluded from participation. Subjects had to be healthy as established by medical history and clinical examination before entering into the study.

- **Study cohorts**

Immunogenicity Analysis Population: The per protocol (PP) population served as the primary population for the analysis of immunogenicity data in this study. The PP population consists of all enrolled

participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint.

Safety Analysis Population: Safety summaries were conducted in the APaT population, which consists of all participants who received study vaccine and had safety follow-up data after the vaccination.

Assessor's comment:

The immunogenicity analysis population includes all participants without significant protocol deviations that might influence the immunogenicity data, while the safety analysis population includes all individuals that have safety follow-up data after vaccination.

The cohort for analysis is endorsed.

- **Statistical methods**

This is an estimation study, and no formal hypothesis testing was performed.

The point estimate for the primary immunogenicity objective was calculated as the proportion of participants with a protective anti-HBs level of ≥10 mIU/mL at 30 days post-challenge with HBVAXPRO. The 95% confidence interval (CI) was calculated based on the exact method proposed by Clopper and Pearson.

The point estimates for the secondary immunogenicity objective were calculated by exponentiating the estimates of the mean of the natural log values. The 95% CIs were derived by exponentiating the bounds of the CIs of the mean of the natural log values based on the t-distribution. Any AE resulting in discontinuation from the study and SAEs will be reported and summarized descriptively.

No interim analyses are planned.

Assessor's comment:

The study was descriptive and no between group comparisons are planned.

The statistical methods are endorsed.

5.2. Results

- **Study participants**

A total of 207 participants were enrolled across 10 study sites in Finland.

All but 2 enrolled participants received HBVAXPRO and completed the study. Two participants withdrew from the study prior to receiving study vaccination.

All 205 participants who received HBVAXPRO were included in immunogenicity analyses for the PP population at Day 1. The data for 3 of these participants were excluded from the immunogenicity analyses for the PP population at Day 30 due to clinically important protocol deviations. All 205 participants were included for safety analysis.

The median age of participants was 8.0 years (range: 8 to 9 years) (Table 3). Nearly all participants were white and not of Hispanic or Latino ethnicity.

Table 2. Participant Characteristics

	HBVAXPRO™	
	n	(%)
Participants in population	207	
Sex		
Male	110	(53.1)
Female	97	(46.9)
Age (Years)		
Children (2-11 years)	207	(100.0)
Mean	8.4	
SD	0.5	
Median	8.0	
Range	8 to 9	
Race		
Multiple	2	(1.0)
White	205	(99.0)
Ethnicity		
Hispanic Or Latino	2	(1.0)
Not Hispanic Or Latino	205	(99.0)
Previously Received Vaxelis® Schedule		
2+1 Schedule (V419-008)	94	(45.4)
3+1 Schedule (V419-007)	113	(54.6)
SD=standard deviation.		

Source: [P013V419: adam-adsl]

Assessor's comment:

Of the 207 participants enrolled, 205 received the HBVAXPRO challenge vaccination and were included in the immunogenicity analysis population on Day 1. On Day 30, 202 participants are included in the immunogenicity analyses population, as for 3 subjects clinically important protocol deviations were reported.

All participants were 8 to 9 year-old at enrolment (Mean age: 8.4 yoa; SD 0.5). There is a good balance between males and females (110 vs 97 participants, respectively); and the previously received Vaxelis schedule (94 vs 113 received previously the 2+1 and 3+1 schedule, respectively). As all participants were enrolled in Finland, nearly all are white and have a non-Hispanic or Latino ethnicity (205 out of 207 participants).

- **Immunogenicity results**

The proportions of participants with anti-HBs level of ≥10 mIU/mL at Day 1 pre-challenge were 40.9% and 49.1% for participants who previously received a 2 + 1 (n=93) or 3 + 1 (n=112) Vaxelis schedule, respectively.

Primary immunogenicity endpoint

All but 1 participant (99.5%) in the PP population had a protective anti-HBs level of ≥10 mIU/mL at 30 days post-challenge with HBVAXPRO (Table 4, response rate).

Table 3. Summary of Anti-HBs at Day 1 and Day 30 (Per-Protocol Population).

Antibody	Endpoint	Timepoint	HBVAXPRO™ (N = 205)		
			n	Observed	95% CI[a]
Anti-HBs	GMC	Day 1 Pre-challenge	205	9.63	(7.88, 11.76)
		Day 30 Post-challenge	202	685.84	(605.67, 776.63)
	Response Rate	Day 30 Post-challenge	202	99.5% (201/202)	(97.3, 100.0)
	% ≥ 4-fold rise	Day 30 Post-challenge	202	96.0% (194/202)	(92.3, 98.3)

[a] For the continuous endpoints, the within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group 95% CIs are based on the exact binomial method proposed by Clopper and Pearson.

N=Number of participants enrolled and vaccinated; n=Number of participants contributing to the analysis.

Response Rate=percentage of participants with a protective anti-HBs level of ≥ 10 mIU/mL at Day 30 post-challenge.

Anti-HBs=hepatitis B surface antibody; CI=confidence interval; GMC=geometric mean concentration (mIU/mL).

Secondary Immunogenicity Endpoint

A robust increase in anti-HBs GMC was demonstrated from pre-challenge at Day 1 (9.63 mIU/mL) to 30 days post-challenge with HBVAXPRO (685.84 mIU/mL) (Table 4).

The distribution of anti-HBs responses at 30 days post-challenge with HBVAXPRO (as displayed by Reverse Cumulative Distribution Curves) was consistent with the anti-HBs GMC estimate at 30 days post-challenge (Figure 2).

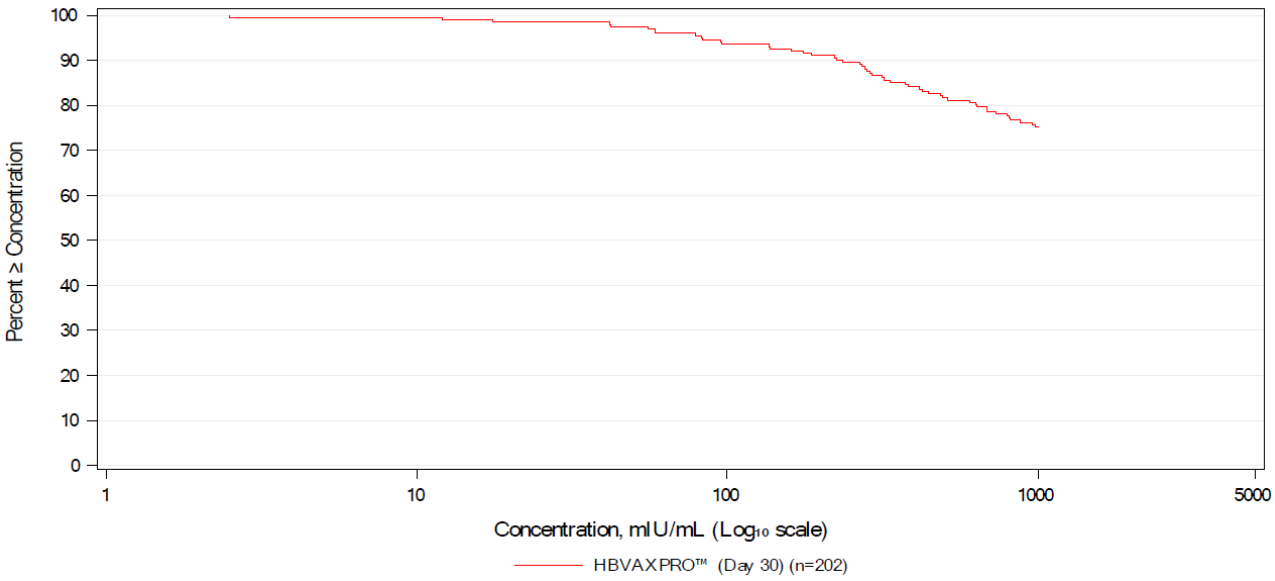


Figure 2. RCDC of Anti-HBs Concentrations at Day 30 Post-Challenge (Per-Protocol Population)

Exploratory Immunogenicity Endpoint

Most participants (96.0%) had a ≥4-fold rise in anti-HBs level from pre-challenge at Day 1 to 30 days post-challenge with HBVAXPRO (Table 4).

Subgroup analyses

Within each subgroup by prior Vaxelis schedule (3 + 1 schedule, 2 + 1 schedule), the following were generally consistent with those observed for the overall population (Table 5; Table 6; Figure 3):

- Proportion of participants with a protective anti-HBs level of ≥10 mIU/mL pre-challenge at Day 1

- Proportion of participants with a protective anti-HBs level of ≥10 mIU/mL at 30 days post-challenge with HBVAXPRO

- Anti-HBs GMCs pre-challenge at Day 1

- Anti-HBs GMCs at 30 days post-challenge with HBVAXPRO

Table 4. Summary of Anti-HBs at Day 1 and Day 30 (for Participants Who Previously Received a 2+1 Vaxelis Schedule in V419-008) (Per-Protocol Population)

			HBVAXPRO™ (N = 93)		
Antibody	Endpoint	Timepoint	n	Observed	95% CI[a]
Anti-HBs	GMC	Day 1 Pre-challenge	93	7.94	(6.01, 10.51)
		Day 30 Post-challenge	93	657.50	(549.14, 787.23)
	Response Rate	Day 1 Pre-challenge	93	40.9% (38/93)	(30.8, 51.5)
		Day 30 Post-challenge	93	100.0% (93/93)	(96.1, 100.0)

[a] For the continuous endpoints, the within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group 95% CIs are based on the exact binomial method proposed by Clopper and Pearson.

N=Number of participants enrolled and vaccinated; n=Number of participants contributing to the analysis.

Response Rate=percentage of participants with a protective anti-HBs level of ≥ 10 mIU/mL.

Anti-HBs=hepatitis B surface antibody; CI=confidence interval; GMC=geometric mean concentration (mIU/mL).

Table 5. Summary of Anti-HBs at Day 1 and Day 30 (for Participants Who Previously Received a 3+1 Vaxelis Schedule in V419-007) (Per-Protocol Population)

			HBVAXPRO™ (N = 112)		
Antibody	Endpoint	Timepoint	n	Observed	95% CI[a]
Anti-HBs	GMC	Day 1 Pre-challenge	112	11.29	(8.51, 14.98)
		Day 30 Post-challenge	109	711.00	(597.44, 846.14)
	Response Rate	Day 1 Pre-challenge	112	49.1% (55/112)	(39.5, 58.7)
		Day 30 Post-challenge	109	99.1% (108/109)	(95.0, 100.0)

[a] For the continuous endpoints, the within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group 95% CIs are based on the exact binomial method proposed by Clopper and Pearson.

N=Number of participants enrolled and vaccinated; n=Number of participants contributing to the analysis.

Response Rate=percentage of participants with a protective anti-HBs level of ≥ 10 mIU/mL.

Anti-HBs=hepatitis B surface antibody; CI=confidence interval; GMC=geometric mean concentration (mIU/mL).

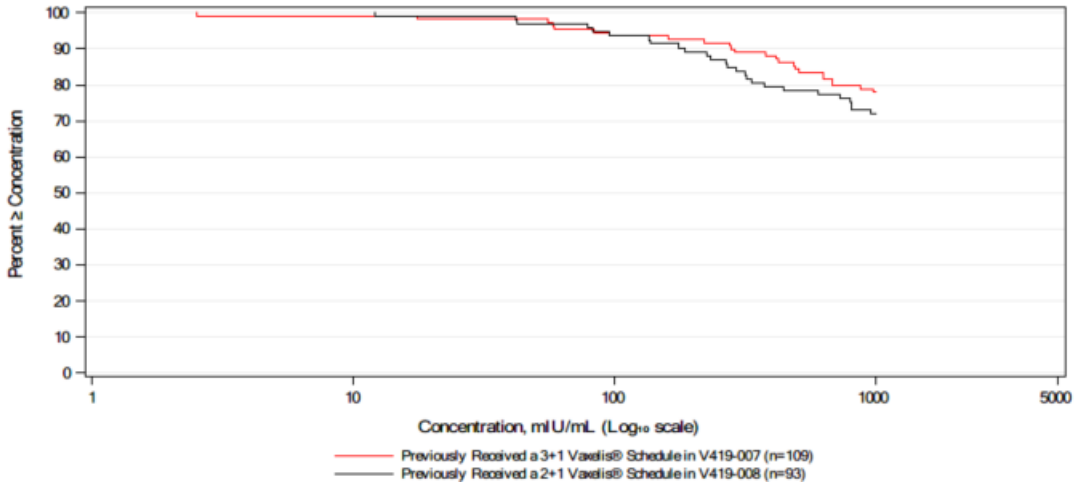


Figure 3. RCDC of Anti-HBs Concentrations at Day 30 Post-Challenge by Vaxelis Schedule (Per-Protocol Population)

Assessor's comment:

At 8-9 years after primary vaccination, protective anti-HBs levels ≥10 mIU/mL were still present in 40.9% and 49.1% of the participants who previously received a 2 + 1 or 3 + 1 Vaxelis® schedule, respectively. Thirty days after receiving the hepatitis B surface antigen challenge HBVAXPRO, nearly all participants (201 out of 202) had seroprotective anti-HBs antibody concentrations.

The mean GMC increased from 9.63 mIU/mL (95% CI: 7.88 - 11.76) pre-challenge, to 685.84 mIU/mL (95% CI: 605.67 - 776.63) 30 days after the challenge. It is unclear if there were any participants with a baseline titer below the LLOQ (5 mIU/mL). Furthermore, 96.0% of the participants showed a ≥4-fold rise in anti-HBs antibody titers, confirming the robust anamnestic response after Heptatis B surface antigen challenge.

No significant differences are observed in the humoral immune response in participants who initially were administered a 3 + 1 or a 2 + 1 Vaxelis schedule, both pre- and post-challenge with HBVAXPRO.

These results suggest there is a long-term persistence of protection against Hepatitis B infection up to at least 8-9 years after primary vaccination with Vaxelis. Even when antibody titers are below the seroprotective level of 10 mIU/mL, an anamnestic response is induced indicating the presence of memory B-cells.

One month after the final Vaxelis dose in the primary vaccination schedule, 98.1% and 99.6% of the participants who received the 2 + 1 or 3 + 1 schedule, respectively, had seroprotective anti-HBs levels (SmPC Vaxelis). The GMCs after primary vaccination of the participants in V419-013 is however not described, making it not possible to assess the magnitude of the anamnestic response.

- **Safety results**

AEs resulting in discontinuation from study and SAEs were to be collected for this study. In the APaT population (vaccinated participants), no AEs resulting in discontinuation from study or SAEs were reported.

One participant experienced an AE of syncope and withdrew from the study prior to receiving HBVAXPRO.

Assessor's comment:

No SAEs and no AEs resulting in discontinuation were reported after vaccination with the hepatitis B surface antigen challenge HBVAXPRO.

The safety profile of Vaxelis remains unchanged.

5.3. Discussion

The study V419-013 is an open-label study conducted at 10 study-sites in Finland. The aim of the study was to evaluate long-term antibody persistence and immune memory 8-9 years after primary vaccination with Vaxelis. Participants 8 to 10 years of age who previously participated in either V419-007 or V419-008 and received a 3 + 1 Vaxelis or 2 + 1 Vaxelis schedule, respectively, were enrolled. All participants were to receive one dose of the HBVAXPRO vaccine as hepatitis B surface antigen challenge.

Vaxelis is indicated for active immunization against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis (caused by poliovirus Types 1, 2, and 3), and invasive disease caused by Haemophilus influenzae type b in children from the age of 6 weeks. The vaccine is administered as a 0.5-mL intramuscular injection in a 2- or 3-dose infant vaccination series (with an interval of at least 1 month between doses) followed by a toddler dose (least 6 months after the last priming dose), depending on local recommendations.

HBVAXPRO is approved in EU for active immunisation against hepatitis B virus infection in individuals from birth through 15 years of age considered at risk of exposure to hepatitis B virus.

Methods

An anti-HBs level ≥10 mIU/mL is accepted as correlate of protection against HBV infection. It is known that when this level is achieved 1 to 3 months after receipt of a complete and adequately administered vaccination course, individuals are considered completely protected against both acute and chronic infection for decades. Reaching anti-HBs levels ≥10 mIU/mL 30 days after a single dose challenge provides acceptable evidence to show persistent protection against HBV infection. Anti-HBs titers were evaluating by the ECi methods (Focus Diagnostics, now Q2 Vaccines).

The study primarily assesses the proportion of participants with a protective anti-HBs level (≥10 mIU/mL) at 30 days post-challenge and secondarily, anti-HBs GMCs pre- and post-challenge. As an exploratory objective, the proportion of participants with a ≥4-fold rise in the level anti-HBs antibodies by 30 days post-challenge were analysed. Analysis of anti-HBs levels was also reported by prior Vaxelis schedule received (3 + 1 or 2 + 1 dose).

Throughout the study, AEs resulting in discontinuation and SAEs were to be collected.

The study was descriptive.

The design, objectives, methods and endpoints of the study are endorsed.

Results:

Of the 207 participants enrolled, 205 participants received the HBVAXPRO challenge vaccination.

At 8-9 years after primary vaccination, protective anti-HBs levels ⩾10 mIU/mL were still present in 40.9% and 49.1% of the participants who previously received a 2 + 1 or 3 + 1 Vaxelis schedule, respectively. Thirty days after receiving the hepatitis B surface antigen challenge HBVAXPRO, nearly all participants (201 out of 202) had seroprotective anti-HBs antibody concentrations.

The mean GMC increased from 9.63 mIU/mL (95% CI: 7.88 - 11.76) pre-challenge, to 685.84 mIU/mL (95% CI: 605.67 - 776.63) 30 days after the challenge. Furthermore, 96.0% of the participants showed a ⩾4-fold rise in anti-HBs antibody titers, confirming the robust anamnestic response after Heptatis B surface antigen challenge.

No significant differences are observed in the humoral immune response in participants who initially were administered a 3 + 1 or a 2 + 1 Vaxelis schedule, both pre- and post-challenge with HBVAXPRO.

These results suggest long-term persistence of protection against Hepatitis B infection up to at least 8-9 years after primary vaccination with Vaxelis. Even when antibody titers are below the seroprotective level of 10 mIU/mL, an anamnestic response is induced indicating the presence of memory B-cells.

No SAEs and no AEs resulting in discontinuation were reported after vaccination with the hepatitis B surface antigen challenge HBVAXPRO. The safety profile of Vaxelis remains unchanged.

Conclusion:

Based on the data from V419-013, it is concluded that 8-9 years after having received a 3 + 1 or 2 + 1 Vaxelis schedule, anti-HBs levels remained above the seroprotection level of 10 mIU/mL in 40.9% and 49.1% of the individuals, respectively. In addition, administration of a hepatitis B surface antigen challenge with HBVAXPRO markedly increased anti-HBs antibody levels, reaching a seroprotective titer above 10 mIU/mL in nearly all subjects. These data demonstrate an anamnestic response and hence long-term persistence of immune memory. Data are consistent with the literature on immune persistence after hepatitis B vaccination.

6. Changes to the Product Information

As a result of this variation, section(s) 5.1 of the SmPC is being updated in order to include information about long-term durability of the immune protection against HBV infection based on study V419-013.

The MAH initially proposed the following changes:

Persistence of the immune response

Long-term persistence of ~~antibody to~~ hepatitis B antibodies and ~~surface antigen~~ immune memory

~~The persistence of a~~Antibody to hepatitis B surface antigen (anti-HBsAg) was measured in children ~~4 or 5 years of age~~ who had received Vaxelis either at 2, 4 and 11-12 months or at 2, 3, 4 and 12 months of age. The proportions of children ~~seroprotected (~~with anti-HBsAg ≥ 10 mIU/mL~~)~~ i.e., seroprotected were:

- 98.1% and 99.6%, respectively, at approximatively 1 month after the final Vaxelis dose (see table 3)

Follow up assessment of available participants (subset from the original studies) showed the proportion of children with anti-HBsAg ≥ 10 mIU/mL to be:

- ~~after those vaccination schedules was 98.1% and 99.6%, respectively, and decreased to~~ 65.~~7~~8% and 70.2%, respectively, at approximatively 5 years of age
- 40.9% and 49.1%, respectively, at 8-9 years of age and just prior to a monovalent hepatitis B vaccine challenge dose ~~approximately 4 years later.~~
- 100% and 99.1%, respectively, approximatively 1 month after receiving the challenge dose

The challenge dose study results confirm persistence of hepatitis B immune response and protection in persons who previously had received Vaxelis.

~~Considerable study data suggest that individuals who have ever had a seroprotective response to hepatitis B vaccination will have a memory response that is protective against clinical disease if exposed to the hepatitis B virus.~~

The CHMP recommended amendments to the initially proposed section on 'Long-term persistence of hepatitis B antibodies and immune memory', mainly in relation to the following points: title of the section, removal of seroprotection rates data that had been previously described in Table 3, rewording of sentence 'Follow up assessment of available participants (subset from the original studies) showed the proportion of children with anti-HBsAg ≥ 10 mIU/mL to be', to specify the number of subjects included in each analyses and in relation to present the data on persistence of immune responses to Hepatitis B in a table, including also the sample size.

Based on the above assessment remarks, the resulting text for Section 5.1 is therefore endorsed:

Persistence of the immune response

~~Long-term persistence of antibody to hH~~epatitis B ~~surface antigen~~immune memory
The persistence of immune responses ~~antibody to hepatitis B surface antigen (anti-HBsAg)~~ was evaluated~~measured~~ in children up to 8 years after primary vaccination with Vaxelis. ~~4 or 5 years of age~~ The proportions of these children with anti-HBsAg ≥ 10 mIU/mL after having ~~who had~~ received Vaxelis either at 2, 4, and 11-12 months or at 2, 3, 4, and 12 ~~-~~months of age, respectively, were:~~.~~ ~~The proportion of children seroprotected (anti-HBsAg ≥ 10 mIU/mL) after those vaccination schedules was 98.1% and 99.6%, respectively, and decreased to 65.7% and 70.2% approximately 4 years later.~~

- 65.8% (119 of 181) and 70.2% (134 of 191), respectively, at 4 or 5 years of age;
- 40.9% (38 of 93) and 49.1% (55 of 112), respectively, at 8 or 9 years of age.

A hepatitis B vaccine challenge dose was given to children 8 or 9 years of age. Approximately 1 month after this challenge dose, the proportions with anti-HBsAg ≥ 10 mIU/mL were 100% (93 of 93) and 99.1% (108 of 109), respectively. These data demonstrate an anamnestic response after a challenge dose, indicating the persistence of hepatitis B immune memory in persons who previously received Vaxelis.

~~Considerable study data suggest that individuals who have ever had a seroprotective response to hepatitis B vaccination will have a memory response that is protective against clinical disease if exposed to the hepatitis B virus.~~

~~Long-term p~~Persistence of antibodies to pertussis antigens
The persistence of pertussis antibodies was measured in children 4 or 5 years of age who had received Vaxelis at 2, 4, and 11-12 months of age. ~~After approximately 4 years, t~~The percentages of these children with anti-pertussis antibodies ≥ the lower limit of quantification ~~above LLOQ~~ were ~~as follows~~: anti-PT 58.4%, anti-FHA 80.9%, anti-PRN 66.1%, and anti-FIM 94.~~3~~4%.

In addition, the CHMP recommended wording for section 4.4 and sections 4.7 and 4.8 of the SmPC were also amended. Minor editorial changes were implemented in sections 4.8 and 6.6 of the SmPC and section 2 of the PL.

Changes are also made throughout the PI to bring it in line with the QRD template version 10.2 rev. 1.

The Package Leaflet (PL) is updated accordingly.

In addition, the list of local representatives in the PL was revised.

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

7. Request for supplementary information

7.1. Major objections

Clinical aspects

None.

7.2. Other concerns

Clinical aspects

1. Information on the manufacturer of the ECi assay and whether the assay is qualified or validated were not found. The applicant is invited to provide this information.
2. Sections 4.4 and 5.1 of the Product Information should be amended as proposed in Attachment 1.

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

8.1. Major objections

None.

8.2. Other concerns

Clinical aspects

Question 1. Information on the manufacturer of the ECi assay and whether the assay is qualified or validated were not found. The applicant is invited to provide this information.

Summary of the MAH's response
The validated Hepatitis B ECi assay used for clinical trial testing is performed using the VITROS ECiQ Immunodiagnostic System (Ortho Clinical Diagnostics) and the VITROS Immunodiagnostic Products Anti-HBs Quantitative Reagent Pack.

The assay was originally qualified for clinical testing at PPD Vaccines & Biologics Laboratory (PPD VBL) in Wayne, Pennsylvania. The assay was transferred to Focus Diagnostics (now Q2 Vaccines), San Juan Capistrano, California in 2014 where method transfer and partial validation were executed prior to using the assay to support clinical testing.

To execute the Hepatitis B ECiQ assay transfer to Focus Diagnostics, a two-step approach, including a method transfer study followed by a partial validation study, was used to insure comparable assay performance at the new laboratory location. The objective of the method transfer study was to evaluate Focus Diagnostics' ability to perform the Hepatitis B ECiQ assay, and the results were evaluated against

pre-specified criteria for control/run validity, assay precision, and concordance and agreement with historical testing results from the Hepatitis B ECiQ assay at PPD VBL. The objective of the partial validation study was to confirm the operating characteristics and performance at Focus Diagnostics and the results were evaluated against pre-specified criteria for control/run validity, verification of limits of quantitation, precision, ruggedness, selectivity (spike and recovery), and dilutional linearity.

The Hepatitis B ECiQ assay was subsequently transferred in 2019 to another lab within the same building at Q2 Vaccines and a partial validation was executed to confirm comparable performance of the assay by assessing controls, sample classification agreement, intermediate precision and concordance parameters against pre-defined acceptance criteria.

Finally, the Applicant would like to reiterate that the test method for the Hepatitis B Enhanced chemiluminescence (ECi) assay was the same for the MAA Phase 3 pivotal clinical studies and this present V419-013 study.

The following test method, method transfer and partial validation reports for the transfer of the assay to Focus Diagnostics, and Q2 Vaccines intra-laboratory transfer report are included for reference:

- 06G0KH: Test Method: TSOP.119.00691 Revision C, Hepatitis B Surface Antibody VITROS ECiQ, Quantitative
- 04M3MC: Transfer Report: AVAL.119.00085 Revision A, Transferability and Equivalency Characteristics for the Focus Diagnostics Hepatitis B Surface Antibody VITROS ECiQ Assay
- 04M3GS: Partial Validation Report: AVAL.119.00124 Revision A, Partial Validation to Establish the Performance Characteristics for the Hepatitis B Surface Antibody VITROS ECiQ Assay at Focus Diagnostics
- 06G0KG: Transfer Report: AVAL.119.00200 Revision B, Transfer Report for Hepatitis B Surface Antibody VITROS ECiQ, Quantitative from Lab 222 to Lab 101 Within SJC Building B

Assessment of the MAH's response – ISSUE RESOLVED

The Hepatitis B ECi assay is a partially validated assay performed by Focus Diagnostics (now Q2 Vaccines).

The ECi assay was the same for this study (V419-013) was the same as for the MAA Phase 3 pivotal clinical studies.

Question 2. Sections 4.4 and 5.1 of the Product Information should be amended as proposed in Attachment 1.

Please refer to the SmPC for the MAH responses and assessment.

After circulation of the response AR, the MAH submitted an updated PI addressing all comments. **All PI issues are now resolved.**

Conclusion

☐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

9. Attachments

1. Product Information (changes highlighted and assessment included)

Reminders to the MAH

1. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion or 5 days after the submission by the MAH of the final language translations, when there is a linguistic review. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU