Protocol Amendment 4

Study ID: 215301

Official Title of Study: A Phase 1/2a, open-label, randomized, controlled, multicountry, dose-escalation study to assess the safety and immunogenicity of AS37 in combination with the Hepatitis B surface antigen (HBsAg), according to a 0-1-month schedule, in healthy, HBs-naïve, adults aged 18-45 years

NCT number: NCT05561673

Date of Document: 17-Sep-2024

Note: The typo appears in the following sections of the Protocol document - 1.1 (Synopsis), 3 (Objectives), and 9.3.1 (Primary Endpoints Analyses). The phrase currently reads “absolute values and changes”, but it should be “absolute values of changes”.

CLINICAL STUDY PROTOCOL

Primary study intervention and number	GSK's Hepatitis B surface antigen (HBsAg) adjuvanted with GSK's AS37 Adjuvant System (GSK2231392A)
Other study interventions	• GSK's Hepatitis B vaccine adjuvanted with aluminum hydroxide (*Engerix-B*, SKF103860) • GSK's Hepatitis B vaccine adjuvanted with GSK's AS04 Adjuvant System (*Fendrix*) • GSK's HBsAg candidate vaccine adjuvanted with GSK's AS03 Adjuvant System (GSK2231392A)
Study identifier and abbreviated title	215301 (EARLY-CLINRES-017)
EudraCT number	2021-005629-25
Date of protocol	Final: 25 April 2022
Date of protocol amendment	Amendment 1 Final: 10 August 2022 Amendment 2 Final: 01 March 2023 Amendment 3 Final: 17 November 2023 Amendment 4 Final: 17 Sep 2024
Title	A Phase 1/2a, open-label, randomized, controlled, multi-country, dose-escalation study to assess the safety and immunogenicity of AS37 in combination with the Hepatitis B surface antigen (HBsAg), according to a 0-1-month schedule, in healthy, HBs-naïve, adults aged 18-45 years
Brief title	A study on the safety and immune response of AS37 together with Hepatitis B antigen in adults aged 18-45 years
Sponsor	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart Belgium
Sponsor signatory	Bach-Yen Nguyen, MD Vice-President, Head of Therapeutic Cluster, Vaccines Clinical Sciences

Medical monitor name and contact information can be found in the local study contact information document.

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.2

Protocol Amendment 4 Sponsor Signatory Approval

Study identifier and abbreviated title	215301 (EARLY-CLINRES-017)
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Sponsor signatory	Bach-Yen Nguyen, MD Vice-President, Head of Therapeutic Cluster, Vaccines Clinical Sciences
Signature	_____
Date	_____

Note: Not applicable if an alternative signature process (e.g., electronic signature or email approval) is used to get the sponsor approval.

Protocol Amendment 4 Investigator Agreement

- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To cooperate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.

Study identifier and abbreviated title	215301 (EARLY-CLINRES-017)
EudraCT number	2021-005629-25
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Investigator name	_____
Signature	_____
Date	_____
PPD **name, function and title**	_____
Signature	_____
Date of signature	_____

SPONSOR INFORMATION

1. Sponsor

GSK

2. Sponsor medical expert for the study

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to the local study contact information document**.**

4. Sponsor study contact for reporting of Serious Adverse Events (SAEs)

GSK central back-up study contact for reporting SAEs: refer to Section 8.4.3.1.

Study contact for reporting SAEs: refer to the local study contact information document.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 4	17 Sep 2024
Amendment 3	17 November 2023
Amendment 2	01 March 2023
Amendment 1	10 August 2022
Original Protocol	25 April 2022

Amendment 4 (17 Sep 2024**)**

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it relates to changes in the conduct of assays addressing tertiary endpoints of the clinical study.

Overall rationale for the current Amendment:

Several factors are driving this amendment: i) the results obtained in the main analysis from immunogenicity data (secondary endpoints) collected from all participants post-Dose 2 (Day 61), ii) CCI [redacted]. Timelines for data availability are also impacting the content of the final analysis and clinical study report.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RESPECTIVE RATIONALE:

Section # and title	Description of change	Brief rationale
Headers, title page, Protocol Amendment Summary of Changes (new)	Headers and title page were updated with new document number, amendment information, and sponsor signatory name; Protocol Amendment Summary of Changes section was updated to include the rationale for this amendment; minor corrections and formatting adjustments were made to add clarification and/or remove discrepancies.	Editorial changes have been implemented as needed.

Section # and title	Description of change	Brief rationale
Section 1.1 Synopsis	Added/updated subheadings to summarize details in the synopsis.	To align with the latest protocol template.
Section 3 Objectives and endpoints	Updated the tertiary endpoints.	CCI [redacted]
Section 6.1.1 Medical devices	Added a section on medical devices.	To align with the latest protocol template.
Section 8.1 Immunogenicity assessments	Updated the paragraph on sample collection for immunogenicity assessments.	To align with the latest protocol template.
Section 8.1.2 Laboratory assays	Updated the methods of laboratory assays. Added a table on assays and subsets.	Availability of alternative assays with higher throughput. To provide details of assays and number of participants in each assay.
CCI [redacted]		
Section 8.6 Pharmacodynamics	Added a section on pharmacodynamics.	To align with the latest protocol template.
CCI [redacted]		

Section # and title	Description of change	Brief rationale
CCI [redacted]		
Section 10.1.1 Regulatory and ethical considerations Section 10.1.3 Informed consent process Section 10.1.4 Data protection Section 10.1.6 Dissemination of clinical study data Section 10.1.7 Data quality assurance Section 10.1.8 Source documents Section 10.1.10 Publication policy	Updated the sections with latest template text.	To align with the latest protocol template.
Section 10.2.2 Protocol-required immunogenicity assessments	Updated the laboratory assay methods.	To reflect change in assay selection.
Section 10.3 Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting	Updated the sections with latest template text.	To align with the latest protocol template.
Section 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Updated the sections with latest template text.	To align with the latest protocol template.
Section 10.6 Appendix 6: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)	Updated the sections with latest template text.	To align with the latest protocol template.
Section 10.9 Appendix 9: List of potential immune-mediated disorders, Table 27 List of pIMDs	Updated the pIMD table.	To align with the latest protocol template.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol title: A Phase 1/2a, open-label, randomized, controlled, multi-country, dose-escalation study to assess the safety and immunogenicity of AS37 in combination with the Hepatitis B surface antigen (HBsAg), according to a 0-1-month schedule, in healthy, HBs naïve, adults aged 18-45 years.

Brief title: A study on the safety and immune response of AS37 together with Hepatitis B antigen in adults aged 18-45 years.

Rationale:

The novel adjuvant named Adjuvant System 37 (AS37) consists of the combination of aluminum hydroxide ($Al(OH)_3$) CCI [redacted], a synthetic toll-like receptor 7 (TLR7) agonist, and has the potential to have a tolerability profile comparable to alum-based vaccines. When combined with an antigen, it has been shown to generate, after a single injection, high concentrations of antigen-specific antibodies.

Preclinical studies of AS37 demonstrated a superior capacity in eliciting an effective immune response when compared to alum-based vaccines in several preclinical models. CCI [redacted] In a Phase 1 clinical study using MenC-CRM antigen and *Menjugate* as control, AS37 formulations containing CCI [redacted] doses of up to 50 µg demonstrated a tolerability profile comparable to alum-based vaccine [Gonzalez-Lopez, 2019]. There was no appreciable difference in functional Ab titers (hSBA), but a dosing effect was observed for MenC PS-specific Ab titers (Enzyme-Linked ImmunoSorbent Assay) and plasmablasts.

Clinically relevant data evaluating how AS37 compares to other adjuvants is lacking. Therefore, this study will be conducted to address this lack of data and differentiate AS37 from other approved Adjuvant Systems (AS03 and AS04), and from an alum-containing control group. CCI [redacted]

HBs-naïve adults aged 18-45 years will receive 2 injections, one month apart of a constant dose of HBs antigen (20 µg) formulated with AS37B (containing 50 µg of CCI [redacted]) or AS37A (containing 100 µg of CCI [redacted]).

Objectives and endpoints:

Objectives	Endpoints
Primary	
To evaluate the reactogenicity and safety in all study groups.	• Percentage of participants with solicited administration site and systemic AEs within 14 days (Day 1 till Day 14) after Dose 1 and Dose 2. • Duration of solicited AEs (administration site and systemic) after Dose 1 and Dose 2. • Percentage of participants with any unsolicited AEs within 31 days (Day 1 till Day 31) after Dose 1 and Dose 2. • Percentage of participants with SAEs, MAEs and AEs leading to study withdrawal throughout the entire study period. • Percentage of participants with pIMDs throughout the entire study period. • The absolute values and changes in hematology and biochemistry parameters post-Dose 1 (Day 8 and Day 31) and post-Dose 2 (Day 38 and Day 61) from baseline (pre-vaccination, Day 1). • Percentage of participants with abnormal laboratory parameter values at pre-vaccination (Day 1), post-Dose 1 (Day 8 and Day 31) and post-Dose 2 (Day 38 and Day 61).
Secondary	
To evaluate the humoral immune response in all study groups.	• GMC of Anti-HBs Ab concentrations at Day 1, Day 31, Day 61 and Day 361. • Anti-HBs seroconversion and seroprotection rates at Day 31, Day 61 and Day 361.

AE = adverse event; **SAE** = serious adverse event; **MAE** = medically attended event; **pIMD** = potential immune-mediated disorder; **GMC** = geometric mean concentration; **HBs** = Hepatitis B surface antigen; **Ab** = antibody.

Refer to Table 3 for details of all objectives and endpoints.

Overall design: This is a Phase 1/2a, dose-escalation, open-label, multi-country study with 5 parallel groups. For details of the study design, refer Section 4.

Number of participants: A minimum of 23 (and maximum of 30) participants per group will be enrolled in this study.

Data monitoring/other committee: Safety monitoring will be conducted by an internal Safety Review Team (SRT). The SRT will review interim and cumulative safety data and will escalate concerns to the Global Safety Board (GSB).

1.2. Schema

Refer to Figure 1 for a schematic presentation of the study design.

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities

Type of contact (V / PC)	Screening Visit	V1	V2	PC1	PC2	V3	PC3	PC4	PC5	V4	V5	PC6	PC7	V6	PC8	PC9	PC10	V7	V8[1]	V9	Notes
Timepoints	**Day -7**	**Day 1**	**Day 2**	**Day 4**	**Day 6**	**Day 8**	**Day 10**	**Day 12**	**Day 15**	**Day 31**	**Day 32**	**Day 34**	**Day 36**	**Day 38**	**Day 40**	**Day 42**	**Day 45**	**Day 61**	**Day 181**	**Day 361**	
Sampling timepoints	**D-7**	**D1**	**D2**	**D4**	**D6**	**D8**	**D10**	**D12**	**D15**	**D31**	**D32**	**D34**	**D36**	**D38**	**D40**	**D42**	**D45**	**D61**	**D181**	**D361**	
Informed consent	●																				See Section 10.1.3 for details
Check inclusion/exclusion criteria	●	○																			Recheck clinical status before randomization and/or first dose of study intervention. See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Collect demographic data	●																				See Section 8.2.1.1 for more information
Medical and vaccination history	●	○																			See Section 8.2.1.2 for more information
Physical examination	●	●								●									●		See Section 8.2.1.3 for more information
Randomization		●																			See Section 6.3 for more information
Study interventions																					
Check contraindications, warnings and precautions to study intervention administration		○								○									○		See Sections 7.1.1 and 8.2.1.5 for more information
Check criteria for temporary delay for enrolment and study intervention administration	○	○								○									○		See Section 5.5 for more information

Type of contact (V / PC)	Screening Visit	V1	V2	PC1	PC2	V3	PC3	PC4	PC5	V4	V5	PC6	PC7	V6	PC8	PC9	PC10	V7	V8[1]	V9	Notes
Timepoints	**Day -7**	**Day 1**	**Day 2**	**Day 4**	**Day 6**	**Day 8**	**Day 10**	**Day 12**	**Day 15**	**Day 31**	**Day 32**	**Day 34**	**Day 36**	**Day 38**	**Day 40**	**Day 42**	**Day 45**	**Day 61**	**Day 181**	**Day 361**	
Sampling timepoints	**D-7**	**D1**	**D2**	**D4**	**D6**	**D8**	**D10**	**D12**	**D15**	**D31**	**D32**	**D34**	**D36**	**D38**	**D40**	**D42**	**D45**	**D61**	**D181**	**D361**	
Urine pregnancy test		●								●									●		See Section 8.2.1.4 for more information
Study group allocation		●																			See Sections 6.3.2 and 6.3.3 for more information
Intervention number allocation for subsequent doses										○									○[1]		
Body temperature before study intervention administration		●								●									●[1]		The preferred location for measuring temperature will be the oral cavity. Fever is defined as temperature ≥38.0°C regardless of the location of measurement
Study intervention administration		●								●									●[1]		See Section 6.1 for more information
Recording of administered study intervention number		●								●									●[1]		
Laboratory Assessment																					
Blood sampling for anti-HBs Ab, anti-HBc Ab and-HBs Antigen screening tests (~5 mL)	●																				See Section 8.1.1 for more information
Blood sampling for antibody determination [redacted] (~20 mL)[2]		●								●								●		●	See Section 8.1.1 for more information
Blood sampling [redacted] (~5 mL)		●	●			●				●	●			●							See Section 8.1.1 for more information

Type of contact (V / PC)	Screening Visit	V1	V2	PC1	PC2	V3	PC3	PC4	PC5	V4	V5	PC6	PC7	V6	PC8	PC9	PC10	V7	V8[1]	V9	Notes
Timepoints	**Day -7**	**Day 1**	**Day 2**	**Day 4**	**Day 6**	**Day 8**	**Day 10**	**Day 12**	**Day 15**	**Day 31**	**Day 32**	**Day 34**	**Day 36**	**Day 38**	**Day 40**	**Day 42**	**Day 45**	**Day 61**	**Day 181**	**Day 361**	
Sampling timepoints	**D-7**	**D1**	**D2**	**D4**	**D6**	**D8**	**D10**	**D12**	**D15**	**D31**	**D32**	**D34**	**D36**	**D38**	**D40**	**D42**	**D45**	**D61**	**D181**	**D361**	
Blood sampling CCI [redacted]) (~5 mL)		●	●			●				●	●			●							See Section 8.1.1 for more information
Blood sampling for CMI response (~50 mL)		●				●				●				●				●		●	See Section 8.1.1 for more information
Blood sampling for hematology/biochemical analysis at screening and for safety monitoring (~7mL)	●	●				●				●				●				●			See Section 8.1.1 for more information
CCI [redacted]																					
Safety assessments																					
Record any concomitant medications/vaccinations		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	See Section 6.9 for more information
Record any intercurrent medical conditions		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	See Section 9.2.1 for more information
Download eDiary application or distribution of eDiary devices and training of participants on how to use eDiaries		○								○											
Recording of solicited events (Days 1–14) post-Dose 1 and Dose 2 of study intervention administration by participants		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○				See Section 10.3.8 for more information

Type of contact (V / PC)	Screening Visit	V1	V2	PC1	PC2	V3	PC3	PC4	PC5	V4	V5	PC6	PC7	V6	PC8	PC9	PC10	V7	V8[1]	V9	Notes
Timepoints	**Day -7**	**Day 1**	**Day 2**	**Day 4**	**Day 6**	**Day 8**	**Day 10**	**Day 12**	**Day 15**	**Day 31**	**Day 32**	**Day 34**	**Day 36**	**Day 38**	**Day 40**	**Day 42**	**Day 45**	**Day 61**	**Day 181**	**Day 361**	
Sampling timepoints	**D-7**	**D1**	**D2**	**D4**	**D6**	**D8**	**D10**	**D12**	**D15**	**D31**	**D32**	**D34**	**D36**	**D38**	**D40**	**D42**	**D45**	**D61**	**D181**	**D361**	
Review of eDiary data by the investigator or delegate			○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○			
Return of eDiary devices or removal of eDiary application from partici-pant personal device																		○			
Recording of unsolicited events (Days 1-31) post-Dose 1 and post-Dose 2 of study intervention administration		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			See Section 10.3.8 for more information
Recording of SAEs, MAEs, pIMDs and pregnancies		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Recording of AEs/SAEs leading to withdrawal from the study		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Study Conclusion																				●	See Section 4.5 for more information

V = visit; **PC** = phone contact; **D** = day; **HBs** = Hepatitis B surface antigen; **HBc** = Hepatitis B core antigen; **CMI** = cell-mediated immunity; **eDiary** = electronic diary; **SAE** = serious adverse event; **MAE** = medically attended event**; pIMD** = potential immune-mediated disorder; **AE** = adverse event; **eCRF** = electronic case record form; CCI [redacted] CCI [redacted].

Note: The double-line border following Day 61 indicates the main analyses that will be performed on all data (i.e., data that are as clean as possible) obtained up to Day 61.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

1Only for participants in the HBs-alum group.
2Note: Participants with anti-HBs Ab concentration < 100 mIU/mL at Day 361 will be offered a dose of *Engerix-B* after the study.

CCI

[redacted]

Table 2 Intervals between study visits

Interval	Optimal length of interval[1]	Allowed interval[2]
Screening Visit → Visit 1	7 days	2-28 days
Visit 1 → Visit 2*	1 day	1 day
Visit 2 → PC1	2 days	2 days
PC1 → PC2	2 days	2 days
Visit 1 → Visit 3	7 days	7-8 days
Visit 3 → PC3	2 days	2 days
PC3 → PC4	2 days	2 days
PC4 → PC5	3 days	3 days
Visit 1 → Visit 4	30 days (1 month)	21-42 days
Visit 4 → Visit 5*	1 day	1 day
Visit 5 → PC6	2 days	2 days
PC6 → PC7	2 days	2 days
Visit 4 → Visit 6	7 days	7-8days
Visit 4 → Visit 7	30 days (1 month)	21-42 days
Visit 4 → Visit 8[3]	150 days (5 months)	136-164 days
Visit 6 → PC8	2 days	2 days
PC8 → PC9	2 days	2 days
PC9 → PC10	3 days	3 days
Visit 7 → Visit 9[4]	300 days (10 months)	286-314 days
Visit 8 → Visit 9[3]	180 days (6 months)	166-194 days

PC = phone contact

[1]Whenever possible the investigator should arrange study visits within this interval.

[2]Participants will not be eligible for inclusion in the Per-Protocol Set for analysis of immunogenicity if they make the study visit outside this interval.

[3]For participants in the HBs-alum group.

[4]For participants in all groups except the HBs-alum group.

CCI [redacted]

2. INTRODUCTION

2.1. Study rationale

The novel adjuvant named AS37 consists of the combination of $Al(OH)_3$ and CCI [redacted] CCI [redacted] a synthetic TLR7 agonist, and has the potential to have a tolerability profile comparable to alum-based vaccines. When combined with an antigen, it has been shown to generate after a single injection, high concentrations of antigen-specific antibodies.

Preclinical studies of AS37 demonstrated a superior capacity in eliciting an effective immune response when compared to alum-based vaccines in several preclinical models. In some specific studies (using cytomegalovirus or *Clostridium difficile* antigens), AS37 generated high levels of Ab concentrations after one dose. In a Phase 1 clinical study using MenC-CRM antigen and *Menjugate* as control, AS37 formulations containing CCI [redacted] doses of up to 50 µg demonstrated a tolerability profile comparable to alum-based vaccine [Gonzalez-Lopez, 2019]. There was no appreciable difference in functional Ab titers (hSBA), but a dosing effect was observed for MenC PS-specific Ab titers (ELISA) and plasmablasts.

Clinically relevant data evaluating how AS37 compares to other adjuvants is lacking. Therefore, this study will be conducted to address this lack of data and differentiate AS37 from other approved Adjuvant Systems (AS03 and AS04), and from an alum-containing control group. CCI [redacted]

HBs-naïve adults aged 18-45 years will receive 2 injections, one month apart of a constant dose of HBs antigen (20 µg) formulated with AS37B (containing 50 µg of CCI [redacted]) or AS37A (containing 100 µg of CCI [redacted]).

2.2. Background

Please refer to the current IB for information regarding preclinical studies of HBs-AS37 investigational vaccine and clinical studies, and the risks and benefits, of HBs-AS03, *Engerix-B* and *Fendrix*.

2.3. Benefit/Risk assessment

2.3.1. Risk assessment

Detailed information about the known and expected benefits and risks and expected adverse events of the study interventions can be found in the IB.

Hypersensitivity reactions may occur following exposure to allergens from a variety of sources including food, aeroallergens, venom, drugs, and immunizations. Vaccines are a mixture of compounds and allergic sensitization can occur to any component. While cutaneous reactions, such as rash or urticaria, are common, anaphylactic reactions are very rare. Administration of the study vaccination is to be preceded by a review of the participants' medical history (especially regarding previous vaccination and possible occurrence of undesirable events) and a clinical examination. All participants will remain under observation at the clinical center for at least 60 minutes after vaccination, with appropriate medical treatment readily available.

Based on the theoretical concern that vaccination with vaccines containing potent immunostimulants (e.g., adjuvant systems) may interfere with immunological self-tolerance, pIMDs are considered AESIs undergoing special safety monitoring for GSK vaccines containing Adjuvant Systems. pIMDs are a subset of adverse events that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology. Risk mitigation strategy includes close monitoring of pIMDs as per study protocol and analysis of safety data generated through clinical trials and other sources. The potential risk of adverse events of possible immune-mediated etiology is mentioned in the ICF. In addition, the ICF advises participants to contact the study doctor or the study staff immediately, should they get any symptoms that they feel may be serious.

The AS37 adjuvant has been tested in a Phase 1 clinical study with MenC antigen and the AS37 formulations containing CCI [redacted] doses from 12.5 to 50 µg had clinically acceptable safety profile, with no clear trend in the incidence of AEs in relation to the dose-escalation. There were no reports of AEs leading to withdrawal or AEs of special interest including new onset chronic diseases. Only one unrelated SAE (joint injury) was reported. However, for the group receiving AS37A (100 µg of CCI [redacted], an increase in number of solicited general AEs as compared with the other AS37 groups and the control was observed. Additionally, in the AS37A group, there were 3 reports (18.8%) of severe solicited systemic AEs (headache, nausea and fever) [Gonzalez-Lopez, 2019]. Therefore, there is a potential risk that AS37A may be more reactogenic than AS37B (50 µg of CCI [redacted]. The risk mitigation measures include staggered vaccination with dose-escalation in AS37 groups, and appropriate safety monitoring with holding rules (see Section 8.2.3).

Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, erythema, and swelling.

In addition to potential risks related to the vaccine, there may be risks related to the blood sampling planned in the study:

- Pain and bruising may occur at the site where blood is drawn; as a mitigation strategy, a topical analgesic may be applied to the site where blood will be taken.
- Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion.
- A nerve may be injured in the process of collecting blood.
- An infection may occur at the injection site.

To mitigate these risks, blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation, redness, nerve injury or infection at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the participant's health.

For details of study procedures, dose, and study design justification, refer to Section 1.3 and Section 4.3.

2.3.2. Benefit assessment

The participants may directly benefit from study intervention administration by being protected against Hepatitis B virus. For participants with insufficient anti-HBs titers at the end of the study, a dose of *Engerix-B* will be offered.

An indirect benefit is that the information obtained in this study will help in determining whether the AS37 adjuvant can be used in the development of future vaccines.

Another benefit for all study participants may include gaining information about their general health status through the medical evaluations/assessments associated with this study (i.e., physical examination).

2.3.3. Overall benefit/risk conclusion

All study vaccines are based on HBsAg, which is a component of registered Hepatitis B vaccines, *Engerix-B* and *Fendrix,* used in this study. *Engerix-B* has established safety and efficacy profile and it is expected that *Fendrix* will provide a good immune response with acceptable reactogenicity compared to *Engerix-B.* The combination of HBsAg and AS37 has not been tested in human to date so information on safety and efficacy of this formulation is currently not available. However, AS37 with MenC antigen has already been tested in humans with no safety concern identified, though a higher systemic reactogenicity with AS37A was observed (see Section 2.3.1).

The combination of HBsAg and AS03 has been tested in humans in one Phase 2 clinical study (NCT00805389) and the tolerability was acceptable, with no serious AEs related to vaccination reported [Burny, 2017].

Measures to minimize risk to study participants are described in this protocol and include, among others, staggered vaccination with dose-escalation in AS37 groups, and appropriate safety monitoring with holding rules. Based on the theoretical concern that vaccination with vaccines containing potent immunostimulants (e.g., adjuvant systems) may interfere with immunological self-tolerance, pIMDs will be monitored as AESIs. Considering the measures taken to minimize the risk to participants in this study, the potential risks are justified by the potential benefits linked to the development of this adjuvant and study participation.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the reactogenicity and safety in all study groups.	• Percentage of participants with solicited administration site and systemic AEs within 14 days (Day 1 till Day 14) after Dose 1 and Dose 2. • Duration of solicited AEs (administration site and systemic) after Dose 1 and Dose 2. • Percentage of participants with any unsolicited AEs within 31 days (Day 1 till Day 31) after Dose 1 and Dose 2. • Percentage of participants with SAEs, MAEs and AEs leading to study withdrawal throughout the entire study period. • Percentage of participants with pIMDs throughout the entire study period. • The absolute values and changes in hematology and biochemistry parameters post-Dose 1 (Day 8 and Day 31) and post-Dose 2 (Day 38 and Day 61) from baseline (pre-vaccination, Day 1).

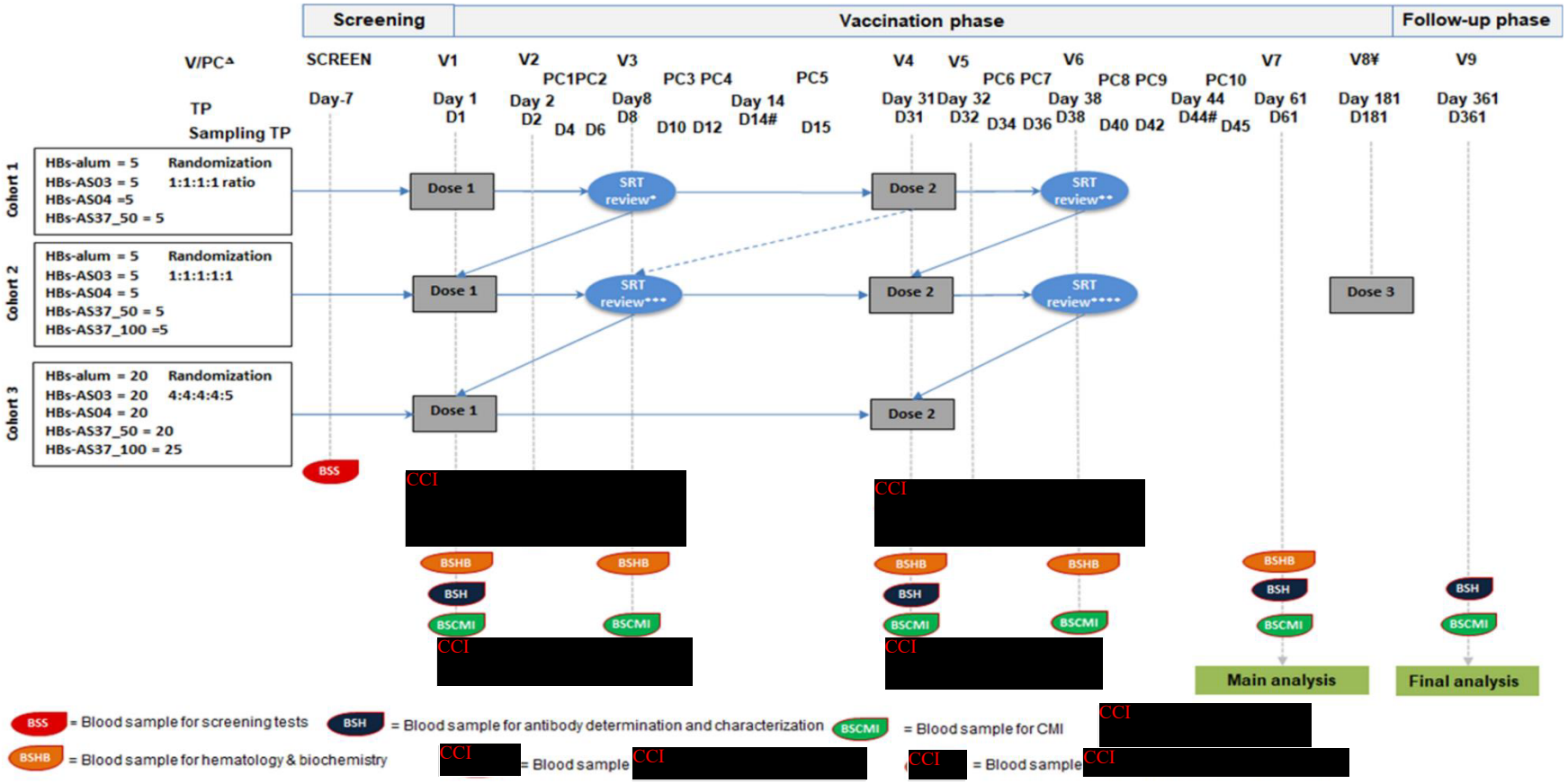
Objectives	Endpoints
	• Percentage of participants with abnormal laboratory parameter values at pre-vaccination (Day 1), post-Dose 1 (Day 8 and Day 31) and post-Dose 2 (Day 38 and Day 61).
Secondary	
To evaluate the humoral immune response in all study groups.	• GMC of Anti-HBs Ab concentrations at Day 1, Day 31, Day 61 and Day 361. • Anti-HBs seroconversion and seroprotection rates at Day 31, Day 61 and Day 361.
Tertiary	
CCI [redacted]	
To evaluate the cell-mediated immune response induced in all study groups.	• Frequency of HBsAg-specific CD4+/CD8+ T-cells per 10^6 CD4+/CD8+ T-cells producing at least 2 activation markers including at least 1 cytokine among IFN-γ, IL-2, TNF-α, IL-13, IL-17, 4-1BB and/or CD40L at Day 1, Day 8, Day 31, Day 38, Day 61 and Day 361. • Frequency of plasmablasts, T Follicular Helper cells (TFH) and memory B-cells (flow cytometry) at Day 1, Day 8, Day 31, Day 38 and Day 61, in a subset of participants. CCI [redacted] • Frequency of HBsAg-specific memory B-cells (ELISPOT) at Day 1, Day 31, Day 61 and Day 361.
CCI [redacted]	

AE = adverse event; **SAE** = serious adverse event; **MAE** = medically attended event; **pIMD** = potential immune-mediated disorder; **GMC** = geometric mean concentration; **HBs** = Hepatitis B surface antigen; **Ab** = antibody; CCI [redacted]
CCI [redacted]
CCI [redacted]

4. STUDY DESIGN

4.1. Overall design

Figure 1 Study design overview



V = visit; **PC** = phone contact; **D** = Day; **N** = number of participants; **SRT** = safety review team; **TP** = timepoint; CCI [redacted]

¥Only for participants in the HBs-alum group

∆Phone contact at Day 4, Day 6, Day 10, Day 12, Day 15, Day 34, Day 36, Day 40, Day 42, and Day 45

*First safety review after the first 5 participants in the HBs-AS37_50 group have completed 7 days safety follow-up post-Dose 1, before administering the second dose to these participants, and before enrolment of the remaining participants in this group in the next cohorts, and the first 5 participants in the HBs-AS37_100 group in the second cohort. The enrolment in the second cohort will start after the second dose is administered to all 20 participants in the first cohort.

**Second safety review after the first 5 participants in the HBs-AS37_50 group have completed 7 days safety follow-up post-Dose 2, before administering the second dose to the remaining participants in this group in the next cohorts.

***Third safety review after the first 5 participants of the HBs-AS37_100 group have completed 7 days safety follow-up post-Dose 1, before administering the second dose to these participants, and before enrolment of the remaining participants in this group in the third cohort. The enrolment in the third cohort will start after the third SRT review.

****Fourth safety review after the first 5 participants in the HBs-AS37_100 group have completed 7 days safety follow-up post-Dose 2, before administering the second dose to the remaining participants in this group in the third cohort.

#Timepoints for safety data cut-off.

CCI [redacted]

Note: Cohort 3 will enroll a minimum of 70 (and maximum of 105) participants distributed between the groups as follows: a minimum of 23 (and maximum of 30) participants in HBs- Alum, HBs-AS03, HBs-AS04, HBs-AS37_50, HBs AS37_100

- **Type of study**: Self-contained.
- **Experimental design**: Phase 1/2a, dose-escalation, open-label, multi-country study with 5 parallel groups.
- **Duration of the study**: ~ 361 days for all participants.
- **Primary completion date**: Day 361.
- **Control**: Active comparators: *Engerix-B, Fendrix* and HBs-AS03.
- **Blinding**: Open-label. Refer to Section 6.4 for details.
- **Data collection**: Standardized eCRF. Solicited events will be collected using a Participant Diary (eDiary).
- **Safety monitoring**: Refer to Section 8.2.3 for the review of safety data by an internal SRT and details of holding rules and safety monitoring.

4.2. Study groups

Refer to Figure 1 and Table 4 for an overview of the study groups.

4.2.1. Overview of the recruitment plan

There will be 3 different cohorts recruited into this study, which will be enrolled in a staggered way. Cohort 1 will enroll 20 participants distributed between the groups as follows: 5 in HBs-Alum, 5 in HBs-AS03, 5 in HBs-AS04, and 5 in HBs-AS37_50. Cohort 2 will enroll 25 participants distributed between the groups as follows: 5 in HBs-Alum, 5 in HBs-AS03, 5 in HBs-AS04, 5 in HBs-AS37_50, and 5 in HBs-AS37_100. Cohort 3 will enroll a minimum of 70 (and maximum of 105) participants distributed among the groups to reach a total sample size across the three cohorts as follows: a minimum of 23 (and maximum of 30) participants in HBs-Alum, HBs-AS03, HBs-AS04, HBs-AS37_50, and HBs-AS37_100. Sample sizes per group are presented in terms of minimums and maximums to allow early stop of enrollment due to reasons of feasibility linked to recruitment of the study population. The choice of the minimum sample size for each group is guided by statistical considerations on the precision of the safety evaluation and on the power for the immunogenicity comparison. For more details, refer to Section 9.4 and Section 9.5.

There will be a screening phase whereby participants will be screened for eligibility before recruitment. The study is planned to be conducted at sites in multiple countries. Recruitment plan will be defined by each participating site.

The recruitment plan may be adapted based on the actual number of participants enrolled in each country. In case a site would fall behind in participant recruitment, a redistribution of the enrolment target per site in the participating countries may be made. This would allow the other participating sites to enroll additional participants to ensure full and timely enrolment of the overall targeted number of participants specified in this protocol.

The procedures for participants identification/recruitment must be approved by the IEC/IRB together with the material intended for participants identification/recruitment and participants use. Refer to the SPM for additional details.

Table 4 Study groups, intervention and blinding

Study groups	Number of participants	Age (Min-Max)	Study interventions	Timing of intervention		
				Visit 1	Visit 4	Visit 8
HBs-alum	23-30	18-45 years	*Engerix-B*	X	X	X
HBs-AS03	23-30		HBsAg/AS03$_A$	X	X	
HBs-AS04	23-30		*Fendrix*	X	X	
HBs-AS37_50	23-30		HBsAg/AS37B*	X	X	
HBs-AS37_100	23-30		HBsAg/AS37A**	X	X	

*AS37B refers to CCI aluminum hydroxide + 50 µg CCI
**AS37A refers to CCI aluminum hydroxide + 100 µg CCI

4.3. Scientific rationale for study design

Previous preclinical and clinical data suggest that AS37 could have the potential to generate a rapid and high-quality immune response, while demonstrating an acceptable safety profile. However, the MenC/AS37 clinical study did not provide a clear answer to several questions CCI that would allow to position this adjuvant in the adjuvant portfolio. The choice of MenC antigens did not allow to benefit from many historical data which were mainly generated with HBsAg. In general, most GSK vaccines are composed of adjuvanted recombinant protein, whereas the MenC study involved a carbohydrate-protein conjugated antigen. Also, using MenC led to the fact that many responses emerging from that study were in primed participants meaning innate immune responses are difficult to interpret. In order to describe a comprehensive set of immune responses (both adaptive and innate), and to document the safety profile of AS37 in combination with a protein-based vaccine in a naïve population, the current study is proposed. A control group receiving licensed Hepatis B vaccine (*Engerix-B*) and 2 other adjuvanted (AS03 and AS04) Hepatitis B vaccines are included to compare with AS37, and potentially position AS37 in the adjuvant portfolio. Although AS37A generated somewhat higher systemic reactogenicity in the MenC study, it is still considered necessary to test this formulation in the current study with appropriate safety oversight and holding rules, because the vaccine constructs are different (conjugate versus protein) and the population in the current study is naïve.

4.4. Justification for dose

The AS37 adjuvant has been used in a previous clinical study (MenC/AS37) where the AS37 formulations containing CCI doses from 12.5 to 50 µg had clinically acceptable safety profile with no clear trend in the incidence of AEs in relation to the dose-escalation. However, for the group receiving AS37A, an increase in the frequency and severity of systemic solicited AEs was observed, as compared with the other AS37 groups and the control (see Section 2.3.1). Therefore, there is a potential risk that AS37A may be more reactogenic than AS37B.

To mitigate this risk, this study will be conducted in a staggered manner whereby initiation of the HBs-AS37_100 group will be conditional to whether any holding rule is met in the HBs-AS37_50 group. Once the first 5 participants of the HBs-AS37_100 group complete the 7 days safety follow-up after the first dose, the data will be evaluated before enrolment of the remaining participants (see Section 8.2.3.1 for more information on the staggered approach and planned safety reviews).

In terms of immunogenicity, including AS37A in the current study is based on the dose effect observed in enzyme linked immunosorbent assay data from the AS37/MenC study. Given the difference in population and vaccine construct versus the MenC study, adding a AS37A group would optimize the probability to differentiate AS37 from other adjuvants included in the study.

4.5. End of Study definition

A participant is considered to have completed the study if he/she returns for the last visit or is available for the last scheduled procedure as described in the protocol.

End of Study (EoS): Date of the LSLV.

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardize the scientific integrity, regulatory acceptability of the study or safety of the participant.

5.1. Inclusion criteria

All participants must satisfy ALL the following criteria at study entry:

- Participants who the investigator believe can and will comply with the requirements of the protocol (e.g., completion of the eDiaries, return for follow-up visits). INC#1
- Written informed consent obtained from the participant prior to performance of any study-specific procedure. INC#2
- Healthy participants as established by medical history, clinical examination and clinical laboratory assessment before entering the study. INC#3
- A male or female between, and including, 18 and 45 years at the time of the first study intervention administration. INC#4
- Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause. INC#5
- Female participants of childbearing potential may be enrolled in the study if the participant: INC#6
  - Has practiced adequate contraception for 1 month prior to study intervention administration, and,

- Has a negative pregnancy test on the day of study intervention administration, and,
- Has agreed to continue adequate contraception during the entire treatment period and for at least 3 months after completion of the study intervention administration series.

Blood sample for simultaneous FSH and estradiol levels may be collected at the discretion of the investigator to confirm non-reproductive potential according to local laboratory reference range.

5.2. Exclusion criteria

The following criteria should be checked at the time of study entry. The potential participant MAY NOT be included in the study if ANY exclusion criterion applies:

5.2.1. Medical conditions

- Previous vaccination against Hepatitis B. EXC#1
- Positive for anti-HBs antibodies or anti-HBc antibodies or HBsAg. EXC#2
- Any previous administration of monophosphoryl lipid (MPL) and/or AS37. EXC#3
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required). EXC#4
- Any confirmed or suspected autoimmune disease. EXC#5
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study interventions. EXC#6
- Recurrent history or uncontrolled neurological disorders or seizures. EXC#7
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study. EXC#8
- Any clinically significant* hematological (hemoglobin level, white blood cell, lymphocyte, neutrophil, eosinophil, platelet and red blood cell count) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine) laboratory abnormality. EXC#9

  *The investigator should use his/her clinical judgment to decide which abnormalities are clinically significant.
- Any past or current malignancies and lymphoproliferative disorders. EXC#10

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug or vaccine) other than the study interventions during the period beginning 30 days before the first dose of study intervention or their planned use during the study period. EXC#11

- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before each dose and ending 30 days after each dose of study intervention administration with the exception of influenza vaccine (pandemic or seasonal). EXC#12
- A vaccine not foreseen by the study protocol administered during the period starting at Visit 1 or 30 days before each dose and ending 30 days after the last dose of study intervention administration*, with the exception of influenza vaccine (pandemic or seasonal). EXC#13

  *In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organized by public health authorities outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine, provided it is licensed/authorized and used according to its Product Information.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab). EXC#14
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months before the first study intervention dose(s). For corticosteroids, this will mean prednisone equivalent ≥20 mg/day. Inhaled and topical steroids are allowed. EXC#15
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the administration of the first dose of study intervention or planned administration during the study period. EXC#16

5.2.3. Prior/Concurrent clinical study experience

Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational intervention. EXC#17

5.2.4. Other exclusions

- Pregnant or lactating female. EXC#18
- Female planning to become pregnant or planning to discontinue contraceptive precautions. EXC#19
- History of chronic alcohol consumption and/or drug abuse. EXC#20
- Any study personnel or their immediate dependents, family, or household members. EXC#21

[redacted]

5.3. Lifestyle considerations

Not applicable for this study.

5.4. Screening failures

A screen failure is an individual who consents to participate in this study but is not randomized to a study intervention.

Limited data for screening failures (at least informed consent date, demographic data, eligibility criteria check, reason for screening failure and any SAEs that occurred at the visit) will be collected and reported in the eCRF.

5.4.1. Rescreening

Participants who met the eligibility criteria in the previous cohorts but could not be randomized as either the cohort threshold was attained, or the screening window had elapsed, can be re-screened.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Individuals who failed initial screening but passed rescreening may be admitted into the study based upon clinical judgment and after consultation with the CSL.

Participants with hematological/biochemical values out of normal range which are expected to be temporary may be rescreened/dosed later within the allowed time interval.

Participants that are rescreened will be recorded with the same participant number. Reason for rescreening will also be recorded.

5.5. Criteria for temporarily delaying enrolment/study intervention administration.

Enrollment/study intervention administration may be postponed within the permitted time interval until transient conditions cited below are resolved:

- Acute disease and/or fever at the time of enrolment and/or study intervention administration. Refer to the SoA (Table 1) for definition of fever and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to study intervention administration.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention.

6.1. Study interventions administered

Table 5 Study interventions administered

	Study intervention 1	Study intervention 2	Study intervention 3	Study intervention 4	Study intervention 5
Study intervention name:	*Engerix-B*	HBsAg/AS03A	*Fendrix*	HBsAg/AS37B* (*CCI $Al(OH)_3$ + 50 µg CCI)	HBsAg/AS37A** (** CCI $Al(OH)_3$ + 100 µg CCI
Study intervention formulation	CCI [redacted]				
Dose Form (presentation)					

	Study intervention 1	**Study intervention 2**	**Study intervention 3**	**Study intervention 4**	**Study intervention 5**
Type	Combination product	Biologic	Combination product	Biologic	Biologic
Use	Comparator	Comparator	Comparator	IMP	IMP
Authorized AxMP/ Unauthorized AxMP	Not applicable				
Route of administration	Intramuscular				
Administration site:					
Location	Deltoid				
Directionality	Not applicable				
Laterality* **	Non-dominant				
Number of doses to be administered	3	2			
Volume to be administered** **	1.0 mL	0.5 mL			
Packaging, labeling and TM	Refer to the SPM for more details				
Manufacturer	GSK				

AxMP = auxiliary medicinal product; **MPL** = monophosphoryl lipid; **SPM** = study procedures manual.

***The non-dominant arm is the preferred arm for injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed.

****Refer to the SPM for the volume after reconstitution

Study participants must be observed closely for at least 60 minutes after the administration of the study interventions. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis or syncope.

6.1.1. Medical devices

- The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are pre-filled syringes for *Engerix-B* and *Fendrix*.
- No other medical devices (not manufactured by or for GSK) are provided for use in this study.
- Instructions for medical device use are provided in SPM.
- All device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Sections 8.4.6 and 10.6) and appropriately managed by GSK.

6.2. Preparation, handling, storage, and accountability

The study interventions must be stored in a secured place within the temperature range specified on the study intervention's label. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

Only authorized study personnel should be allowed access to the study interventions. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the SPM for more details on storage and handling of the study interventions.

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

Participant identification numbers will be assigned sequentially to the individuals who have consented to participate in the study. Each study center will be allocated a range of participant identification numbers.

6.3.2. Randomization to study intervention

The randomization of supplies within blocks will be performed at GSK, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK. Entire blocks will be shipped to the study centers/warehouse(s).

6.3.3. Intervention allocation to the participant

The randomization algorithm will use a minimization procedure accounting for center and sex, as well as cohort to improve balance between groups for the SRT reviews.

Once a participant identification number is allocated, the randomization system will determine study group and will provide the study intervention number to be used for the first dose. The study intervention number(s) to be used for subsequent dosing will be provided by the same automated Internet-based system (SBIR).

The actual treatment number used for first vaccination of the participant must be recorded by the investigator in the eCRF (Randomization/Treatment Allocation section).

When an automated, Internet-based system, SBIR is not available, please refer to the SBIR user guide or SPM for specific instructions.

Refer to the SPM for additional information about the study intervention number allocation.

6.4. Blinding and unblinding

This is an open-label study.

The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention groups and the identity of the participant.

6.5. Study intervention compliance

When the study intervention is administered at the site, participants will receive it directly from the investigator or designee, under medical supervision. The date of administration of each study intervention dose in the clinic will be recorded in the source documents.

6.6. Dose modification

Section is not applicable.

6.7. Continued access to study intervention after the end of the study

The investigator is encouraged to share the immunological assay results of non-responders with the study participants.

An extra dose of *Engerix-B* to be provided by GSK will be offered at the end of the study to non-responders (anti-HBs Ab concentration <100 mIU/mL) by the investigator irrespective of the study intervention received in the study.

6.8. Treatment of overdose

Section is not applicable.

6.9. Concomitant therapy

At each study visit/contact the investigator or his/her delegate should question the participant about all medications/products taken, and vaccinations received by the participant.

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF:

- All concomitant medication associated with an adverse event, including vaccines/products, except vitamins and dietary supplements, administered during a 31-day follow-up after each dose of study intervention (i.e., day of vaccination and 30 subsequent days).
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines. Please refer to Sections 5.2.2 and 9.2.1 for further details.

- All concomitant medication which may explain/cause/be used to treat an SAE/pIMD including vaccines/products, as defined in Sections 8.4.1 and 10.3.2. These must also be recorded in the Expedited Adverse Event Report.

The LML should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of study intervention. A participant who discontinued study intervention may continue other study procedures (e.g., safety or immunogenicity), planned in the study protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

- AE requiring expedited reporting to GSK. Refer to Section 10.3.10.1 for details.
- Unsolicited non-serious AE.
- Solicited AE.
- Not willing to be vaccinated.
- Other (specify).

7.1.1. Contraindications to subsequent study intervention(s) administration

The eligibility for subsequent study intervention administration must be confirmed before administering any additional dose.

Participants who meet any of the criteria listed below or criteria listed in Sections 5.2.1 and 5.2.2 should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures, at the investigator's discretion (Section 10.3.8.2). All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to study intervention or non-study concomitant vaccine/product, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant if he/she continues to participate in the study.
- Anaphylaxis following the administration of study interventions.

- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the participant to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgment prior to administering the next dose of the study intervention(s). Refer to Section 10.3.5.1 for the definition of pIMDs.

7.2. Participant discontinuation/withdrawal from the study

A participant is considered to have withdrawn from the study if no new study procedure has been performed or no new information has been collected for him/her since the date of withdrawal/last contact.

From an analysis perspective, a study 'withdrawal' refers to any participant who did not return for the concluding visit planned in the protocol.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses.

The primary reason for study withdrawal will be documented in the eCRF, based on the list below:

- AEs requiring expedited reporting to GSK. Refer to Section 10.3.10.1 for details.
- Unsolicited non-serious AEs.
- Solicited AE.
- Withdrawal by participant, not due to an AE. *
- Migrated/moved from the study area.
- Lost to follow-up.
- Sponsor study termination.
- Other (specify).

*If a participant is withdrawn from the study because he/she has withdrawn consent and the reason for withdrawal was provided, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.8.2).

7.3. Lost to follow-up

A participant will be considered 'lost to follow-up' if he/she fails to return for scheduled visits and cannot be contacted by the study site.

Please refer to the SPM for a description of actions to be taken before considering the participant lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are only permitted when necessary for the management of immediate safety concerns for the participant.

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team becomes aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.

Study procedures and their timing are summarized in the SoA (Section 1.3).

All screening evaluations must be completed, and the results reviewed before confirming that potential participants meet all eligibility criteria.

The investigator will maintain a log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

Procedures conducted as part of routine clinical management (e.g., hematologic profiles), and obtained before the participant signed the ICF, may be used for screening and/or for establishing a clinical baseline (provided the procedure met protocol specified criteria and was performed within the time frame defined in the SoA (Section 1.3)).

The SPM provides the investigator and site personnel with detailed administrative and technical information that does not impact participant safety.

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be followed. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Safety follow-up may be made by a telephone call, other means of virtual contact or home visit (from the site staff or from the home care service system), if appropriate.
- If the eDiary device was provided to the participant, it may be returned to the study center by conventional mail after the end of the relevant data collection period (refer to the SPM for details). If the eDiary app was provided to the participant for use on their personal device, the app can be disabled remotely.
- Biological samples may be collected at a different location* other than the study site or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

*Note: It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff, and documented delegation of responsibilities in this location. This alternate location may need to be covered by proper insurance for the conduct of study on participants by investigator and study center staff other than the designated study center and must be compliant according to local laws and/or regulations.

- If despite best efforts it is not possible to collect the biological samples within the interval pre-defined in the protocol (see Table 2), then the interval may be extended up to a maximum length of 60 days after Visit 1 to Visit 4 and after Visit 4 to Visit 7.

The impact on the Per-Protocol Set for immunogenicity will be determined on a case-by-case basis.

8.1. Immunogenicity assessments

Biological samples will be used for research planned in the protocol and for purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol.

If allowed by informed consent, the samples collected in this study may also be used for further research to better understand the study disease(s) under evaluation and/or further characterize the immune response to the study vaccine(s) and/or to further understand other diseases and/or inform the development of new products. In addition, the samples may be used to develop new research methods, assays, and tests. To this end, all participants in countries where this is allowed will also be asked to give consent to further research at the time they give consent to join the study. Biological samples may also be shared with a contracted partner for further research. The further research will be subject to prior IEC/IRB approval, if required by local legislation.

Information on further research and its rationale can be obtained from GSK.

Sample testing will be done in accordance with the recorded consent of the individual participant.

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

8.1.1. Biological samples

An overall volume of ~490.5 mL per participant will be collected during the entire study period, over a one-year period. Refer to Table 6 and SoA (Section 1.3) for details of volumes collected for different assessments.

Table 6 Biological samples

Sample type	Quantity	Unit	Timepoint	
Blood sampling for anti-HBs Ab, anti-HBc Ab and-HBs Antigen screening tests	~8.5	mL	SCREEN (Day -7)	All screened
Blood sampling for antibody determination CCI [redacted]	~20		Day 1, Day 31, Day 61 and Day 361	All participants
Blood sampling CCI [redacted]	~5		CCI [redacted]	
Blood sampling CCI [redacted]	~5			
Blood sampling for CMI response	~50		Day 1, Day 8, Day 31, Day 38, Day 61 and Day 361	All participants
Blood sampling for hematology/biochemical analysis at screening and for safety monitoring	~7		SCREEN (Day -7)	All screened
			Day 1, Day 8, Day 31, Day 38, and Day 61	All participants

8.1.2. Laboratory assays

Table 7 Laboratory assays at screening

Timepoint	Study timing	Blood analyzed for:	Laboratory
Day -7	Screening Visit (SCREEN)	Anti-HBs antibodies, anti-HBc antibodies, HBsAg	GSK*

*GSK designated central laboratory

Table 8 Laboratory assays

Assay type	System	Component	Challenge	Method	Laboratory*
Humoral Immunity (antibody quantification and characterization)	Serum	HBs-specific Ab quantification		Chemiluminescence immunoassay (CLIA)	GSK**
	CCI [redacted]				
CMI	PBMC	Anti-HBs-specific CD4+/CD8+ T-cells	HBs peptide pool	Intracellular cytokine staining / Flow cytometry	GSK**
	PBMC	CCI [redacted] CCI [redacted] and Memory B-cells	HBs antigen	Flow cytometry	GSK**
	CCI [redacted]				
	PBMC	Memory B-cells	HBs antigen or peptide pool	B-cell ELISPOT	GSK**
CCI [redacted]					

CCI [redacted]

The addresses of clinical laboratories used for sample analysis are provided in a separate document accompanying this study protocol.

GSK clinical laboratories have established a Quality System supported by procedures. The activities of GSK clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

8.1.3. Immunological read-outs

Refer to Table 9 for the number of participants planned to be evaluated per time point and laboratory assessment. CCI [redacted]

Table 9 Laboratory testings and timepoints

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-Dose	All	~150	Anti-HBsAg-specific antibodies (quantification CCI [redacted])
				HBs-specific CD4+/CD8+ T-cells
				HBs-specific memory B-cells
				CCI [redacted]
		CCI [redacted]		and Memory B-cells
CCI [redacted]				CCI [redacted]
				and Memory B-cells
Visit 4 (Day 31)	Pre-Dose 2	All	~150	Anti-HBsAg-specific antibodies (quantification CCI [redacted])
				HBs-specific CD4+/CD8+ T-cells
				HBs-specific memory B-cells
				CCI [redacted]
		CCI [redacted]		and Memory B-cells
CCI [redacted]				CCI [redacted]

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
				CCI [redacted]
Visit 6 (Day 38)	Post-Dose 2	All	~150	
		CCI [redacted]		and Memory B-cells
Visit 7 (Day 61)	Post-Dose 2	All	~150	Anti-HBsAg-specific antibodies (quantification CCI [redacted])
				HBs-specific CD4+/CD8+ T-cells
				HBs-specific memory B-cells
		CCI [redacted]		CCI [redacted]
				and Memory B-cells
				CCI [redacted]
Visit 9 (Day 361)	Post-Dose 2 or post-Dose 3 for participants receiving HBs/Alum	All	~150	Anti-HBsAg-specific antibodies (quantification CCI [redacted])
				HBs-specific CD4+/CD8+ T-cells
				HBs-specific memory B-cells

HBsAg = hepatitis B surface antigen; **HBs** = hepatitis B surface; **CD** = cluster of differentiation.
Details of assay subsets is described in Section 6.3.5.

8.1.4. Clinical safety laboratory assessments

Refer to Section 10.2.1 for the list of clinical laboratory safety assessments required by the protocol. These assessments must be conducted according to the clinical laboratory manual and the SoA.

8.1.5. Immunological correlates of protection

For the Hepatitis B surface antigen, the conventional correlate of protection (CoP) is anti-HBs antibody concentrations above 10 mIU/mL [Kane, 2000].

The investigator is encouraged to share the immunological assay results of non-responders with the study participants.

After the end of the study, GSK will provide investigators with data that may potentially be relevant to the care of their respective participants. This may include the results of research immunological assays (as detailed in Section 8.1) that the investigator may consider to be indicative of responders and non-responders in the study.

An extra dose of *Engerix-B* will be offered by the investigator at the end of the study to non-responders irrespective of the study intervention received in the study (as described in Section 6.7).

8.2. Safety assessments

The investigator and his/her designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant's withdrawal from the study interventions. Refer to the SoA (Section 1.3) for the timepoints for safety assessments.

8.2.1. Pre-intervention administration procedures

8.2.1.1. Collection of demographic data

Record demographic data such as date of birth, sex and race in the participant's eCRF.

8.2.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history* by interviewing the participant or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention in the eCRF.

*Any vaccines administered within 30 days before Visit 1 (Day -29 to Day 1).

8.2.1.3. Physical examination

At screening, perform a targeted physical examination based on the clinical history of the patient and collect temperature, vital signs at rest (heart rate and respiratory rate, blood pressure), height, weight and BMI.

During Visit 1, Visit 4 and Visit 8, perform a physical examination and collect temperature, vital signs at rest (heart rate and respiratory rate, blood pressure). Collected information should be recorded in the eCRF.

Vital signs are to be taken before blood collection for laboratory tests and will consist of one pulse and one blood pressure measurement.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to Section 5.5 for the list of criteria for temporary delay of study intervention administration.

Physical examination at each visit after the study intervention administration visits, will be performed only if the participant indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

8.2.1.4. Pregnancy test

Female participants of childbearing potential must perform a urine pregnancy test before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

Refer to Section 10.4.3.1 for the information on study continuation for participants who become pregnant during the study.

8.2.1.5. Warnings and precautions to administration of study intervention

Warnings and precautions to administration of *Engerix-B* and *Fendrix*, as listed in their respective Prescribing Information (PI), must be checked at each visit with planned administration of study intervention.

8.2.2. Clinical safety laboratory tests

Refer to Section 10.2.1.

8.2.3. Study holding rules and safety monitoring

This study will be overseen by an internal SRT. Four safety reviews by the SRT are planned during the study conduct. In addition, ad hoc SRT reviews can be triggered in case any safety concern is observed.

If any safety concern is identified by the investigator (i.e., meeting of holding rules (see Section 7.2), or any other safety concern), he/she will inform GSK Global Safety immediately (within 24 hours), and vaccination may be put on hold at all sites as a consequence. Following an internal review, GSK will then decide to suspend, modify or continue the conduct of the study. This decision will be documented and provided in writing to the investigators.

8.2.3.1. Staggered administration of study intervention

The study will be conducted following a staggered design, and the initiation of the HBs-AS37_100 group will be conditional to whether any holding rule is met in the HBs-AS37_50 group.

If ≥ 2 participants from the HBs-AS37 groups are to be vaccinated at the same study site on the same day, these participants should be vaccinated sequentially with at least 60 minutes apart to allow monitoring of any acute event, such as anaphylactic reaction.

During the first SRT review, all available safety data will be reviewed once the first 5 participants in the HBs-AS37_50 group have completed 7 days safety follow-up post-Dose 1 (and data are available for analysis), before administering the second dose to these participants, and before enrolment of the remaining participants in this group in the next cohorts, and the first 5 participants in the HBs-AS37_100 group in the second cohort. The enrolment in the second cohort will start after the second dose is administered to all 20 participants in the first cohort.

During the second SRT review, all available safety data will be reviewed once the first 5 participants in the HBs-AS37_50 group have completed 7 days safety follow-up post-Dose 2, before administering the second dose to the remaining participants in this group in the next cohorts.

During the third SRT review, all available safety data will be reviewed once the first 5 participants of the HBs-AS37_100 group have completed 7 days safety follow-up post-Dose 1, before administering the second dose to these participants, and before enrolment of the remaining participants in this group in the third cohort. The enrolment in the third cohort will start after the third SRT review.

During the fourth SRT review, all available safety data will be reviewed once the first 5 participants in the HBs-AS37_100 group have completed 7 days safety follow-up post-Dose 2, before administering the second dose to the remaining participants in this group, in the third cohort.

Seven days safety follow-up data will also include hematological and biochemical laboratory parameters tested at Day 8 post-study intervention administration.

The investigator can only start vaccinating the participants in the AS37 groups with the second dose or in a subsequent cohort upon notification from the sponsor and receipt of written documentation of a favorable outcome of the scheduled SRT reviews.

8.2.3.2. Outcome of safety evaluation

- If no safety signal is observed, the favorable outcome of the safety evaluations will be documented and provided in a written way, authorizing the investigator to start the administration of the subsequent dose of study intervention to participants, as well as enrolment and study intervention administration to the remaining participants in the next step of the study.
- If any of the holding rules 2a-d (Table 10) is met, vaccination will be put on hold, but other procedures relating to safety, immunology and monitoring will continue.
- If any of the holding rules 1a-d (Table 10) is met, or if a signal is identified during ongoing safety monitoring, the study may be put on hold if needed for safety reasons.
- Following an internal review, GSK will then decide to suspend, modify or continue the conduct of the study. This decision will be documented and provided in writing to the investigators.

- The study CSL will be accountable for notifying all investigators of the decision whether to suspend, modify or continue the conduct of the study on all groups or on selected groups.

8.2.3.3. Study holding rules

Study holding rules are defined in Table 10. Holding rules 1a-d will be assessed by the investigator on a continuous basis and meeting any of these holding rules will trigger a hold of vaccination irrespective of number of participants enrolled and/or timing of the event relative to vaccination. Holding rules 2a-d will be assessed by the SRT during the scheduled meetings for evaluation of safety data.

The initiation of the HBs-AS37_100 group will be conditional to whether any holding rule is met in the HBs-AS37_50 group and can only occur upon review of the available safety data during the SRT meetings scheduled as per the staggered approach (see Section 8.2.3.2).

If a safety signal is observed during the SRT review, or if any of the holding rules is met, the SRT can recommend to: (1) continue the study, (2) modify the study, or (3) stop the study. The SRT can recommend stopping vaccination in all groups, or only in a specific study group, while proceeding with vaccination in the other groups. The SRT recommendation should be communicated to the GSB Chair, who will make the final decision on the path forward. GSB Chair must immediately be notified if a holding rule is met.

Table 10 Study holding rules

Holding rule	Event	Number/percentage of participants per group
1a	Death or any **life-threatening SAE** regardless of causality	≥1
1b	Any **SAE** considered at least possibly related to the study intervention as per Investigator or Sponsor assessment	≥1
1c	Any **withdrawal** from the study (by investigator or participant request) following a Grade 3 AE	≥1
1d	Any administration site or systemic solicited AE leading to **hospitalization** or **necrosis** at the injection site, each with an event onset within the 7-day (Day 1-7) post-study intervention period	≥1
2a	Any **Grade 3 solicited administration site AE** (lasting 48h or more as Grade 3) in an investigational group, with an event onset within the 7-day (Day 1-7) post-study intervention period	20%
2b	Any **Grade 3 solicited systemic AE** (lasting 48h or more as Grade 3) in an investigational group, with an event onset within the 7-day (Day 1-7) post-intervention period	20%
2c	Any **Grade 3 unsolicited AE** in an investigational group, that can be reasonably attributed to the study intervention, with an event onset within the 7-day (Day 1-7) post-study intervention period or Any **Grade 3 or above abnormality** in pre-specified hematological or biochemical **laboratory parameters*** in an investigational group at Day 8 post-study intervention	20%
2d	Any **Grade 3 non-serious AE** considered as, at least, possibly related to the study intervention as per Investigator or Sponsor assessment, independent of within or not within the same system-organ-class	≥2

AE = adverse event; **SAE** = serious adverse event; **FDA** = Food and Drugs Administration
*Refer to Table 22 for the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

If the investigator becomes aware of a holding rule 1a-d being met, he/she must suspend administration of the study intervention and inform GSK immediately Refer to Table 13 for contact information.

The following communication sequence must be followed:

- The concerned site staff must put study intervention administration on hold.
- The concerned site staff must immediately inform their local GSK contact defined in Section 8.4.3.1.
- LML will inform the other sites of his/her country, LMLs of other countries and the CSL.
- All informed site staff will confirm to their local contact that action has been taken providing appropriate documentation to GSK.
- GSK will further evaluate the case with the SRT and GSB and will take the decision to restart, modify, or stop the study. All site staff will be informed about that final decision by their local GSK contact.

GSK will inform the investigator if holding rules 2a-d are met (see Section 8.2.3.2).

8.3. Other assessments

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[redacted]

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and other safety reporting

8.4.1. Time period and frequency for collecting AE, SAE and other safety information

Table 11 Timeframes for collecting and reporting of safety information

Event	Pre-Dose*		Dose 1				Dose2				Dose 3				Study Conclusion
			D1	D14	D31		D31	D44	D61		D181	D194	D211		
Administration site and systemic solicited events															
Unsolicited AEs															
AEs/SAEs leading to withdrawal from the study															
SAEs															
SAEs related to the study intervention															
SAEs related to study participation or concurrent GSK medication/vaccine															
Pregnancy															
pIMDs															
MAEs															

D = day; **M** = month; **AE** = adverse event; **SAE** = serious adverse event; **pIMD** = potential immune-mediated disorder; **MAE** = medically attended event

*i.e., consent obtained

The investigator or designee will record and immediately report all SAEs in enrolled participants to the sponsor or designee via the Expedited AE Reporting Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.10. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. See Section 10.3.10.1 for more information on the events requiring expedited reporting to GSK.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 11. Investigators are not obligated to actively seek AEs or SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in Table 13.

8.4.2. Method of detecting AEs and SAEs, pregnancies and other events

Detection and recording of AE/SAE/pIMD/pregnancies are detailed in Section 10.3.8.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.9.

Open-ended and non-leading verbal questioning of participants is the preferred method of acquiring information related to an AE/SAE/pIMD/pregnancy.

8.4.2.1. Clinically significant abnormal laboratory findings

The investigator must review the laboratory report, document that he/she did so, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All clinically significant abnormal laboratory test values reported during the study or within 31 days after the last dose of study intervention should be repeated until the values return to normal/baseline, or until they are no longer considered significantly abnormal by the investigator or LML. Refer to Section 10.3.6 for more information on clinically abnormal laboratory assessments that qualify as an AE or SAE.
- If such values do not return to normal/baseline after an interval judged reasonable by the investigator, the etiology of the abnormal value should be identified, and the sponsor notified.

8.4.3. Regulatory reporting requirements for SAEs, pregnancies and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pIMD/pregnancy, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 12. This is essential for meeting GSK legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/pIMDs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in Section 10.3.9.2.

Local regulatory requirements and sponsor policy for preparation of an investigator safety report of Suspected Unexpected Serious Adverse Reactions (SUSAR) must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has the legal responsibility to notify local authorities/regulatory agencies about the safety of an investigational study intervention. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC and investigators.

Refer to Section 10.3.10 for further details regarding the reporting of SAEs/pIMDs/pregnancies.

Table 12 Timeframes for submitting SAE, pIMD, pregnancy and other events reports to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	24 hours*	electronic pregnancy report	24 hours*	electronic pregnancy report
pIMDs	24 hours** ‡‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

*Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.
‡‡The investigator will be required to confirm review of the SAE/pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/pIMD.

8.4.3.1. Contact information for reporting SAEs, pIMDs, pregnancies and study holding rules

Table 13 Contact information for reporting SAEs, pIMDs, pregnancies and study holding rules

Study contact for questions regarding SAEs, pIMDs, pregnancies Refer to the local study contact information document	**Study contact for reporting of study holding rules** As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the LML
Back-up study contact for reporting SAEs, pIMDs, pregnancies. Available 24/24 hours and 7/7 days: **GSK Global Safety** Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: ogm28723@gsk.com	**Back-up study contact for escalation of holding rules.** CSL

8.4.4. Treatment of AEs

Any medication administered for the treatment of an SAE/pIMDs should be recorded in the Expedited Adverse Event Report of the participant's eCRF page/screen (refer to Section 10.3.10.1).

8.4.5. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in his/her/their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator or his/her back-up.

8.4.6. Medical device deficiencies

The study intervention *Engerix-B* and *Fendrix* is a combination product constituted of a device and biologic product (e.g., pre-filled syringes). Refer to the Glossary of terms for the definition of combination product and medical device deficiency.

8.4.6.1. Detection, follow-up and prompt reporting of medical device deficiency

The investigator is responsible for the detection, documentation and prompt reporting of any medical device deficiency occurring during the study to GSK. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 10.6 for definitions and details on recording and reporting of these events.

The investigator will ensure that follow-up includes any additional investigations to elucidate the nature and/or related of the device deficiency to the incident. Follow-up applies to all participants, including those who discontinue study intervention or the study.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and reported to GSK within 24 hours.

8.4.6.2. Regulatory reporting of medical device deficiency when used as combination product

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to GSK. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to Section 10.6 for details of reporting.

The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

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8.9. Immunogenicity assessments

Immunogenicity is described in Section 8.1.

8.10. Health outcomes

Not applicable for this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

No confirmatory statistical hypotheses are to be tested. All analyses are descriptive. The use of these descriptive analyses will be limited to hypotheses generation or to supportive analyses of other confirmatory analyses or hypotheses generation.

9.2. Analysis sets

Table 14 Analysis sets

Analysis Set	Description
Screened	All participants who were screened for eligibility.
Enrolled	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening procedure). NOTE: Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (i.e., met eligibility but not needed) are excluded from the Enrolled Set as they did not enter the study.
Exposed	All participants who received at least 1 dose of the study intervention. Analysis per group using the Enrolled Set is based on the administered intervention.
Per-Protocol	All eligible participants who received all doses as per protocol, had immunogenicity results post-dose, complied with dosing/blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.
CCI [redacted]	

9.2.1. Criteria for elimination from analysis

If the participant meets one of the criteria mentioned below or ones listed in Section 7.1.1, he/she may be eliminated from Per-Protocol analysis.

Participants may be eliminated from the Per-Protocol Set for immunogenicity if, during the study, they incur an intercurrent medical condition that could alter their immune response (i.e., varicella, HIV, lymphoma) or are confirmed to have an alteration of their initial immune status. For further details on criteria for elimination from Per-Protocol set, refer to the Statistical Analysis Plan.

9.3. Statistical analyses

The SAP will be finalized prior to the First Subject First Visit and it will include a more technical and detailed description of the statistical analyses. This section is a summary of the planned statistical analyses.

The analyses will be descriptive with the aim to characterize the safety/reactogenicity and immunogenicity of the vaccine groups.

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final clinical study report (CSR).

9.3.1. Primary endpoints analyses

The analysis of the primary objective will be performed on the Exposed Set (ES).

Endpoint description	Analysis set	Statistical analysis methods
Reactogenicity and Safety	Exposed	Descriptive statistics: • Percentage of participants with solicited administration site and systemic AEs within 14 days (Day 1 till Day 14) and severity grading will be tabulated with exact 95% CI for each group after Dose 1 and Dose 2 of the study intervention and overall. • Descriptive statistics of duration of solicited AEs (administration site and systemic) will be tabulated for each group after Dose 1 and Dose 2 of the study intervention and overall. • Percentage of participants with any unsolicited AEs within 31 days (Day 1 till Day 31) and severity grading will be tabulated with exact 95% CI for each group after Dose 1 and Dose 2 of the study intervention and overall. • Percentage of participants with SAEs, related SAEs, MAEs and AEs leading to study withdrawal throughout the entire study period will be tabulated with exact 95% CI for each group. • Percentage of participants with pIMDs throughout the entire study period will be tabulated with exact 95% CI for each group. • Descriptive statistics of the absolute values and changes in hematology and biochemical parameters from baseline at each protocol specified timepoints will be tabulated for each group. • Percentage of participants with abnormal laboratory parameter values will be tabulated with exact 95% CI for each group pre-vaccination, after Dose 1 and after Dose 2 of the study intervention and overall.

AE = adverse event; **CI** = confidence interval; **SAE** = serious adverse event; **MAE** = medically attended event; **pIMD** = potential immune-mediated disorder.

9.3.2. Secondary endpoints analyses

The analysis of the secondary objective will be performed on the Per-Protocol Set (PPS). If 5% or more of the vaccinated participants are eliminated from the PPS at one timepoint, an additional sensitivity analysis will be performed on the ES.

Endpoint description	Analysis set	Statistical analysis methods
Immunogenicity	Per-Protocol	Descriptive statistics: • Anti-HBs antibody GMCs and their 95% CI will be tabulated and represented graphically for each group at each timepoint. • GMCs ratios, their 95% CI and related p-value for difference will be tabulated for post-Dose 1 and Dose 2 for all pairwise comparisons between groups. CCI [redacted] • Antibody concentrations will be displayed using reverse cumulative curves for each protocol defined timepoint. • Percentage of participants above seroconversion and seroprotection threshold will be tabulated with exact 95% CI for each group at each protocol specified timepoint. • Seroconversion and seroprotection rates will be compared, and the 95% CI and related p-value for the difference will be tabulated for post-Dose 1 and Dose 2 for all pairwise comparisons between groups. CCI [redacted]

GMC = geometric mean concentration; **CI** = confidence interval; **ANCOVA** = Analysis of Covariance

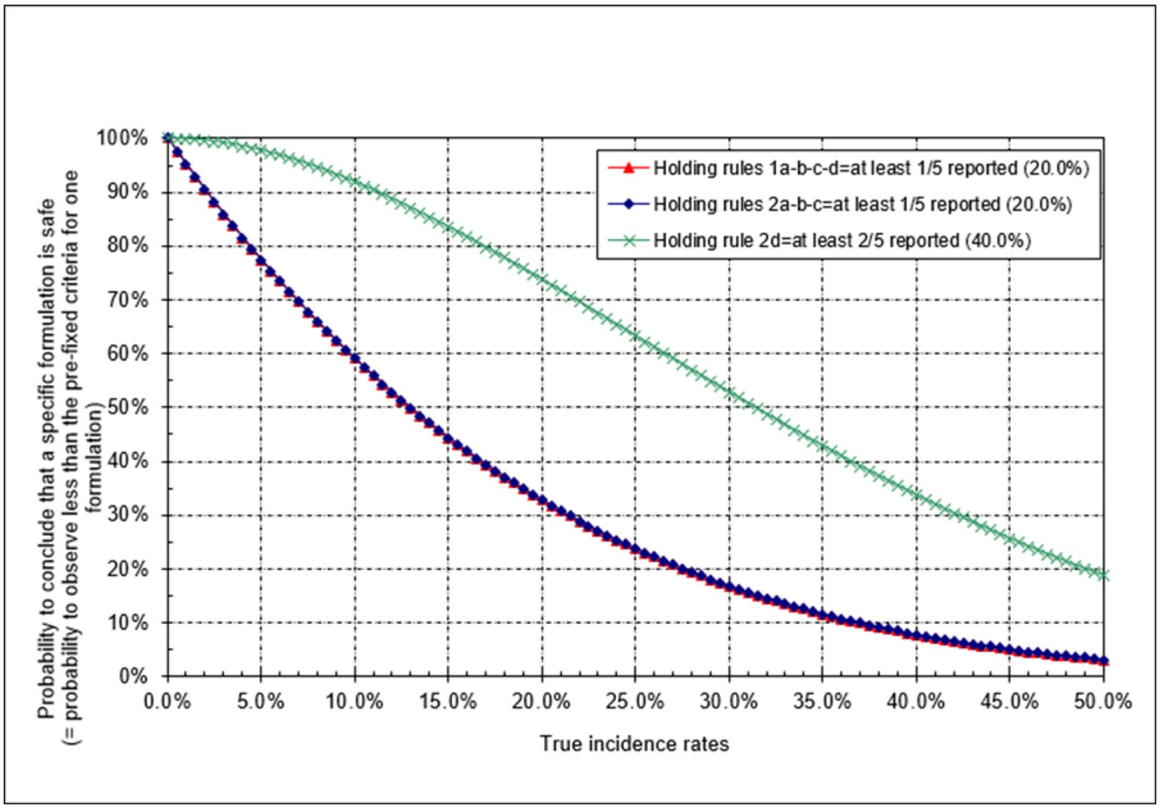
9.4. Interim analyses

There will be no interim analyses, a main analysis is planned on data collected post-Dose 2 (Day 61 – Visit 7) and a final analysis including data up to study end (Day 361 - Visit 9). However, there will be interim safety monitoring.

Interim safety monitoring will be performed based on all the available safety data after 5 participants from each of the AS37 groups have completed the 7 days safety follow-up period post-Dose 1 and post-Dose 2, applying the safety holding rules as described in Table 10. Holding rules 1a-d from Table 10 will be assessed by the investigator on a continuous basis, holding rules 2a-d from Table 10 will be assessed by the SRT during the scheduled meeting for evaluation of safety data. These interim safety evaluations will be used to decide on the enrolment of the remaining participants and administration of the second dose in the AS37 groups, as well as the enrolment of the first 5 participants in HBs-AS37_100 group (when evaluating the first 5 participants post-Dose 1 from the HBs-AS37_50 group).

Figure 2 shows the probability of meeting the holding rules described in Table 10, for a group of sentinel participants (5 participants).

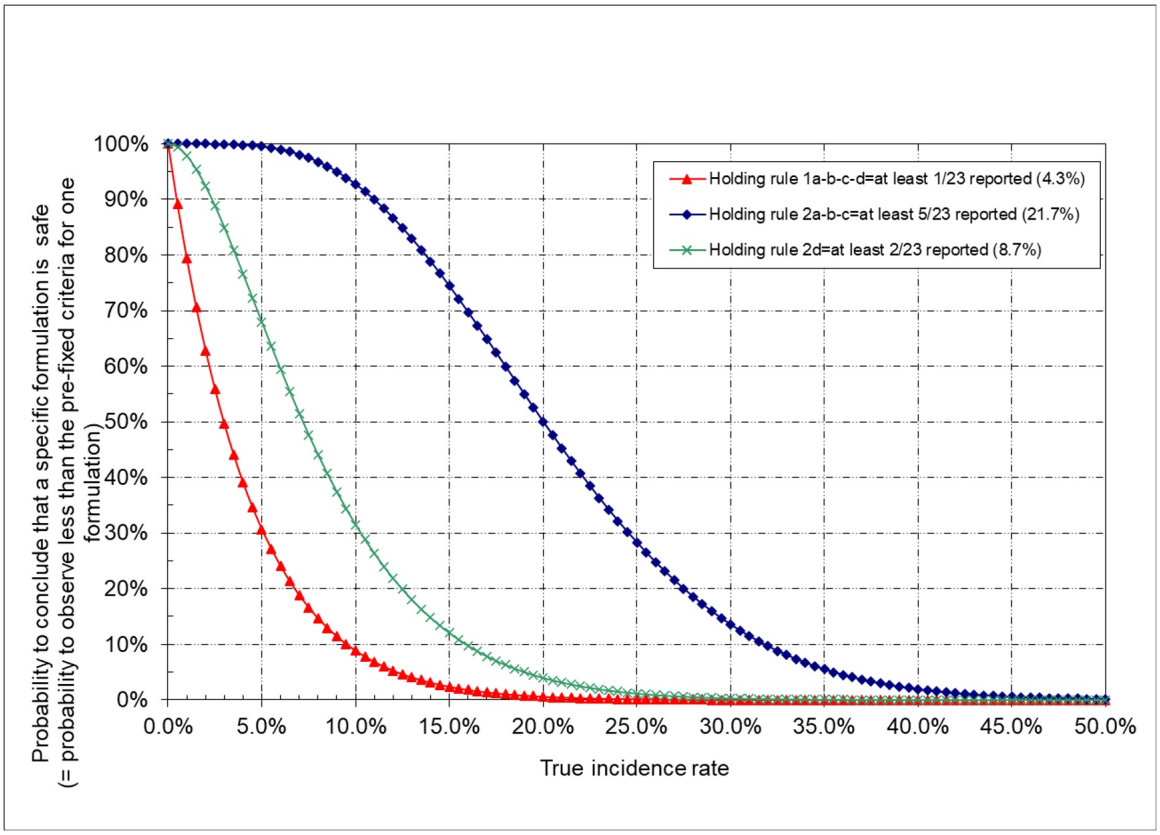
Figure 2 Risk assessment curves for study holding rules after 5 participants (sentinel participants)*



*The binomial distribution was used to obtain the probabilities displayed in this figure

Figure 3 shows the probability of meeting the holding rules described in Table 10, for each whole group (23 participants).

Figure 3 Risk assessment curves for study holding rules after 23 participants (minimum sample size for a whole group) *



*A binomial distribution was used to obtain the probabilities displayed in this figure

9.4.1. Sequence of analyses

9.4.1.1. Main analysis

The main analysis will be performed on safety and reactogenicity data (primary endpoints) and immunogenicity data (secondary endpoints) when all data post-Dose 2 (Day 61 – Visit 7) are cleaned and available. CCI [redacted].

9.4.1.2. Final analysis

The final analysis on primary and secondary endpoints (safety, reactogenicity and immunogenicity data) and CCI [redacted]

An integrated CSR containing all the primary, secondary and when available tertiary data will be written and made available to the investigators. Tertiary endpoints data that become available at a later stage will be documented in annex(es) to the CSR and will be made available to the investigators at that time.

9.5. Sample size determination

A minimum of 23 (and maximum of 30) participants per group will be enrolled in this study. The target sample size has been reduced from 30 to 23 participants per group for reasons of feasibility, as discussed in Section 4.2.1. CCI [redacted]

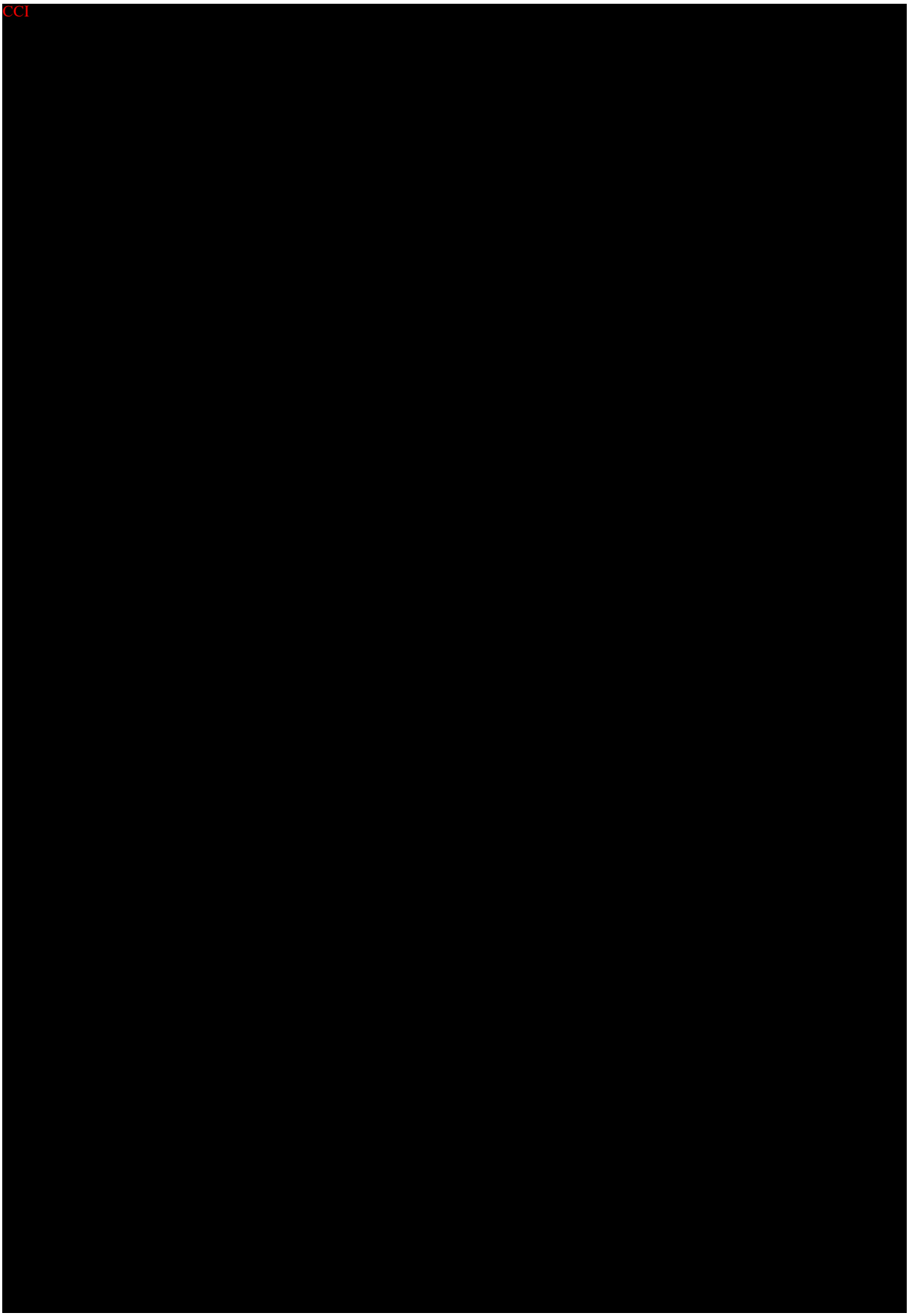
The sample size is not based on formal hypothesis testing and is typical for this kind of study where a treatment is tested for the first-time in human. CCI [redacted]

The primary objectives of the study are to assess the reactogenicity and safety of each vaccine dose throughout the study. CCI [redacted]

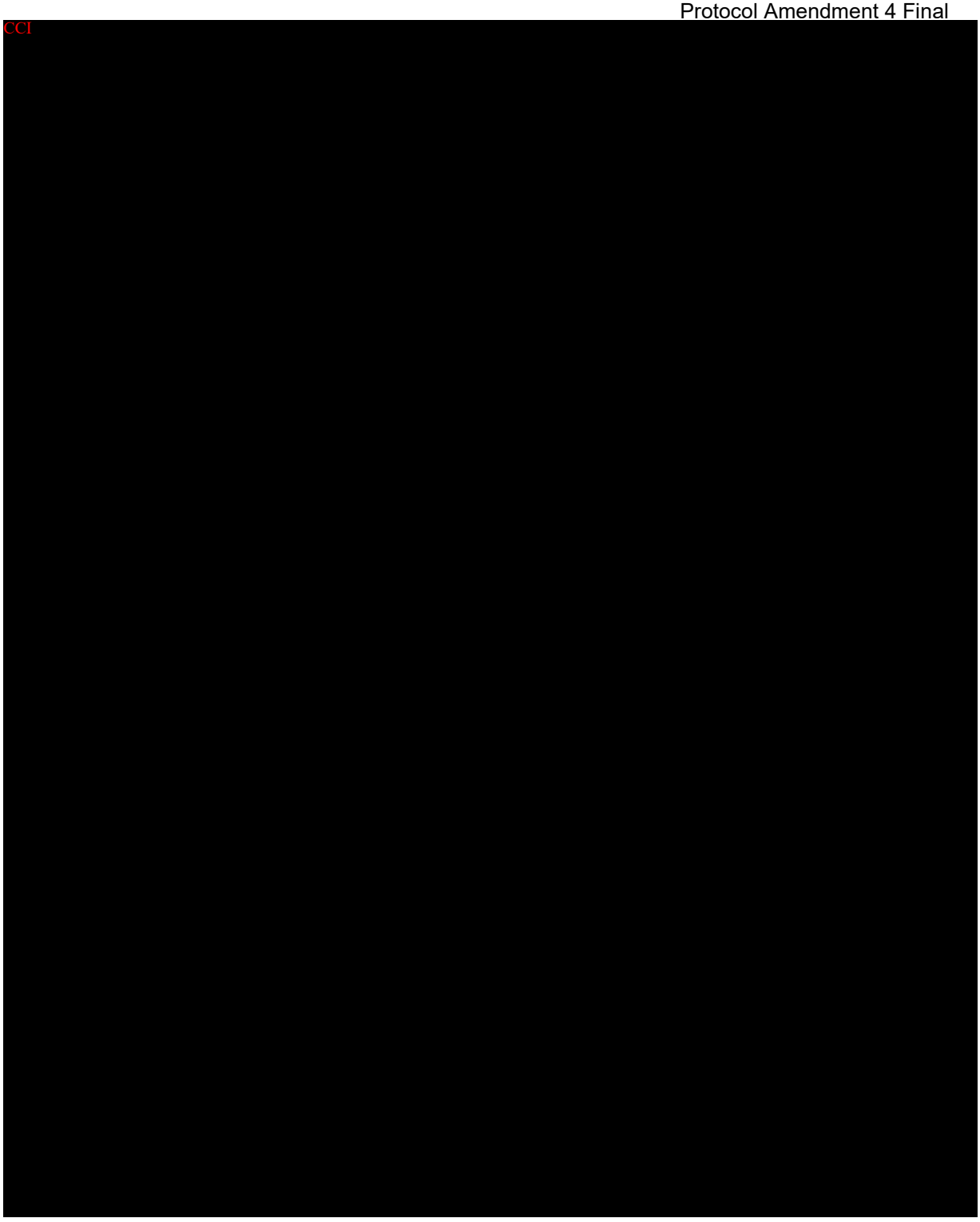
CCI [redacted]

CCI [redacted]

CCI



CCI



10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3. Informed consent process

The investigator or his/her representative must fully explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Freely given and written/witnessed informed consent must be obtained from each participant as appropriate, prior to participation in the study.

Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

Sample testing will be done in accordance with the recorded consent of the individual participant. The medical record must include a statement that written or witnessed informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented if a new version of the ICF(s) or an ICF addendum is released during their participation in the study.

A copy of the ICF(s) must be provided to the participants.

Participants who are rescreened are required to sign a new ICF, only if there are changes to the original ICF.

10.1.4. Data protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets transferred to the sponsor will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study, in accordance with the Data Privacy Notice that will be sent to the site staff.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, that their data will be used as described in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.5. Committees' structure

The protocol will be reviewed and approved by an IEC/IRB before study initiation (see Section 10.1.1 for further details).

Safety monitoring will be conducted by an internal SRT. The SRT will review interim and cumulative safety data and will escalate concerns to the GSB (see Section 8.2.3).

10.1.6. Dissemination of clinical study data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.

GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.

GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.7. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents, including source documents (see Glossary of terms for the exact definition of essential and source documents). The document storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential study documents may be added or removed where justified (in advance of study initiation) based on their importance and relevance to the study. When a copy is used to replace an original document (e.g., source documents, eCRF), the copy should fulfill the requirements for certified copies (see Glossary of terms for the exact definition of certified copies).

All participant data related to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants (see Glossary of terms for the exact definition of source documents) that supports information entered in the eCRF.

Guidance on completion of eCRFs will be provided in eCRF completion guidelines.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies for such review and inspection.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data (see Glossary of terms for the exact definition of source data).

Study monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be fully explained if necessary (e.g., via an audit trail). The safety and rights of participants must be protected, and the study conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Quality tolerance limits (QTLs) will be pre-defined in the Quality Management Plan to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

Study records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 25 years from issuance of the final CSR/equivalent summary or in accordance with Applicable Law, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

When source data are sent for external assessment or adjudication (e.g., endpoint adjudication committee; expert reader), source data are stored by the external body for 25 years.

10.1.8. Source documents

Source documents provide evidence to establish the existence of the participant and substantiate the integrity of collected data. The investigator should maintain a record of the location(s) of their source documents.

Data transcribed into the eCRF from source documents must be consistent with those source documents; any discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data and documents can be found in the Glossary of terms.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Source data are shared with third parties contracted by GSK for external assessment or adjudication (e.g., endpoint adjudication committee; expert reader). The non-exhaustive list of source data shared may include, discharge summaries, imaging reports, scans, videos, pathology reports, biological specimens, ECG reports, etc. Participant names or any information which would make the participant identifiable or is not essential for the external assessment or adjudication will be redacted by the investigator sites prior to transfer. Details of the participant information redaction strategy are provided in the relevant third party manuals and/or study plans. These source data will be used by the third party solely for the purpose indicated within this protocol.

10.1.9. Study and site start and closure

First act of recruitment

The start of study is defined as First Subject First Visit (FSFV) at a country-level.

Study/site termination

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study sites will occur upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and enough notice in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any Contract Research Organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

At the end of the study, the investigator will:

- Review data collected to ensure accuracy and completeness.
- Complete the Study Conclusion screen in the eCRF.

10.1.10. Publication policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Clinical laboratory tests

10.2.1. Protocol-required safety laboratory assessments

The addresses of the clinical laboratories in charge of the testing can be found in the "List of Clinical Laboratories and Key Vendors".

Table 20 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Hematology	Platelet count, Red blood cell count, Hemoglobin level, White blood cell count, Neutrophils, Lymphocytes, Monocytes, Eosinophils
Clinical chemistry	Sodium, Potassium, Chloride, Bicarbonate, Blood urea nitrogen, Creatinine, Liver function tests (ALT, AST) C-reactive protein
Other screening tests	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)] • Serology: Hepatitis B surface antigen [HBsAg], anti-HBs antibodies, anti-HBc antibodies • All study-required laboratory assessments will be performed by a central laboratory.

The tests detailed in Table 20 will be performed by the central laboratory.

Table 21 Hematology and biochemistry read-outs

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-Dose 1	All	~150	Platelet count, RBC count, Hemoglobin level, WBC count, Neutrophils, Lymphocytes,
Visit 3 (Day 8)	Post-Dose 1	All	~150	

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 4 (Day 31)	Pre-Dose 2	All	~150	Monocytes, Eosinophils, Sodium, Potassium, Chloride, Bicarbonate, Blood urea nitrogen, Creatinine, Liver function tests (ALT, AST), C-reactive protein
Visit 6 (Day 38)	Post-Dose 2	All	~150	
Visit 7 (Day 61)	Post-Dose 2	All	~150	

WBC = white blood cells; **RBC** = red blood cells; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase

Grading of laboratory parameters (Table 21) will be based on the Food and Drug Administration [FDA, 2007] Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" as presented in Table 22.

Table 22 Toxicity Grading Scales for Hematology and Biochemistry Parameters Applicable for this Study

Component	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Hematology (whole blood)				
Hemoglobin (g/dL) – female	11.0 - 12.0	9.5 - 10.9	8.0 - 9.4	< 8.0
Hemoglobin (g/dL) – male	12.5 - 13.5	10.5 - 12.4	8.5 - 10.4	< 8.5
Hemoglobin (g/dL) - female change from baseline value	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (g/dL) - male change from baseline value	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC increase (cell/mm^3)	10 800 - 15 000	15 001 - 20 000	20 001 - 25 000	> 25 000
WBC decrease (cell/mm^3)	2500 - 3500	1500 - 2499	1000 - 1499	< 1 000
Lymphocytes Decrease (cell/mm^3)	750 – 1000	500 – 749	250 - 499	< 250
Neutrophils Decrease (cell/mm^3)	1500 – 2000	1000 – 1499	500 - 999	< 500
Eosinophils (cell/mm^3)	650 – 1500	1501 – 5000	> 5000	Hyper-eosinophilic
Platelets decrease (cell/mm^3)	125 000 - 140 000	100 000 - 124 000	25 000 - 99 000	< 25 000
Biochemistry (serum)				
AST and ALT (increase by factor)	1.1 - 2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 10 x ULN	> 10.0 x ULN
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkaliemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Creatinine (mg/dL)	1.5 - 1.7	1.8 - 2.0	2.1 - 2.5	> 2.5 or requires dialysis
Blood urea nitrogen (mg/dL)	23 – 26	27 – 31	> 31	Requires dialysis

WBC = white blood cells; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **ULN** = upper limit of the normal range

FDA toxicity grading for red blood cell count, bicarbonate, chloride and C-reactive protein is not available. Laboratory ranges of normality should be consulted for these parameters. See Section 10.3.6 for further information on clinical laboratory parameters qualifying as AEs or SAEs, and Section 10.3.9.1 for the assessment of intensity.

10.2.2. Protocol-required immunogenicity assessments

10.2.2.1. Total Ig Anti-Hepatitis B Surface antigen CLIA

The ADVIA Centaur Anti-HBS2 assay is a sandwich immunoassay using direct, chemiluminometric technology. HBsAg (ad and ay) are covalently coupled to magnetic latex particles in the Solid Phase. In the Lite Reagent, the HBsAg (ad and ay) is labeled with acridinum ester. Non-magnetic latex particles are added from the ancillary well. The sample is incubated simultaneously with Lite Reagent, Solid Phase and Ancillary Reagent. Antibody-antigen complexes will form if anti-HBs is present in the sample. A direct relationship exists between the amount of anti-HBs activity present in the patient sample and the amount of relative light units (RLUs) detected by the system.

Note: ad and ay are 2 different subtypes of S antigen.

10.2.2.3. Intracellular cytokine staining for HBs-specific CD4+/CD8+ T-cells

The assay quantifies the Hepatitis B Surface Protein-specific CD4+/CD8+ T-cells elicited after vaccination or natural infection, with data on polyfunctionality of T-cells.

ICS has been used to assess CMI responses as previously described [Moris, 2011].

Briefly, thawed PBMCs are stimulated in vitro with Hepatitis B Surface Protein peptides (1 peptide pool, 15mer overlapping by 11) or with culture medium only in the presence of anti-CD28 and anti-CD49d antibodies. After 2 h of incubation at 37 ˚C, Brefeldin A is added to inhibit cytokine secretion during an additional overnight incubation. Cells are subsequently harvested, stained with live/dead dye and then fixed. Fixed cells are then permeabilized and stained with fluorescently labeled antibodies specific for the following immune markers:

- CD3, CD4, CD8: phenotyping T-cells.
- CD40L (CD154), 4-1BB: expressed on activated CD4 and CD8 T-cells, respectively [Chattopadhyay, 2005; Frentsch, 2005; Samten, 2000; Stubbe, 2006].
- IL-2: key for the development, survival, and function of T-cells [Boyman, 2012].
- TNF-α: anti-viral/intracellular factor, pro-inflammatory cytokine, cytotoxicity [Sedger, 2014].
- IFN-γ: anti-viral factor, associated with the Th1 profile (and CD8) T-cells [Schoenborn, 2007].
- IL-13: associated with the Th2 profile [Bao, 2015].
- IL-17: associated with the Th17 profile [Korn, 2009].

Acquisition of data is performed via a flow cytometer, and data analysis is performed on FlowJo software.

Other cell populations (e.g., plasmablast, memory B cells or TFH cells), or other activation markers or cytokines produced by different cell types may also be evaluated by flow cytometry. Further details on these assessments will be available in the Annex Clinical Study Report.

10.2.2.5. B-cell ELISPOT assay

B-cell ELISPOT will be used to quantify vaccine antigen-specific memory B-cells which are responsible for long term (humoral) memory and will be the cells recalled during an infection subsequent to vaccination. This assay is designed to evaluate the frequency (per million memory B-cells) of HBs-specific memory B-cells from peripheral blood samples.

PBMCs are stimulated with Cytosine phosphate Guanine (CpG) for 5 days to induce *in vitro* cell differentiation. Differentiated cells (plasmablasts) are then incubated with IgG antibody directed against immunoglobulins (to quantify total memory B-cells) or with the recombinant HBs protein (to quantify vaccine specific memory B-cells) coated on nitrocellulose plates. Antibodies bound to their target are revealed by the addition of a secondary antibody, an antibody/substrate complex allowing colorimetric detection. Finally, the plate(s) are read and analyzed on an ELISPOT reader. This B-cells ELISPOT is an optimized assay.

The clinical testing will be performed at GSK laboratory (Rixensart, Belgium).

CCI

10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of an AE

An AE is any untoward medical occurrence (an unfavorable/unintended sign - including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a clinical study participant that is temporally associated with the study intervention. The AE may or may not be considered related to the study intervention.

10.3.1.1. Events Meeting the AE Definition
• Significant or unexpected worsening or exacerbation of the condition/indication under study. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- Signs, symptoms that require medical attention (e.g., hospital stays, physician visits and emergency room visits).
- Significant failure of an expected pharmacologic or biological action.
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.

10.3.1.2. Events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a participant before the first dose of study intervention These events will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

10.3.2. Definition of an SAE

An SAE is any untoward medical occurrence that:
a. Results in death.
b. Is life-threatening. Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c. Requires hospitalization or prolongation of existing hospitalization. Note: In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in disability/incapacity. Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant.
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
g. Other situations. Medical or scientific judgment must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should be considered serious. Examples of such events are invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; and convulsions that do not result in hospitalization.

10.3.3. Solicited events

Solicited events are predefined administration site events and systemic events for which the participant is specifically questioned, and which are noted by the participant in their eDiary.

a. Solicited administration site events

The following administration site events will be solicited:

Table 23 Solicited administration site events

Pain at administration site
Redness at administration site
Swelling at administration site

b. Solicited systemic events

The following systemic events will be solicited:

Table 24 Solicited systemic events

Fever
Fatigue
Myalgia
Arthralgia
Headache
Chills
Malaise
Loss of appetite
Nausea
Vomiting
Diarrhea

Note: participants will be instructed to measure and record the oral temperature in the evening. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the eDiary. Other options for temperature records include the axilla, ear canal and forehead; but oral temperature remains the preferred option.

10.3.4. Unsolicited AEs

An unsolicited AE is an AE that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow-up for solicited events. Unsolicited events must have been spontaneously communicated by a participant who has signed the informed consent. Unsolicited AEs include both serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or an emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended or perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

10.3.5. Adverse events of special interest (AESIs)

pIMDs are the only AESIs collected during this study.

10.3.5.1. Potential immune-mediated disorders

Potential immune-mediated disorders (pIMDs) include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 27 (refer to Section 10.3.8.1 for reporting details).

The investigator must exercise his/her medical/scientific judgment to determine whether other diseases have an autoimmune origin (i.e., pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

In addition, the investigator should categorize each pIMD either as a new onset condition (if it started following vaccination) or as an exacerbation of a preexisting chronic condition (if it exacerbated following vaccination) in the eCRF.

When there is enough evidence to make any of the diagnoses mentioned in Table 27, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) will be available to investigators at study start.

Once a pIMD is diagnosed (serious or non-serious) in a study participant, the investigator (or designate) must complete, date and sign an electronic Expedited Adverse Events Report.

The list of pIMDs is provided in Section 10.9 (Appendix 9).

10.3.6. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings assessments (hematology or clinical chemistry) or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Sections 10.3.1 and 10.3.2).

The investigator must exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

10.3.7. Events or outcomes not qualifying as AEs or SAEs

10.3.7.1. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any abnormal pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an SAE. Please refer to Section 10.3.2 for definition of SAE.

Note: The pregnancy itself should always be recorded on an electronic pregnancy report. The following should always be considered as SAE and will be reported as described in Section 10.3.8 and Section 10.3.10:

- Spontaneous pregnancy loss, including:
  - Spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation).
  - Ectopic and molar pregnancy.
  - Stillbirth (intrauterine death of fetus after 22 weeks of gestation).

    Note: the 22 weeks cut-off in gestational age is based on WHO-International Classification of Diseases 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (that is death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC] guidelines) identified in the offspring of a study participant (either during pregnancy, at birth or later) regardless of whether the fetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccine will be reported to GSK Global Safety as described in Section 10.3.10. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

10.3.8. Recording and follow-up of AEs, SAEs, pIMDs and pregnancies

The participants will be instructed to contact the investigator immediately should they experience any signs or symptoms they perceive as serious.

When an AE/SAE occurs, it is the investigator's responsibility to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF. The investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers will be blinded on copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event, based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE instead of individual signs/symptoms.

Electronic Diary (eDiary) will be used in this study to capture solicited administration site or systemic events. The participant should be trained on how and when to complete the eDiary.

Participants should be trained on using the eDiary. This training must be documented in the participant's source record.

Verify completed eDiary (via the web portal) during discussions with the participant at subsequent contacts (visit or phone call) after Dose 1 and Dose 2 of the study intervention administration.

Any unreturned eDiary will be sought from the participant through telephone call(s) or any other convenient procedure.

Refer to the SPM for more information regarding the use of eDiary.

10.3.8.1. Time period for collecting and recording AEs, SAEs, MAEs, pIMDs and pregnancies

All solicited events that occur up to 14 days following administration of Dose 1 and Dose 2 of study intervention (Day 1 to Day 14 and Day 31 to Day 44, respectively) must be recorded into the eDiary, irrespective of intensity. All other AEs occurring within 31 days following Dose 1 and Dose 2 of study intervention administration should be recorded onto the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

The time period for collecting and recording of SAEs, MAEs, pIMDs, and pregnancies will begin at the first receipt of study interventions and will continue throughout the whole study period.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study intervention until the participant is discharged from the study. SAEs related to study participation or to a concurrent GSK medication/vaccine will be collected from the time consent is obtained until the participant is discharged from the study.

10.3.8.2. Follow-up of AEs, SAEs, pIMDs, pregnancies

After the initial AE/SAE/pIMD/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and pIMDs (Section 10.3.5.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

10.3.8.2.1. Follow-up during the study

AEs/pIMDs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study or the participant is lost to follow-up.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

10.3.8.2.2. Follow-up after the participant is discharged from the study

The investigator will provide any new or updated relevant information to GSK on a previously reported SAE/pIMD using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the SAE/pIMD as fully as possible.

10.3.8.2.3. Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, if the investigator becomes aware of any SAE occurring as a result of a post-study pregnancy AND it is considered by the investigator to be reasonably related to the study intervention, he/she must report this information to GSK as described in Section 10.3.10.

10.3.8.3. Updating of SAE, pIMD and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, pIMD or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the study contact for reporting SAEs (refer to Section 8.4.3.1 or to GSK Global Safety department within the defined reporting timeframes specified in Table 12.

10.3.9. Assessment of intensity and toxicity

10.3.9.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:

Table 25 Intensity scales for solicited events

Event	Intensity grade	Parameter
Pain at administration site	0	None
	1	Mild: Pain that does not interfere with activity
	2	Moderate: Pain that interferes with activity
	3	Severe: Pain that prevents daily activity
Redness at administration site	0	< 25 mm
	1	25 - 50 mm
	2	51 - 100 mm
	3	> 100 mm
Swelling at administration site	0	< 25 mm
	1	25 - 50 mm
	2	51 - 100 mm
	3	> 100 mm
Temperature*	0	< 38.0 °C
	1	38.0 – 38.4 °C
	2	38.5 – 38.9 °C
	3	≥ 39.0 °C
Headache	0	None
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia	0	None
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia	0	None
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity
Chills	0	None

Event	Intensity grade	Parameter
	1	Mild: Chills present but do not interfere with activity
	2	Moderate: Chills that interfere with normal activity
	3	Severe: Chills that prevent normal activity
Malaise	0	None
	1	Mild: Malaise present but do not interference with activity
	2	Moderate: Malaise that interferes with normal activity
	3	Severe: Malaise that prevents normal activity
Loss of appetite	0	None
	1	Mild: Loss of appetite without decreased oral intake
	2	Moderate: Loss of appetite with decreased oral intake but without weight loss
	3	Severe: Loss of appetite with decreased oral intake and weight loss
Nausea	0	None
	1	Mild: Nausea present but not interfering with oral intake
	2	Moderate: Nausea leading to decreased oral intake
	3	Severe: Nausea leading to minimal to no oral intake
Vomiting	0	None
	1	Mild: 1 - 2 episodes/24 hours
	2	Moderate: 2 episodes/24 hours
	3	Severe: Requires outpatient IV hydration
Diarrhea	0	None
	1	2 - 3 loose stools/24 hours
	2	4 - 5 loose stools/24 hours
	3	6 or more watery stools/24 hours or requires outpatient IV hydration

IV = intravenous
*Refer to the SoA (Section 1.3) for the definition of fever and the preferred location for temperature measurement

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgment.

The intensity should be assigned to 1 of the following categories:

1 (mild) = An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

2 (moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.

3 (severe) = An AE which prevents normal, everyday activities (for example, prevent attendance at work and would necessitate the administration of corrective therapy).

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 10.3.2.

10.3.9.2. Assessment of causality

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgment. Where several different interventions were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all interventions.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult the IB and/or PI for marketed products to assist in making his/her assessment.

Causality should be assessed by the investigator using the following question: *Is there a reasonable possibility that the unsolicited AE may have been caused by the study intervention?*

YES: There is a reasonable possibility that the study intervention contributed to the AE.

NO: There is no reasonable possibility that the AE is causally related to the administration of the study intervention. There are other, more likely causes and administration of the study intervention is not suspected to have contributed to the AE.

If an event meets the criteria to be determined 'serious' (see Section 10.3.2), additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol-required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the study intervention, if applicable.
- An error in study intervention administration.
- Other cause (specify).

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to GSK.

The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.9.3. Medically attended visits

For each solicited and unsolicited AE the participant experiences, the participant will be asked if he/she received medical attention (defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the eCRF/paper Expedited Adverse Events Report, and/or, if applicable eDiary.

10.3.9.4. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

10.3.10. Reporting of SAEs, pIMDs, pregnancies

10.3.10.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in an enrolled participant, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE. It must be completed as thoroughly as possible, with all available details of the event.

The SAE report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to Table 12 for the details on timeframes for reporting of SAEs/pIMD/pregnancies.

The investigator will be required to confirm the review of SAE causality by ticking the ‘reviewed’ box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

Refer to Section 10.3.10.2 for information on back-up systems in case the electronic reporting system does not work.

10.3.10.2. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designee) must fax or email a completed, dated and signed paper Expedited Adverse Events Report to the study contact for reporting SAEs (refer to Sponsor Information) or to GSK Global Safety department within 24 hours of becoming aware of the SAE.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours after the electronic reporting system is working again. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1. Definitions

10.4.1.1. Woman of childbearing potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

- Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below).

10.4.1.2. Women not considered as women of childbearing potential

Women in the following categories are considered WONCBP:

- Premenarchal Tanner stage 1 (prepubertal)

  Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

  Additional evaluation should be considered if a participant's fertility status is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention.
- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

- Postmenopausal female

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use a non-hormonal, highly effective contraception method if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception guidance

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 26).

Table 26 Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent*   ***Failure rate of <1% per year when used consistently and correctly***
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation. • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Injectable • Oral
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation. • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Male partner sterilization prior to the female participant's entry into the study, and this male is the sole partner for that participant, *The information on the male sterility can come from the site personnel's review of the participant's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner.*

Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

*Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

10.4.3. Collection of pregnancy information

10.4.3.1. Female participants who become pregnant

Refer to Sections 8.4.1, 8.4.2, 10.3.8.1, 10.3.8.2, and 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female participant who becomes pregnant during the study will discontinue study intervention or be withdrawn from the study.

CCI

[redacted]

10.6. Appendix 6: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.6.1. Definition of medical device AE and ADE

- Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether considered related to a medical device or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved.
- An ADE is an AE related to the use of a medical device. This definition includes any AE resulting from:
  - Insufficient or inadequate instructions for use (i.e., user error), or
  - Any malfunction of a medical device, or
  - Intentional misuse of the medical device.

10.6.2. Definition of medical device SAE, SADE and USADE

A medical device SAE is any SAE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: – A life-threatening illness or injury. The term ‘life-threatening' in the definition of ‘serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. – A permanent impairment of a body structure or a body function. – Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. – Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. – Chronic disease (MDR 2017/745)
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
SADE definition
• A SADE is defined as an ADE that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the IB.

10.6.3. Recording and reporting of medical device AE, ADEs, SADEs and USADE

- Any device deficiency must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- Email/Facsimile transmission of the paper 'Medical device or combination product with device deficiency/incident report form' is the preferred method to transmit this information to the sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of 'Medical device or combination product with device deficiency/incident report form' sent by overnight mail or courier service.
- Contacts for reporting can be found in Section 8.4.3.1.
- GSK will review all device deficiencies, determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

10.7. Appendix 7: Country-specific requirements

10.7.1. Requirements for Germany

EXPLANATORY STATEMENT CONCERNING SEX DISTRIBUTION (ARTICLE 7, PARAGRAPH 2 (12) OF THE GERMAN GCP ORDER)

There is no intention to conduct specific analyses investigating the relationship between the sex of the participants and the efficacy, immunogenicity or safety of the GSK's HBsAg adjuvanted with the different adjuvants systems. The ratio of male to female participants recruited into the EARLY-CLINRES-017 study is expected to be in line with the demographics of the population of healthy, HBs-naïve adults aged 18-45 years in the Member State.

10.8. Appendix 8: Abbreviations and glossary of terms

10.8.1. List of abbreviations

CCI [redacted]

ADE: Adverse Device Effect

CCI [redacted]

AE: Adverse Event

AESI: Adverse Event of Special Interest

AI: Artificial Intelligence

ALT: Alanine Aminotransferase

CCI [redacted]

AST: Aspartate Aminotransferase

CDC: Centers for Disease Control

CLIA: Chemiluminescence Immunoassay

CLS: Clinical Laboratory Sciences

CMI: Cell-Mediated Immunity

CoP: Correlate of Protection

CPMG: Carr-Purcell-Meiboom-Gill

CSL: Clinical Science Lead

CSR: Clinical Study Report

eCRF: electronic Case Report Form

ELISA Enzyme-linked Immunosorbent Assay

EMA: European Medicines Agency

EoS: End of Study

FDA: Food and Drug Administration, United States of America

FSH: follicle-stimulating hormone

FTIH: First-Time in Human

GCP: Good Clinical Practice

GMC: Geometric Mean Concentration

GSB Global Safety Board

GSK: GlaxoSmithKline

HBsAg: Hepatitis B surface Antigen

IAF: Informed Assent Form

IB: Investigator's Brochure

ICF: Informed Consent Form

ICH: International Council for Harmonisation

ICMJE: International Committee of Medical Journal Editors

IDMC: Independent Data Monitoring Committee

IEC: Independent Ethics Committee

IND: Investigational New Drug

IRB: Institutional Review Board

LAR: Legally Acceptable Representative

LML: Local Medical lead

LSLV: Last Subject Last Visit

MAE: Medically Attended Adverse Event

MedDRA: Medical Dictionary for Regulatory Activities

CCI [redacted]

MPL: Monophosphoryl Lipid

CCI [redacted]

PBMC: Peripheral Blood Mononuclear Cell

PC: Phone Contact

PI: Personal Information

pIMD:	Potential Immune-Mediated Disorder
QTL:	Quality Tolerance Limit
RBC:	Red Blood Cell
RLU:	Relative Light Unit
SADE:	Serious Adverse Device Effect
SAE:	Serious Adverse Event
SBIR:	Source data Base for Internet Randomization
SD:	Standard Deviation
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SoA:	Schedule of Activity
SPM:	Study Procedures Manual
SRT:	Safety Review Team
SUSAR:	Suspected Unexpected Serious Adverse Reactions
CCI [redacted]	
TFH	T Follicular Helper
USADE:	Unanticipated Serious Adverse Device Effect
WHO:	World Health Organization
WOCBP:	Woman of Childbearing Potential
WONCBP:	Woman of Non-childbearing Potential

10.8.2. Glossary of terms

Adverse drug reaction:	An adverse event (AE) where a causal relationship between a medicinal product and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. In the context of a clinical trial, an ADR can be serious or nonserious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Combination product:	Combination product comprises any combination of: • Drug • Device • Biological product Each drug, device and biological product included in a combination product is a constituent part.
Comparator:	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Co-administered (concomitant) products:	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and therefore is not part of the objective of the study.

eDiary:	Electronically recorded patient data and automated data entries on, for example, a handheld mobile device, tablet, or computer.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrollment:	The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the Per-Protocol analysis.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intervention:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Investigational medicinal product:	A pharmaceutical form of an active substance or placebo being tested or used as reference in a clinical trial, including products already with a marketing authorization but used as assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information of the authorized form.
Investigator:	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
Last subject last visit:	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).

Medical device deficiency:	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject.
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way, as an active drug or intervention/treatment being studied.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical study was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The ICH defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit:	This term refers to the visit conducted in the place other than the study site.
Self-contained study:	Study with objectives not linked to the data of another study.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.

Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical study).
Study intervention:	Term used throughout the clinical study to cover all types of investigational and non-investigational products including medical devices and vaccines intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.
Study monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
SUSAR	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator’s Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

10.9. Appendix 9: List of potential immune-mediated disorders

Table 27 List of pIMDs

Blood disorders and coagulopathies	Cardio-pulmonary inflammatory disorders	Endocrine disorders

– Antiphospholipid syndrome
– Autoimmune aplastic anemia
– Autoimmune hemolytic anemia, including:
  – Warm antibody hemolytic anemia
  – Cold antibody hemolytic anemia
– Autoimmune lymphoproliferative syndrome (ALPS)
– Autoimmune neutropenia
– Autoimmune pancytopenia
– Autoimmune thrombocytopenia
  – Frequently used related terms include: “autoimmune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura (ITP)”, “idiopathic immune thrombocytopenia”, “primary immune thrombocytopenia”.
– Evans syndrome
– Pernicious anemia
– Thrombosis with thrombocytopenia syndrome (TTS)
– Thrombotic thrombocytopenic purpura
  – Also known as “Moschcowitz-syndrome” or “microangiopathic hemolytic anemia”
	– Idiopathic Myocarditis/Pericarditis, including:
	  – Autoimmune / Immune-mediated myocarditis
	  – Autoimmune / Immune-mediated pericarditis
	  – Giant cell myocarditis
	– Idiopathic pulmonary fibrosis, including:
	  – Idiopathic interstitial pneumonia (Interstitial lung disease, Pulmonary fibrosis, Immune-mediated pneumonitis)
	  – Pleuroparenchymal fibroelastosis (PPFE)
	– Pulmonary alveolar proteinosis (PAP)
	  – Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis”
		– Addison’s disease
		– Autoimmune / Immune-mediated thyroiditis, including:
		  – Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)
		  – Atrophic thyroiditis
		  – Silent thyroiditis
		  – Thyrotoxicosis
		– Autoimmune diseases of the testis and ovary, including:
		  – Autoimmune oophoritis
		  – Autoimmune ovarian failure
		  – Autoimmune orchitis
		– Autoimmune hyperlipidemia
		– Autoimmune hypophysitis
		– Diabetes mellitus type I
		– Graves’ or Basedow’s disease, including:
		  – Marine Lenhart syndrome
		  – Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
		– Insulin autoimmune syndrome
		– Polyglandular autoimmune syndrome, including:
		  – Polyglandular autoimmune syndrome type I, II and III

Eye disorders	Gastrointestinal disorders	Hepatobiliary disorders
– Ocular Autoimmune / Immune-mediated disorders, including: – Acute macular neuroretinopathy (also known as acute macular outer retinopathy) – Autoimmune/Immune-mediated retinopathy – Autoimmune/Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia – Cogan's syndrome: an oculo-audiovestibular disease – Ocular pemphigoid – Ulcerative keratitis – Vogt-Koyanagi-Harada disease	– Autoimmune / Immune-mediated pancreatitis – Celiac disease – Inflammatory Bowel disease, including: – Crohn's disease – Microscopic colitis – Terminal ileitis – Ulcerative colitis – Ulcerative proctitis	– Autoimmune cholangitis – Autoimmune hepatitis – Primary biliary cirrhosis – Primary sclerosing cholangitis
Musculoskeletal and connective tissue disorders	**Neuroinflammatory/neuromuscular disorders**	**Renal disorders**
– Gout, including: – Gouty arthritis – Idiopathic inflammatory myopathies, including: – Dermatomyositis – Inclusion body myositis – Immune-mediated necrotizing myopathy – Polymyositis – Mixed connective tissue disorder – Polymyalgia rheumatica (PMR) – Psoriatic arthritis (PsA) – Relapsing polychondritis – Rheumatoid arthritis, including: – Rheumatoid arthritis associated conditions – Juvenile idiopathic arthritis	– Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants, including: – Acute necrotising myelitis – Bickerstaff's brainstem encephalitis – Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) – Myelin oligodendrocyte glycoprotein antibody-associated disease – Neuromyelitis optica (also known as Devic's disease) – Noninfective encephalitis/ encephalomyelitis / myelitis – Postimmunization encephalomyelitis	– Autoimmune/Immune-mediated glomerulonephritis, including: – IgA nephropathy – IgM nephropathy – C1q nephropathy – Fibrillary glomerulonephritis – Glomerulonephritis rapidly progressive – Membranoproliferative glomerulonephritis – Membranous glomerulonephritis – Mesangioproliferative glomerulonephritis – Tubulointerstitial nephritis and uveitis syndrome

– Palindromic rheumatism – Still's disease – Felty's syndrome – Sjogren's syndrome – Spondyloarthritis, including: – Ankylosing spondylitis – Juvenile spondyloarthritis – Keratoderma blenorrhagica – Psoriatic spondylitis – Reactive Arthritis – Undifferentiated spondyloarthritis – Systemic Lupus Erythematosus, including: – Lupus associated conditions (e.g., Cutaneous lupus erythematosus, Lupus nephritis, etc.) – Complications such as shrinking lung syndrome (SLS) – Systemic Scleroderma (Systemic Sclerosis), including: – Raynaud's syndrome – Systemic sclerosis with diffuse scleroderma – Systemic sclerosis with limited scleroderma (also known as CREST syndrome)	– Guillain-Barré syndrome (GBS)*, including: – Variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN) – Idiopathic cranial nerve palsies/paresis and inflammations (neuritis), including: – Cranial nerve neuritis (e.g., Optic neuritis) – Idiopathic nerve palsies/paresis (e.g., Bell's palsy) – Melkersson-Rosenthal syndrome – Multiple cranial nerve palsies/paresis – Multiple Sclerosis (MS), including: – Clinically isolated syndrome (CIS) – Malignant MS (the Marburg type of MS) – Primary-progressive MS (PPMS) – Radiologically isolated syndrome (RIS) – Relapsing-remitting MS (RRMS) – Secondary-progressive MS (SPMS) – Uhthoff's phenomenon – Myasthenia gravis, including: – Ocular myasthenia – Lambert-Eaton myasthenic syndrome – Narcolepsy (with or without presence of unambiguous cataplexy) – Peripheral inflammatory demyelinating neuropathies and plexopathies, including – Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) – Antibody-mediated demyelinating neuropathy – Chronic idiopathic axonal polyneuropathy (CIAP) – Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g., multifocal acquired demyelinating sensory	

	and motor neuropathy also known as Lewis-Sumner syndrome) – Multifocal motor neuropathy (MMN) – Transverse myelitis (TM), including: – Acute partial transverse myelitis (APTM) – Acute complete transverse myelitis (ACTM)	
Skin and subcutaneous tissue disorders	**Vasculitis**	**Other (including multisystemic)**
– Alopecia areata – Autoimmune / Immune-mediated blistering dermatoses, including: – Bullous Dermatitis – Bullous Pemphigoid – Dermatitis herpetiformis – Epidermolysis bullosa acquisita (EBA) – Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease – Pemphigus – Erythema multiforme – Erythema nodosum – Lichen planus, including: – Liquen planopilaris – Localised Scleroderma (Morphoea) – Eosinophilic fasciitis (also called Shulman syndrome) – Psoriasis – Pyoderma gangrenosum	– Large vessels vasculitis*, including: – Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) – Giant cell arteritis (also called temporal arteritis) – Takayasu's arteritis – Medium sized and/or small vessels vasculitis*, including: – Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) – Behcet's syndrome – Buerger's disease (thromboangiitis obliterans) – Churg–Strauss syndrome (allergic granulomatous angiitis) – Erythema induratum (also known as nodular vasculitis) – Henoch-Schonlein purpura (also known as IgA vasculitis) – Microscopic polyangiitis – Necrotizing vasculitis – Polyarteritis nodosa – Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) – Granulomatosis with polyangiitis	– Anti-synthetase syndrome – Capillary leak syndrome – Frequently used related terms include: "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome" – Goodpasture syndrome – Frequently used related terms include: "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)" – Immune-mediated enhancement of disease, including: – Vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE) – Immunoglobulin G4 related disease – Langerhans' cell histiocytosis

– Reactive granulomatous dermatitis, including:
  – Interstitial granulomatous dermatitis
  – Palisaded neutrophilic granulomatous dermatitis
– Stevens-Johnson Syndrome (SJS), including:
  – Toxic Epidermal Necrolysis (TEN)
  – SJS-TEN overlap
– Sweet's syndrome, including:
  – Acute febrile neutrophilic dermatosis
– Vitiligo
		– Multisystem inflammatory syndromes, including:
		  – Kawasaki's disease
		  – Multisystem inflammatory syndrome in adults (MIS-A)
		  – Multisystem inflammatory syndrome in children (MIS-C)
		– Overlap syndrome
		– Raynaud's phenomenon
		– Sarcoidosis, including:
		  – Loefgren syndrome
		– Susac's syndrome

10.10. Appendix 10: Protocol Amendment history

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 4	17 Sep 2024
Amendment 3	17 November 2023
Amendment 2	01 March 2023
Amendment 1	10 August 2022
Original Protocol	25 April 2022

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC.

Amendment 3 (17 November 2023)

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because the change in the recruitment plan consists of a decrease in the target sample size with a consequent change in the precision of the statistical analysis.

Overall rationale for the Protocol Amendment 3:

Vaccination against Hepatitis B has been introduced with varying degrees depending on the countries where the study participants reside. Anti-HBs seroprevalence (essentially due to previous vaccination) in the adult population screened in the trial is therefore high and has led to a high screening failure rate (45%) and inadequate enrollment in the clinical study.

The target sample size for the study has therefore been revisited and guided by statistical considerations on the precision of the safety evaluation and on the power for the immunogenicity comparison. The enrollment in the study will therefore be stopped earlier than initially expected to target a minimum of 23 and a maximum of 30 participants in each study group (HBs- Alum, HBs-AS03, HBs-AS04, HBs-AS37_50, and HBs AS37_100).

Summary of changes table of previous amendment (Amendment 3):

Section # and title	Description of change	Brief rationale
Headers, title page, Protocol Amendment Summary of Changes (new)	Headers and title page were updated with new document number and amendment information; Protocol Amendment Summary of Changes section was updated to include the rationale for this amendment; minor corrections and formatting adjustments were made to add clarification and/or remove discrepancies.	Editorial changes have been implemented as needed.
CCI [redacted]		
Table 14 Analysis sets	CCI [redacted]	To align with the Statistical Analysis Plan
CCI [redacted]		
Section 9.3.2 Secondary endpoints analysis	The statistical analysis proposed for seroconversion and seroprotection rates was updated	No correction for baseline characteristics is considered needed for the analysis on seroconversion and seroprotection rates

Section # and title	Description of change	Brief rationale
Section 9.4.1.1 Main analysis	Description of endpoints included in the main analysis.	To addressing operational changes
CCI [redacted]		

Amendment 2 (1 March 2023)

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it significantly impacts the scientific value and procedures undertaken by participants in the study.

Overall rationale for the Protocol Amendment 2: CCI [redacted]

Summary of changes table of previous amendment (Amendment 2):

Section # and title	Description of change	Brief rationale
1.3 Table 1 Schedule of activities	CCI [redacted]	
3. Table 3 Study objectives and endpoints		
4. Figure 1 Study design overview		
5.2 Exclusion criteria		
5.4.1 Rescreening		
CCI [redacted]		
8.3 Other assessments		
9.2 Table 14 Analysis sets		
9.4.1.1 Main analysis		
CCI [redacted]		

Amendment 1 (10 August 2022)

This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety monitoring of participants.

Overall rationale for the Protocol Amendment 1: Following the review of the protocol by Medicines and Healthcare products Regulatory Agency (MHRA), the protocol is being amended to

- Update the study holding rules: Study holding rule (1b) related to serious adverse event (SAE) has been reworded and an additional holding (2d) rule related to non-serious adverse event (AE) has been added.
- Delete reference to emergency unblinding: Since the study is open-label, any reference to unblinding in the protocol has been deleted.
- Minor correction and clarification: A minor error has been corrected in Table 2 (Intervals between study visits) and a clarification on including the cohort in the minimization procedure has been added in the Section 6.3.3 (Intervention allocation to the participant). Figure 2 and Figure 3 have been updated to include additional holding rule added as per MHRA recommendation.

Summary of changes table of previous amendments (Amendment 1):

Section # and title	Description of change	Brief rationale
8.2.3.3 Study holding rule	The study holding rules in Table 10 are being updated.	Study holding rules updated as per MHRA recommendation
9.4. Interim analyses	Figure 2 and Figure 3 have been updated	To include in Figure 2 and Figure 3 an additional holding rule added as per MHRA recommendation, along with other holding rules already displayed in these figures
6.3.5.1 Emergency unblinding	This section is being deleted	The study is open-label and this section is not applicable.
1.3 Schedule of activities	A minor error in Visit interval in Table 2 has been corrected	A minor error has been corrected.
6.3.3 Invention allocation to the participant	A clarification to include cohort in the minimization procedure has been added.	Clarification added for minimization procedure.

11. REFERENCES

CCI [redacted]

CDC Metropolitan Atlanta Congenital Defects Program (MACDP), url: https://www.cdc.gov/ncbddd/birthdefects/macdp.html

CCI [redacted]

EMA Guideline on pregnancy exposure, 2006.

FDA. Guidance For Industry: Toxicity Grading Scale For Healthy Adult And Adolescent Volunteers Enrolled In Preventive Vaccine Clinical Trials. 2007, url: https://www.fda.gov/media/73679/download

CCI [redacted]

Gonzalez-Lopez A, Oostendorp J, Koernicke T, et al. Adjuvant effect of TLR7 agonist adsorbed on aluminum hydroxide (AS37): A Phase I randomized, dose escalation study of an AS37-adjuvanted meningococcal C conjugated vaccine. Clin Immunol. 2019;209:108275.

CCI [redacted]

CCI

[redacted]

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