EMA/562093/2023
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/003982/II/0126

Invented name: Vaxelis

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

Marketing authorisation holder (MAH): MCM Vaccine B.V.

Note

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	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	03 Jul 2023	03 Jul 2023
☐	CHMP Rapporteur Assessment Report	07 Aug 2023	27 Jul 2023
☐	CHMP members comments	21 Aug 2023	21 Aug 2023
☐	Updated CHMP Rapporteur Assessment Report	24 Aug 2023	24 Aug 2023
☐	Start of written procedure	29 Aug 2023	29 Aug 2023
☐	Request for Supplementary Information	31 Aug 2023	31 Aug 2023
☐	Submission of Responses	29 Sep 2023	29 Sep 2023
☐	Re-start of procedure	02 Oct 2023	02 Oct 2023
☐	CHMP Rapporteur Assessment Report	06 Nov 2023	31 Oct 2023
☐	CHMP members comments	20 Nov 2023	20 Nov 2023
☐	Updated CHMP Rapporteur Assessment Report	23 Nov 2023	23 Nov 2023
☐	Start of written procedure	28 Nov 2023	28 Nov 2023
☒	Opinion	30 Nov 2023	30 Nov 2023

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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 16 June 2023 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

Update of sections 4.2 and 5.1 of the SmPC in order to add information on interchangeable use of Vaxelis with other hexavalent vaccines based on final results from Study V419-016.
In addition, the MAH took this opportunity to introduce minor editorial changes.

The requested variation proposed amendments to the Summary of Product Characteristics.

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

VAXELIS (DTaP-HB-IPV-Hib) is a hexavalent combination vaccine indicated for primary and booster vaccination in infants and toddlers for the prevention of diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis caused by poliovirus Types 1, 2, and 3, and invasive disease caused by *Haemophilus influenzae* type b. It can be used as a 2- or 3- dose primary series beginning at 6 weeks of age (with an interval of at least 1 month between doses), followed by a booster dose, given at least 6 months after the primary series.

VAXELIS was approved in the EU in 2016 and is currently licensed in over 30 countries worldwide.

VAXELIS is one of the 3 hexavalent paediatric vaccines approved in the EU, together with HEXYON (DTaP2-HB-IPV-Hib) and INFANRIX hexa (DTaP3-HBV-IPV/Hib). In clinical practice, switching between childhood hexavalent vaccines is sometimes necessary, which results in a "mixed" vaccine schedule. This may occur due to changes in vaccine availability, changes in procurement, vaccine shortages, relocation, or care provider preference.

The purpose of the Phase 4 study V419-016 was to evaluate the safety, tolerability, and immunogenicity of a booster dose of VAXELIS administered to healthy participants approximately 11 to 13 months of age who previously received a 2-dose primary infant series of either VAXELIS (Group 1: V,V,V) or HEXYON (Group 2: H,H,V) as part of their routine vaccinations.

Data of this study could support switching to VAXELIS after a primary series with another hexavalent vaccine. The MAH proposed to update sections 4.2 and 5.1 of the SmPC.

The primary safety objective was to evaluate the safety and tolerability of a booster dose of VAXELIS with respect to the proportion of participants with adverse events (AEs), i.e. with solicited (from Days 1 to 5 after study vaccination) and unsolicited (from Days 1 to 15 after study vaccination) AEs, and SAEs (including fatal SAEs, from Day 1 through completion of study participation i.e. 30 days post-vaccination). Body temperatures, concomitant medications, non-study vaccinations, use of any analgesic or antipyretic on the day of vaccination were also documented. There were no AEs of special interest in the study, nor laboratory evaluation.

The primary and secondary immunogenicity objectives were to describe the response rates to antigens contained in VAXELIS and/or HEXYON 30 days after the booster dose of VAXELIS. Description of the antigen-specific GMCs at pre-dose and 30 days post-booster with VAXELIS were amongst the exploratory objectives.

The antibody (Ab) thresholds used as cut-offs for response rates for anti-DT Ab (0.1 IU/ml), anti-TT Ab (0.1 IU/ml), anti-poliovirus Ab (1:8 dilution), anti-HBs Ab (10 mIU/ml), anti-PRP Ab (1 µg/mL) are consistent with established immunological correlate of protection (ICP). For pertussis, there are currently no ICP established. The MAH proposed endpoints based on assay LLOQ for pertussis antigens. Those criteria are arbitrary and differ from those previously used in the CDP of VAXELIS and defined in the SmPC. However, as the aim of the study is to evidence a booster effect, vaccine response rate defined on arbitrary criteria is deemed acceptable as this cannot be avoided in the absence of ICP. In addition, GMCs were presented which allowed relevant assessment of the magnitude of the booster effect.

As of database lock, 168 participants were enrolled in the study. A total of 85 and 82 toddlers were administered with a booster dose of VAXELIS respectively in Group 1 (V, V, V) and Group 2 (H, H, V).

Most of the 167 toddlers who were administered with VAXELIS as a booster at the age of 11 to 13 months, i.e. at least 6 months post-primary vaccination either with VAXELIS or HEXYON, experienced one or more solicited AEs (within 5 days post-vaccination). AEs were generally mild to moderate in intensity. Fever was observed in most of the children and was < 40°C for most of them. Unsolicited AEs were recorded up to 15 days post-vaccination and a total of 42.4% and 50.0% of the toddlers in Group 1 and Group 2 respectively experienced one or more unsolicited AEs related to the study vaccine. A total of 8 toddlers (9.8%) in Group 2 experienced severe AEs. No severe AEs was recorded in Group 1. No SAE was deemed related to the vaccine.

The boost with VAXELIS elicited specific Ab to each antigen contained in both VAXELIS and/or HEXYON. At least 89% of the children had a seroresponse defined as associated with protection against diphtheria, tetanus, hepatitis B, clinical paralysis due to polioviruses, and invasive *Haemophilus influenzae* type b disease. Higher immune responses to pertussis antigens were observed post-boost when compared to pre-boost, both in terms of seroresponse and Ab GMCs.

There are various limitation to the study including the limited sample size, the open-label design and absence of participants randomization and stratifications by sex or other characteristics (such as concomitant medication or vaccination), which preclude appropriate interpretations of results comparison between groups. Number of participants enrolled in each country and in each site were not balanced between both groups. Prior and concomitant medications, treatment and vaccines were not balanced between groups, which is probably related to the local practices (country and region/site). Additional analyses by country and according to the use of analgesic/antipyretic on the day of vaccination are overall consistent with the results of the whole PP population in terms of seroresponder rates. Higher incidence of solicited systemic AEs was observed in participants who used analgesic/antipyretic on the day of vaccination versus those who did not. Because of the limited number of toddlers per group, interpretation should be cautious and no firm conclusion can be drawn.

The study was conducted in 3 countries (Germany, Spain and Italy: 13 sites). The recommendation in these 3 countries is a 2-dose regimen at 2 and 4 months of age, but other EU countries recommend a 3-dose regimen. Age recommended for the primary vaccination but also for the booster dose also varies depending on EU countries, as well as the hexavalent vaccine to be used for both primary and boost vaccinations. These vaccines differ in terms of composition for the pertussis antigens, in terms of conjugate for the *Haemophilus influenzae* type B polysaccharide, and in terms of their respective amount

of some antigens. However, it is considered that the booster effect of VAXELIS will also be observed in these different settings.

The benefit-risk balance of VAXELIS remains positive. There are various limitations to the submitted Phase 4 V419-016 study, but it is acknowledged that in clinical practice mixed schedules were and are probably used in different EU countries. In addition, the reactogenicity and safety profile of VAXELIS is well-known as it has been widely used since 2016. The application is recommended for approval.

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

Update of sections 4.2 and 5.1 of the SmPC in order to add information on interchangeable use of Vaxelis with other hexavalent vaccines based on final results from Study V419-016.
In addition, the MAH took this opportunity to introduce minor editorial changes.

☒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 Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

The Vaxelis SmPC sections 4.2 and 5.1 have been updated to include information on interchangeable use of Vaxelis with other hexavalent vaccines. Vaxelis may be used as a booster dose in children who received another hexavalent vaccine for their primary series.

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

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

5. Introduction

VAXELIS (DTaP-HB-IPV-Hib) is a hexavalent combination vaccine indicated for primary and booster vaccination in infants and toddlers for the prevention of diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis caused by poliovirus Types 1, 2, and 3, and invasive disease caused by *Haemophilus influenzae* type b. It can be used as a 2- or 3- dose primary series beginning at 6 weeks of age (with an interval of at least 1 month between doses), followed by a booster dose, given at least 6 months after the primary series.

VAXELIS was approved in the European Union (EU) in 2016 and is currently licensed in over 30 countries worldwide.

VAXELIS is one of the 3 hexavalent paediatric vaccines approved in the EU, together with HEXYON (DTaP2-HB-IPV-Hib) and INFANRIX hexa (DTaP3-HBV-IPV/Hib).

In clinical practice, switching between childhood hexavalent vaccines is sometimes necessary, which results in a "mixed" vaccine schedule. This may occur due to changes in vaccine availability, changes in procurement, vaccine shortages, relocation, or care provider preference.

The purpose of the submitted Phase 4 study V419-016 was to evaluate the safety, tolerability, and immunogenicity of a booster dose of VAXELIS administered to healthy participants approximately 11 to 13 months of age who previously received a 2-dose primary infant series of either VAXELIS (Group 1: V,V,V) or HEXYON (Group 2: H,H,V) as part of their routine vaccinations.

This application summarizes the safety and immunogenicity of VAXELIS when used as a booster dose in children who previously received a 2-dose primary series of VAXELIS or HEXYON from Study V419-016, in support of an update to VAXELIS Product Information. There is no proposed change in indication.

6. Clinical Immunogenicity aspects

V419-016 is a Phase 4, Open-label, Multicenter Study to Evaluate the Safety, Tolerability, and Immunogenicity of VAXELIS in Healthy Children Previously Vaccinated With a 2-Dose Primary Infant Series of Either VAXELIS or HEXYON.

6.1. Methods – analysis of data submitted

6.1.1. Study design

The study was an open-label study of VAXELIS in healthy participants approximately 11 to 13 months of age who previously received a 2-dose primary infant series of either VAXELIS (Group 1: V,V,V) or HEXYON (Group 2: H,H,V) at 2 and 4 months of age as part of routine vaccination. A 0.5-mL intramuscular dose of VAXELIS was to be administered to all study participants at Visit 1 (Day 1).

The study was conducted at 13 centers in 3 countries.

The study design is depicted in Figure 1 below.

Figure 9-1
Study Design

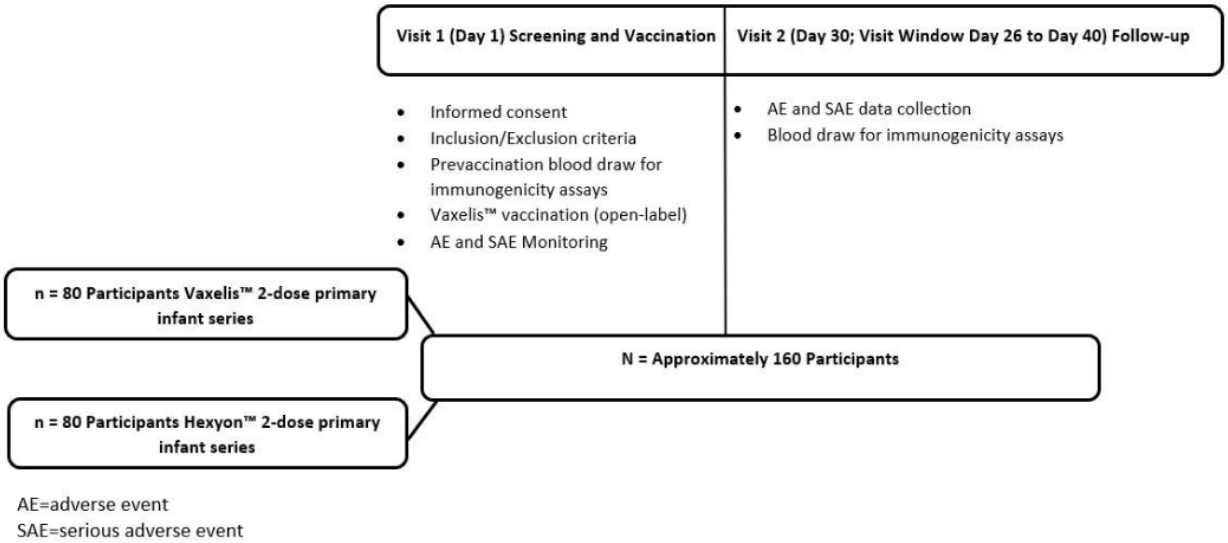

Figure 1. Study design (Figure 9-1, Study report)

This study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its Standard Operating Procedures (SOPs) for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

Assessor's comment

V419-016 is a Phase 4 study to evaluate the safety, tolerability, and immunogenicity of a booster dose of VAXELIS given to toddlers 11 to 13 months of age who previously received a 2-dose primary infant series of either VAXELIS (Group 1: V,V,V) or HEXYON (Group 2: H,H,V).

Data from this study would support switching to VAXELIS after a primary series with another hexavalent vaccine. The primary series consisted in 2 doses given 2 months apart. Either VAXELIS or HEXYON was given to infants at 2 and 4 months of age as part of their routine vaccination. The boost with VAXELIS, open-label, was administered approximately at 11-13 months of age (i.e. at least 6 months post-primary vaccination).

The study was conducted in Germany, Spain and Italy. The 2-dose primary vaccination is recommended in those countries from 2 months of age. Refer to section 6.2.3.

6.1.2. Study participants

Inclusion criteria

The participant was included in the study if the participant met any of the following key criteria for inclusion in the study included (but were not limited to), the participants:

• Were male or female participants approximately 11 to 13 months of age *(≥327 days to ≤396 days inclusive)*

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

• Had received a 2-dose infant primary series of either Vaxelis or Hexyon at approximately 2 and 4 months of age (based on a review of medical history), respectively.

Exclusion criteria

The participant was excluded from the study if the participant met any of the following key criteria for exclusion from the study included (but not limited to) the participants:

• Had a known or suspected impairment of immunological function.

• Had a history of Hib, HB, diphtheria, tetanus, pertussis, or poliovirus infection.

• Was born to a mother with a known history of HB infection.

• *Had a recent febrile illness (defined as rectal temperature ≥38.1° C [≥100.5° F] or axillary temperature ≥37.8° C [≥100.0° F]) occurring at or within 72 hours prior to receipt of study vaccine.

• Had encephalopathy of unknown etiology, occurring within 7 days following prior vaccination with a pertussis-containing vaccine.

• Had an uncontrolled neurologic disorder or uncontrolled epilepsy.

• Had a health or developmental disorder that, based on the clinical judgment of the investigator, could affect evaluation of the vaccine.

• Had received or is expected to receive immunosuppressive agents during the conduct of the study.

• *Met 1 or more of the following systemic corticosteroid exclusion criteria:

- Had received systemic corticosteroids (equivalent of ≥2 mg/kg total daily dose of prednisone or ≥20 mg/d for persons weighing >10 kg) for ≥14 consecutive days and has not completed treatment at least 30 days before study entry.

- Had received any systemic corticosteroids within 14 days before study vaccination.

- Was expected to require any systemic corticosteroids during conduct of the study.

- Note: Topical, ophthalmic, and inhaled steroids are permitted.

• *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 prior to Visit 2 blood draw.

- Exception: Participant received non-study paediatric licensed non-live vaccines on same day as study vaccine is given (Day 1).

- Exception: Non-live influenzae vaccine was administered but given at least 7 days before receipt of study vaccine or at least 15 days after receipt of study vaccine.

• *Had received any licensed live vaccine within 30 days before receipt of study vaccine or was scheduled to receive any live vaccine prior to Visit 2 blood draw.

• *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 are not considered an exclusion criterion.

• *Had participated in another clinical study of an investigational product within 2 months before study vaccination at Visit 1 (Day 1) or planned to participate anytime during the duration of the current clinical study. Participants previously or currently enrolled in a COVID-19 vaccine clinical study, or enrolled in observational studies may be included; these were reviewed on a case-by-case basis for approval by the Sponsor.

• Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

For items with an asterisk (*), if the participant met these exclusion criteria, Visit 1 could have been rescheduled for a time when these criteria were not met.

6.1.3. Study interventions

The study interventions are presented in Table 1 and in Table 2.

Table 1. Study interventions (Table 4, Protocol)

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength	Dosage Level	Route of Admin.	Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Group 1: V,V,V	Experimental	Vaxelis™	Biological/ Vaccine	Sterile Suspension (Prefilled Syringe)	Refer to product labeling	0.5 mL	IM	Single dose at Visit 1	Experimental	IMP	Central
Group 2: H,H,V	Experimental	Vaxelis™	Biological/ Vaccine	Sterile Suspension (Prefilled Syringe)	Refer to product labeling	0.5 mL	IM	Single dose at Visit 1	Experimental	IMP	Central

Admin.=administration; EEA=European Economic Area; H=Hexyon™; IM=intramuscular; IMP=investigational medicinal product; mL=milliliter; NIMP=noninvestigational medicinal product; V=Vaxelis™

The classification of IMP and NIMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

Table 2. Vaccine composition (Table 1, Protocol)

One dose (0.5 mL) contains the following antigens:			
Vaxelis™		**Hexyon™**	
Antigen	**Amount in Vaxelis™**	**Antigen**	**Amount in Hexyon™**
Diphtheria toxoid	Not less than 20 IU	Diphtheria toxoid	Not less than 20 IU
Tetanus toxoid	Not less than 40 IU	Tetanus toxoid	Not less than 40 IU
Bordetella pertussis antigens Pertussis toxoid (PT) Filamentous haemagglutinin (FHA) Pertactin (PRN)[a] Fimbriae Types 2[a] and 3[a] (FIM2/3)	 20 micrograms 20 micrograms 3 micrograms 5 micrograms	*Bordetella pertussis* antigens Pertussis toxoid (PT) Filamentous haemagglutinin (FHA)	 25 micrograms 25 micrograms
Hepatitis B surface antigen	10 micrograms	Hepatitis B surface antigen	10 micrograms
Poliovirus (inactivated) Type 1 (Mahoney) Type 2 (MEF-1) Type 3 (Saukett)	 40 D antigen units 8 D antigen units 32 D antigen units	Poliovirus (inactivated) Type 1 (Mahoney) Type 2 (MEF-1) Type 3 (Saukett)	 40 D antigen units 8 D antigen units 32 D antigen units
Haemophilus influenzae type b polysaccharide (Polyribosylribitol phosphate [PRP]) conjugated to meningococcal protein	3 micrograms 50 micrograms	*Haemophilus influenzae* type b polysaccharide (Polyribosylribitol phosphate [PRP]) conjugated to tetanus protein	12 micrograms 22-36 micrograms

IU=international units; MEF=Middle East Forces

See Summary of Product Characteristics for complete details of the vaccine composition.

[a] Not contained in Hexyon™.

6.1.4. Objectives and endpoints

The different objectives are listed in Table 3.

Table 3. Objectives and endpoints

Primary Objective	**Primary Endpoint**
Objective: To evaluate the safety and tolerability of a booster dose of Vaxelis™ with respect to the proportion of participants with adverse events (AEs).	• Solicited injection-site AEs from Day 1 through Day 5 postvaccination • Solicited systemic AEs from Day 1 through Day 5 postvaccination • Unsolicited AEs from Day 1 through Day 15 postvaccination • Serious adverse events (SAEs) through completion of study participation
Objective: To describe the response rates to antigens contained in both Vaxelis™ and Hexyon™ 30 days after a booster dose of Vaxelis™	Antibody responses to: • diphtheria toxoid • tetanus toxoid • pertussis toxoid (PT) • filamentous hemagglutinin (FHA) • *Haemophilus influenzae* type b polyribosylribitol phosphate (Hib PRP) • hepatitis B surface antigen (HBsAg) • poliovirus serotypes 1, 2, and 3 at 30 days postvaccination with Vaxelis™
Secondary Objectives	**Secondary Endpoints**
Objective: To describe the response rates to the pertussis antigens contained in Vaxelis™, but not in Hexyon™, 30 days after a booster dose of Vaxelis™.	Antibody responses to: • pertactin (PRN) • fimbriae 2/3 (FIM 2/3) at 30 days postvaccination with Vaxelis™

Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Objective: To describe the antigen-specific geometric mean concentrations (GMCs) at predose and 30 days post booster dose with Vaxelis™, and the proportion of participants with a ≥4-fold rise from Day 1 (predose) to 30 days post booster dose with Vaxelis™, for each antigen contained in Vaxelis™.	Antibody responses to: • diphtheria toxoid • tetanus toxoid • PT • FHA • PRN • FIM 2/3 • Hib-PRP • HBsAg • poliovirus serotypes 1, 2, and 3 at Day 1 (predose) and 30 days postvaccination with Vaxelis™

The endpoints used to evaluate the immune responses to the antigens contained in VAXELIS and HEXYON are shown in Table 4 and in Table 5.

Table 4. List of primary endpoints (Table 2, Protocol)

Antigen	Endpoint
Diphtheria toxoid	% ≥0.1 IU/mL
Tetanus toxoid	% ≥0.1 IU/mL
PT	% vaccine response[a]
FHA	% vaccine response[a]
Hib-PRP	% ≥1.0 µg/mL
HBsAg	% ≥10 mIU/mL
Poliovirus 1	% Nab ≥1:8 dilution
Poliovirus 2	% Nab ≥1:8 dilution
Poliovirus 3	% Nab ≥1:8 dilution

FHA=filamentous hemagglutinin; Hib=*Haemophilus influenzae* type b; HBsAg=hepatitis B surface antigen; IU=international unit; LLOQ=lower limit of quantitation; Nab=neutralizing antibodies; PRP=polyribosylribitol phosphate; PT=pertussis toxoid

[a] The pertussis vaccine response is defined as follows:
1) If prevaccination <LLOQ, then postvaccination should be ≥4 × the LLOQ.
2) If prevaccination ≥LLOQ but <2 × the LLOQ, then postvaccination should achieve a 4-fold rise (postvaccination/prevaccination ≥4).
3) If prevaccination ≥2 × the LLOQ, then postvaccination should achieve a 2-fold response (postvaccination/prevaccination ≥2).

Table 5. List of secondary endpoints (Table 3, Protocol)

Antigen	Endpoint
PRN	% vaccine response[a]
FIM 2/3[b]	% vaccine response[a]

FIM=fimbriae; LLOQ=lower limit of quantitation; PRN=pertactin

[a] The pertussis vaccine response is defined as follows:
1) If prevaccination <LLOQ, then postvaccination should be ≥4 × the LLOQ.
2) If prevaccination ≥LLOQ but <2 × the LLOQ, then postvaccination should achieve a 4-fold rise (postvaccination/prevaccination ≥4).
3) If prevaccination ≥2 × the LLOQ, then postvaccination should achieve a 2-fold response (postvaccination/prevaccination ≥2).

[b] Antibodies to FIM 2 and FIM 3 are measured together.

Assessor's comment

The Objectives are overall endorsed.

Please refer to the section 7.1 for the safety endpoints.

The primary immunogenicity endpoints are overall endorsed. Seroprotection or seroconversion rates were to be measured at 30 days post-boost.

The antibody (Ab) thresholds used for anti-DT Ab (0.1 IU/ml), anti-TT Ab (0.1 IU/ml), anti-poliovirus Ab (1:8 dilution), anti-HBs Ab (10 mIU/ml) are consistent with established immunological correlate of protection.

For diphtheria, it is commonly agreed that a level of 0.01 IU/mL is the lowest level providing some degree of protection, and 0.1 IU/mL is considered a protective level of circulating antitoxin. Levels of 1.0 IU/mL and greater are associated with long-term protection.
Similarly, for tetanus, it is generally accepted that levels at 0.01 IU/mL provides considerable protection, whereas a level of 0.1 IU/mL corresponds to virtually complete protection against the disease.
Poliovirus neutralizing antibody levels above the 1 : 8 dilution threshold are correlates of protection against clinical paralysis.
Vaccine-induced protection against HBV infection is defined as having an anti-HBs level of 10 mIU/mL or higher, measured 1 to 3 months after receipt of a complete and adequately administered vaccination course.

The threshold used for anti-PRP Ab (1 µg/mL) is the threshold associated with long-term protection. Serum anti-PRP Ab levels greater than 0.15 µg/mL are associated with short-term protection whereas anti-PRP Ab level required for protection against carriage is greater than 5 µg/mL. The selected threshold is endorsed.

For pertussis, there are currently no immunological correlates of protection that are established. The MAH proposed endpoints based on assay LLOQ for pertussis antigens. The vaccine response is defined as follows:

- If pre-vaccination Ab titers are < LLOQ, post-vaccination Ab titers should be ≥4x LLOQ

- If pre-vaccination Ab titers are ≥ LLOQ but <2x LLOQ, post-vaccination Ab titers should be ≥4x pre-vaccination values

- If pre-vaccination Ab titers are ≥ 2x LLOQ, post-vaccination Ab titers should be ≥2x pre-vaccination values

Those criteria are arbitrary and differ from those previously used in the CDP of VAXELIS and defined in the SmPC:

'Vaccine response: If pre-dose 1 antibody concentration < LLOQ, then post-booster antibody concentration should be ≥ LLOQ; If pre-dose 1 antibody concentration ≥ LLOQ, then the post-booster antibody concentration should be ≥ pre-dose 1 levels.'

The LLOQ of the assay used to measure the pertussis Ab is 2.00 EU/mL for each pertussis Ab, which also differ from those previously used (LLOQ = 4 EU/mL are for anti-PT, anti-PRN and anti-FIM; and LLOQ = 3 EU/mL for anti-FHA).

Different criteria were also used in the CDP of HEXYON and INFANRIX hexa.

As the aim of the study is to evidence a booster effect, vaccine response rate defined on arbitrary criteria is deemed acceptable as this cannot be avoided in the absence of ICP. In addition, GMCs are presented which will allow relevant assessment of the magnitude of the booster effect.

Please also refer to section 6.1.8 for the description of the assays.

6.1.5. Sample size

This study plan to enrol approximately 160 participants (80 in each group), which will allow estimation of the primary immunogenicity endpoints with a reasonable 95% CI.

This is based on the following assumptions: 1) a 5% non-evaluability rate (76 evaluable participants per group), and 2) underlying response rates for VAXELIS following a booster dose based on the study results from V419-008 [Silfverdal, S. A., et al 2016].

6.1.6. Randomization and blinding

Participants in this study were allocated by non-random assignment. No stratification based on age, sex, or other characteristics will be used in this study.

Blinding was not applicable as this was an open-label study.

Assessor's comment

Participants were not randomized, thus, the participant distribution per country and per site were not balanced, which might, in theory, bias the results. However, all participants received VAXELIS as a booster dose and no difference in the monitoring of the AEs is expected. In addition, protocol deviations were recorded.

There were no stratifications by age which is acceptable as the age range of the participant to be enrolled was clearly defined and narrow (≥327 days to ≤396 days inclusive). There were no stratifications by sex or other characteristics (such as concomitant medication or vaccination) although this might have been of scientific value.

The open-label design might bias the reactogenicity/safety results, but this is not considered as a major concern as the safety profile of VAXELIS is already well known.

6.1.7. Statistical methods

Analysis populations

Per-protocol (PP)

The PP population served as the population for the analysis of immunogenicity data. The PP population consists of all enrolled participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint. Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include, but are not limited to:

- Failure to receive study vaccine at Visit 1 (Day 1).
- Receipt of a prohibited medication or prohibited vaccine within the study window.
- Collection of blood sample at Visit 2 outside the prespecified window (Day 26 to Day 40).

All Participants as Treated (APaT)

The APaT population consists of all participants who received study vaccination.

Statistical Methods for Key Immunogenicity Analyses

No statistical hypothesis testing were performed for immunogenicity analyses. For the immunogenicity endpoints, the response rates to each antigen in VAXELIS and the corresponding 95% confidence intervals (CIs) were to be provided, for each group. The CIs were to be calculated based on the exact binomial method proposed by Clopper and Pearson.

Please refer to section 7.1 for the statistical methods for key safety analyses.

Interim analyses and multiplicity

No interim analyses are planned.

No multiplicity adjustment is needed for the primary immunogenicity objective as there is no hypothesis testing.

Subgroup Analyses

Subgroup analyses based on receipt of pertussis vaccine during pregnancy by the participant's biological mother (ie, received vs not received) were to be performed for the pertussis immunogenicity endpoints.

6.1.8. Immunogenicity assessment

Sera from participants were used to measure the immune responses to the antigens summarized in Table 4 and Table 5 using the assays provided below.

Blood collection, storage, and shipment instructions for serum samples were provided in the operations/laboratory manual.

Anti-Diphtheria Toxoid, Tetanus Toxoid, and Pertussis Antigen Serology Assay

The Meso Scale Discovery Electrochemiluminescence is a multiplexed serological assay that allows for the simultaneous quantification of human antibodies to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN, and FIM). In this assay, each well of a 96-well microtiter plate is precoated in precise positions with the 6 different antigens in a multispot fashion. Following incubation with serum samples, antigen-specific antibodies bind to the respective antigens. The captured antibodies are then detected using a sulfotag conjugated anti-human IgG conjugate. Electrical stimulation of the conjugate in the presence of a chemiluminescent substrate results in the generation of a light signal from each specific spot that is captured by a camera in relative light units. The signal generated is directly proportional to the amount of antibodies present in the sample, which is quantified using software and based on an established reference standard sample curve. The LLOQ for diphtheria antibody is 0.005 IU/mL, for tetanus antibody is 0.01 IU/mL, and for each pertussis antibody is 2.00 EU/mL.

Haemophilus Influenzae Type b IgG ELISA

The Hib IgG ELISA for the in-vitro measurement of specific IgG antibodies against Hib capsular polysaccharide in human serum uses the Vacczyme Human Anti-Haemophilus influenzae Type b Enzyme Immunoassay Kit purchased from The Binding Site (catalog # MK016), which was further validated for use in clinical studies. The kit contains microtiter wells precoated with Hib polysaccharide antigen conjugated to human serum albumin. Diluted serum is added to the microtiter wells and allowed to incubate. After incubation and washing to remove non-bound serum proteins, HRP-conjugated rabbit anti-human IgG is added, which binds to any captured Hib-specific IgG molecules. After another wash step, tetramethylbenzidine substrate is added; the ensuing color development reaction is then stopped at a defined time point by the addition of a dilute acid solution. The OD is measured at 450 nm and is directly proportional to the amount of anti-Hib IgG present in the serum specimen. Levels of anti-Hib IgG are quantified by interpolation from a standard curve that has been calibrated to the FDA lot 1983 reference serum. LLOQ and ULOQ are 0.15 and 5.29 µg/mL.

Hepatitis B Enhanced Chemiluminescence (ECi) Assay

The purpose of the hepatitis B ECi assay is to detect total antibody to human plasma-derived HBsAg subtypes ad and ay before and after vaccination with HBsAg-containing vaccine(s).
This is the primary assay used to evaluate the serological response to the vaccine(s). The assay is a solid phase sandwich enzyme-labeled immunoassay. Results for the assay are reported in mIU/mL.
This assay involves the reaction of anti-HBs in a test sample with HBsAg coated onto the wells. A HRP-labeled HBsAg conjugate then forms a complex with the bound anti-HBs, forming an "antigen sandwich". Unbound materials are removed by washing. A reagent that contains luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent

increases the level and duration of the light produced. The amount of HRP conjugate bound and subsequent light produced is indicative of the concentration of anti-HBs present in the sample.
Three internally prepared control serum pools, consisting of a high-positive, low-positive, and negative control, are used to monitor the performance of the assay. These pools are each prepared from 4 individual human immune sera obtained from an external vendor.
Additionally, there are anti-HBs positive and negative manufacturer-supplied controls, which are prepared from freeze-dried recalcified human plasma. The hepatitis B WHO International reference standard at 10 mIU/mL is also run as a control in every assay. The LLOQ of the assay is 5 mIU/mL.

Poliovirus Neutralization Assay

Anti-poliovirus types 1, 2, and 3 will be measured by neutralization assay. Serial dilutions of sera are mixed with challenge poliovirus and incubated with cultured Vero cells that are sensitive to poliovirus. Specific neutralizing antibodies contained in the sera bind to and neutralize the challenge poliovirus. The neutralized poliovirus does not affect cellular viability, and these cells continue to metabolize and release CO2, reducing the pH of the culture medium. Cell survival correlates with the change in the pH indicator (phenol red to yellow at pH ≤7.0) contained in the medium. In the absence of neutralizing antibodies, the challenge poliovirus reduces cellular metabolism and CO2 production. Therefore, the pH does not decrease and a color change is not detected. The poliovirus mouse inoculation test measures the functional serum antibody response to poliovirus by utilizing Vero cells MEF-1, and Saukett, respectively) as the challenge virus. The Karber method is used to determine the serum dilution that neutralized 50% of the challenge virus. Results are expressed as titers (1:dilution). The LLOQ for each of the antibodies to poliovirus types 1, 2, and 3 assays is 1:4.

Assessor's comment

All the assays are validated. The MAH clarified that, with the exception of the Hepatitis B ECi assay, assays were not previously used in the CDP of VAXELIS and provided with main characteristics of the assays.
For Ab values below the LLOQ, the value of 0.5 × LLOQ was used for analysis when calculating GMCs. The value of the LLOQ was used for analysis when calculating the GMFR and proportions of participants with a ≥4-fold rise in antibody level. For values greater than the upper limit of quantification (ULOQ), a value of the ULOQ was used for analysis. This is considered acceptable.

6.2. Results

6.2.1. Participant flow

The planned enrolment total was 160 participants. As of database lock, 168 participants were enrolled across 13 study sites in Germany, Italy, and Spain. All but 1 enrolled participant in Group 1 (V,V,V) received VAXELIS at Day 1 and completed the study, and all 82 participants in Group 2 (H,H,V) were vaccinated with VAXELIS at Day 1 and completed the study. Three participants were not enrolled (screen failures).

Important protocol deviations were reported for 14 (16.3%) participants in Group 1 (V,V,V), and 15 (18.3%) participants in Group 2 (H,H,V). Of these, 11 (12.8%) participants in Group 1 (V,V,V) and 13 (15.9%) participants in Group 2 (H,H,V) had important protocol deviations that were considered to be clinically important (The different objectives are listed in Table 6).

No protocol deviations were classified as a serious GCP compliance issue.

Table 6. Summary of important protocol deviations considered to be clinically important (all enrolled participants) (Table 10-2, Study report)

	Group 1 (V,V,V)		Group 2 (H,H,V)	
	n	(%)	n	(%)
Participants in population	86		82	
with one or more important protocol deviations considered to be clinically important	11	(12.8)	13	(15.9)
with no important protocol deviations considered to be clinically important	75	(87.2)	69	(84.1)
Inclusion/ Exclusion Criteria	**1**	**(1.2)**	**0**	**(0.0)**
Participant is not approximately 11 months to 13 months of age (327 days to 396 days) inclusive, at the time of obtaining the informed consent.	1	(1.2)	0	(0.0)
Prohibited Medications	**1**	**(1.2)**	**0**	**(0.0)**
Participant received any prohibited, licensed, live or non-live vaccine during the conduct of the study, prior to the Visit 2 blood draw.	1	(1.2)	0	(0.0)
Trial Procedures	**9**	**(10.5)**	**13**	**(15.9)**
Participant's immunogenicity blood sample was drawn outside the protocol-defined window for that time point.	4	(4.7)	1	(1.2)
Participant's immunogenicity blood sample was not drawn or could not be tested due to an error by the site in processing and/or handling of the sample.	5	(5.8)	12	(14.6)

Every participant is counted a single time for each applicable row and column.
H=Hexyon™; V=Vaxelis™.
Group 1 (V,V,V)=Participants had previously received 2 doses of Vaxelis™ at approximately 2 and 4 months of age.
Group 2 (H,H,V)=Participants had previously received 2 doses of Hexyon™ at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl] [P016V419: sdtm-dv; suppdv]

Immunogenicity Analysis Populations

The primary, secondary, and exploratory immunogenicity analyses were conducted using the PP population, defined as all enrolled participants without deviations from the protocol that may have substantially affected the results of the immunogenicity endpoints.

The majority of enrolled participants (Group 1 [V,V,V]: 72 [83.7%], and Group 2 [H,H,V]: 77 [93.9%]) were included in the IgG analyses at both Day 1 and Day 30.

Table 7. Participants accounting for immunogenicity analyses of the PP population (All enrolled participants) (Table 14.1-6, Study report)

	Group 1 (V,V,V)		Group 2 (H,H,V)	
	n	(%)	n	(%)
Participants enrolled	86		82	
Participants included in analyses by timepoint				
Day 1	79	(91.9)	82	(100.0)
Day 30	74	(86.0)	77	(93.9)
Both Day 1 and Day 30 timepoints	72	(83.7)	77	(93.9)
Reasons for exclusions from analyses[a]				
Participant-level exclusions[b]	**2**	**(2.3)**	**0**	**(0.0)**
Age at vaccination out of window	1	(1.2)	0	(0.0)
Enrolled but not vaccinated	1	(1.2)	0	(0.0)
Visit-level exclusions - Day 1	**5**	**(5.8)**	**0**	**(0.0)**
Missing serology results[c]	5	(5.8)	0	(0.0)
Visit-level exclusions - Day 30	**10**	**(11.6)**	**5**	**(6.1)**
Blood draw out of window	4	(4.7)	1	(1.2)
Missing serology results[c]	6	(7.0)	4	(4.9)
Prohibited concomitant medication or vaccination	1	(1.2)	0	(0.0)

Percentages are calculated based on the number of participants enrolled.

[a] Participants may have more than one reason for exclusion. Participants are displayed in all applicable categories.

[b] Participant-level exclusions result in exclusion from analyses at all timepoints. These participants do not also appear in the visit-level exclusion rows.

[c] Missing serology results for all 11 antigens, which may be due to discontinuation prior to serum sample collection, failure to provide a serum sample, and serum sample lost or damaged.

Source: [P016V419: adam-adsl; adpdev; adimm]

Safety Analysis Population

Safety analyses were performed using the APaT population, defined as all enrolled participants who received study intervention.

Assessor's comment

As of database lock, 168 participants were enrolled in the study. A total of 85 and 82 toddlers were administered with VAXELIS respectively in Group 1 (V, V, V) and Group 2 (H, H, V). All completed the study.

As mentioned above, the study was conducted in 3 countries. There were 6 sites in Germany, 2 sites in Italy and 5 sites in Spain. Number of participants enrolled in each country and in each site were not balanced between both groups (Table 14.2-2, study report), which, together with the open-label design and the absence of data post-primary vaccination, add limitations to results interpretation (comparison between groups).

Out of the 24 reported protocol deviations considered to be clinically important, the most frequent was that the participant blood sample could not be drawn or processed appropriately (n=22), which does not impact the safety reporting. One participant was outside the allowed age range at the time of obtaining informed consent (327 days to 396 days) and one participant received any prohibited, licensed, live or non-live vaccine during the conduct of the study, prior to the visit 2 blood draw.

Safety analyses were performed using the APaT population, defined as all enrolled participants who received study intervention, whereas immunogenicity analyses were conducted using the PP population, defined as all enrolled participants without deviations from the protocol that may have substantially affected the results of the immunogenicity endpoints. The number of participants included in the PP population varies by timepoint. A total of 79/86 subjects of Group 1 and 82/82 subjects of Group 2 were included in the PP population for the Day 1 timepoint. For Day 30 analyses, 74/86 toddlers of Group 1 and 77/82 toddlers of Group 2 were included in the PP population. Thus, overall, a higher number of participants of Group 1 were excluded when compared to Group 2. The main reasons for exclusion were missing serology results and blood draw out of window.

6.2.2. Recruitment

The first subject was enrolled on 31 March 2022 (first participant first visit) and the last subject completed on 30 August 2022 (last participant last visit). The database lock date was 24 January 2023.

6.2.3. Baseline data

Demographic and baseline characteristics

Main demographic and baseline characteristics are presented in Table 8.

Table 8. Participant characteristics (all participants as treated) (Table 10-3, Study report)

	Group 1 (V,V,V)		Group 2 (H,H,V)	
	n	(%)	n	(%)
Participants in population	85		82	
Sex				
Male	41	(48.2)	49	(59.8)
Female	44	(51.8)	33	(40.2)
Age (Days)				
327-396	84	(98.8)	82	(100.0)
≥397	1	(1.2)	0	(0.0)
Mean	348.3		344.7	
SD	18.2		16.4	
Median	341.0		341.0	
Range	327 to 397		327 to 396	
Race				
Asian	1	(1.2)	0	(0.0)
White	84	(98.8)	82	(100.0)
Ethnicity				
Hispanic Or Latino	45	(52.9)	60	(73.2)
Not Hispanic Or Latino	34	(40.0)	21	(25.6)
Not Reported	0	(0.0)	1	(1.2)
Unknown	6	(7.1)	0	(0.0)
History of maternal pertussis vaccination during pregnancy				
Yes	66	(77.6)	66	(80.5)
No	16	(18.8)	15	(18.3)
Unknown	3	(3.5)	1	(1.2)

SD=standard deviation.
H=Hexyon™; V=Vaxelis™.
Group 1 (V,V,V)=Participants had previously received 2 doses of Vaxelis™ at approximately 2 and 4 months of age.
Group 2 (H,H,V)=Participants had previously received 2 doses of Hexyon™ at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl]

Table 9. Age at vaccination (Table 1-1 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)

	Germany		Italy		Spain		Total	
	Group 1 (VVV) (N=30)	Group 2 (HHV) (N=22)	Group 1 (VVV) (N=11)	Group 2 (HHV) (N=0)	Group 1 (VVV) (N=44)	Group 2 (HHV) (N=60)	Group 1 (VVV) (N=85)	Group 2 (HHV) (N=82)
Age at 1st vaccination (Days)								
Mean (SD)	74.6 (15.7)	71.4 (12.6)	67.4 (8.32)	NA	65.5 (6.26)	66.7 (7.81)	69.0 (11.5)	68.0 (9.49)
Median [Min, Max]	70.0 [62.0, 140]	67.5 [56.0, 109]	63.0 [62.0, 85.0]	NA	63.5 [57.0, 93.0]	64.0 [61.0, 105]	65.0 [57.0, 140]	65.0 [56.0, 109]
Age at 2nd vaccination (Days)								
Mean (SD)	150 (19.2)	136 (17.9)	144 (19.1)	NA	128 (5.07)	136 (13.7)	138 (17.3)	136 (14.8)
Median [Min, Max]	150 [121, 217]	131 [118, 185]	145 [124, 190]	NA	126 [122, 145]	132 [122, 198]	132 [121, 217]	131 [118, 198]

Medical History

Reported medical history conditions by System Organ Class (SOC) are presented in Table 14.1-8 of the study report. A total of 38.8% and 40.2% of participants of Group 1 and Group 2 respectively had one or more conditions.

Prior and Concomitant Medications/Treatments/Vaccines

Prior medication (within 30 days prior to vaccination at Day 1) were reported for 58.8% and 29.3% of the participants in, respectively, Group 1 and Group 2 (Table 14.1-9 of the study report). Prior non-study vaccination (within 14 days prior to vaccination at Day 1) were reported for 3 Group 1-subjects only (Table 14.1-10 of the study report).

Concomitant medications were reported for 80.0% and 64.6% of the participants in Group 1 and Group 2, respectively (Table 14.1-11, study report).
In Group 1, concomitant non-study vaccinations were reported for 80.0% of the participants, and in Group 2 concomitant non-study vaccinations were reported for 92.7% of the participants (Table 10).

Table 10. Participants with specific concomitant vaccinations (incidence >0% in one or more vaccination groups) (all participants as treated population) (Table 14.1-12, study report)

	Group 1 (V,V,V)		Group 2 (H,H,V)	
	n	(%)	n	(%)
Participants in population	85		82	
with one or more concomitant vaccinations	68	(80.0)	76	(92.7)
with no concomitant vaccinations	17	(20.0)	6	(7.3)
ANTIINFECTIVES FOR SYSTEMIC USE				
VACCINES	**68**	**(80.0)**	**76**	**(92.7)**
MEASLES VACCINE LIVE (ENDERS-EDMONSTON);MUMPS VACCINE LIVE (JERYL LYNN);RUBELLA VACCINE LIVE (WISTAR RA 27/3)	9	(10.6)	44	(53.7)
MEASLES VACCINE LIVE (SCHWARTZ);MUMPS VACCINE LIVE (RIT 4385);RUBELLA VACCINE LIVE (WISTAR RA 27/3)	17	(20.0)	0	(0.0)
MEASLES VACCINE;MUMPS VACCINE;RUBELLA VACCINE	12	(14.1)	0	(0.0)
MENINGOCOCCAL VACCINE A/C/Y/W CONJ (TET TOX)	37	(43.5)	45	(54.9)
MENINGOCOCCAL VACCINE C CONJ (TET TOX)	1	(1.2)	1	(1.2)
PNEUMOCOCCAL VACCINE CONJ 13V (CRM197)	62	(72.9)	74	(90.2)
PNEUMOCOCCAL VACCINE CONJ 7V (CRM197)	4	(4.7)	2	(2.4)

Every participant is counted a single time for each applicable specific concomitant vaccination. A participant with multiple concomitant vaccinations within a vaccination category is counted a single time for that category. Each specific concomitant vaccination is listed under all relevant vaccination classes based on the vaccination's generic name, regardless of route of administration or reason for use.
WHO-DD GLOBALB3Sep22 was used in the reporting of this study.

Source: [P016V419: adam-adsl; adcm]

Assessor's comment

Demographic and baseline characteristics were generally comparable between the 2 groups.
There was however a trend for relatively less males in Group 1 (48.2%) than in Group 2 (59.8%). Median age at inclusion was similar for both groups (341.0 days). Median age at primary vaccination first dose was overall comparable between countries and groups. Medians age range from 63.0 days (Italy, Group 1) to 74.6 days (Germany, Group 1). Medians age at second vaccination were more variable, ranging from 126 days (Spain, Group1) to 150 days (Germany, Group 1).

Except 1 toddler, all were white with a higher proportion of Hispanic/Latino in Group 2 (73.2%) when compared to Group 1 (52.9%). A total of 77.6% and 80.5% of the mothers included in Group 1 and Group 2 respectively had an history of maternal pertussis vaccination during pregnancy.

As mentioned earlier, the study was conducted in different countries which might have an impact on the results. The MAH provided summaries of the proportions of participants meeting specified VAXELIS antigen responses at 30 days post-vaccination per country. GMTs were not provided. Overall, the immunogenicity results stratified by country are consistent with those of whole PP population. Seroresponder rates are comparable for Group 1 (Germany, Italy, Spain) and for Group 2 (Germany, Spain) across countries. For the safety results, refer to section 7.2.3.

Medical history conditions were overall comparable between both groups. There was a trend for higher participants reporting with gastrointestinal disorders in Group 2 (13.4%, n=11/82) versus Group 1 (7.1%,n= 6/85). The most frequently reported medical history conditions were all comprised in the SOC infections and infestations' and were, in Group 1, nasopharyngitis (11.8%, n=10/85), upper respiratory tract infection (10.6%, n=9/85), and gastroenteritis (7.1%, n=6/85). The most frequently reported medical history conditions in Group 2 were upper respiratory tract infection (18.3%, n=15/82), conjunctivitis (12.2%, n=10/82), and bronchiolitis (8.5%, n=7/82).

Prior and concomitant medications, treatment and vaccines are not balanced between groups, which is probably related to the local practices (country and region/site).

Proportions of participants (treated population, Table 14.1-9 of the study report) with specific prior medications (within 30 days prior administration of VAXELIS) were 58.8% (n=50/85) in Group 1 and 29.3% (24/82) in Group 2. Main differences between groups were for the following medication categories (difference ≥ 5%): stomatological preparations (8.2% vs 1.2%), vitamins (47.1% vs 23.2%), nasal preparations (9.4% vs 2.4%), and ophthalmologicals (11.8% vs 4.9%).

It is not known whether prior medications could have an impact on the reactogenicity/safety and immunogenicity of the booster administration. This is a limitation of the study but it is acknowledged that study design would not allow to address this aspect.

Proportions of participants (treated population, Table 14.1-11 of the study report) with specific concomitant medications were 80.0% (n=68/85) in Group 1 and 64.6% (n=53/82) in Group 2. Main differences were for the following medication categories (difference ≥ 5%): stomatological preparations (14.1% vs 2.4%), vitamins (47.1% vs 23.2%), anti-acne preparations (15.3% vs 9.8%), other dermatological preparations (16.5% vs 11.0%), other gynecologicals (15.3% vs 9.8%), urologicals (8.2% vs 2.4%), analgesics (45.9% vs 51.2%), nasal preparations (9.4% vs 2.4%), throat preparations (15.3% vs 9.8%) and otologicals (9.4% vs 2.4%).
As for prior medications, it is not known whether concomitant medications could have an impact on the reactogenicity/safety and immunogenicity of the booster administration. This is a limitation of the study but it is acknowledged that study design would not allow to address this aspect.

Proportions of participants (treated population, Table 10) with specific concomitant vaccinations were 80.0% (n=68/85) in Group 1 and 92.7% (n=76/82) in Group 2. MMR vaccines were administered in 44.7% of the toddlers in Group 1 versus 53.7% of toddlers included in Group 2. The MMR vaccine administered was always the same in Group 2, whereas 3 different vaccine types were administered in Group 1. A total of 43.5% and 54.9% of the toddlers of Group 1 and Group 2 respectively received a meningococcal vaccine (all except 2 subjects received the A/C/W/Y conjugated vaccine) and a total of

77.6% and 92.6% of the toddlers of Group 1 and Group 2 respectively received a conjugated pneumococcal vaccine (PPV13 for the majority of them).
As indicated in the SmPC, section 4.5, VAXELIS may be administered simultaneously with pneumococcal polysaccharide conjugate vaccines, rotavirus vaccines, measles, mumps, rubella (MMR) and varicella containing vaccines and meningococcal C conjugate vaccines.

Overall, all these differences between groups limit the result interpretation.

6.2.4. Immunogenicity results

6.2.4.1. Primary and secondary Immunogenicity Endpoints

Table 11 summarises the proportions of participants with antibody-specific responses to each antigen contained in VAXELIS and HEXYON meeting the thresholds specified in 6.1.4.

Table 11. Summary of the proportions of participants meeting specified VAXELIS antigen responses at 30 days post-vaccination (PP population) (Table 11-1, Study report)

Antigen	Endpoint	Group 1 (V,V,V) (N = 85)		Group 2 (H,H,V) (N = 82)	
		Observed Response Percentage (m/n)	95% CI[a]	Observed Response Percentage (m/n)	95% CI[a]
Primary Endpoints					
Diphtheria toxoid	% ≥0.1 IU/mL	100.0 (69/69)	(94.8, 100.0)	98.6 (73/74)	(92.7, 100.0)
Tetanus toxoid	% ≥0.1 IU/mL	98.6 (68/69)	(92.2, 100.0)	98.6 (73/74)	(92.7, 100.0)
Pertussis - PT	% vaccine response[b]	98.4 (63/64)	(91.6, 100.0)	94.4 (67/71)	(86.2, 98.4)
Pertussis - FHA	% vaccine response[b]	98.4 (63/64)	(91.6, 100.0)	90.1 (64/71)	(80.7, 95.9)
Hib-PRP	% ≥1.0 µg/mL	89.0 (65/73)	(79.5, 95.1)	90.8 (69/76)	(81.9, 96.2)
HBsAg	% ≥10 mIU/mL	100.0 (56/56)	(93.6, 100.0)	94.2 (65/69)	(85.8, 98.4)
Poliovirus 1	% Nab ≥1:8 dilution	100.0 (66/66)	(94.6, 100.0)	95.7 (66/69)	(87.8, 99.1)
Poliovirus 2	% Nab ≥1:8 dilution	100.0 (66/66)	(94.6, 100.0)	100.0 (69/69)	(94.8, 100.0)
Poliovirus 3	% Nab ≥1:8 dilution	97.0 (64/66)	(89.5, 99.6)	100.0 (69/69)	(94.8, 100.0)
Secondary Endpoints					
Pertussis - FIM 2/3[c]	% vaccine response[b]	95.3 (61/64)	(86.9, 99.0)	69.0 (49/71)	(56.9, 79.5)
Pertussis - PRN[c]	% vaccine response[b]	92.2 (59/64)	(82.7, 97.4)	22.5 (16/71)	(13.5, 34.0)

[a] The within-group CIs are based on the exact binomial method proposed by Clopper and Pearson.
N=Number of participants allocated and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.
CI=confidence interval; FHA=filamentous hemagglutinin; FIM 2/3=fimbriae types 2 and 3; HBsAg=hepatitis B surface antigen; Hib=haemophilus influenzae type b; IU=international unit; Nab=neutralizing antibodies; PRN=pertactin; PRP=polyribosylribitol phosphate; PT=pertussis toxin.
[b] The pertussis vaccine response is defined as follows:
1) If prevaccination <LLOQ, then postvaccination should be ≥4 × the LLOQ.
2) If prevaccination ≥LLOQ but <2 × the LLOQ, then postvaccination should achieve a 4-fold rise (postvaccination/prevaccination ≥4).
3) If prevaccination ≥2 × the LLOQ, then postvaccination should achieve a 2-fold response (postvaccination/prevaccination ≥2).
[c] Antigen contained only in Vaxelis™.
H=Hexyon™; V=Vaxelis™.
Group 1 (V,V,V)=Participants had previously received 2 doses of Vaxelis™ at approximately 2 and 4 months of age.
Group 2 (H,H,V)=Participants had previously received 2 doses of Hexyon™ at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adimm]

Assessor's comment

Specific Ab to each antigen contained in both VAXELIS and HEXYON were observed at 30 days post-boost.

At Day 1 (pre-vaccination), proportion of participants showing Ab titers equal or above the Ab thresholds associated with protection against diphtheria, tetanus, clinical paralysis due to polioviruses and hepatitis B were overall comparable between groups, with 95% CIs overlapping (Table 24). In contrast, anti-PRP Ab levels were not comparable between groups. Only 1 out of 81 participant of Group 2 (H,H,V) had anti-PRP Ab levels equal or above the threshold associated with long-term protection, versus 51/79 (64.6%) of Group 1 (Table 24). Proportion of participants who achieved short term protective concentration of anti Hib-PRP ≥0.15 µg/mL was calculated (Table 25). Although the percentages of participants with Ab levels ≥ 0.15 µg/mL was higher than those with Ab levels ≥1.0 µg/mL, the percentage observed in Group 2 was still lower than the percentage observed in Group 1 (27.2% [22/81] versus 87.3% [69/79]), indicating the importance of the booster dose. Proportion of responders at Day 1 (pre-vaccination) were not presented for the pertussis antigens PT and FHA because of no Ab threshold associated with protection. GMTs specific for PT and FHA at Day 1 were presented at initial submission, which is deemed sufficient.

More than 98% of the participants of both groups reach the Ab threshold associated with protection against diphtheria and tetanus. Only 1 toddler from Group 2 did not mount Ab levels ≥0.1 IU/mL to diphtheria toxoid, and one toddler to tetanus toxoid. It is not known if it is the same child. More than 95% are considered protected against clinical paralysis due to polioviruses based on results of the different poliovirus neutralization assays. Three subjects of Group 2 had anti-poliovirus 1 Ab titers and 2 subjects of Group 1 had anti-poliovirus 3 Ab titers below the defined thresholds. The vast majority (>89%) of the participants had anti-PRP Ab levels equal or above the threshold associated with long-term protection (65/73 and 69/76 in Group 1 and Group 2 respectively). Anti-HBs Ab levels were ≥ 10 mIU/mL (associated with vaccine-induced protection) in more than 94% of the participants, corresponding to 4/69 toddlers of Group 2 with an Ab level below the threshold of 10 mIU/mL.
Percentages of participants reaching the Ab threshold associated with protection against diphtheria, tetanus, clinical paralysis due to polioviruses, hepatitis B and long-term protection against Haemophilus Influenzae Type b at 1 month post-vaccination were always higher than at Day 1 (pre-vaccination).

Vaccine response rates were >90% for common pertussis antigens (PT and FHA) in both groups. As expected, vaccine response rates were lower in Group 2 for PRN and FIM 2/3, both antigens being only contained in VAXELIS. Seroresponse rate for PRN in Group 2 was very low (22.5%).

Participant's legally acceptable representative were to document on the VRC the use of any analgesic or antipyretic on the day of vaccination. A total of 55 participants used analgesic/antipyretic on the day of vaccination, n= 27/85 (32%) in Group 1 and n=28/82 (34%) in Group 2. No other analgesic/antipyretic, or immunosuppressant medication, than paracetamol or ibuprofen were reported on the day of vaccination.
In terms of percentages of participants achieving thresholds associated with protection against diphtheria, tetanus, clinical paralysis due to polioviruses, hepatitis B and long-term protection against *Haemophilus Influenzae* Type b, no differences were observed between participants who used analgesic/antipyretic on the day of vaccination and those who did not. Results were overall consistent with those of whole PP population.

6.2.4.2. Exploratory Immunogenicity Endpoints

Table 12 summarises the GMC of the antibody responses at day 1 and at day 30 post-vaccination with VAXELIS.

Table 12. Summary of antibody responses for all antigens contained in VAXELIS (PP population) (Table 11-2, Study report)

			Group 1 (V,V,V) (N = 85)			Group 2 (H,H,V) (N = 82)		
	Endpoint	Timepoint	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Diphtheria toxoid	GMC	Day 1	73	0.08	(0.06, 0.11)	79	0.08	(0.07, 0.10)
		Day 30	69	3.24	(2.69, 3.89)	74	1.93	(1.55, 2.39)
	% ≥ 4-fold rise	Day 1 to Day 30	64	98.4% (63/64)	(91.6, 100.0)	71	95.8% (68/71)	(88.1, 99.1)
Tetanus toxoid	GMC	Day 1	73	0.17	(0.14, 0.23)	79	0.14	(0.12, 0.17)
		Day 30	69	7.73	(5.88, 10.16)	74	3.92	(3.07, 4.99)
	% ≥ 4-fold rise	Day 1 to Day 30	64	95.3% (61/64)	(86.9, 99.0)	71	97.2% (69/71)	(90.2, 99.7)
Pertussis - PT	GMC	Day 1	73	6.91	(5.35, 8.93)	79	7.15	(5.86, 8.72)
		Day 30	69	172.27	(138.99, 213.53)	74	59.41	(48.58, 72.67)
	% ≥ 4-fold rise	Day 1 to Day 30	64	98.4% (63/64)	(91.6, 100.0)	71	85.9% (61/71)	(75.6, 93.0)
Pertussis - FHA	GMC	Day 1	73	8.39	(6.70, 10.49)	79	29.52	(24.90, 35.00)
		Day 30	69	99.01	(80.89, 121.20)	74	147.03	(124.94, 173.02)
	% ≥ 4-fold rise	Day 1 to Day 30	64	90.6% (58/64)	(80.7, 96.5)	71	60.6% (43/71)	(48.3, 72.0)
Pertussis - FIM 2/3[b]	GMC	Day 1	73	18.01	(13.47, 24.06)	79	1.21	(1.08, 1.37)
		Day 30	69	337.60	(250.90, 454.27)	74	13.50	(10.75, 16.96)
	% ≥ 4-fold rise	Day 1 to Day 30	64	89.1% (57/64)	(78.8, 95.5)	71	69.0% (49/71)	(56.9, 79.5)
Pertussis - PRN[b]	GMC	Day 1	73	2.68	(2.08, 3.45)	79	1.39	(1.20, 1.61)
		Day 30	69	115.88	(84.02, 159.83)	74	3.21	(2.49, 4.14)
	% ≥ 4-fold rise	Day 1 to Day 30	64	92.2% (59/64)	(82.7, 97.4)	71	22.5% (16/71)	(13.5, 34.0)

			Group 1 (V,V,V) (N = 85)			Group 2 (H,H,V) (N = 82)		
	Endpoint	Timepoint	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Hib-PRP	GMC	Day 1	79	1.25	(0.92, 1.70)	81	0.11	(0.10, 0.13)
		Day 30	73	5.85	(4.28, 8.00)	76	5.12	(3.88, 6.76)
	% ≥ 4-fold rise	Day 1 to Day 30	71	54.9% (39/71)	(42.7, 66.8)	75	96.0% (72/75)	(88.8, 99.2)
HBsAg	GMC	Day 1	69	30.88	(21.55, 44.23)	73	32.38	(21.21, 49.44)
		Day 30	56	1111.50	(784.67, 1574.46)	69	470.60	(292.00, 758.43)
	% ≥ 4-fold rise	Day 1 to Day 30	52	96.2% (50/52)	(86.8, 99.5)	63	84.1% (53/63)	(72.7, 92.1)
Poliovirus 1	GMC	Day 1	62	38.94	(24.12, 62.86)	78	31.86	(21.29, 47.68)
		Day 30	66	2135.80	(1448.73, 3148.73)	69	1569.33	(958.73, 2568.81)
	% ≥ 4-fold rise	Day 1 to Day 30	53	90.6% (48/53)	(79.3, 96.9)	66	90.9% (60/66)	(81.3, 96.6)
Poliovirus 2	GMC	Day 1	62	57.90	(37.28, 89.92)	78	53.12	(33.76, 83.60)
		Day 30	66	3020.62	(2162.92, 4218.44)	69	3470.29	(2441.36, 4932.86)
	% ≥ 4-fold rise	Day 1 to Day 30	53	96.2% (51/53)	(87.0, 99.5)	66	95.5% (63/66)	(87.3, 99.1)
Poliovirus 3	GMC	Day 1	62	30.28	(18.87, 48.57)	78	33.78	(23.10, 49.39)
		Day 30	66	1161.50	(687.73, 1961.64)	69	2554.44	(1704.39, 3828.46)

			Group 1 (V,V,V) (N = 85)			Group 2 (H,H,V) (N = 82)		
	Endpoint	Timepoint	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Poliovirus 3	% ≥ 4-fold rise	Day 1 to Day 30	53	88.7% (47/53)	(77.0, 95.7)	66	93.9% (62/66)	(85.2, 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 allocated and vaccinated; n=Number of participants contributing to the analysis.
CI=confidence interval; GMC=geometric mean concentration (µg/mL); FHA=filamentous hemagglutinin; FIM 2/3=fimbriae types 2 and 3; HBsAg=hepatitis B surface antigen; Hib=haemophilus influenzae type b; IU=international unit; Nab=neutralizing antibodies; PRN=pertactin; PRP=polyribosylribitol phosphate; PT=pertussis toxin.
[b] Antigen contained only in Vaxelis™.
H=Hexyon™; V=Vaxelis™.
Group 1 (V,V,V)=Participants had previously received 2 doses of Vaxelis™ at approximately 2 and 4 months of age.
Group 2 (H,H,V)=Participants had previously received 2 doses of Hexyon™ at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adimm]

Assessor's comment

Pre-boost (Visit 1), Ab-specific GMCs for DT, TT, PT, HBsAg and Polioviruses 1-3 were comparable between groups.

Higher anti-PRP Ab GMC was observed in Group 1 (1.25, 95% CI of 0.92-1.70) when compared to Group 2 (0.11, 95%CI of 0.10-0.13). Anti-PRP Ab GMC of Group 2 were lower than the LLOQ (0.15 µg/mL).

Specific Ab GMCs to FHA and to FIM 2/3 were respectively higher and lower in Group 2 when compared to Group 1 (FHA-Ab titers of 29.52 vs 8.39 and FIM 2/3-Ab titers of 1.21 vs 18.01 in Group 1 and Group 2 respectively, 95% CI non-overlapping). PRN-Ab were low in both groups (2.68 and 1.39 for Group 1 and Group 2 respectively). FIM 2/3-Ab and PRN Ab titers of Group 2 were lower than the LLOQ (2.00 EU/mL).

Responses post-primary vaccination are not known, no conclusion can thus be drawn on the kinetics of the persistence of the immune response following primary vaccination with VAXELIS or HEXYON. Maternal immunisation could also have an impact on the (memory) responses.

At 30 days post-boost with VAXELIS specific Ab to each antigen contained in both VAXELIS and HEXYON were observed. Higher Ab GMCs were observed for DT, TT, PT, FIM 2/3, PRN and HBsAg in Group 1 when compared to Group 2. FIM 2/3 and PRN Ab titers remain low in Group 2 as expected since the infants were not primed with these antigens.
Higher FHA-Ab titers were observed in Group 2 when compared to Group 1, as observed pre-boost.
Ab titers specific to Hib-PRP and the 3 polioviruses were overall comparable between groups.

Observation were confirmed by reverse cumulative distribution curves (Figures 14.2-1 to 14.2-11 of the study report).

No conclusion can be drawn on these group comparisons as the study was open-label, non-randomized, conducted in 3 different countries (and 13 sites), with/without previous medication, and with/without concomitant administration of medication and/or vaccines. Subgroup analyses were not presented according to all these variables.
Stratified descriptive immunogenicity data for participants with/without use of analgesic/antipyretic on the day of vaccination in terms of GMCs were provided. As mentioned above, a total of 55 participants used analgesic/antipyretic on the day of vaccination. However, GMC Ab responses are not available for all the participants, resulting in limited number of participants per group. Ab GMC results were overall consistent with those of whole PP population.
Subgroup analysis of the vaccine responses to pertussis antigens according to pertussis maternal immunisation during the pregnancy was also presented (Tables 14.2-3 and 14.2-4 of study report). No data pre-boost were provided. GMCs post-primary vaccination, pre- and post-boost were neither provided. Only 11 infants in each group were born from mothers not vaccinated during their pregnancies, which also preclude appropriate comparison.

The only conclusion that can be drawn is that maternal immunisation with pertussis antigen does not seem to interfere with a booster vaccination with VAXELIS, hence adequate memory induced by the primary vaccination, either with VAXELIS or HEXYON.

6.3. Discussion

Methods

V419-016 is a Phase 4 study to evaluate the safety, tolerability, and immunogenicity of a booster dose of VAXELIS given to toddlers 11 to 13 months of age who previously received a 2-dose primary infant series of either VAXELIS (Group 1: V,V,V) or HEXYON (Group 2: H,H,V).

Data of this study would support switching to VAXELIS after a primary series with another hexavalent vaccine. The primary series consisted in 2 doses given 2 months apart. Either VAXELIS or HEXYON was given to infants at 2 and 4 months of age as part of their routine vaccination. The boost with VAXELIS, open-label, was administered approximately at 11-13 months of age (i.e. at least 6 months post-primary vaccination).

The study was conducted in Germany, Spain and Italy. The 2-dose primary vaccination is recommended in those countries at 2 and 4 months of age, and the boost is recommended at 11 months.

The primary immunogenicity objective was to describe the response rates to antigens contained in both VAXELIS and HEXYON 30 days after the booster dose of VAXELIS. The secondary objective was to describe the response rates to antigens contained in both VAXELIS, but not in HEXYON, 30 days after the booster dose of VAXELIS. Description of the antigen-specific GMCs at pre-dose and 30 days post-booster with VAXELIS were amongst the exploratory objectives. The Objectives are overall endorsed.

The primary immunogenicity endpoints are overall endorsed. Seroprotection or seroconversion rates were to be measured at 30 days post-boost. The antibody (Ab) thresholds used for anti-DT Ab (0.1 IU/ml), anti-TT Ab (0.1 IU/ml), anti-poliovirus Ab (1:8 dilution), anti-HBs Ab (10 mIU/ml), anti-PRP Ab (1 µg/mL) are consistent with established immunological correlate of protection (ICP). For pertussis, there are currently no ICP that are established. The MAH proposed endpoints based on assay LLOQ for pertussis antigens. Those criteria are arbitrary and differ from those previously used in the CDP of VAXELIS and defined in the SmPC. However, as the aim of the study is to evidence a booster effect, vaccine response rate defined on arbitrary criteria is deemed acceptable as this cannot be avoided in the absence of ICP. In addition, GMCs are presented which will allow relevant assessment of the magnitude of the booster effect.

This study planned to enrol approximately 160 participants (80 in each group). Participants were not randomized, thus, the participant distribution per country and per site was not balanced, which might, in theory, bias the results. There was no stratification by age which is acceptable as the age range of the participants to be enrolled was clearly defined and narrow (≥327 days to ≤396 days inclusive). There was no stratifications by sex or other characteristics (such as concomitant medication or vaccination) although this might have been of scientific value.

The PP population served as the population for the analysis of immunogenicity data. The PP population consists of all enrolled participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint. No statistical hypothesis testing were performed for immunogenicity analyses.

The different immunogenicity assays used are validated assays. With the exception of the Hepatitis B ECi assay, these assays were not previously used in the CDP of VAXELIS. Main characteristics of the assays are provided.

Results

Participants and baseline data

As of database lock, 168 participants were enrolled in the study. A total of 85 and 82 toddlers were administered with VAXELIS respectively in Group 1 (V, V, V) and Group 2 (H, H, V). All completed the study. All participants included in Italy received a VAXELIS primary series (Group 1). Number of participants in this country is limited (n=11).

Demographic and baseline characteristics were generally comparable between the 2 groups. There was however a trend for relatively less males in Group 1 (48.2%) as compared to Group 2 (59.8%). Median age was similar for both groups (341.0 days). Except for 1 toddler, all were white with a higher proportion of Hispanic/Latino in Group 2 (73.2%) when compared to Group 1 (52.9%). A total of 77.6% and 80.5% of the mothers included in Group 1 and Group 2, respectively, had an history of maternal pertussis vaccination during pregnancy.

Proportions of participants with specific prior or concomitant medications or vaccinations were different between groups. It is not known whether prior or concomitant medications could have an impact on the reactogenicity/safety and immunogenicity of the booster administration, this is a limitation of the study.

Stratified descriptive data for participants with/without use of analgesic/antipyretic on the day of vaccination, both for reactogenicity (solicited local and systemic adverse events) and for immunogenicity were nevertheless submitted (see below).

Immunogenicity results

VAXELIS elicited specific Ab to each antigens contained in both VAXELIS and HEXYON.

At 30 days post-boost with VAXELIS, more than 98% of the participants of both groups reach the Ab threshold associated with protection against diphtheria and tetanus. More than 95% are considered protected against clinical paralysis due to polioviruses based on results of the different poliovirus neutralization assays. The vast majority (>89%) of the participants had anti-PRP Ab levels equal or above the threshold associated with long-term protection. Anti-HBs Ab levels were ≥ 10 mIU/mL (associated with vaccine-induced protection) in more than 94% of the participants. Vaccine response rates were >90% for common pertussis antigens (PT and FHA) in both groups. As expected, vaccine response rates were lower in Group 2 for PRN and FIM 2/3, both antigens being only contained in VAXELIS.

Percentages of participants reaching the Ab threshold associated with protection against diphtheria, tetanus, clinical paralysis due to polioviruses, hepatitis B and long-term protection against *Haemophilus Influenzae* type b at 1 month post-vaccination were always higher than at Day 1 (pre-vaccination), indicating the usefulness of a booster dose.

At 30 days post-boost with VAXELIS, higher Ab GMCs were observed for DT, TT, PT, FIM 2/3, PRN and HBsAg in Group 1 when compared to Group 2. FIM 2/3 and PRN Ab titers remain low in Group 2 as expected since the infants were not primed with these antigens. Higher FHA-Ab titers were observed in Group 2 when compared to Group 1, as observed pre-boost. Ab titers specific to Hib-PRP and the 3 polioviruses were overall comparable between groups.

No conclusion can be drawn on these group comparisons as the study was open-label, non-randomized, conducted in 3 different countries (and 13 sites), with/without previous medication, and with/without concomitant administration of medication and/or vaccines. Subgroup analyses were not presented according to all these variables. Although, as per study design, no robust interpretation could be done, immunogenicity results stratified by country or for participants with/without use of analgesic/antipyretic on the day of vaccination were shown to be overall consistent with those of whole PP population (seroprotection rates).
Subgroup analysis of the vaccine responses to pertussis antigens according to pertussis maternal immunisation during the pregnancy were also presented. Results suggest that maternal immunisation with pertussis antigen does not interfere with a booster vaccination with VAXELIS, hence adequate memory seems to be induced by the primary vaccination, either with VAXELIS or HEXYON.

Conclusion

A boost with VAXELIS given at least 6 months after primary vaccination with 2 doses of either VAXELIS or HEXYON elicited specific Ab to each antigen contained in both VAXELIS and/or HEXYON.

At least 89% of the children had a seroresponse defined as associated with protection against diphtheria, tetanus, hepatitis B, clinical paralysis due to polioviruses, and invasive *Haemophilus influenzae* type b disease. Percentages of participants reaching these seroresponses at 1 month post-vaccination were always higher than at Day 1 (pre-vaccination).

Higher immune responses to pertussis antigens were observed post-boost when compared to pre-boost, both in terms of seroresponse and Ab GMCs.

Because of the various limitations of the study, results comparison between groups cannot be appropriately interpreted.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

V419-016, a Phase 4, open-label study to evaluate the safety, tolerability, and immunogenicity of VAXELIS (V419) given as a booster to healthy participants approximately 11 to 13 months of age who previously received a 2-dose primary infant series of either VAXELIS (Group 1: V,V,V) or HEXYON (Group 2: H,H,V).

The primary safety objective was to evaluate the safety and tolerability of a booster dose of VAXELIS with respect to the proportion of participants with adverse events (AEs).

The safety endpoints include:

- Number of participants with solicited injection-site AEs from Day 1 through Day 5 post-vaccination with VAXELIS.
- Number of participants with solicited systemic AEs from Day 1 through Day 5 post-vaccination with VAXELIS.
- Number of participants with unsolicited AEs from Day 1 through Day 15 post-vaccination with VAXELIS.
- Number of participants with an SAE, a vaccine-related SAE, discontinuation due to an AE, and death, from Day 1 through completion of study participation.
- Participants body temperature measured from Day 1 through Day 5 post-vaccination with VAXELIS.

Body temperatures, solicited and unsolicited AEs, concomitant medications, non-study vaccinations, use of any analgesic or antipyretic on the day of vaccination were documented by the participant's legally acceptable representative by using a paper vaccination report card (VRC).

Solicited AEs for this study are summarized in Table 13. All solicited injection-site AEs are considered related to study intervention.

Table 13. Solicited Adverse events (Table 6, Protocol)

Type of Solicited Adverse Event	Predefined Solicited Adverse Events (Preferred Term)	Solicited Time Period
Injection-site	Injection-site swelling Injection-site redness (erythema) Injection-site pain or tenderness (pain)	Day 1 through Day 5 postvaccination
Systemic	Vomiting Drowsiness (somnolence) Appetite lost (decreased appetite) Irritability	Day 1 through Day 5 postvaccination

Unsolicited AEs for this study are events that are 1) not predefined in Table 13 or 2) predefined in Table 13, but reported at any time outside the solicited time period. The investigator assessed unsolicited AEs that meet the definition of an AE or SAE with respect to seriousness, intensity, and causality.

Safety analyses were performed using the APaT population, defined as all enrolled participants who received study intervention. At least 1 temperature measurement obtained after study intervention was required for inclusion in the analyses of temperature.

Safety and tolerability were assessed by clinical review of AEs and post-vaccination temperatures. The overall safety endpoints and specific AEs were summarized by providing the number and percentage of participants with AEs. The 95% within-group CIs for the percentages of participants with the event were provided. Within-group CIs were calculated based on the exact binomial method proposed by Clopper and Pearson.

Table 14. Analysis strategy for safety parameters (Table 7, Protocol)

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Within-group CI
Overall Safety Assessment	Solicited injection-site swelling (Days 1 through 5)	X	X
	Solicited injection-site redness/erythema (Days 1 through 5)	X	X
	Solicited injection-site tenderness/pain (Days 1 through 5)	X	X
	Solicited vomiting (Days 1 through 5)	X	X
	Solicited drowsiness/somnolence (Days 1 through 5)	X	X
	Solicited appetite lost/decreased appetite (Days 1 through 5)	X	X
	Solicited irritability (Days 1 through 5)	X	X
	Unsolicited AEs (Days 1 through 15)	X	X
	Any AE	X	X
	Any vaccine-related AE	X	X
	Any SAE	X	X
	Any vaccine-related SAE	X	X
	Discontinuation from study due to AE	X	X
	AE that resulted in death	X	X
	SOCs	X	X
	Maximum temperature measurements (Days 1 through 5)	X	X

AE=adverse event; CI=confidence interval; SAE=serious adverse event; SOC=System Organ Class

There were no safety topics of special interest.

There were no laboratory safety evaluations required by the protocol.

If the underlying incidence of an SAE is 1.00% (1 of every 100 participants receiving the vaccine), there is an 80% chance of observing at least 1 SAE among 160 participants. If the underlying incidence of an SAE is 0.43% (1 of every 231 participants receiving the vaccine), there is a 50% chance of observing at least 1 SAE among 160 participants. If no SAEs are observed among the 160 participants, this study provides 95% confidence that the underlying percentage of participants with SAE is <1.85% (1 in every 53 participants).

The extent of exposure was summarized by the number and proportion of participants vaccinated with VAXELIS.

Assessor's comment

V419-016 is a Phase 4 study to evaluate the safety, tolerability, and immunogenicity of a booster dose of VAXELIS given to toddlers 11 to 13 months of age who previously received a 2-dose primary infant series of either VAXELIS (Group 1: V,V,V) or HEXYON (Group 2: H,H,V).

Reactogenicity and safety assessments included monitoring and recording of solicited and unsolicited AEs, SAEs (including fatal SAEs). Body temperatures, concomitant medications, non-study vaccinations, use of any analgesic or antipyretic on the day of vaccination were also documented.

Solicited AEs were evaluated from Days 1 to 5 after study vaccination. Solicited local AEs included swelling, redness (erythema), or pain (tenderness). All solicited injection-site AEs were considered related to study intervention.

Solicited systemic AEs included vomiting, drowsiness (somnolence), appetite lost, and irritability. The causality of solicited systemic AEs was assessed by the investigators.

The number of solicited AEs to be monitor were limited. However, VAXELIS is widely used with a well-known reactogenicity/safety profile.

Unsolicited AEs were evaluated from Days 1 to 15 after study vaccination. Those are AEs defined as a solicited AE but with an onset of more than 5 days following vaccination or are AEs with an onset within 15 days following vaccination that are not defined as a solicited AE.

The investigators used their clinical judgment to assess the causal relatedness and the intensity/size of an AE or SAE.

Occurrence of SAEs, discontinuation due to an AE and death were reported from Day 1 through completion of study participation (i.e. 30 days post-vaccination). There were no AEs of special interest in the study, nor laboratory evaluation.

Analyses were performed in the APaT population which consisted of all randomized participants who received study vaccination.

Safety methods and endpoints are overall endorsed.

7.2. Results

7.2.1. Exposure

Please refer to section 6.2.3.

7.2.2. Summary of adverse events

Vaccine-related AEs were reported for the majority of participants in both groups.

Table 15. Summary of adverse events (Table 12-1, Study report)

	Group 1 (V,V,V)			Group 2 (H,H,V)		
	n	(%)	95% CI[a]	n	(%)	95% CI[a]
Participants in population	85			82		
with one or more adverse events	83	(97.6)	(91.8, 99.7)	76	(92.7)	(84.8, 97.3)
injection-site	71	(83.5)		62	(75.6)	
systemic	79	(92.9)		69	(84.1)	
with no adverse event	2	(2.4)		6	(7.3)	
with vaccine-related[b] adverse events	83	(97.6)	(91.8, 99.7)	76	(92.7)	(84.8, 97.3)
injection-site	71	(83.5)		62	(75.6)	
systemic	79	(92.9)		68	(82.9)	
with serious adverse events	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
with serious vaccine-related adverse events	0	(0.0)	(0.0, 4.2)	0	(0.0)	(0.0, 4.4)
who died	0	(0.0)	(0.0, 4.2)	0	(0.0)	(0.0, 4.4)

[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.
[b] Determined by the investigator to be related to the vaccine.
Reported adverse events include nonserious adverse events that occurred from Day 1 through Day 15 postvaccination with Vaxelis™, and serious adverse events that occurred throughout the duration of study.
CI=confidence interval.
H=Hexyon™; V=Vaxelis™.
Group 1 (V,V,V)=Participants had previously received 2 doses of Vaxelis™ at approximately 2 and 4 months of age.
Group 2 (H,H,V)=Participants had previously received 2 doses of Hexyon™ at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adae]

Assessor's comment

A trend for a higher proportion of participants with one or more adverse events was observed for Group 1 when compared for Group 2, but still with 95% CI overlapping. All except 1 systemic AE were considered by the investigator as related to the vaccine. No vaccine-related SAEs, deaths, or discontinuations due to AEs were reported in the study.

7.2.3. Solicited local and systemic adverse events

Table 16 summarizes the proportion of participants who experienced at least one solicited AEs. Solicited events accounted for the majority of all AEs.

Table 16. Participants with solicited adverse events (Incidence > 0% in one or more vaccination groups) (all participants as treated population) (Table 12-2, Study report)

	Group 1 (V,V,V)			Group 2 (H,H,V)		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	85			82		
with one or more solicited adverse events	82	(96.5)		71	(86.6)	
with no solicited adverse events	3	(3.5)		11	(13.4)	
Solicited injection site adverse events	**71**	**(83.5)**	**(73.9, 90.7)**	**62**	**(75.6)**	**(64.9, 84.4)**
Injection site erythema	45	(52.9)	(41.8, 63.9)	41	(50.0)	(38.7, 61.3)
Injection site pain	63	(74.1)	(63.5, 83.0)	46	(56.1)	(44.7, 67.0)
Injection site swelling	45	(52.9)	(41.8, 63.9)	33	(40.2)	(29.6, 51.7)
Solicited systemic adverse events	**78**	**(91.8)**	**(83.8, 96.6)**	**57**	**(69.5)**	**(58.4, 79.2)**
Decreased appetite	37	(43.5)	(32.8, 54.7)	30	(36.6)	(26.2, 48.0)
Irritability	66	(77.6)	(67.3, 86.0)	48	(58.5)	(47.1, 69.3)
Somnolence	55	(64.7)	(53.6, 74.8)	39	(47.6)	(36.4, 58.9)
Vomiting	3	(3.5)	(0.7, 10.0)	7	(8.5)	(3.5, 16.8)

[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.

Every participant is counted a single time for each applicable row and column.

Injection site swelling, injection site redness/erythema, injection site tenderness/pain, vomiting, drowsiness/somnolence, appetite lost/decreased appetite, and irritability were solicited from Day 1 through Day 5 following vaccination.

MedDRA version 25.1 was used in the reporting of this study.

CI=confidence interval.

H=Hexyon™; V=Vaxelis™.

Group 1 (V,V,V)=Participants had previously received 2 doses of Vaxelis™ at approximately 2 and 4 months of age.

Group 2 (H,H,V)=Participants had previously received 2 doses of Hexyon™ at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adae]

All injection-site AEs were considered vaccine-related. Proportions of participants with vaccine-related systemic AEs is shown in the Table 17 below. Table 18 shows temperature data collected up to 5 days post-vaccination.

Table 17. Participants with solicited systemic adverse events related to study vaccine (Incidence > 0% in one or more vaccination groups) (all participants as treated population) (Table 12-3, Study report)

	Group 1 (V,V,V)			Group 2 (H,H,V)		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	85			82		
with one or more solicited systemic adverse events related to study vaccine	78	(91.8)		56	(68.3)	
with no solicited systemic adverse events related to study vaccine	7	(8.2)		26	(31.7)	
Decreased appetite	37	(43.5)	(32.8, 54.7)	29	(35.4)	(25.1, 46.7)
Irritability	63	(74.1)	(63.5, 83.0)	47	(57.3)	(45.9, 68.2)
Somnolence	55	(64.7)	(53.6, 74.8)	39	(47.6)	(36.4, 58.9)
Vomiting	3	(3.5)	(0.7, 10.0)	3	(3.7)	(0.8, 10.3)

[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.

Every participant is counted a single time for each applicable row and column.

Vomiting, drowsiness/somnolence, appetite lost/decreased appetite, and irritability were solicited from Day 1 through Day 5 following vaccination.

Relatedness to study vaccine was determined by the investigator.

MedDRA version 25.1 was used in the reporting of this study.

CI=confidence interval.

H=Hexyon™; V=Vaxelis™.

Group 1 (V,V,V)=Participants had previously received 2 doses of Vaxelis™ at approximately 2 and 4 months of age.

Group 2 (H,H,V)=Participants had previously received 2 doses of Hexyon™ at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adae]

Table 18. Summary of maximum temperature by Brighton collaboration cut points (all participants as treated population) (Table 12-6, Study report)

	Group 1 (V,V,V)			Group 2 (H,H,V)		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	85			82		
without temperature data (Day 1 through Day 5)[b]	0	(0.0)	(0.0, 4.2)	0	(0.0)	(0.0, 4.4)
with temperature data (Day 1 through Day 5)	85	(100.0)	(95.8, 100.0)	82	(100.0)	(95.6, 100.0)
Maximum Temperature (Rectal or Rectal Equivalent)						
< 100.4 °F (38.0 °C)	16	(18.8)	(11.2, 28.8)	24	(29.3)	(19.7, 40.4)
≥ 100.4 °F (38.0 °C) and < 101.3 °F (38.5 °C)	25	(29.4)	(20.0, 40.3)	22	(26.8)	(17.6, 37.8)
≥ 101.3 °F (38.5 °C) and < 102.2 °F (39.0 °C)	23	(27.1)	(18.0, 37.8)	17	(20.7)	(12.6, 31.1)
≥ 102.2 °F (39.0 °C) and < 103.1 °F (39.5 °C)	15	(17.6)	(10.2, 27.4)	9	(11.0)	(5.1, 19.8)
≥ 103.1 °F (39.5 °C) and < 104.0 °F (40.0 °C)	3	(3.5)	(0.7, 10.0)	6	(7.3)	(2.7, 15.2)
≥ 104.0 °F (40.0 °C) and < 104.9 °F (40.5 °C)	3	(3.5)	(0.7, 10.0)	2	(2.4)	(0.3, 8.5)
≥ 104.9 °F (40.5 °C) and < 105.8 °F (41.0 °C)	0	(0.0)	(0.0, 4.2)	2	(2.4)	(0.3, 8.5)
≥ 105.8 °F (41.0 °C)	0	(0.0)	(0.0, 4.2)	0	(0.0)	(0.0, 4.4)

[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson.
[b] Includes participants whose temperature methods were unreported or unable to be converted to Rectal equivalent for Day 1 through Day 5 following vaccination.
Percentages for the maximum temperature categories are calculated based on the number of participants with temperature data.
Multiple occurrences of maximum temperature are counted only once.
Non-Rectal temperatures have been converted to Rectal equivalent.
CI=confidence interval.
H=Hexyon™; V=Vaxelis™.
Group 1 (V,V,V)=Participants had previously received 2 doses of Vaxelis™ at approximately 2 and 4 months of age.
Group 2 (H,H,V)=Participants had previously received 2 doses of Hexyon™ at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; advstemp]

Assessor's comment

Most toddlers experienced one or more solicited AEs (96.5% in Group 1 and 86.6% in Group 2). Overall, a trend for higher proportions of toddlers experiencing one or more solicited injection site and solicited systemic AEs was observed in Group 1 when compared to Group 2. 95% CI were not overlapping for the solicited systemic AEs. These differences in percentages might be explained by the limited sample size but also by country-biased, differences in prior and concomitant medications or vaccinations.

Overall, the solicited AEs results stratified by country are consistent with those of whole PP population. Percentage of solicited injection site AEs observed in Group 1 tends to be higher in Spain (93.2%, 95% CI: 81.3-98.6) when compared to those of Germany (73.3%, 95% CI: 54.1-87.7) and Italy (72.7%, 95% CI: 39.0-94.0). For solicited systemics AEs, percentage observed in Group 1 in Italy (63.6%, 95% CI: 30.8-89.1) is lower than those of both other countries (Spain: 95.5%, 95% I: 84.5-99.4; Germany: 96.7%, 95% 82.8-99.9) but the number of participants in Italy is too limited to draw definitive conclusion (n=11).
A total of 55 participants used analgesic/antipyretic on the day of vaccination, n= 27/85 (32%) in Group 1 and n=28/82 (34%) in Group 2. No other analgesic/antipyretic, or immunosuppressant medication, than paracetamol or ibuprofen were reported on the day of vaccination.
Solicited systemic AEs were reported in all Group 1 participants and in 23/28 (82.1) of the Group 2 participants who used analgesic/antipyretic on the day of vaccination, which is higher than the

percentages observed in participants who did not (87.9% and 63.0 % in Group 1 and in Group 2, respectively). A trend for higher percentage of Group 2 participants experiencing solicited injection site AEs was also observed in participants who used analgesic/antipyretic on the day of vaccination (82.1%) versus those who did not (72.2%). In Group 1, the percentage of participants experiencing solicited injection site AEs was similar in participants who used analgesic/antipyretic on the day of vaccination (85.2%) versus those who did not (82.8%).
Because the limited sample size per group, interpretation should be cautious and no firm conclusion can be drawn.
The most frequently reported solicited injection-site AE was injection-site pain, with a trend for a higher proportion of participants with this AE in Group 1 (74.1%) vs Group 2 (56.1%). Irritability was the most frequently reported solicited systemic AEs (77.6% in Group 1 vs 58.5% in Group 2).

All solicited injection-site AEs were considered related to VAXELIS administration as per protocol. Most of the solicited systemic AEs were also considered vaccine-related by the investigator.

A total of 80 and 66 participants of Group 1 and Group 2 respectively had one or more solicited AEs graded by intensity (Table 12-4, Study report). Of those 40.0% and 39.0% were considered as mild, 47.1% (n=40/85) and 28.0% (n=23/82) as moderate and 7.1% (n=6/85) and 13.4% (n=11/82) as severe in Group 1 and Group 2 respectively.

Solicited injection-site erythema or swelling were also categorized by size (Table 12-5, Study report). Most of the injection-site erythema AEs were ≤1 inch (34/45 for Group 1 and 28/41 for Group 2). 4/45 and 9/41 were between 1 and ≤2, 7/45 and 3/41 between 2 and ≤3, and 0/45 and 1/41 between 3 and ≤4, for Group 1 and Group 2 respectively. The same trend was observed for the solicited injection-site swelling.

Fever was collected from Day 1 to Day 5 post-vaccination. Fever ≥38°C was observed in 81.2% and 71.6% of Group 1 and Group 2 subjects respectively. Fever ≥39°C was observed in 24.7% and 23.2% of Group 1 and Group 2 subjects respectively. Fever ≥40°C was measured in 3.5% and 4.8% of the subjects respectively included in Group 1 and Group 2.

7.2.4. Unsolicited adverse events

Table 19 summarizes the number of participants with unsolicited adverse events per group in total and per SOC.

Table 20 summarizes the number of participants with unsolicited adverse events related to study vaccine per group, in total and per event.

Table 7-3 in the *RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis* summarizes the number of participants with unsolicited adverse events by maximum intensity per group, in total and per SOC. Of the participants with unsolicited AEs graded by intensity, the majority had events with a maximum intensity of mild or moderate in both groups.

Table 19. Participants with unsolicited AEs (Incidence > 0% in the one or more vaccination groups) (all participants as treated population) (Table 7-1 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)

	Group 1 (VVV)			Group 2 (HHV)		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	85			82		
with one or more unsolicited adverse events	44	(51.8)		52	(63.4)	
with no unsolicited adverse events	41	(48.2)		30	(36.6)	
Congenital, familial and genetic disorders	**1**	**(1.2)**	**(0.0, 6.4)**	**0**	**(0.0)**	**(0.0, 4.4)**
Tooth hypoplasia	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Gastrointestinal disorders	**9**	**(10.6)**	**(5.0, 19.2)**	**10**	**(12.2)**	**(6.0, 21.3)**
Abdominal pain	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Diarrhoea	1	(1.2)	(0.0, 6.4)	6	(7.3)	(2.7, 15.2)
Enteritis	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Flatulence	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Nausea	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Teething	4	(4.7)	(1.3, 11.6)	1	(1.2)	(0.0, 6.6)
Tooth development disorder	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Vomiting[b]	2	(2.4)	(0.3, 8.2)	1	(1.2)	(0.0, 6.6)
General disorders and administration site conditions	**36**	**(42.4)**	**(31.7, 53.6)**	**44**	**(53.7)**	**(42.3, 64.7)**
Injection site bruising	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Injection site granuloma	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Injection site haematoma	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Injection site induration	0	(0.0)	(0.0, 4.2)	6	(7.3)	(2.7, 15.2)
Injection site pruritus	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Injection site warmth	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Malaise	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Pyrexia	34	(40.0)	(29.5, 51.2)	40	(48.8)	(37.6, 60.1)
Infections and infestations	**13**	**(15.3)**	**(8.4, 24.7)**	**12**	**(14.6)**	**(7.8, 24.2)**
Bronchiolitis	1	(1.2)	(0.0, 6.4)	1	(1.2)	(0.0, 6.6)
COVID-19	3	(3.5)	(0.7, 10.0)	3	(3.7)	(0.8, 10.3)
Conjunctivitis	1	(1.2)	(0.0, 6.4)	2	(2.4)	(0.3, 8.5)
Ear infection	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Gastroenteritis	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Gastroenteritis adenovirus	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)

	Group 1 (VVV)			Group 2 (HHV)		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Hand-foot-and-mouth disease	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Nasopharyngitis	3	(3.5)	(0.7, 10.0)	2	(2.4)	(0.3, 8.5)
Pharyngotonsillitis	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Rhinitis	2	(2.4)	(0.3, 8.2)	0	(0.0)	(0.0, 4.4)
Upper respiratory tract infection	1	(1.2)	(0.0, 6.4)	3	(3.7)	(0.8, 10.3)
Viral rash	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Injury, poisoning and procedural complications	**2**	**(2.4)**	**(0.3, 8.2)**	**0**	**(0.0)**	**(0.0, 4.4)**
Arthropod bite	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Head injury	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Investigations	**0**	**(0.0)**	**(0.0, 4.2)**	**2**	**(2.4)**	**(0.3, 8.5)**
Body temperature increased	0	(0.0)	(0.0, 4.2)	2	(2.4)	(0.3, 8.5)
Reproductive system and breast disorders	**0**	**(0.0)**	**(0.0, 4.2)**	**1**	**(1.2)**	**(0.0, 6.6)**
Balanoposthitis	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Respiratory, thoracic and mediastinal disorders	**3**	**(3.5)**	**(0.7, 10.0)**	**2**	**(2.4)**	**(0.3, 8.5)**
Cough	1	(1.2)	(0.0, 6.4)	1	(1.2)	(0.0, 6.6)
Rhinorrhoea	2	(2.4)	(0.3, 8.2)	2	(2.4)	(0.3, 8.5)
Sneezing	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Skin and subcutaneous tissue disorders	**4**	**(4.7)**	**(1.3, 11.6)**	**5**	**(6.1)**	**(2.0, 13.7)**
Dermatitis	1	(1.2)	(0.0, 6.4)	1	(1.2)	(0.0, 6.6)
Dermatitis diaper	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Digital pulpitis	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Macule	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Pruritus	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Rash	1	(1.2)	(0.0, 6.4)	1	(1.2)	(0.0, 6.6)
Urticaria	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)

[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.

Every participant is counted a single time for each applicable row and column.

Reported adverse events include nonserious adverse events that occurred from Day 1 through Day 15 postvaccination with Vaxelis, and serious adverse events that occurred throughout the duration of study.

MedDRA version 25.1 was used in the reporting of this study.

CI=confidence interval.

H=Hexyon; V=Vaxelis.

Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.

Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adae]

Table 20. Participants with unsolicited AEs related to study vaccine (Incidence > 0% in the one or more vaccination groups) (all participants as treated population) (Table 7-2 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)

	Group 1 (VVV)			Group 2 (HHV)		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	85			82		
with one or more unsolicited adverse events related to study vaccine	36	(42.4)		41	(50.0)	
with no unsolicited adverse events related to study vaccine	49	(57.6)		41	(50.0)	
Body temperature increased	0	(0.0)	(0.0, 4.2)	2	(2.4)	(0.3, 8.5)
Injection site bruising	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Injection site granuloma	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Injection site haematoma	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Injection site induration	0	(0.0)	(0.0, 4.2)	6	(7.3)	(2.7, 15.2)
Injection site pruritus	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Injection site warmth	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Pyrexia	34	(40.0)	(29.5, 51.2)	34	(41.5)	(30.7, 52.9)
Rash	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)

[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.
Every participant is counted a single time for each applicable row and column.
Reported adverse events include nonserious adverse events that occurred from Day 1 through Day 15 postvaccination with Vaxelis, and serious adverse events that occurred throughout the duration of study.
Relatedness to study vaccine was determined by the investigator.
MedDRA version 25.1 was used in the reporting of this study.
CI=confidence interval.
H=Hexyon; V=Vaxelis.
Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.
Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adae]

Assessor's comment

A total of 44/85 (51.8%) and 52/82 (63.4%) of the toddlers in Group 1 and Group 2 respectively experienced one or more unsolicited AEs. Percentages of unsolicited AEs per SOC were overall comparable except for the SOC *General disorder and administration site conditions* with a trend for higher percentages in Group 2 (53.7%) when compared to Group 1 (42.4%). There were 6/44 (7.3%) of the Group 2 participants who experienced induration at the site of injection versus 0 in Group 1. Although no difference of percentages between groups for the SOC *Gastrointestinal disorders* was observed, higher number of toddlers experienced diarrhoea in Group 2 (7.3%: 6/10) when compared to Group 1 (1.2%: 1/9).

A total of 36/85 (42.4%) and 41/82 (50.0%) of the toddlers in Group 1 and Group 2 respectively experienced one or more unsolicited AEs related to the study vaccine. The main difference was the 7.3% of the Group 2 participants who experienced induration at the site of injection versus 0 in Group 1.

Among the toddlers who experienced one or more unsolicited AEs, a higher percentage of toddlers in Group 2 versus Group 1 experienced severe AEs: 9.8% (8 severe AEs: 6 pyrexia, 1 nausea, 1 urticaria) vs 0%, respectively.

7.2.5. Serious adverse events and fatal serious adverse events

One SAE of adenovirus gastroenteritis was reported for 1 participant in Group 2 and was considered by the investigator to be not related to study intervention.

There were no deaths due to AEs reported in this study.

Assessor's comment

One SAE of adenovirus gastroenteritis was reported for 1 participant in Group 2.
On Day 8 the participant experienced weight loss, vomiting, and diarrhoea and was admitted to the hospital. The participant was diagnosed with adenovirus gastroenteritis (moderate, onset on Day 3) and treated with IV fluid supplements. On Day 15 adenovirus gastroenteritis was considered resolved.
The event was considered by the investigator to be not related to study intervention.
On Day 37, the last known date, the participant completed the study.

7.2.6. Post-marketing experience

VAXELIS was approved in the EU via Centralized Procedure on 15-FEB-2016 (including the UK), in the US on 21-DEC-2018, in Switzerland on 28-AUG-2019, and in Australia on 22-MAR-2022. A separate Great Britain registration was grandfathered in post-Brexit on 01-JAN-2021. VAXELIS is currently registered and approved in over 30 countries worldwide.

The estimated number of marketed VAXELIS doses distributed worldwide since market introduction (15-FEB-2016 to 28-FEB-2023) was approximately 14,306,679. Patient exposure estimates were calculated from the Company's internal distribution data from the Worldwide Financial Reporting System and the Financial Sharing Area database. Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide.

Cumulatively, approximately 3,576,669 to 14,306,679 individuals are estimated to have been exposed to the vaccine, based on the assumption that each individual received 1 to 4 doses depending on country-specific vaccination schedules (2 + 1 or 3 + 1 schedule) and that all the distributed doses were administered.

The EU Summary of Product Characteristics was updated in FEB-2020 to include "Hypotonic-hyporesponsive episode" to the list of post-marketing AEs, based on a cumulative assessment of post-marketing data from the Marketing Authorisation Holder global safety database.

In DEC-2021, the EU Summary of Product Characteristics was updated to include "convulsions with or without fever" to the list of Other Side Effects, and on 26-JAN-2023 to add "Hypersensitivity" including "Anaphylactic reactions" to the list of adverse drug reactions with a frequency of "Rare".

No important identified risks, important potential risks, or missing information were associated with VAXELIS as described in the current EU Risk Management Plan (Version 3.1, dated 25-FEB-2020). Based on a review of post-marketing data available as of 13-FEB-2023, no new safety issues were identified from this review. The Applicant will continue to monitor the safety of VAXELIS through routine pharmacovigilance.

7.3. Discussion

V419-016 is a Phase 4 study to evaluate the safety, tolerability, and immunogenicity of a booster dose of VAXELIS given to toddlers 11 to 13 months of age who previously received a 2-dose primary infant series of either VAXELIS (Group 1: V,V,V) or HEXYON (Group 2: H,H,V).

Reactogenicity and safety assessments included monitoring and recording of solicited and unsolicited AEs, and SAEs (including fatal SAEs). Body temperatures, concomitant medications, non-study vaccinations, use of any analgesic or antipyretic on the day of vaccination were also documented. There were no AEs of special interest in the study, nor laboratory evaluation.

Analyses were performed in the APaT population which consisted of all randomized participants who received study vaccination.

Safety methods and endpoints are overall endorsed.

Exposure

As of database lock, 168 participants were enrolled. A total of 85 and 82 toddlers were administered with VAXELIS (open-label) respectively in Group 1 (V, V, V) and Group 2 (H, H, V).

Main demographic and baseline characteristics were generally comparable between the 2 groups.

Prior and concomitant medications, treatment and vaccines were not balanced between groups, which is probably related to the local practices (country and region/site). Indeed, the study was conducted in 3 countries, 13 sites. Number of participants enrolled in each country and in each site were not balanced between both groups, which, together with the open-label design, add limitations to results interpretation (comparison between groups).

Solicited AEs

Solicited AEs were evaluated from Days 1 to 5 after study vaccination. Solicited local AEs included swelling, redness, and pain. Solicited systemic AEs included vomiting, drowsiness, appetite lost, and irritability. The number of solicited AEs to be monitor were limited. However, VAXELIS is widely used with a well-known reactogenicity/safety profile.

Most toddlers experienced one or more solicited AEs (96.5% in Group 1 and 86.6% in Group 2). Overall, a trend for higher proportions of toddlers experiencing one of more solicited injection site and solicited systemic AEs was observed in Group 1 when compared to Group 2. 95% CI were not overlapping for the solicited systemic AEs. These differences in percentages might be explained by the limited sample size but also by country-biased, differences in prior and concomitant medications or vaccinations.

The most frequently reported solicited injection-site AE was injection-site pain, with a trend for a higher proportion of participants with this AE in Group 1 (74.1%) vs Group 2 (56.1%). Irritability was the most frequently reported solicited systemic AEs (77.6% in Group 1 vs 58.5% in Group 2).

All solicited injection-site AEs were considered related to VAXELIS administration as per protocol. Most of the solicited systemic AEs were also considered vaccine-related by the investigator.

Most of the solicited AEs were of mild to moderate intensity (92.5% and 83.3% of the AEs graded by intensity in Group 1 and Group 2 respectively). Solicited injection-site erythema or swelling were also categorized by size, and most of them were ≤ 1 inch.

Fever was collected from Day 1 to Day 5 post-vaccination. Fever ≥38° C was observed in 81.2% and 71.6% of Group 1 and Group 2 subjects respectively. Fever ≥40° C was measured in 3.5% and 4.8% of the subjects respectively included in Group 1 and Group 2.

Unsolicited AEs

Unsolicited AEs were evaluated from Days 1 to 15 after study vaccination. Those are AEs defined as a solicited AE but with an onset of more than 5 days following vaccination or are AEs with an onset within 15 days following vaccination that are not defined as a solicited AE.

A total of 44/85 (51.8%) and 52/82 (63.4%) of the toddlers in Group 1 and Group 2 respectively experienced one or more unsolicited AEs. A total of 36/85 (42.4%) and 41/82 (50.0%) of the toddlers in Group 1 and Group 2 respectively experienced one or more unsolicited AEs related to the study vaccine. The main difference was the 7.3% of the Group 2 participants who experienced induration at the site of injection versus 0 in Group 1.

Among the toddlers who experienced one or more unsolicited AEs, a higher percentage of toddlers in Group 2 versus Group 1 experienced severe AEs: 9.8% (8 severe AEs: 6 pyrexia, 1 nausea, 1 urticaria) vs 0%, respectively. .

SAEs and fatal SAEs, AEs leading to withdrawal from the study

Occurrence of SAEs, discontinuation due to an AE and death were reported from Day 1 through completion of study participation (i.e. 30 days post-vaccination).

One SAE of adenovirus gastroenteritis was reported for 1 participant in Group 2. The event was considered by the investigator to be not related to study intervention.

There were no deaths due to AEs reported in this study. There were no discontinuations due to an AE reported in this study.

Conclusion

The reactogenicity and safety profile of VAXELIS is well-known as it has been widely used since 2016.

In study V419-016, most of the 167 toddlers who were administered with VAXELIS as a booster at the age of 11 to 13 months, i.e. at least 6 months post-primary vaccination either with VAXELIS or HEXYON, experienced one or more solicited AEs (within 5 days post-vaccination). AEs were generally mild to moderate intensity. Fever was observed in most of the children and was < 40°C for most of them. Unsolicited AEs were recorded up to 15 days post-vaccination and a total of 36/85 (42.4%) and 41/82 (50.0%) of the toddlers in Group 1 and Group 2 respectively experienced one or more unsolicited AEs related to the study vaccine. A total of 8 toddlers (9.8%) in Group 2 experienced severe AEs. No severe AEs was recorded in Group 1. No SAE was deemed related to the vaccine.

Because of the design and settings of the study, no strict comparison between groups can be done.

8. Changes to the Product Information

As a result of this variation, sections 4.2 and 5.1 of the SmPC are being updated in order to add information on interchangeable use of Vaxelis with other hexavalent vaccines based on final results from Study V419-016 (no update of the Package Leaflet (PL) needed).

The SmPC changes to sections 4.2 and 5.1 initially proposed by the MAH were the following:

4.2 Posology and method of administration

Posology

Primary vaccination:

The primary vaccination schedule consists of two or three doses, with an interval of at least 1 month between doses, and may be given from 6 weeks of age, in accordance with the official recommendations.

Where a dose of hepatitis B vaccine is given at birth, Vaxelis can be used for supplementary doses of hepatitis B vaccine from the age of 6 weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used. Vaxelis can be used for a mixed hexavalent/pentavalent/hexavalent combined vaccine immunisation schedule.

Booster vaccination:

~~After a 2-dose or a 3-dose primary series vaccination with Vaxelis, a~~ A booster dose should be ~~given~~ administered at least 6 months after the last priming dose and can be given to children who have previously been vaccinated with Vaxelis or any other hexavalent vaccine~~. Booster dose should be given~~, in accordance with the official recommendations. When a booster dose with a hexavalent DTaP (diphtheria, tetanus, and acellular pertussis) containing vaccine is not available~~As a minimum~~, a dose of Hib vaccine must be administered, as a minimum.

Section 5.1

Interchangeability Study
In an open-label study, Vaxelis was given as a booster dose to 167 healthy children approximately 11-13 months of age who previously received a 2-dose primary series of either Vaxelis (N=85) or another

hexavalent vaccine with 2 pertussis components (DTaP2-IPV-HepB-Hib; N=82) as part of routine vaccination. A booster dose of Vaxelis was well tolerated and induced comparable immune responses in both groups to all antigens contained in both Vaxelis and DTaP2-IPV-HepB-Hib. In children primed with Vaxelis, higher responses to antigens contained only in Vaxelis (pertussis PRN and FIM 2, 3) were observed.

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed.

The below amendments to the MAH initial proposals for sections 4.2 and 5.1 were recommended as part of the assessment.

Section 4.2

Booster vaccination:

After a 2-dose or a 3-dose primary series vaccination with Vaxelis, a booster dose should be given at least 6 months after the last priming dose. Vaxelis may be used as a booster dose in children who received another hexavalent vaccine for their primary series. ~~Booster dose should be given in accordance with the official recommendations.~~When a booster dose with a hexavalent DTaP (diphtheria, tetanus, and acellular pertussis) containing vaccine is not available~~As a minimum~~, a dose of Hib vaccine must be administered, as a minimum.

Section 5.1

Regarding PT and FIM, similar response rates and higher GMCs were observed both post-primary and post-booster in comparison to control vaccine. Lower FHA, PRN, IPV1 (Inactivated poliovirus vaccine) and IPV3 immune responses were observed after a 2-dose primary schedule (2, 4 months), although the clinical relevance of these data remains uncertain. Pertussis response rates were similar to the control vaccine for all pertussis antigens after the booster dose.

The immunogenicity of Vaxelis administered to children over 15 months of age has not been studied in clinical trials.

In an open-label study, Vaxelis was given as a booster dose to 167 healthy children approximately 11-13 months of age who previously received a 2-dose primary series of either Vaxelis (N=85) or another hexavalent vaccine with 2 pertussis components (DTaP-HB-IPV-Hib; N=82) as part of routine vaccination. A booster dose of Vaxelis was well tolerated and induced an increase of the humoral immune responses to all antigens. At 30 days post-boost, at least 89% of the children had a seroresponse defined as protective against diphtheria, tetanus, hepatitis B, poliomyelitis, and invasive *Haemophilus influenzae* type b disease.

The MAH submitted an amended SmPC, according to the recommendations above.

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

9. Request for supplementary information

9.1. Major objections

None

9.2. Other concerns

Clinical aspects

Q1 The study was conducted in Germany, Spain and Italy. The 2-dose primary vaccination is recommended in those countries, but based on information currently available at ECDC, it appears that the age for vaccination varies between these countries (2 and 4 months of age in Germany and Spain, 3 and 5 months of age in Italy). In all 3 countries the boost is recommended at 11 months. The MAH is invited to provide the age of the participants at the time of primary vaccination.

Q2 The MAH is requested to provide the status of the serological assays, as well as main characteristics. The MAH should clarify if these assays were previously used in the CDP of VAXELIS. If the assays used are not those previously used and/or not validated, the MAH is invited to specify and justify reason(s) for not using qualified/validated tests (or at least IVD tests if applicable).

Q3 The study was conducted in different countries which might have an impact on the results. The MAH is invited to present the results (for the safety and immunogenicity) by country.

Q4 Specific Ab to each antigen contained in both VAXELIS and HEXYON were observed at 30 days post-boost. Ab GMCs but not seroprotection/seroresponse rates were presented at Day 1. Data should be presented.

Q5 The MAH is required to submit stratified descriptive immunogenicity data for participants with/without use of analgesic/antipyretic on the day of vaccination, both in terms of seroprotection/seroresponse rates and in terms of GMCs, for the 2 groups and to discuss differences observed in each group and between groups.

Q6 The MAH is required to submit stratified descriptive data for participants with/without use of analgesic/antipyretic on the day of vaccination, both for solicited local and for systemic adverse events, for the 2 groups, and to discuss differences observed in each group and between groups.

Q7 For transparency and clarity in the EPAR (and even if it concerns only a limited number of AEs), it is requested to the MAH to clarify for each group: the percentage of unsolicited AEs in total and per SOC, of related unsolicited AEs in total and per SOC, and of unsolicited AEs by maximum intensity in total and per SOC. Any differences observed between the 2 groups should be discussed.

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

10.1. Other concerns

Clinical aspects

Question 1

The study was conducted in Germany, Spain and Italy. The 2-dose primary vaccination is recommended in those countries, but based on information currently available at ECDC, it appears that the age for vaccination varies between these countries (2 and 4 months of age in Germany and Spain, 3 and 5 months of age in Italy). In all 3 countries the boost is recommended at 11 months. The MAH is invited to provide the age of the participants at the time of primary vaccination.

Summary of the MAH's response

The primary series vaccination was performed at around 2 and 4 months as recommended per local standard of care in all countries participating in the trial. Of note, recommendations in Italy from the Ministero della Salute specify that the hexavalent vaccine primary series should be administered as soon as possible from the 61st day of life, that is two months of age, in line with what is prescribed in the other countries participating in the study.

A summary of the age of the participants at the time of primary vaccination performed as part of the standard of care before entering the study is provided in Table 21.

The language of the study protocol allowed some flexibility in the timing of the primary series and did not mandate a specific interval around the primary series vaccination dates, to account for the disruption caused by SARS-CoV-2 pandemic in the vaccination program with significant backlogs in the vaccination campaigns reported in all participating countries. Despite this allowed flexibility Table 1-1 illustrates that the mean age of first vaccination was similar between groups and countries. While there was somewhat more variation for the second vaccination, this variation is most conspicuous within the VVV group (particularly between Germany and Spain), but not between groups. When taken as a whole, as intended in the study, the mean age of vaccination for the first and second doses are similar between the VVV and HHV groups (Table 21).

Table 21. Age at vaccination (Table 1-1 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)

	Germany		Italy		Spain		Total	
	Group 1 (VVV) (N=30)	Group 2 (HHV) (N=22)	Group 1 (VVV) (N=11)	Group 2 (HHV) (N=0)	Group 1 (VVV) (N=44)	Group 2 (HHV) (N=60)	Group 1 (VVV) (N=85)	Group 2 (HHV) (N=82)
Age at 1st vaccination (Days)								
Mean (SD)	74.6 (15.7)	71.4 (12.6)	67.4 (8.32)	NA	65.5 (6.26)	66.7 (7.81)	69.0 (11.5)	68.0 (9.49)
Median [Min, Max]	70.0 [62.0, 140]	67.5 [56.0, 109]	63.0 [62.0, 85.0]	NA	63.5 [57.0, 93.0]	64.0 [61.0, 105]	65.0 [57.0, 140]	65.0 [56.0, 109]
Age at 2nd vaccination (Days)								
Mean (SD)	150 (19.2)	136 (17.9)	144 (19.1)	NA	128 (5.07)	136 (13.7)	138 (17.3)	136 (14.8)
Median [Min, Max]	150 [121, 217]	131 [118, 185]	145 [124, 190]	NA	126 [122, 145]	132 [122, 198]	132 [121, 217]	131 [118, 198]

Assessment of the MAH's response

The MAH clarified that the primary vaccination in Italy is also recommended from 2 months of age as per the recommendations from the Ministero della Salute. This is thus in line with the recommendations of both other countries.

The MAH provided a Table presenting the age at vaccination per country and per group (overall and within in each country). Mean (SD) and Median (Min, Max) were included in the Table.

Median age at first vaccination was overall comparable between countries and groups.
Medians age range from 63.0 days (Italy, Group 1) to 74.6 days (Germany, Group 1). There were some flexibility for age at administration, most probably mimicking the real life. Minimum and maximum ages at first dose were 56.0 days (Germany, Group 2) and 140 days (Germany, Group 1).
Medians age at second vaccination were more variable, ranging from 126 days (Spain, Group1) to 150 days (Germany, Group 1). Minimum and maximum ages at first dose were 118 days (Germany, Group 2) and 217 days (Germany, Group 1).

Issue resolved.

Question 2

The MAH is requested to provide the status of the serological assays, as well as main characteristics. The MAH should clarify if these assays were previously used in the CDP of VAXELIS. If the assays used are not those previously used and/or not validated, the MAH is invited to specify and justify reason(s) for not using qualified/validated tests (or at least IVD tests if applicable).

Summary of the MAH's response

The MAH specified that all serological assays used in V419-016 were validated.

The MAH specified that since late stage Vaxelis Clinical Development Program (CDP) - primary conducted during the years 2011-2014 - adjustments and improvements have been made to certain assays and all assays have been validated.

More specifically:

Concerning the Hepatitis B Surface Antibody Enhanced Chemiluminescence (HBV ECiQ) Quantitative Test, used to quantitatively detect total antibodies to hepatitis B virus (HBV) surface antigen (anti-HBs) in human serum : same assay was used as the one of Vaxelis's CDP, transferred and revalidated at Q2 solutions in 2022. Results of revalidation were submitted Table 22 and indicate that transferring this assay to a different laboratory did not affect its main characteristics in terms of limits of quantitation, precision, ruggedness, selectivity/recovery and dilutional linearity.

Table 22: HBV ECiQ validation parameter summary (source Table 2-1 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)

Assay Characteristic	Result	Expectation
Limits of Quantitation (mIU/mL, undilute)	[5, 1000]	[5, 1000]
Total Precision (Antibody Concentration %RSD)	6.8%	≤25%
Assay Ruggedness (Maximum % difference in antibody concentration between factor levels)	<2%	<30%
Selectivity (% Recovery) (at 5 mIU/mL)	107.7%	50% - 200%
Selectivity (% Recovery) (at 10 mIU/mL)	100.7%	67% - 150%
Selectivity (% Recovery) (at ≥20 mIU/mL)	83.6% - 94.8%	75% - 130%
Dilutional Linearity (% Bias per 10-fold dilution)	-12.6%	≤2.0-fold per 10-fold dilution

Concerning the *Haemophilus influenzae* type b (Hib) Enzyme Immunoassay (EIA) ELISA, for the measurement of specific IgG antibodies against the Hib capsular polysaccharide, polyribosylribitol-phosphate (PRP): the assay is different from the one that was used in the CDP of Vaxelis, which was the Hib total antibody radioimmunoassay (RIA) retired in 2016. The novel assay to quantify anti-PRP specific

IgG (Hib EIA) is performed using the Binding Site Human Anti-Haemophilus influenzae type b Enzyme Immunoassay Kit. Diluted serum is added to microtiter wells coated with Hib polysaccharide antigen conjugated to human serum albumin. Anti-Hib IgG antibodies in the sample bind to the Hib polysaccharide antigen. After incubation and washing to remove unbound serum proteins, horseradish peroxidase (HRP)-conjugated rabbit anti-human IgG is added and binds to any captured Hib-specific IgG molecules. After another wash step, tetramethylbenzidine (TMB) substrate is added; the ensuing color development reaction is then stopped by the addition of a dilute phosphoric acid solution. The optical density (OD) is measured and is directly proportional to the amount of Hib IgG present in the serum specimen. Levels of Hib IgG are quantified by interpolation from a standard curve that is calibrated to the FDA Lot 1983 reference standard and are reported as µg/mL. This Hib-EIA assay used for V419-016 clinical testing was validated at Q2 Solutions. Parameters assessed for validation were limits of quantitation, repeatability, intermediate precision, linearity and recovery and a summary of the validation parameter was presented in Table 23.

Table 23: Hib EIA validation parameter summary (source Table 2-2 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)

Assay Characteristic	Result	Expectation
Limits of Quantitation (µg/mL)	[0.15, 5.29]	[0.15, max sample available not to exceed 9.0]
Repeatability	4 – 20.74%	≤20%
Intermediate Precision	15 – 23%	≤25%
Linearity	Slope: 0.99 – 1.10 R^2: >0.99	Slope: 0.8-1.25 R^2: ≥0.95
Recovery	85 – 113%	75 – 125%

Concerning the multiplexed serological assay used to measure IgG antibodies to Diphtheria Toxoid (DT), Tetanus Toxoid (TT), Pertussis Toxin (PT), Filamentous Haemagglutinin (FHA), Pertactin (PRN), and Fimbrial Agglutinogens (FIM 2/3): this assay is different from the 6 different assays used in the CDP of Vaxelis. For V419-016 clinical testing, IgG specific to these different antigens were measured using a validated multiplexed electrochemiluminescence (ECL) assay format at Sanofi's Global Clinical Immunology (GCI) lab (Swiftwater, PA). The aim was to improve efficiency and throughput compared to the previously utilized ELISA format for the CDP of Vaxelis.

Concerning the Micro Metabolic Inhibition Tests (MIT) performed to measure functional anti-poliovirus types 1, 2, and 3 neutralizing antibodies: these assays are similar to the of the CDP of Vaxelis of Focus Diagnostics, Inc.. The novel MIT assays used for V419-016 clinical testing were validated at Sanofi's Global Clinical Immunology (GCI) lab (Swiftwater, PA).

Assessment of the MAH's response

The MAH specified in their answer that all serological assays used for V419-016 clinical testing were validated.

The only assay that was equal to the one used in the CDP of VAXELIS, is the one to quantify total antibodies to hepatitis B virus (HBV) surface antigen (anti-HBs) in human serum (HBV ECiQ). This assay was transferred and revalidated at Q2 Solutions in 2022. The MAH provided a summary of the validation parameters of HBV ECiQ, which included the results of this revalidation of the assay. In terms of limits of quantitation, precision, ruggedness, selectivity/recovery and dilutional linearity results indicate that

transferring this assay to a different laboratory did not affect its main analytical characteristics.

The serological assay to quantify specific IgG antibodies against the Hib capsular polysaccharide, polyribosylribitol- phosphate (PRP) that was used for the CDP of VAXELIS was no longer available and was replaced by the Hib-EIA assay. This assay is considered adequate for the purposes of V419-016 clinical testing, in terms of the estimated ranges of the limits of quantitation, repeatability, intermediate precision, linearity and recovery (Table 23).

The MAH did not submit the validation report of the multiplexed serological assay applied for the simultaneous quantification of human antibodies to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN, and FIM). This assay is different from the 6 separate assays that were used for the CDP of VAXELIS.

The MAH did not submit the validation reports of the Micro Metabolic Inhibition Tests (MIT) performed to measure functional anti-poliovirus types 1, 2, and 3 neutralizing antibodies.

Issue not pursued.

Question 3

The study was conducted in different countries which might have an impact on the results. The MAH is invited to present the results (for the safety and immunogenicity) by country.

Summary of the MAH's response

As a non-randomized, open-label, multicenter, descriptive study in 3 countries (Spain, Germany, Italy), V419-016 was not designed to assess differences in safety and immunogenicity by country. Participants received their primary series of either Vaxelis or Hexyon prior to study participation. Of note, participants enrolled in Italy all received a Vaxelis primary series, as this was the vaccine offered at participating sites. Despite these caveats, the seroresponses and solicited adverse events results stratified by country show that the safety and immunogenicity of the Vaxelis booster dose does not meaningfully differ between countries, and the country specific immunogenicity and safety are consistent with the population as a whole, as shown in data below.

<u>Immunogenicity</u>

Vaxelis elicited antibody-specific responses to each antigen contained in both Vaxelis and Hexyon in each of the participating countries as assessed by the proportions of participants with antibody-specific responses at 30 days following a booster dose of Vaxelis. The proportions of participants with antibody-specific responses to each antigen contained in both Vaxelis and Hexyon were generally comparable between the 2 groups at 30 days following a booster dose of Vaxelis, irrespective of the country considered. The proportions of participants with antibody-specific responses to pertussis FIM 2/3 and pertussis PRN (antigens contained only in Vaxelis) were higher in Group 1 (VVV) compared with Group 2 (HHV) at 30 days following a booster dose of Vaxelis, irrespective of the country considered (Tables 3-1 to 3-3).

Overall, the immunogenicity results stratified by country are consistent with what is seen in the whole study population, with comparable immunogenicity observed between groups irrespective of the country considered. When considering the two groups separately among the countries that contributed with participants in the group, immunogenicity results were generally comparable for Group 1 (VVV) (Spain, Germany, Italy), as well as for Group 2 (HHV) (Spain, Germany).

<u>Safety</u>

Overall, the solicited adverse events results stratified by country are consistent with what is seen in the whole study population. The proportions of participants with solicited AEs were generally comparable between the 2 groups following a booster dose of Vaxelis, irrespective of the country considered. When considering the two groups separately among the countries that contributed participants in that group, solicited adverse events where comparable for Group 1 (VVV) (Spain, Germany, Italy), as well as for Group 2 (HHV) (Spain, Germany) (Tables 3-4 to 3-6).

Assessment of the MAH's response

As requested, the MAH provided immunogenicity and safety results by country. It is acknowledge that the study was not designed for such comparison, results are nevertheless considered relevant/of interest for completeness in the reporting of V419-016 study results.

All participants included in Italy received a VAXELIS primary series (Group 1). Number of participants in this country is limited (n=11). Overall, number of toddlers by group in each country is limited.

The MAH provided summaries of the proportions of participants meeting specified VAXELIS antigen responses at 30 days post-vaccination per country. GMTs were not provided. Overall, the immunogenicity results stratified by country are consistent with those of whole PP population. Seroresponder rates are comparable for Group 1 (Germany, Italy, Spain) and for Group 2 (Germany, Spain) across countries.

The MAH provided summaries of the proportions of participants with solicited AEs per country. Overall, the solicited AEs results stratified by country are consistent with those of whole PP population. Percentage of solicited injection site AEs observed in Group 1 tends to be higher in Spain (93.2%, 95% CI: 81.3-98.6) when compared to those of Germany (73.3%, 95% CI: 54.1-87.7) and Italy (72.7%, 95% CI: 39.0-94.0). For solicited systemics AEs, percentage observed in Group 1 in Italy (63.6%, 95% CI: 30.8-89.1) is lower than those of both other countries (Spain: 95.5%, 95% I: 84.5-99.4; Germany: 96.7%, 95% 82.8-99.9) but the number of participants in Italy is too limited to draw definitive conclusion (n=11).

Issue resolved.

Question 4

Specific Ab to each antigen contained in both VAXELIS and HEXYON were observed at 30 days post-boost. Ab GMCs but not seroprotection/seroresponse rates were presented at Day 1. Data should be presented.

Summary of the MAH's response

The proportion of responders at Day 1 is presented for all antigens shared by Vaxelis and Hexyon in Table 24. The endpoints used to evaluate the immune responses at Day 1 are the same used to evaluate the responses at Day 30 as per primary endpoint of the study with the addition of the short-term correlate of protection for Hib. Pertussis antigens are not presented in the table since there are currently no established immunological correlates of protection and the seroresponse rates calculated at Day 30 were dependent on the fold increase over Day 1 concentrations.

Of note: Day 1 data reflect the 2 dose primary series given prior to study entry. Overall, the proportion of responders at Day 1 is comparable for all antigens between the groups, with the exception of Hib. At Day 1 prior to the booster dose, the proportion of participants who achieved the long-term protective concentration of anti-Hib-PRP IgG ≥1.0 µg/mL was higher in the VVV group 51/79 (64.6%), compared to the HHV group 1/81 (1.2%). Additional post hoc analysis (Table 25) showed that the proportion of participants who achieved short term protective concentration of anti Hib-PRP ≥0.15 µg/mL was also higher in the VVV group (69/79, 87.3%) compared to the HHV group (22/81, 27.2%). These data further

support the evidence that the PRP-OMPC conjugation used in Vaxelis, result in a more robust immune response following even a 2-dose primary series as compared to the PRP-T conjugation used in Hexyon and Infanrix hexa , as already observed in previously published studies [2 – 4].

Table 24. Summary of the proportions of participants meeting specified Vaxelis antigen responses at Day 1 pre-vaccination (PP population) (Table 4-1 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)

Antigen	Endpoint	Group 1 (VVV) (N = 85)		Group 2 (HHV) (N = 82)	
		Observed Response Percentage (m/n)	95% CI[a]	Observed Response Percentage (m/n)	95% CI[a]
Diphtheria toxoid	% ≥0.1 IU/mL	38.4 (28/73)	(27.2, 50.5)	41.8 (33/79)	(30.8, 53.4)
Tetanus toxoid	% ≥0.1 IU/mL	78.1 (57/73)	(66.9, 86.9)	69.6 (55/79)	(58.2, 79.5)
Hib-PRP	% ≥1.0 µg/mL	64.6 (51/79)	(53.0, 75.0)	1.2 (1/81)	(0.0, 6.7)
HBsAg	% ≥10 mIU/mL	76.8 (53/69)	(65.1, 86.1)	72.6 (53/73)	(60.9, 82.4)
Poliovirus 1	% Nab ≥1:8 dilution	77.4 (48/62)	(65.0, 87.1)	78.2 (61/78)	(67.4, 86.8)
Poliovirus 2	% Nab ≥1:8 dilution	85.5 (53/62)	(74.2, 93.1)	80.8 (63/78)	(70.3, 88.8)
Poliovirus 3	% Nab ≥1:8 dilution	72.6 (45/62)	(59.8, 83.1)	76.9 (60/78)	(66.0, 85.7)

[a] The within-group CIs are based on the exact binomial method proposed by Clopper and Pearson.
N=Number of participants allocated and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.
CI=confidence interval; HBsAg=hepatitis B surface antigen; Hib=haemophilus influenzae type b; IU=international unit; Nab=neutralizing antibodies; PRP=polyribosylribitol phosphate.
H=Hexyon; V=Vaxelis.
Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.
Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adimm]

Table 25. Summary of the proportions of participants meeting specified Vaxelis antigen responses at Day 1 pre-vaccination (Hib-PRP ≥0.15 µg/mL) (PP population) (Table 4-2 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)

Antigen	Endpoint	Group 1 (VVV) (N = 85)		Group 2 (HHV) (N = 82)	
		Observed Response Percentage (m/n)	95% CI[a]	Observed Response Percentage (m/n)	95% CI[a]
Hib-PRP	% ≥0.15 µg/mL	87.3 (69/79)	(78.0, 93.8)	27.2 (22/81)	(17.9, 38.2)

[a] The within-group CIs are based on the exact binomial method proposed by Clopper and Pearson.
N=Number of participants allocated and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.
CI=confidence interval; Hib=haemophilus influenzae type b; PRP=polyribosylribitol phosphate.
H=Hexyon; V=Vaxelis.
Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.
Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adimm]

Assessment of the MAH's response

The MAH provided a Table including the proportion of responders at Day 1 (pre-vaccination) for all antigens shared by VAXELIS and HEXYON, except for the pertussis antigens PT and FHA because of no Ab threshold associated with protection. GMTs specific for PT and FHA at Day 1 were presented at initial submission, which is deemed sufficient.

Proportion of participants showing Ab titers equal or above the Ab thresholds associated with protection against diphtheria, tetanus, clinical paralysis due to polioviruses and hepatitis B were overall comparable between groups (95% CI overlapping). In contrast, anti-PRP Ab levels were not comparable between groups. Only 1 out of 81 participant of Group 2 (H,H,V) had anti-PRP Ab levels equal or above the threshold associated with long-term protection, versus 51/79 (64.6%) of Group 1. Proportion of participants who achieved short term protective concentration of anti Hib-PRP ≥0.15 µg/mL was calculated. Although the percentages of participants with Ab levels ≥0.15 µg/mL was higher than those with Ab levels ≥1.0 µg/mL, the percentage observed in Group 2 was still lower than the percentage observed in Group 1 (27.2% [22/81] versus 87.3% [69/79]), indicating the importance of the booster dose.

Issue resolved.

Question 5

The MAH is required to submit stratified descriptive immunogenicity data for participants with/without use of analgesic/antipyretic on the day of vaccination, both in terms of seroprotection/seroresponse rates and in terms of GMCs, for the 2 groups and to discuss differences observed in each group and between groups.

Summary of the MAH's response
As requested, the MAH analyzed the use of analgesic and anti-inflammatory medications on the immunogenicity of Vaxelis. A total of 55 participants who used analgesic/antipyretic on the day of vaccination were identified (Group 1 VVV n=27; Group 2 HHV n=28). Analgesic/antipyretic reported as concomitant medications on the day of vaccination included paracetamol or ibuprofen. One participant reported the use of both paracetamol and ibuprofen. No other analgesic/antipyretic, or immunosuppressant medication, were reported on the day of vaccination. V419-016 was not designed to assess the effects of antipyretic/analgesic use on vaccination and only 33% of participants received these medications. Caution should be used when interpreting any differences in responses with these small numbers.

Seroprotection/seroresponse rates stratified by use of analgesic/antipyretic are shown in Table 26 and Table 27 and are consistent with the population as a whole.

The proportions of participants with antibody-specific responses to each antigen contained in both Vaxelis and Hexyon were generally comparable between the 2 groups at 30 days following a booster dose of Vaxelis, regardless of the use of analgesic/antipyretic on the day of vaccination. The proportions of participants with antibody-specific responses to pertussis PRN and FIM2/3 were higher in Group 1 (VVV) compared with Group 2 (HHV) regardless of the use of analgesic/antipyretic on the day of vaccination.

Similarly, Day 30 postvaccination antibody GMCs for participants without and with analgesic/antipyretic use are shown in Table 28 and Table 29 and are consistent with the population as a whole.

Analgesic/antipyretic use on the day of vaccination did not affect between-group comparisons for example: Antibody-specific GMCs for diphtheria toxoid, tetanus toxoid, pertussis PT, pertussis FIM 2/3, pertussis PRN, and HBsAg were numerically higher in Group 1 (VVV) compared with Group 2 (HHV), regardless of the use of analgesic/antipyretic on the day of vaccination. Antibody specific GMC's for poliovirus 1-3 were numerically lower in the HHV group participants and the antibody-specific GMCs for HBsAg in the VVV group participants who used analgesic/antipyretic. However the seroresponse rates remains generally comparable within the groups regardless of analgesic/antipyretics use and these differences are not considered clinically meaningful.

Overall, the use of analgesic/antipyretic resulted in minimal, if any, differences in the immunogenicity profile between the two arms or within each arm of the study.

*Table 26. Summary of the proportions of participants meeting specified Vaxelis antigen responses at 30 days post-vaccination (PP population) (participants **without** analgesic or antipyretic administered on the day of vaccination) (Table 5-1 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)*

Antigen	Endpoint	Group 1 (VVV) (N = 58)		Group 2 (HHV) (N = 54)	
		Observed Response Percentage (m/n)	95% CI[a]	Observed Response Percentage (m/n)	95% CI[a]
Primary Endpoints					
Diphtheria toxoid	% ≥0.1 IU/mL	100.0 (49/49)	(92.7, 100.0)	97.9 (47/48)	(88.9, 99.9)
Tetanus toxoid	% ≥0.1 IU/mL	98.0 (48/49)	(89.1, 99.9)	97.9 (47/48)	(88.9, 99.9)
Pertussis - PT	% vaccine response[b]	97.8 (44/45)	(88.2, 99.9)	93.5 (43/46)	(82.1, 98.6)
Pertussis - FHA	% vaccine response[b]	97.8 (44/45)	(88.2, 99.9)	89.1 (41/46)	(76.4, 96.4)
Hib-PRP	% ≥1.0 µg/mL	90.2 (46/51)	(78.6, 96.7)	95.9 (47/49)	(86.0, 99.5)
HBsAg	% ≥10 mIU/mL	100.0 (37/37)	(90.5, 100.0)	92.9 (39/42)	(80.5, 98.5)
Poliovirus 1	% Nab ≥1:8 dilution	100.0 (46/46)	(92.3, 100.0)	97.7 (43/44)	(88.0, 99.9)
Poliovirus 2	% Nab ≥1:8 dilution	100.0 (46/46)	(92.3, 100.0)	100.0 (44/44)	(92.0, 100.0)
Poliovirus 3	% Nab ≥1:8 dilution	97.8 (45/46)	(88.5, 99.9)	100.0 (44/44)	(92.0, 100.0)
Secondary Endpoints					
Pertussis - FIM 2/3[c]	% vaccine response[b]	93.3 (42/45)	(81.7, 98.6)	71.7 (33/46)	(56.5, 84.0)
Pertussis - PRN[c]	% vaccine response[b]	93.3 (42/45)	(81.7, 98.6)	26.1 (12/46)	(14.3, 41.1)

[a] The within-group CIs are based on the exact binomial method proposed by Clopper and Pearson.
N=Number of participants allocated and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.
CI=confidence interval; FHA=filamentous hemagglutinin; FIM 2/3=fimbriae types 2 and 3; PRN=pertactin; PT=pertussis toxin.
[b] The pertussis vaccine response is defined as follows:
1) If prevaccination <LLOQ, then postvaccination should be ≥4 × the LLOQ.
2) If prevaccination ≥LLOQ but <2 × the LLOQ, then postvaccination should achieve a 4-fold rise (postvaccination/prevaccination ≥4).
3) If prevaccination ≥2 × the LLOQ, then postvaccination should achieve a 2-fold response (postvaccination/prevaccination ≥2).
[c] Antigen contained only in Vaxelis.
H=Hexyon; V=Vaxelis.
Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.
Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adimm]

*Table 27. Summary of the proportions of participants meeting specified Vaxelis antigen responses at 30 days post-vaccination (PP population) (participants **with** analgesic or antipyretic administered on the day*

of vaccination) (Table 5-2 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)

Antigen	Endpoint	Group 1 (VVV) (N = 27)		Group 2 (HHV) (N = 28)	
		Observed Response Percentage (m/n)	95% CI[a]	Observed Response Percentage (m/n)	95% CI[a]
Primary Endpoints					
Diphtheria toxoid	% ≥0.1 IU/mL	100.0 (20/20)	(83.2, 100.0)	100.0 (26/26)	(86.8, 100.0)
Tetanus toxoid	% ≥0.1 IU/mL	100.0 (20/20)	(83.2, 100.0)	100.0 (26/26)	(86.8, 100.0)
Pertussis - PT	% vaccine response[b]	100.0 (19/19)	(82.4, 100.0)	96.0 (24/25)	(79.6, 99.9)
Pertussis - FHA	% vaccine response[b]	100.0 (19/19)	(82.4, 100.0)	92.0 (23/25)	(74.0, 99.0)
Hib-PRP	% ≥1.0 µg/mL	86.4 (19/22)	(65.1, 97.1)	81.5 (22/27)	(61.9, 93.7)
HBsAg	% ≥10 mIU/mL	100.0 (19/19)	(82.4, 100.0)	96.3 (26/27)	(81.0, 99.9)
Poliovirus 1	% Nab ≥1:8 dilution	100.0 (20/20)	(83.2, 100.0)	92.0 (23/25)	(74.0, 99.0)
Poliovirus 2	% Nab ≥1:8 dilution	100.0 (20/20)	(83.2, 100.0)	100.0 (25/25)	(86.3, 100.0)
Poliovirus 3	% Nab ≥1:8 dilution	95.0 (19/20)	(75.1, 99.9)	100.0 (25/25)	(86.3, 100.0)
Secondary Endpoints					
Pertussis - FIM 2/3[c]	% vaccine response[b]	100.0 (19/19)	(82.4, 100.0)	64.0 (16/25)	(42.5, 82.0)
Pertussis - PRN[c]	% vaccine response[b]	89.5 (17/19)	(66.9, 98.7)	16.0 (4/25)	(4.5, 36.1)

[a] The within-group CIs are based on the exact binomial method proposed by Clopper and Pearson.
N=Number of participants allocated and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.
CI=confidence interval; FHA=filamentous hemagglutinin; FIM 2/3=fimbriae types 2 and 3; PRN=pertactin; PT=pertussis toxin.
[b] The pertussis vaccine response is defined as follows:
1) If prevaccination <LLOQ, then postvaccination should be ≥4 × the LLOQ.
2) If prevaccination ≥LLOQ but <2 × the LLOQ, then postvaccination should achieve a 4-fold rise (postvaccination/prevaccination ≥4).
3) If prevaccination ≥2 × the LLOQ, then postvaccination should achieve a 2-fold response (postvaccination/prevaccination ≥2).
[c] Antigen contained only in Vaxelis.
H=Hexyon; V=Vaxelis.
Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.
Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adimm]

*Table 28. Summary of Ab responses for all antigens contained in Vaxelis (PP population) (participants **without** analgesic or antipyretic administered on the day of vaccination) (Table 5-3 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)*

			Group 1 (VVV) (N = 58)			Group 2 (HHV) (N = 54)		
	Endpoint	Timepoint	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Diphtheria toxoid	GMC	Day 1	49	0.08	(0.05, 0.11)	52	0.09	(0.07, 0.11)
		Day 30	49	3.13	(2.51, 3.91)	48	1.90	(1.44, 2.52)
	% ≥ 4-fold rise	Day 1 to Day 30	45	97.8% (44/45)	(88.2, 99.9)	46	97.8% (45/46)	(88.5, 99.9)
Tetanus toxoid	GMC	Day 1	49	0.18	(0.13, 0.25)	52	0.13	(0.10, 0.17)
		Day 30	49	6.92	(4.89, 9.79)	48	3.85	(2.86, 5.18)
	% ≥ 4-fold rise	Day 1 to Day 30	45	93.3% (42/45)	(81.7, 98.6)	46	97.8% (45/46)	(88.5, 99.9)
Pertussis – PT	GMC	Day 1	49	7.91	(5.63, 11.12)	52	7.65	(5.92, 9.89)
		Day 30	49	186.74	(143.87, 242.38)	48	62.12	(47.76, 80.80)
	% ≥ 4-fold rise	Day 1 to Day 30	45	97.8% (44/45)	(88.2, 99.9)	46	87.0% (40/46)	(73.7, 95.1)
Pertussis – FHA	GMC	Day 1	49	8.88	(6.54, 12.05)	52	29.91	(24.03, 37.24)
		Day 30	49	101.93	(79.53, 130.63)	48	146.06	(117.08, 182.22)
	% ≥ 4-fold rise	Day 1 to Day 30	45	86.7% (39/45)	(73.2, 94.9)	46	60.9% (28/46)	(45.4, 74.9)
Pertussis – FIM 2/3[b]	GMC	Day 1	49	20.39	(14.23, 29.22)	52	1.14	(1.02, 1.27)
		Day 30	49	388.29	(270.23, 557.93)	48	13.62	(10.46, 17.73)
	% ≥ 4-fold rise	Day 1 to Day 30	45	91.1% (41/45)	(78.8, 97.5)	46	71.7% (33/46)	(56.5, 84.0)
Pertussis – PRN[b]	GMC	Day 1	49	2.73	(1.98, 3.75)	52	1.48	(1.21, 1.81)
		Day 30	49	112.17	(77.86, 161.59)	48	3.64	(2.64, 5.03)

			Group 1 (VVV) (N = 58)			Group 2 (HHV) (N = 54)		
	Endpoint	Timepoint	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Pertussis - PRN[b]	% ≥ 4-fold rise	Day 1 to Day 30	45	93.3% (42/45)	(81.7, 98.6)	46	26.1% (12/46)	(14.3, 41.1)
Hib-PRP	GMC	Day 1	53	1.37	(0.94, 2.01)	54	0.11	(0.09, 0.14)
		Day 30	51	6.03	(4.20, 8.68)	49	5.61	(4.00, 7.87)
	% ≥ 4-fold rise	Day 1 to Day 30	49	49.0% (24/49)	(34.4, 63.7)	49	98.0% (48/49)	(89.1, 99.9)
HBsAg	GMC	Day 1	45	32.75	(20.85, 51.43)	47	25.60	(14.98, 43.75)
		Day 30	37	1346.35	(928.06, 1953.18)	42	411.61	(222.81, 760.41)
	% ≥ 4-fold rise	Day 1 to Day 30	33	97.0% (32/33)	(84.2, 99.9)	38	81.6% (31/38)	(65.7, 92.3)
Poliovirus 1	GMC	Day 1	41	42.67	(23.80, 76.50)	52	42.90	(25.62, 71.83)
		Day 30	46	2110.57	(1298.07, 3431.66)	44	2553.35	(1569.94, 4152.78)
	% ≥ 4-fold rise	Day 1 to Day 30	35	91.4% (32/35)	(76.9, 98.2)	43	93.0% (40/43)	(80.9, 98.5)
Poliovirus 2	GMC	Day 1	41	64.04	(35.45, 115.69)	52	70.76	(40.67, 123.10)
		Day 30	46	2918.28	(1924.20, 4425.92)	44	4609.67	(3200.11, 6640.08)
	% ≥ 4-fold rise	Day 1 to Day 30	35	97.1% (34/35)	(85.1, 99.9)	43	97.7% (42/43)	(87.7, 99.9)
Poliovirus 3	GMC	Day 1	41	30.18	(16.84, 54.08)	52	41.80	(26.19, 66.72)
		Day 30	46	1283.61	(711.57, 2315.53)	44	3036.39	(1867.38, 4937.23)

			Group 1 (VVV) (N = 58)			Group 2 (HHV) (N = 54)		
	Endpoint	Timepoint	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Poliovirus 3	% ≥ 4-fold rise	Day 1 to Day 30	35	91.4% (32/35)	(76.9, 98.2)	43	93.0% (40/43)	(80.9, 98.5)

[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 allocated and vaccinated; n=Number of participants contributing to the analysis.

CI=confidence interval; GMC=geometric mean concentration (µg/mL); FHA=filamentous hemagglutinin; FIM 2/3=fimbriae types 2 and 3; HBsAg=hepatitis B surface antigen; Hib=haemophilus influenzae type b; IU=international unit; Nab=neutralizing antibodies; PRN=pertactin; PRP=polyribosylribitol phosphate; PT=pertussis toxin.

[b] Antigen contained only in Vaxelis.

H=Hexyon; V=Vaxelis.

Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.

Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adimm]

*Table 29. Summary of Ab responses for all antigens contained in Vaxelis (PP population) (participants **with** analgesic or antipyretic administered on the day of vaccination) (Table 5-3 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)*

			Group 1 (VVV) (N = 27)			Group 2 (HHV) (N = 28)		
	Endpoint	Timepoint	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Diphtheria toxoid	GMC	Day 1	24	0.08	(0.05, 0.14)	27	0.08	(0.05, 0.12)
		Day 30	20	3.51	(2.46, 5.02)	26	1.98	(1.38, 2.83)
	% ≥ 4-fold rise	Day 1 to Day 30	19	100.0% (19/19)	(82.4, 100.0)	25	92.0% (23/25)	(74.0, 99.0)
Tetanus toxoid	GMC	Day 1	24	0.17	(0.11, 0.25)	27	0.17	(0.11, 0.25)
		Day 30	20	10.13	(6.61, 15.53)	26	4.04	(2.58, 6.34)
	% ≥ 4-fold rise	Day 1 to Day 30	19	100.0% (19/19)	(82.4, 100.0)	25	96.0% (24/25)	(79.6, 99.9)
Pertussis - PT	GMC	Day 1	24	5.25	(3.67, 7.49)	27	6.27	(4.56, 8.63)
		Day 30	20	141.39	(95.10, 210.19)	26	54.72	(39.48, 75.84)
	% ≥ 4-fold rise	Day 1 to Day 30	19	100.0% (19/19)	(82.4, 100.0)	25	84.0% (21/25)	(63.9, 95.5)
Pertussis - FHA	GMC	Day 1	24	7.46	(5.54, 10.05)	27	28.78	(21.66, 38.23)
		Day 30	20	92.23	(63.36, 134.25)	26	148.83	(117.16, 189.05)
	% ≥ 4-fold rise	Day 1 to Day 30	19	100.0% (19/19)	(82.4, 100.0)	25	60.0% (15/25)	(38.7, 78.9)
Pertussis - FIM 2/3[b]	GMC	Day 1	24	13.97	(8.38, 23.27)	27	1.37	(1.03, 1.81)
		Day 30	20	239.65	(141.52, 405.82)	26	13.29	(8.43, 20.96)
	% ≥ 4-fold rise	Day 1 to Day 30	19	84.2% (16/19)	(60.4, 96.6)	25	64.0% (16/25)	(42.5, 82.0)
Pertussis - PRN[b]	GMC	Day 1	24	2.59	(1.67, 4.02)	27	1.24	(1.02, 1.51)
		Day 30	20	125.51	(61.52, 256.07)	26	2.55	(1.66, 3.91)

	Endpoint	Timepoint	Group 1 (VVV) (N = 27)			Group 2 (HHV) (N = 28)		
			n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Pertussis - PRN[b]	% ≥ 4-fold rise	Day 1 to Day 30	19	89.5% (17/19)	(66.9, 98.7)	25	16.0% (4/25)	(4.5, 36.1)
Hib-PRP	GMC	Day 1	26	1.03	(0.59, 1.78)	27	0.11	(0.08, 0.15)
		Day 30	22	5.45	(2.83, 10.46)	27	4.34	(2.61, 7.23)
	% ≥ 4-fold rise	Day 1 to Day 30	22	68.2% (15/22)	(45.1, 86.1)	26	92.3% (24/26)	(74.9, 99.1)
HBsAg	GMC	Day 1	24	27.65	(14.61, 52.30)	26	49.53	(24.48, 100.25)
		Day 30	19	765.22	(359.72, 1627.83)	27	579.59	(259.38, 1295.07)
	% ≥ 4-fold rise	Day 1 to Day 30	19	94.7% (18/19)	(74.0, 99.9)	25	88.0% (22/25)	(68.8, 97.5)
Poliovirus 1	GMC	Day 1	21	32.57	(13.17, 80.51)	26	17.58	(9.53, 32.43)
		Day 30	20	2194.98	(1099.43, 4382.21)	25	666.28	(239.60, 1852.77)
	% ≥ 4-fold rise	Day 1 to Day 30	18	88.9% (16/18)	(65.3, 98.6)	23	87.0% (20/23)	(66.4, 97.2)
Poliovirus 2	GMC	Day 1	21	47.56	(24.67, 91.70)	26	29.94	(13.52, 66.29)
		Day 30	20	3269.82	(1793.34, 5961.93)	25	2105.47	(1020.01, 4346.06)
	% ≥ 4-fold rise	Day 1 to Day 30	18	94.4% (17/18)	(72.7, 99.9)	23	91.3% (21/23)	(72.0, 98.9)
Poliovirus 3	GMC	Day 1	21	30.47	(12.64, 73.46)	26	22.06	(11.35, 42.86)
		Day 30	20	922.91	(289.94, 2937.70)	25	1884.46	(889.64, 3991.73)

	Endpoint	Timepoint	Group 1 (VVV) (N = 27)			Group 2 (HHV) (N = 28)		
			n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Poliovirus 3	% ≥ 4-fold rise	Day 1 to Day 30	18	83.3% (15/18)	(58.6, 96.4)	23	95.7% (22/23)	(78.1, 99.9)

[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 allocated and vaccinated; n=Number of participants contributing to the analysis.

CI=confidence interval; GMC=geometric mean concentration (µg/mL); FHA=filamentous hemagglutinin; FIM 2/3=fimbriae types 2 and 3; HBsAg=hepatitis B surface antigen; Hib=haemophilus influenzae type b; IU=international unit; Nab=neutralizing antibodies; PRN=pertactin; PRP=polyribosylribitol phosphate; PT=pertussis toxin.

[b] Antigen contained only in Vaxelis.

H=Hexyon; V=Vaxelis.

Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.

Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adimm]

Assessment of the MAH's response

The MAH provided the requested analyses, i.e. immune responses at 1 month post-vaccination according to the use of analgesic and anti-inflammatory medications on the day of vaccination. It is acknowledged that the study was not designed for such comparison, results are nevertheless of interest.

A total of 55 participants used analgesic/antipyretic on the day of vaccination, n= 27/85 (32%) in Group 1 and n=28/82 (34%) in Group 2. However, GMC Ab responses are not available for all the participants, resulting in limited number of participants per group. No other analgesic/antipyretic, or immunosuppressant medication, than paracetamol or ibuprofen were reported on the day of vaccination.

In terms of percentages of participants achieving thresholds associated with protection against diphtheria, tetanus, clinical paralysis due to polioviruses, hepatitis B and long-term protection against Haemophilus Influenzae Type b, no differences between participants who used analgesic/antipyretic on the day of vaccination and those who did not were observed.

Results were overall consistent with those of whole PP population.

In terms of Ab GMCs, results were also overall consistent with those of whole PP population except for the specific responses to polioviruses, particularly for Group 2. In addition, trend for lower Ab GMCs for all 3 polioviruses were observed for participants of Group 2 who used analgesic/antipyretic on the day of vaccination versus those of Group 2 who did not. However, 95% CIs were large and still overlapping. A trend for lower anti-HBsAg Ab was observed in Group 1 participants who used analgesic/antipyretic on

the day of vaccination when compared to those who did not.

Such results might be explained by the limited sample size per group. The clinical relevance is considered limited since percentages of participants reaching the Ab thresholds associated with protection were high in all groups.

Issue resolved.

Question 6

The MAH is required to submit stratified descriptive data for participants with/without use of analgesic/antipyretic on the day of vaccination, both for solicited local and for systemic adverse events, for the 2 groups, and to discuss differences observed in each group and between groups.

Summary of the MAH's response

V419-016 was not designed to look at antipyretic/analgesic use with vaccination and only around 33% of participants received these medications. Therefore, any differences should be interpreted with caution.

Solicited adverse events stratified by use of analgesic/antipyretic are shown in Table 30 and Table 31. There are 27 and 28 participants who used antipyretic/analgesic in Group 1 (VVV) and Group 2 (HHV) respectively.

Overall, the proportions of participants with solicited AEs were generally comparable between the 2 groups following a booster dose of Vaxelis, regardless of the use of analgesic/antipyretic on the day of vaccination. Within each group no clinically meaningful differences were seen in the reporting of solicited local or systemic AEs for those participants with or without analgesic/antipyretic use.

Overall, no difference in the local and systemic solicited events profile was observed between and within groups regardless of the use of analgesic/antipyretic on the day of vaccination.

*Table 30. Participants with solicited AEs (Incidence > 0% in the one or more vaccination groups) (all participants as treated population) (Participants **without** analgesic or antipyretic administered on the day of vaccination) (Table 6-1 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)*

	Group 1 (VVV)			Group 2 (HHV)		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	58			54		
with one or more solicited adverse events	55	(94.8)		45	(83.3)	
with no solicited adverse events	3	(5.2)		9	(16.7)	
Solicited injection site adverse events	**48**	**(82.8)**	**(70.6, 91.4)**	**39**	**(72.2)**	**(58.4, 83.5)**
Injection site erythema[b]	30	(51.7)	(38.2, 65.0)	26	(48.1)	(34.3, 62.2)
Injection site pain[b]	44	(75.9)	(62.8, 86.1)	28	(51.9)	(37.8, 65.7)
Injection site swelling[b]	32	(55.2)	(41.5, 68.3)	21	(38.9)	(25.9, 53.1)
Solicited systemic adverse events	**51**	**(87.9)**	**(76.7, 95.0)**	**34**	**(63.0)**	**(48.7, 75.7)**
Decreased appetite[b]	23	(39.7)	(27.0, 53.4)	14	(25.9)	(15.0, 39.7)
Irritability[b]	43	(74.1)	(61.0, 84.7)	28	(51.9)	(37.8, 65.7)
Somnolence[b]	35	(60.3)	(46.6, 73.0)	24	(44.4)	(30.9, 58.6)
Vomiting[b]	3	(5.2)	(1.1, 14.4)	5	(9.3)	(3.1, 20.3)

[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.
Every participant is counted a single time for each applicable row and column.
Injection site swelling, injection site redness/erythema, injection site tenderness/pain, vomiting, drowsiness/somnolence, appetite lost/decreased appetite, and irritability were solicited from Day 1 through Day 5 following vaccination.
MedDRA version 25.1 was used in the reporting of this study.
CI=confidence interval.
H=Hexyon; V=Vaxelis.
Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.
Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adae]

*Table 31. Participants with solicited AEs (Incidence > 0% in the one or more vaccination groups) (all participants as treated population) (Participants **with** analgesic or antipyretic administered on the day of vaccination) (Table 6-2 of AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)*

	Group 1 (VVV)			Group 2 (HHV)		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	27			28		
with one or more solicited adverse events	27	(100.0)		26	(92.9)	
with no solicited adverse events	0	(0.0)		2	(7.1)	
Solicited injection site adverse events	**23**	**(85.2)**	**(66.3, 95.8)**	**23**	**(82.1)**	**(63.1, 93.9)**
Injection site erythema[b]	15	(55.6)	(35.3, 74.5)	15	(53.6)	(33.9, 72.5)
Injection site pain[b]	19	(70.4)	(49.8, 86.2)	18	(64.3)	(44.1, 81.4)
Injection site swelling[b]	13	(48.1)	(28.7, 68.1)	12	(42.9)	(24.5, 62.8)
Solicited systemic adverse events	**27**	**(100.0)**	**(87.2, 100.0)**	**23**	**(82.1)**	**(63.1, 93.9)**
Decreased appetite[b]	14	(51.9)	(31.9, 71.3)	16	(57.1)	(37.2, 75.5)
Irritability[b]	23	(85.2)	(66.3, 95.8)	20	(71.4)	(51.3, 86.8)
Somnolence[b]	20	(74.1)	(53.7, 88.9)	15	(53.6)	(33.9, 72.5)
Vomiting[b]	0	(0.0)	(0.0, 12.8)	2	(7.1)	(0.9, 23.5)

[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.
Every participant is counted a single time for each applicable row and column.
Injection site swelling, injection site redness/erythema, injection site tenderness/pain, vomiting, drowsiness/somnolence, appetite lost/decreased appetite, and irritability were solicited from Day 1 through Day 5 following vaccination.
MedDRA version 25.1 was used in the reporting of this study.
CI=confidence interval.
H=Hexyon; V=Vaxelis.
Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.
Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.
Source: [P016V419: adam-adsl; adae]

Assessment of the MAH's response

The MAH provided the requested analyses, i.e. incidence of solicited AEs at 1 month post-vaccination according to the use of analgesic and anti-inflammatory medications on the day of vaccination. It is acknowledged that the study was not designed for such comparison, results are nevertheless considered relevant/of interest for completeness in the reporting of V419-016 study results.

A total of 55 participants used analgesic/antipyretic on the day of vaccination, n= 27/85 (32%) in Group 1 and n=28/82 (34%) in Group 2. No other analgesic/antipyretic, or immunosuppressant medication, than paracetamol or ibuprofen were reported on the day of vaccination.

Solicited systemic AEs were reported in all Group 1 participants and in 23/28 (82.1%) of the Group 2 participants who used analgesic/antipyretic on the day of vaccination, which is higher than the percentages observed in participants who did not (87.9% and 63.0% in Group 1 and in Group 2, respectively). A trend for higher percentage of Group 2 participants experiencing solicited injection site AEs was also observed in participants who used analgesic/antipyretic on the day of vaccination (82.1%) versus those who did not (72.2%). In Group 1, the percentage of participants experiencing solicited injection site AEs was similar in participants who used analgesic/antipyretic on the day of vaccination (85.2%) versus those who did not (82.8%)

Because of the limited sample size per group, interpretation should be cautious and no firm conclusion can be drawn.

Issue resolved.

Question 7

For transparency and clarity in the EPAR (and even if it concerns only a limited number of AEs), it is requested to the MAH to clarify for each group: the percentage of unsolicited AEs in total and per SOC, of

related unsolicited AEs in total and per SOC, and of unsolicited AEs by maximum intensity in total and per SOC. Any differences observed between the 2 groups should be discussed.

Summary of the MAH's response

The requested information is provided in:.

- Table 32 summarizes the number of participants with unsolicited adverse events per group in total and per SOC.
- Table 33 summarizes the number of participants with unsolicited adverse events related to study vaccine per group, in total and per event.
- Table 7-3 in the RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis summarizes the number of participants with unsolicited adverse events by maximum intensity per group, in total and per SOC. Of the participants with unsolicited AEs graded by intensity, the majority had events with a maximum intensity of mild or moderate in both groups.

Table 32. Participants with unsolicited AEs (Incidence > 0% in the one or more vaccination groups) (all participants as treated population) (Table 7-1 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)

	Group 1 (VVV)			Group 2 (HHV)		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	85			82		
with one or more unsolicited adverse events	44	(51.8)		52	(63.4)	
with no unsolicited adverse events	41	(48.2)		30	(36.6)	
Congenital, familial and genetic disorders	**1**	**(1.2)**	**(0.0, 6.4)**	**0**	**(0.0)**	**(0.0, 4.4)**
Tooth hypoplasia	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Gastrointestinal disorders	**9**	**(10.6)**	**(5.0, 19.2)**	**10**	**(12.2)**	**(6.0, 21.3)**
Abdominal pain	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Diarrhoea	1	(1.2)	(0.0, 6.4)	6	(7.3)	(2.7, 15.2)
Enteritis	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Flatulence	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Nausea	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Teething	4	(4.7)	(1.3, 11.6)	1	(1.2)	(0.0, 6.6)
Tooth development disorder	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Vomiting[b]	2	(2.4)	(0.3, 8.2)	1	(1.2)	(0.0, 6.6)
General disorders and administration site conditions	**36**	**(42.4)**	**(31.7, 53.6)**	**44**	**(53.7)**	**(42.3, 64.7)**
Injection site bruising	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Injection site granuloma	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Injection site haematoma	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Injection site induration	0	(0.0)	(0.0, 4.2)	6	(7.3)	(2.7, 15.2)
Injection site pruritus	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Injection site warmth	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Malaise	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Pyrexia	34	(40.0)	(29.5, 51.2)	40	(48.8)	(37.6, 60.1)
Infections and infestations	**13**	**(15.3)**	**(8.4, 24.7)**	**12**	**(14.6)**	**(7.8, 24.2)**
Bronchiolitis	1	(1.2)	(0.0, 6.4)	1	(1.2)	(0.0, 6.6)
COVID-19	3	(3.5)	(0.7, 10.0)	3	(3.7)	(0.8, 10.3)
Conjunctivitis	1	(1.2)	(0.0, 6.4)	2	(2.4)	(0.3, 8.5)
Ear infection	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Gastroenteritis	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Gastroenteritis adenovirus	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)

	Group 1 (VVV)			Group 2 (HHV)		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Hand-foot-and-mouth disease	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Nasopharyngitis	3	(3.5)	(0.7, 10.0)	2	(2.4)	(0.3, 8.5)
Pharyngotonsillitis	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Rhinitis	2	(2.4)	(0.3, 8.2)	0	(0.0)	(0.0, 4.4)
Upper respiratory tract infection	1	(1.2)	(0.0, 6.4)	3	(3.7)	(0.8, 10.3)
Viral rash	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Injury, poisoning and procedural complications	**2**	**(2.4)**	**(0.3, 8.2)**	**0**	**(0.0)**	**(0.0, 4.4)**
Arthropod bite	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Head injury	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Investigations	**0**	**(0.0)**	**(0.0, 4.2)**	**2**	**(2.4)**	**(0.3, 8.5)**
Body temperature increased	0	(0.0)	(0.0, 4.2)	2	(2.4)	(0.3, 8.5)
Reproductive system and breast disorders	**0**	**(0.0)**	**(0.0, 4.2)**	**1**	**(1.2)**	**(0.0, 6.6)**
Balanoposthitis	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Respiratory, thoracic and mediastinal disorders	**3**	**(3.5)**	**(0.7, 10.0)**	**2**	**(2.4)**	**(0.3, 8.5)**
Cough	1	(1.2)	(0.0, 6.4)	1	(1.2)	(0.0, 6.6)
Rhinorrhoea	2	(2.4)	(0.3, 8.2)	2	(2.4)	(0.3, 8.5)
Sneezing	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Skin and subcutaneous tissue disorders	**4**	**(4.7)**	**(1.3, 11.6)**	**5**	**(6.1)**	**(2.0, 13.7)**
Dermatitis	1	(1.2)	(0.0, 6.4)	1	(1.2)	(0.0, 6.6)
Dermatitis diaper	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Digital pulpitis	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Macule	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Pruritus	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Rash	1	(1.2)	(0.0, 6.4)	1	(1.2)	(0.0, 6.6)
Urticaria	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)

[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.

Every participant is counted a single time for each applicable row and column.

Reported adverse events include nonserious adverse events that occurred from Day 1 through Day 15 postvaccination with Vaxelis, and serious adverse events that occurred throughout the duration of study.

MedDRA version 25.1 was used in the reporting of this study.

CI=confidence interval.

H=Hexyon; V=Vaxelis.

Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.

Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adae]

Table 33. Participants with unsolicited AEs related to study vaccine (Incidence > 0% in the one or more vaccination groups) (all participants as treated population) (Table 7-2 of RESPONSE TO AGENCY QUESTIONS - Study V419-016: interchangeable use of Vaxelis)

	Group 1 (VVV)			Group 2 (HHV)		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	85			82		
with one or more unsolicited adverse events related to study vaccine	36	(42.4)		41	(50.0)	
with no unsolicited adverse events related to study vaccine	49	(57.6)		41	(50.0)	
Body temperature increased	0	(0.0)	(0.0, 4.2)	2	(2.4)	(0.3, 8.5)
Injection site bruising	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Injection site granuloma	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Injection site haematoma	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Injection site induration	0	(0.0)	(0.0, 4.2)	6	(7.3)	(2.7, 15.2)
Injection site pruritus	0	(0.0)	(0.0, 4.2)	1	(1.2)	(0.0, 6.6)
Injection site warmth	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)
Pyrexia	34	(40.0)	(29.5, 51.2)	34	(41.5)	(30.7, 52.9)
Rash	1	(1.2)	(0.0, 6.4)	0	(0.0)	(0.0, 4.4)

[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.
Every participant is counted a single time for each applicable row and column.
Reported adverse events include nonserious adverse events that occurred from Day 1 through Day 15 postvaccination with Vaxelis, and serious adverse events that occurred throughout the duration of study.
Relatedness to study vaccine was determined by the investigator.
MedDRA version 25.1 was used in the reporting of this study.
CI=confidence interval.
H=Hexyon; V=Vaxelis.
Group 1 (VVV)=Participants had previously received 2 doses of Vaxelis at approximately 2 and 4 months of age.
Group 2 (HHV)=Participants had previously received 2 doses of Hexyon at approximately 2 and 4 months of age.

Source: [P016V419: adam-adsl; adae]

Assessment of the MAH's response

The MAH provided the requested analyses.

A total of 44/85 (51.8%) and 52/82 (63.4%) of the toddlers in Group 1 and Group 2 respectively experienced one or more unsolicited AEs. Percentages of unsolicited AEs per SOC were overall comparable except for the SOC *General disorder and administration site conditions* with a trend for higher percentages in Group 2 (53.7%) when compared to Group 1 (42.4%). There were 6/44 (7.3%) of the Group 2 participants who experienced induration at the site of injection versus 0 in Group 1. Although no difference of percentages between groups for the SOC *Gastrointestinal disorders* was observed overall, higher percentage of toddlers experienced diarrhea in Group 2 (7.3%: 6/10) when compared to Group 1 (1.2%: 1/9).

A total of 36/85 (42.4%) and 41/82 (50.0%) of the toddlers in Group 1 and Group 2 respectively experienced one or more unsolicited AEs related to the study vaccine. The main difference was the 7.3% of the Group 2 participants who experienced induration at the site of injection versus 0 in Group 1.

Among the toddlers who experienced one or more unsolicited AEs, a higher percentages of toddlers in Group 2 versus Group 1 experienced severe AEs: 9.8% (8 severe AEs: 6 pyrexia, 1 nausea, 1 urticaria) vs 0%, respectively.

Issue resolved.

Conclusion

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