Statistical Analysis Plan Amendment 5

Study ID: 204852

Official Title of Study: A first-time-in human (FTIH), Phase I/II, randomized, multicentric, single-blind, controlled dose-escalation study to evaluate the reactogenicity, safety, immunogenicity and efficacy of GSK Biologicals' HBV viral vector vaccines given in a prime-boost schedule with sequential or coadministration of adjuvanted proteins therapeutic vaccine (GSK3528869A) in chronic Hepatitis B patients (18-65 years old) well controlled under nucleo(s)tide analogue (NA) therapy

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TITLE PAGE

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Study Number:	204852
Compound Number:	GSK3528869A
Abbreviated Title:	TH HBV VV-001
Sponsor Name:	GlaxoSmithKline Biologicals SA (GSK)
Regulatory Agency Identifier Number(s)	2017-001452-55
Registry	**ID**
Registry name	Registry ID
Clintrials.gov	NCT03866187

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	16 November 2021	30 July 2021 (Protocol amendment 7)	Not Applicable	Original version
SAP amendment 1	03 November 2022	16 June 2022 (Protocol amendment 9)	Analyses related to qHBsAg, HBV DNA and CMI were updated. Subgroup analysis was added. CCI [redacted]	Updated to be aligned with protocol amendment 9

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			CCI [redacted]	
SAP amendment 2	01 March 2023	23 September 2022 (Protocol Amendment 10 BEL) 16 June 2022 (Protocol amendment 9)		
SAP amendment 3	20 March 2024	22 June 2023 (Protocol Amendment 11)	Additional of modified per protocol set.	
SAP amendment 4	04 June 2024	22 June 2023 (Protocol Amendment 11)	Align the definition of HBV DNA breakthrough in a new section 4.1.7; Update LLOQ of Anti-HBs.	Updates are necessary for clarification.
SAP amendment 5	02 Jan 2025	22 June 2023 (Protocol Amendment 11)	Revise analysis sets and plan for premature ending.	Updates are necessary for the final analysis due to the early termination of the study.

1. INTRODUCTION

The purpose of this SAP is to describe the planned statistical analyses for Study TH HBV VV-001 (204852).

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety of escalating doses of the HBV viral vector vaccines (prime-boost) and/or adjuvanted proteins vaccines in patients with chronic HBV infection who are virally suppressed on NA therapy.	• Occurrence of adverse events (AEs) from vaccination up to Day 337: – Occurrence of each solicited local and general symptoms within 7 days after each vaccination (from day of vaccination to six days after vaccination). – Occurrence of unsolicited AEs within 30 days after each vaccination (from day of vaccination to 29 days after vaccination). – Occurrence of hematological, biochemical or urinalysis laboratory abnormalities within 30 days after each vaccination (from day of vaccination to 29 days after vaccination). – Occurrence of serious adverse events (SAEs) up to six months after the last dose. – Occurrence of potential immune-mediated diseases (pIMDs) up to six months after the last dose. – Occurrence of liver-disease related AEs up to six months after the last dose. – Occurrence of hematological adverse events of special interest (AESIs) up to six months after the last dose.

Objectives	Endpoints
	– Occurrence of medically attended events (MAEs) up to six months after the last dose
Secondary	
• To assess the immunogenicity of escalating doses of the HBV viral vector vaccines (prime-boost) and/or adjuvanted proteins vaccines in patients with chronic HBV infection who are virally suppressed on NA therapy.	**Immunogenicity** • Immunogenicity with respect to HBV components of the viral vectored vaccines and adjuvanted proteins vaccines, at predefined time points. – Anti-HBc antibodies: seropositivity and concentration. – Anti-HBs antibodies: seroconversion and concentration; anti-HBs ≥10 mIU/ml and ≥100 mIU/ml. – Frequency of HBc- and HBs-specific $CD4^+$ T-cells and $CD8^+$ T-cells: $CD4^+$ T-cells responder, $CD8^+$ T-cells responder.
• To assess the efficacy of the HBV viral vector vaccines (prime-boost) and/or adjuvanted proteins vaccines in patients with chronic HBV infection who are virally suppressed on NA therapy. Proof-of-principle (PoP) will be achieved if – At least [cci]% of patients (i.e. a lower limit of the 80% CI of at least 15%) in one vaccine group show at least 10-fold decrease (i.e. 1-log difference) in qHBsAg or show HBsAg loss at Day 337 versus Day 1, or – If there is at least a 10-fold difference in mean HBsAg concentration between a vaccine group at Day 337 and the respective control group (i.e. the criterion is to observe a point estimate of at least 10-fold	**Efficacy** • qHBsAg: number of patients with ≥ 0.5 log decrease, ≥ 1-log decrease, HBsAg loss and log-changes since pre-vaccination. • Number of patients with HBsAg loss and anti-HBs seroconversion. • Mean qHBsAg in each group

Objectives	Endpoints
decrease between the groups with statistical significance, i.e., 80% CI on the ratio not including 1).	
• To assess the long-term safety of escalating doses of the HBV viral vector vaccines (prime-boost) and/or adjuvanted proteins vaccines in patients with chronic HBV infection who are virally suppressed on NA therapy.	**Safety** • Occurrence of AEs from vaccination up to Day 841 – Occurrence of any SAEs throughout the study period. – Occurrence of SAEs causally related to an investigational vaccine throughout the study period. – Occurrence of MAEs throughout the study period. – Occurrence of pIMDs throughout the study period. – Occurrence of liver disease-related AEs throughout the study period. – Occurrence of spontaneous local or general bleeding with thrombocytopenia (< 50,000 platelets/mm^3). – Occurrence of anemia with Hb < 9.5 g/dl. – Occurrence of AEs and SAEs leading to study withdrawal. • Pregnancy and pregnancy outcome throughout the study period

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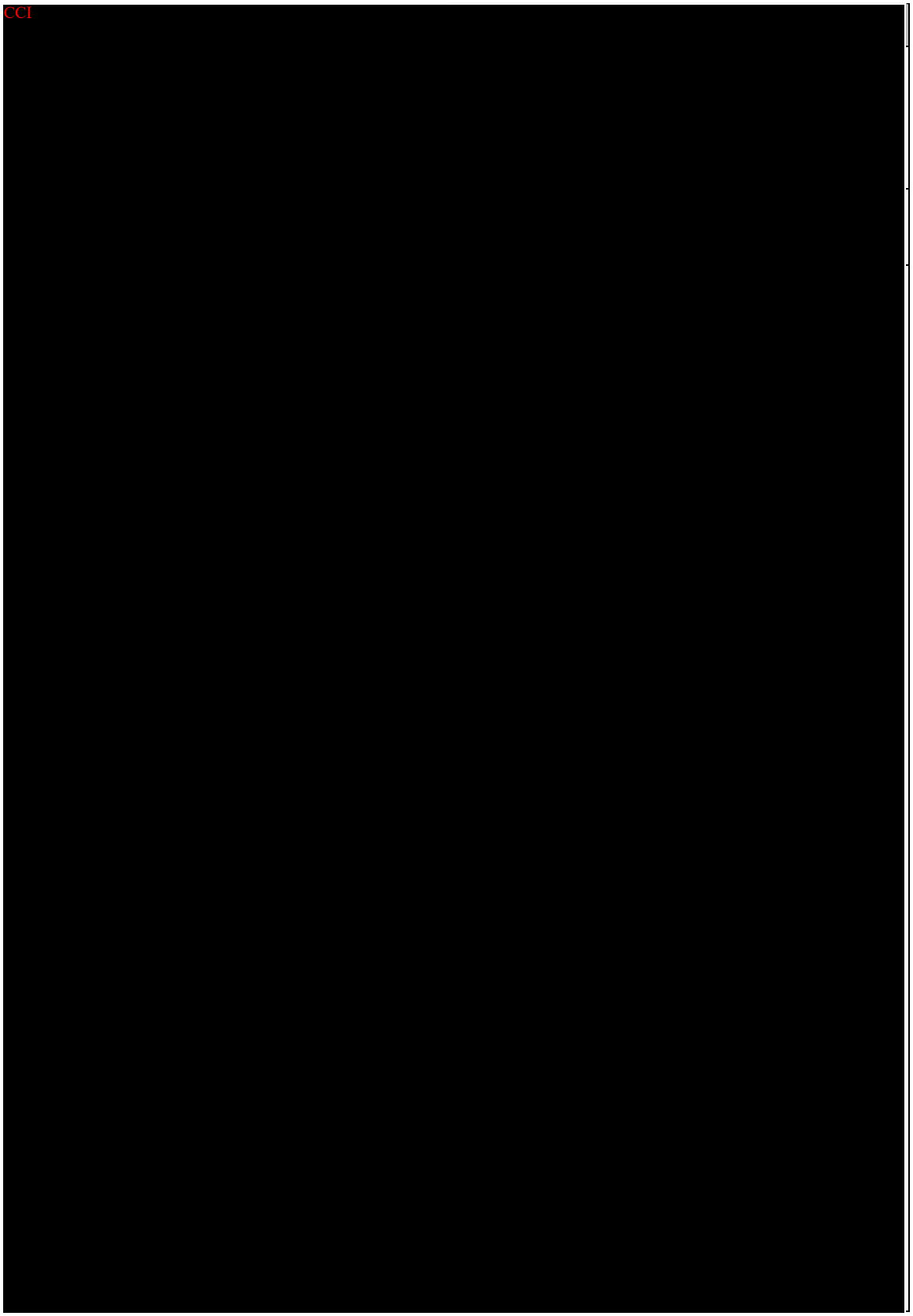
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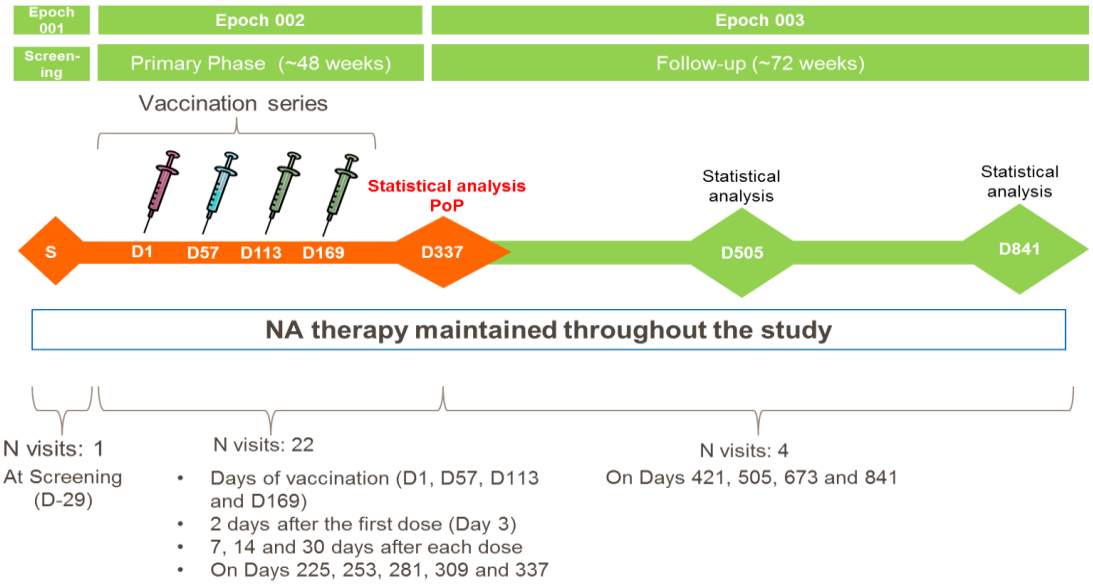
pIMD: potential immune-mediated disease. AE: adverse event; SAE: serious adverse event.

1.2. Study Design

Figure 1 Study design overview



D: Day; N: Total number; NA: Nucleo(s)tides analogues; PoP: Proof-of-principle; S: Screening

D: Day; N: Approximate number of patients to be enrolled and vaccinated. Note that prior moving to Step B, safety assessment of at least CCI patients who completed Visit 8 in Step A, may be considered sufficient, if approved by local authorities.

* Step A, B and C will be performed in a staggered manner.

- Experimental design: FTIH, Phase I/II, single-blind, randomized, controlled, multi-centric, multi-country study with a staggered design.
- Duration of the study:
  - Epoch 001: The Screening Visit will take place approximately 30 days before the planned first vaccine administration (Day -29).
  - Epoch 002: The primary phase will start on the day of the first vaccine administration until 6 months after the last vaccine dose (Day 337).
  - Epoch 003: The follow-up phase will start at the end of the primary phase (Day 337) and will last 18 months (up to Day 841).
- Primary completion Date (PCD): Visit 22 (Day 337)
- End of Study (EoS): Last testing results released of samples collected at Visit 26

- Study groups:

Table 1 Study groups and treatments

Study group	Study treatment
A1	D1: ChAd155-hli-HBV 5x10^9 vp, D57: MVA-HBV 2x10^7 pfu, D113: HBc-HBs/AS01$_{B-4}$ 20-20 µg, D169: HBc-HBs/AS01$_{B-4}$ 20-20 µg
A2	D1: HBc-HBs/AS01$_{B-4}$ 20-20 µg, D57: HBc-HBs/AS01$_{B-4}$ 20-20 µg, D113: HBc-HBs/AS01$_{B-4}$ 20-20 µg, D169: HBc-HBs/AS01$_{B-4}$ 20-20 µg
A3*	D1: PBS, D57: PBS, D113: PBS, D169: PBS
B1	D1: ChAd155-hli-HBV 5x10^{10} vp, D57: MVA-HBV 2x10^8 pfu, D113: HBc-HBs/AS01$_{B-4}$ 80-80 µg, D169: HBc-HBs/AS01$_{B-4}$ 80-80 µg
B2	D1: HBc-HBs/AS01$_{B-4}$ 80-80 µg, D57: HBc-HBs/AS01$_{B-4}$ 80-80 µg, D113: HBc-HBs/AS01$_{B-4}$ 80-80 µg, D169: HBc-HBs/AS01$_{B-4}$ 80-80 µg
B3	D1: PBS, D57: PBS, D113: ChAd155-hli-HBV 5x10^{10} vp, D169: MVA-HBV 2x108 pfu
C1	D1: ChAd155-hli-HBV 5x10^{10} vp & HBc-HBs/AS01$_{B-4}$ 80-80 µg, D57: MVA-HBV 2x10^8 pfu & HBc-HBc-HBs/AS01$_{B-4}$ 80-80 µg, D113: MVA-HBV 2x108 pfu & HBc- HBc-HBs/AS01$_{B-4}$ 80-80 µg, D169: MVA-HBV 2x108 pfu & HBc- HBc-HBs/AS01$_{B-4}$ 80-80 µg
C2	D1: PBS, D57: PBS, D113: ChAd155-hli-HBV 5x10^{10} vp & HBc-HBs/AS01$_{B-4}$ 80-80 µg, D169: MVA-HBV 2x10^8 pfu & HBc-HBs/AS01$_{B-4}$ 80-80 µg

*Patients of Group A3 will be unblinded at the end of primary phase (Epoch 002) and will be given the option to continue in follow-up phase (Epoch 003) in Step A or to participate in Step B or C provided that all eligibility criteria are met.

- Control:
  - For safety assessment:
    - Group A3 (placebo control) will be used for Step A.
    - For Step B and Step C, Group B3 and C2 data obtained up to Day 113 (placebo control up to Day 113) will be used respectively.
  - For PoP efficacy objective:
    - For Step B and Step C, Group B3 and C2 data obtained up to Day 113 (placebo control up to Day 113) will be used as placebo control, respectively.
- Vaccination schedules: Heterogeneous prime-boost-boost-boost on Day 1, 57, 113, 169.
- Treatment allocation: Following the assessment of eligibility (*i.e.*, after Screening conclusion), patients will be randomized using a centralized randomization system on internet (SBIR) before the first study vaccine administration. The randomization ratio in each step are: Step A: 1:1:1; Step B: 2:1:1; Step C: 2:1. Study products administration must take place as soon as possible after randomization.
- Step-wise approach: The study will be conducted in three consecutive steps as described in Figure 2.

- Blinding:

Table 2 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	Not applicable
Epoch 002	Single-blind*
Epoch 003	Single-blind

* Patients of Group A3 will be unblinded at the end of primary phase (Epoch 002) and will be given the option to continue in follow-up phase (Epoch 003) in Step A or to participate in Step B or C provided that all eligibility criteria are met.

- Sampling schedule:
  - Blood samples for serological markers of HBV, HCV, HDV and HIV, and autoimmune antibodies will be collected at the Screening Visit.
  - Blood samples for hematology and biochemistry will be collected at all time points throughout the study except on Days 3, 31, 87, 143, 199, 253 * and 309 * that are not mandatory and can be collected at the discretion of the Investigator. In case of abnormal parameters, blood samples may be collected at additional unscheduled visits.

  *For patients in Step B and Step C, blood collection is cancelled for Days 253 and 309.

  - Blood samples for markers of hepatic fibrosis (FibroTest) and HCC (α-fetoprotein) will be collected at the Screening Visit and on Day 337, 505 and 841.
  - Blood samples for HBsAg, HBV-DNA (and, if deemed necessary, new HBV markers) will be collected at the Screening Visit and every month since the vaccination during the primary phase and all time points during the follow-up phase, except on Days 3 *, 31 *, 87, 143, 199, 253 † and 309 † that are not mandatory and can be collected at the discretion of the Investigator.

  * For patients participating to TH HBV VV-031 HBS:001 study, blood collection specific to that study remains mandatory for Days 3 and 31.

  † For patients in Step B and Step C, blood collection is cancelled for Days 253 and 309.

  - Blood samples for humoral response to HBV antigens will be collected on Day 1, 15, 71, 113, 127, 183, 337, 505 and 841.
  - Blood samples for cell-mediated immune response to HBV antigens will be collected on Day 1, 15, 57, 64, 71, 113, 127, 169, 183, 337, 505 and 841.
  - CCI [redacted]
  - Blood samples for serum repository will be collected on Day 1, 71, 113, 127, 183, 337, 505 and 841.

– Blood samples in case of a TTS event should be collected within 2 weeks of the diagnosis of the TTS for exploratory testing. This blood sample can be collected at the next study visit or at an unscheduled visit in case the next study visit is >2 weeks from the TTS diagnosis. The blood sample collection for TTS event reported during the follow-up phase is optional.

– Urine samples for urinalysis will be collected at all time points during the primary phase of the study, except on Days 3 *, 31 *, 87, 143, 199, 253 † and 309 † that are not mandatory and can be collected at the discretion of the Investigator.

* For patients participating in TH HBV VV-031 HBS:001 study, urine collection specific to that study remains mandatory for Days 3 and 31.

† For patients in Step B and Step C, urine collection is cancelled for Days 253 and 309.

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- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring: Internal Safety Review Committee (iSRC). An external expert with a clinical expertise in hepatology will work together with the iSRC to review the safety data and contribute to the decision-making process to hold or continue the study.
- CCI

- Provision for patients in placebo group of Step A (Group A3): Patients randomized in the Group A3 that have received placebo in Step A will be informed about the treatment assignment after completing their Day 337 visit in Step A and will be given the option to continue in the follow-up phase (Epoch 003) in Step A or to participate in Step B or Step C.
- Holding rules and safety monitoring:

  This study will be overseen by an iSRC operating under a charter. The analysis plan for iSRC review is presented in a separate iSRC SAP and TFL.

The group labels listed in table below will be used for the analysis. Analysis summaries will be generated separately for each step, namely Step A, Step B and Step C.

Group order in tables	Group label in tables	Group definition for footnote
Step A		
1	Group A1	Patients who receive a dose of ChAd155-hli-HBV (low dose) at Day 1, a dose of MVA-HBV (low dose) at Day 57 and 2 doses of HBc-HBs-AS01B (low dose) at Day 113 and at Day 169 sequentially
2	Group A2	Patients who receive 4 doses of HBc-HBs-AS01B (low dose) at Day 1, Day 57, Day 113 and Day 169
3	Group A3	Subjects who receive 4 doses of Placebo at Day 1, Day 57, Day 113 and Day 169
Step B		
1	Group B1	Patients who receive a dose of ChAd155-hli-HBV at Day 1, a dose of MVA-HBV at Day 57 and 2 doses of HBc-HBs-AS01B at Day 113 and at Day 169 sequentially
2	Group B2	Patients who receive 4 doses of HBc-HBs-AS01B at Day 1, Day 57, Day 113 and Day 169
3	Group B3	Patients who receive 2 doses of Placebo at Day 1 and Day 57, a dose of ChAd155-hli-HBV at Day 113 and a dose of MVA-HBV at Day 169 sequentially
Step C		
1	Group C1	Patients who receive a dose of ChAd155-hli-HBV co-administered with HBc-HBs-AS01B at Day 1 and 3 doses of MVA-HBV co-administered with HBc-HBs-AS01B at Day 57, Day 113 and Day 169.
2	Group C2	Patients who receive 2 doses of Placebo at Day 1 and at Day 57, a dose of ChAd155-hli-HBV co-administered with HBc-HBs-AS01B at Day 113 and a dose of MVA-HBV co-administered with HBc-HBs-AS01B at Day 169.

2. STATISTICAL HYPOTHESES

2.1. Multiplicity Adjustment

The comparisons will be descriptive with the aim to characterize the difference in efficacy between the groups and are not adjusted for multiplicity.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria
Enrolled set	All patients who have signed the ICF (ICF date) is available will be considered for enrolled set.
Exposed set (ES)	The Exposed set (ES) will include all patients with study vaccine administration documented. • A safety/reactogenicity analysis based on the ES will include all patients who received at least one vaccine dose. • An efficacy/immunogenicity analysis based on ES will include all vaccinated patients for whom efficacy/immunogenicity post-vaccination data are available. The ES analysis will be performed per treatment randomization actually administered at Dose 1.
Per-Protocol set for Efficacy (PPS-E337)	The per-protocol cohort for efficacy will include all evaluable patients, i.e., those who were included in the ES and: • Who received all vaccine doses (at Day 1, Day 57, Day 113 and Day 169) according to protocol procedures including correct administration route and compliance with the protocol defined interval. • Who complied with the allowed interval between Dose 4 (Day 169) and Visit 22 (Day 337). • Who did not receive a concomitant medication/product/vaccine leading to elimination from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to elimination from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination efficacy results are available for at least one post-vaccination time point will be considered in the analysis. Scope of the data: • qHBsAg: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 20 and Visit 22. Note: Visits 19 and 21 were cancelled for Step B and C. • Allowed Interval: – Maximum interval between study vaccinations will be 63 days. In case of lab abnormalities, the interval will be extended to 84 days.
Per-Protocol set for Immunogenicity (PPS-I337)	The per-protocol cohort for immunogenicity will include all evaluable patients, i.e., those who were included in the ES and: • Who received all vaccine doses (at Day 1, Day 57, Day 113 and Day 169) according to protocol procedures including correct administration route and compliance with the protocol defined interval. • Who did not receive a concomitant medication/product/vaccine leading to exclusion from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to exclusion from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination immunogenicity results are available for at least one assay will be considered in the analysis • Scope of the data: HBV-DNA and new viral markers: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14 Visit 17, Visit 18, Visit 20 and Visit 22. Note: Visits 19 and 21 were cancelled for Step B and C.CMI response: Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16 and Visit 22. Humoral response to HBV antigens: Visit 4, Visit 8, Visit 10, Visit 12, Visit 16 and Visit 22. • Allowed Interval: – Maximum interval between study vaccinations will be 63 days. In case of lab abnormalities, the interval will be extended to 84 days.
Per-Protocol set for Immunogenicity up to 14-days	The per-protocol cohort for 14-days post dose 2 for Immunogenicity will include all evaluable patients, i.e., those who were included in the ES and: • Who received 2 vaccine doses (at Day 1 and Day 57) according to protocol procedures including correct administration route and compliance with the protocol defined interval. • Who complied with the allowed interval between Dose 2 (Day 57) and Visit 8 (Day 71)

Analysis Set	Definition / Criteria
post dose 2 (PPS-I71)	• Who did not receive a concomitant medication/product/vaccine leading to exclusion from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to exclusion from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination Immunogenicity results are available for at least one-time point till 14-days post dose 2. Scope of the data: CMI response: Visit 4, Visit 6, Visit 7 and Visit 8 The analysis on this PPS will be done only if there are significant eliminations for the analysis to avoid inadvertent unblinding of the patients. If not, this analysis will be done on the Exposed set with available data.
Per-Protocol set for Efficacy up to Day 505 (PPS-E505)	The per-protocol cohort for efficacy will include all evaluable patients from PPS-E337, i.e., those who were included in the PPS-E337 and: • Who did not receive a concomitant medication/product/vaccine leading to exclusion from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to exclusion from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination efficacy results are available for at least one post-vaccination time point till day 505. Scope of the data: qHBsAg: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 20, Visit 22, Visit 23 and Visit 24. Note: Visits 19 and 21 were cancelled for Step B and C. The data of the patients from the timepoint of meeting these elimination criteria will be excluded from the analysis. But, data up to this timepoint will be included in the analysis.
Per-Protocol set for Efficacy up to Day 841 (PPS-E841)	The per-protocol cohort for efficacy will include all evaluable patients from PPS-E505, i.e., those who were included in the PPS-E505 and: • Who did not receive a concomitant medication/product/vaccine leading to exclusion from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to exclusion from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination efficacy results are available for at least one post-vaccination time point till day 841. Scope of the data: qHBsAg: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 20, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26. Note: Visits 19 and 21 were cancelled for Step B and C. The data of the patients from the timepoint of meeting these elimination criteria will be excluded from the analysis. But, data up to this timepoint will be included in the analysis.
Per-Protocol set for Immunogenicity up to Day 505 (PPS-I505)	The per-protocol cohort for Immunogenicity will include all evaluable patients PPS-I337, i.e., those who were included in the PPS-I337 and: • Who did not receive a concomitant medication/product/vaccine leading to exclusion from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to exclusion from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination Immunogenicity results are available for at least one-assay till day 505. Scope of the data: HBV-DNA and new viral markers: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14 Visit 17, Visit 18, Visit 20, Visit 22, Visit 23 and Visit 24. CMI response: Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16, Visit 22 and Visit 24. Humoral response to HBV antigens: Visit 4, Visit 8, Visit 10, Visit 12, Visit 16, Visit 22 and Visit 24

Analysis Set	Definition / Criteria
	Note: Visits 19 and 21 were cancelled for Step B and C. The data of the patients from the timepoint of meeting these elimination criteria will be excluded from the analysis. But, data up to this timepoint will be included in the analysis.
Per-Protocol set for Immunogenicity up to Day 841 (PPS-I841)	The per-protocol cohort for Immunogenicity will include all evaluable patients PPS-I505, i.e., those who were included in the PPS-I505 and: • Who did not receive a concomitant medication/product/vaccine leading to exclusion from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to exclusion from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination Immunogenicity results are available for at least one-assay till day 841. Scope of the data: HBV-DNA and new viral markers: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14 Visit 17, Visit 18, Visit 20, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26. CMI response: Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16, Visit 22, Visit 24 and Visit 26. Humoral response to HBV antigens: Visit 4, Visit 8, Visit 10, Visit 12, Visit 16, Visit 22, Visit 24 and Visit 26. Note: Visits 19 and 21 were cancelled for Step B and C. The data of the patients from the timepoint of meeting these elimination criteria will be excluded from the analysis. But, data up to this timepoint will be included in the analysis.
Modified Per-Protocol set for Efficacy (mPPS-E337)	The modified per-protocol cohort for efficacy will include all evaluable patients, i.e., those who were included in the ES and: • Who received all vaccine doses (at Day 1, Day 57, Day 113 and Day 169) according to protocol procedures including correct administration route and compliance with the protocol defined interval. • Who complied with the allowed interval between Dose 4 (Day 169) and Visit 22 (Day 337). • Who did not receive a concomitant medication/product/vaccine leading to elimination from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to elimination from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination efficacy results are available for at least one post-vaccination time point will be considered in the analysis. Scope of the data: • qHBsAg: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 20 and Visit 22. Note: Visits 19 and 21 were cancelled for Step B and C. • Allowed Interval: Maximum interval between study vaccinations will be 111 days for all the participants included in step A, step B and step C.
Modified Per-Protocol set for Immunogenicity (mPPS-I337)	The modified per-protocol cohort for immunogenicity will include all evaluable patients, i.e., those who were included in the ES and: • Who received all vaccine doses (at Day 1, Day 57, Day 113 and Day 169) according to protocol procedures including correct administration route and compliance with the protocol defined interval. • Who did not receive a concomitant medication/product/vaccine leading to exclusion from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to exclusion from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination immunogenicity results are available for at least one-assay will be considered in the analysis • Scope of the data: HBV-DNA and new viral markers: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14 Visit 17, Visit 18, Visit 20 and Visit 22.

Analysis Set	Definition / Criteria
	Note: Visits 19 and 21 were cancelled for Step B and C. CMI response: Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16 and Visit 22. Humoral response to HBV antigens: Visit 4, Visit 8, Visit 10, Visit 12, Visit 16 and Visit 22. • Allowed Interval: Maximum interval between study vaccinations will be 111 days for all the participants included in step A, step B and step C.
Modified Per-Protocol set for Efficacy up to Day 505 (mPPS-E505)	The modified per-protocol cohort for efficacy will include all evaluable patients from mPPS-E337, i.e., those who were included in the PPS-E337 and: • Who did not receive a concomitant medication/product/vaccine leading to exclusion from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to exclusion from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination efficacy results are available for at least one post-vaccination time point till day 505. Scope of the data: qHBsAg: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 20, Visit 22, Visit 23 and Visit 24. Note: The data of the patients from the timepoint of meeting these elimination criteria will be excluded from the analysis. But, data up to this timepoint will be included in the analysis • Allowed Interval: Maximum interval between study vaccinations will be 111 days for all the participants included in step A, step B and step C.
Modified Per-Protocol set for Efficacy up to Day 841 (PPS-E841)	The per-protocol cohort for efficacy will include all evaluable patients from PPS-E505, i.e., those who were included in the PPS-E505 and: • Who did not receive a concomitant medication/product/vaccine leading to exclusion from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to exclusion from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination efficacy results are available for at least one post-vaccination time point till day 841. Scope of the data: qHBsAg: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 20, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26. Note: The data of the patients from the timepoint of meeting these elimination criteria will be excluded from the analysis. But, data up to this timepoint will be included in the analysis. • Allowed Interval: Maximum interval between study vaccinations will be 111 days for all the participants included in step A, step B and step C.
Modified Per-Protocol set for Immunogenicity up to Day 505 (PPS-I505)	The per-protocol cohort for Immunogenicity will include all evaluable patients mPPS-I337, i.e., those who were included in the PPS-I337 and: • Who did not receive a concomitant medication/product/vaccine leading to exclusion from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to exclusion from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination Immunogenicity results are available for at least one-assay till day 505. Scope of the data: HBV-DNA and new viral markers: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14 Visit 17, Visit 18, Visit 20, Visit 22, Visit 23 and Visit 24. CMI response: Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16, Visit 22 and Visit 24. Humoral response to HBV antigens: Visit 4, Visit 8, Visit 10, Visit 12, Visit 16, Visit 22 and Visit 24 Note: Visits 19 and 21 were cancelled for Step B and C. The data of the patients from the timepoint of meeting these elimination criteria will be excluded from the analysis. But, data up to this timepoint will be included in the analysis.

Analysis Set	Definition / Criteria
	• Allowed Interval: Maximum interval between study vaccinations will be 111 days for all the participants included in step A, step B and step C.
Modified Per-Protocol set for Immunogenicity for Day 841 (mPPS-I841)	The modified per-protocol cohort for Immunogenicity will include all evaluable patients mPPS-I505, i.e., those who were included in the PPS-I505 and: • Who did not receive a concomitant medication/product/vaccine leading to exclusion from the per-protocol analysis, as described in protocol section 6.7.2. • Who did not present with a medical condition leading to exclusion from the per-protocol analysis, as described in protocol section 6.8. • For whom post-vaccination Immunogenicity results are available for at least one-assay till day 841. Scope of the data: HBV-DNA and new viral markers: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14 Visit 17, Visit 18, Visit 20, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26. CMI response: Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16, Visit 22, Visit 24 and Visit 26. Humoral response to HBV antigens: Visit 4, Visit 8, Visit 10, Visit 12, Visit 16, Visit 22, Visit 24 and Visit 26. Note: Visits 19 and 21 were cancelled for Step B and C. The data of the patients from the timepoint of meeting these elimination criteria will be excluded from the analysis. But, data up to this timepoint will be included in the analysis. • Allowed Interval: Maximum interval between study vaccinations will be 111 days for all the participants included in step A, step B and step C.
Efficacy Set for final analysis (mPPS-E)	The modified per-protocol cohort for analysis of efficacy will be defined by visit/time-point and will include evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria) from the Exposed Set and have any efficacy endpoint measures available. Scope of the data: qHBsAg: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 20, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26. Note: Subjects have different follow-up visits since the study is early terminated. The data of the patients up to the timepoint of meeting these elimination criteria will be included in the analysis. • Allowed Interval: Maximum interval between study vaccinations will be 111 days for all the participants included in Step A, Step B and Step C.
Immunogenicity Set for final analysis (mPPS-I)	The modified per-protocol cohort for analysis of immunogenicity will be defined by visit/time-point and will include evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria) from the Exposed Set and have any immunogenicity endpoint measures available. Scope of the data: HBV-DNA and new viral markers: Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14 Visit 17, Visit 18, Visit 20, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26. Note: HBV-DNA has same planned visits as qHBsAg and will be analyzed within efficacy. CMI response: Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16, Visit 22, Visit 24 and Visit 26. Humoral response to HBV antigens: Visit 4, Visit 8, Visit 10, Visit 12, Visit 16, Visit 22, Visit 24 and Visit 26. Note: Subjects have different follow-up visits since the study is early terminated. The data of the patients up to the timepoint of meeting these elimination criteria will be included in the analysis. • Allowed Interval: Maximum interval between study vaccinations will be 111 days for all the participants included in Step A, Step B and Step C.

3.1. Criteria for eliminating data from Analysis Sets

Elimination codes will be used to identify participants to be eliminated from analysis sets. Details for each set are provided below.

3.1.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraudulent data) will be used for identifying subjects to be eliminated from ES.

3.1.2. Elimination from Per-protocol Set (PPS)

A subject will be eliminated from the PPS under the following conditions:

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
900	Invalid informed consent or fraudulent data	All	All
1030	Study vaccine not administered at all	All	All (except for enrolled set)
1040	Administration of concomitant vaccine(s) forbidden in the protocol: • Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period. • A vaccine not foreseen by the study protocol administered during the period starting 14 days before each dose and ending 30 days after administration of the last vaccine(s) dose, with the exception of annual influenza vaccine or pandemic influenza vaccine.	All	PPS-E337/PPS-I337, PPS-E505/PPS-I505, PPS-E841/PPS-I841, PPS-I71/ mPPS-E337/mPPS-I337, mPPS-E505/mPPS-I505, mPPS-E841/mPPS-I841 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards.
1050	Randomisation failure	All	PPS-E337/PPS-I337, PPS-E505/PPS-I505, PPS-E841/PPS-I841, PPS-I71/ mPPS-E337/mPPS-I337, mPPS-E505/mPPS-I505, mPPS-E841/mPPS-I841 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards.
1070	Vaccination not according to protocol: • Incomplete vaccination course • Subject was vaccinated with the correct vaccine but containing a lower volume • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) • Route of the study vaccine is not intramuscular	All	PPS-E337/PPS-I337, PPS-E505/PPS-I505, PPS-E841/PPS-I841, PPS-I71/ mPPS-E337/mPPS-I337, mPPS-E505/mPPS-I505, mPPS-E841/mPPS-I841 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards.

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
	• Wrong reconstitution of administered vaccine		
1080	• Vaccine temperature deviation (non GMP use):	All	PPS-E337/PPS-I337, PPS-E505/PPS-I505, PPS-E841/PPS-I841, PPS-I71/ mPPS-E337/mPPS-I337, mPPS-E505/mPPS-I505, mPPS-E841/mPPS-I841 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards.
1090	Expired vaccine administered	All	PPS-E337/PPS-I337, PPS-E505/PPS-I505, PPS-E841/PPS-I841, PPS-I71/ mPPS-E337/mPPS-I337, m PPS-E505/mPPS-I505, mPPS-E841/mPPS-I841 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards.
2010	Protocol violation (inclusion/exclusion criteria)	All	PPS-E337/PPS-I337, PPS-E505/PPS-I505, PPS-E841/PPS-I841, PPS-I71/ mPPS-E337/mPPS-I337, mPPS-E505/mPPS-I505, mPPS-E841/mPPS-I841 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards.
2040	Administration of any medication forbidden by the protocol: • Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period • Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥ 10 mg/day or equivalent. Inhaled and topical steroids are allowed. • Immunoglobulins and/or any blood products administered within 30 days before the blood sampling	All up to Day 337	PPS-E337/PPS-I337/mPPS-E337/mPPS-I337 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards.
2041	Administration of any medication forbidden by the protocol: • Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period	Day 337 to Day 505	PPS-E505/PPS-I505/mPPS-E505/mPPS-I505 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards.

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
	• Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥ 10 mg/day or equivalent. Inhaled and topical steroids are allowed. • Immunoglobulins and/or any blood products administered within 30 days before the blood sampling		
2042	Administration of any medication forbidden by the protocol: • Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period • Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥ 10 mg/day or equivalent. Inhaled and topical steroids are allowed. • Immunoglobulins and/or any blood products administered within 30 days before the blood sampling	Day 505 to Day 841	PPS-E841/PPS-I841/mPPS-E841/mPPS-I841 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards.
2050	Underlying medical condition forbidden by the protocol • Patients may be eliminated from the per-protocol cohort for efficacy/immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status. • Patients may be eliminated from the per-protocol cohort for efficacy/immunogenicity if they develop a concurrent infection with HDV and/or HIV or an immunodeficiency disorder.	All up to Day 337	PPS-E337/PPS-I337/mPPS-E337/mPPS-I337 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards
2051	Underlying medical condition forbidden by the protocol • Patients may be eliminated from the per-protocol cohort for efficacy/immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status. • Patients may be eliminated from the per-protocol cohort for efficacy/immunogenicity if they develop a concurrent infection with HDV and/or HIV or an immunodeficiency disorder.	Day 337 to Day 505	PPS-E505/PPS-I505 /mPPS-E505/mPPS-I505 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2052	Underlying medical condition forbidden by the protocol • Patients may be eliminated from the per-protocol cohort for efficacy/immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status. • Patients may be eliminated from the per-protocol cohort for efficacy/immunogenicity if they develop a concurrent infection with HDV and/or HIV or an immunodeficiency disorder.	Day 505 to Day 841	PPS-E841/PPS-I841/mPPS-E841/mPPS-I841 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards
2080	Subjects did not comply with vaccination schedule*: • Dose 1 to Dose 2 = 53-63 days • Dose 2 to Dose 3 = 53-63 days • Dose 3 to Dose 4 = 53-63 days	Day 57, Day 113, Day 169	PPS-E337/PPS-I337, PPS-E505/PPS-I505, PPS-E841/PPS-I841, PPS-I71
2081	Subjects did not comply with vaccination schedule: • Dose 1 to Dose 2 = 53-63 days	Day 57, Day 64, Day 71	PPS-I71
2090	Subjects did not comply with blood sample schedule • Dose 4 to BL at Visit 22= 147 – 188 days	Day 337	PPS-E337/PPS-I337/mPPS-E337/mPPS-I337 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit only
2091	Subjects did not comply with blood sample schedule Dose 2 to BL at Visit 8 = 12-18days	Day 71	PPS-I71 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit only
2100	Serological results not available post-vaccination • Anti-HBc and Anti-HBs results	Day 337	PPS-I337 /mPPS-I337 For finaly analysis set mPPS-I: Eliminate from Visit only
2101	Serological results not available post-vaccination • Anti-HBc and Anti-HBs results	Day 421, Day 505,	PPS-I505 /mPPS-I505 For finaly analysis set mPPS-I: Eliminate from Visit only
2102	Serological results not available post-vaccination • Anti-HBc and Anti-HBs results	Day 673, Day 841	PPS-I841 /mPPS-I841 For finaly analysis set mPPS-I: Eliminate from Visit only
2120	Obvious incoherence or abnormality or error in data • Anti-HBc and Anti-HBs results	All	PPS-I337, PPS-I505, PPS-I841/ mPPS-I337, mPPS-I505, mPPS-I841 For finaly analysis set mPPS-I: Eliminate from Visit only
3100	Serological results not available post-vaccination • qHBs results	Day 337	PPS-E337/ mPPS-E337 For finaly analysis set mPPS-E: Eliminate from Visit only

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
3101	Serological results not available post-vaccination • qHBs results	Day 421, Day 505,	PPS-E505/ mPPS-E505 For finaly analysis set mPPS-E: Eliminate from Visit only
3102	Serological results not available post-vaccination • qHBs results	Day 673, Day 841	PPS-E841/ mPPS-E841 For finaly analysis set mPPS-E: Eliminate from Visit only
3120	Obvious incoherence or abnormality or error in data • qHBs results	All	PPS-E337, PPS-E505, PPS-E841/ mPPS-E337, mPPS-E505, mPPS-E841 For finaly analysis set mPPS-E: Eliminate from Visit only
4080	Subject did not comply with the expanded vaccination interval**: • Dose 1 to Dose 2 = Max 111 days • Dose 2 to Dose 3 = Max 111 days • Dose 3 to Dose 4 = Max 111 days	Day 57, Day 113, Day 169	PPS-E337/PPS-I337, PPS-E505/PPS-I505, PPS-E841/PPS-I841, mPPS-E337/mPPS-I337, mPPS-E505/mPPS-I505, mPPS-E841/mPPS-I841 For finaly analysis sets, mPPS-E/mPPS-I: Eliminate from Visit and onwards Note: Sensitivity analysis for subjects with 2080 but included in 4080 will be considered. mPPS-E337/mPPS-I337,m PPS-E505/mPPS-I505, mPPS-E841/mPPS-I841/mPPS-E/mPPS-I, considering the extended interval.

*In case abnormal biochemistry or hematology parameter(s) are detected but do not fulfil the contraindication for subsequent vaccination, the interval can be extended to 84 days.
In case of special circumstances, this interval between two subsequent doses can be extended up to 84 days.
**For all subjects: If a subject did not receive a study dose within allowed interval from administration of the previous vaccine dose, study vaccination should continue provided that maximum interval of 111 days between doses is respected.

3.1.3. Safety Set for Solicited AEs

Patients included in Exposed set will be the safety set for solicited AEs.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

The qHBsAg GMC ratio between groups at week 24 post last vaccine dose (Visit 22 at Day 337) will be computed with CIs using an ANCOVA model on the logarithm 10 transformation of the concentrations. The ANCOVA model will include the vaccine group and the country as fixed effects and the pre-vaccination concentration as covariate.

4.1.2. Definitions

- For the HBV antigens and antibodies:

  A seronegative participant will be defined as a participant whose antigen/antibody titer/concentration is below the cut-off (LLOQ) value of the assay. A seropositive participant is a participant whose antigen/antibody titer/concentration is greater than or equal to the cut-off/LLOQ value of the assay. The following cut-offs/LLOQs will apply:

  – qHBsAg = 0.05IU/mL
  – HBeAg = 0.06 U/mL
  – Anti-HBs = 7.65mIU/mL
  – Anti-HBc = TBD
  – Anti-HBe = 0.06 U/mL
  – HBV DNA qPCR = 10 IU/mL

Note: For Anti-HBs, the limit of detection (LOD) is 6.2 mIU/mL.

HBc- and HBs-specific CD4+/CD8+ T-cell responder is defined as patient with post-vaccination / pre-vaccination ratio in CD4+/CD8+ T-cells polypositive (at least 2 markers including at least 1 cytokine) response above the maximum ratio observed into placebo controls (Group A3 for Step A, Group B3 over the timepoints up to Day 113 for Step B, Group C2 over the timepoints up to Day 113 for Step C, respectively).

4.1.3. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. If there are multiple assessments collected at the same scheduled time, the average of these assessments will be used as the baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Baseline of estimated glomerular filtration rate (eGFR) is defined as the mean of all pre-dose values, from screening to Day 1 pre-dose assessment.

4.1.4. Rescue Medication Definition

Any newly initiated medication for the management of HBV DNA reversion and with proven anti HBV activity (including PrEP for HIV that contains NA).

4.1.5. Seroconversion Definition

The appearance of antibodies (i.e., concentrations/titre greater than or equal to the LLOQ) in the serum of participants seronegative before GSK3528869A administration.

4.1.6. HBsAg or HBV DNA reversion Definition

HBsAg >LLOQ or HBV DNA >LLOQ, confirmed by 2 consecutive visits at least 1 month apart among those subjects who have HBsAg<LLOQ and HBV DNA<LLOQ. Actual dates will be used for derivation.

4.1.7. HBV DNA Virologic Breakthrough Definition

HBV DNA virologic breakthrough is defined as any increase in serum HBV DNA by >1 log10 from nadir, or redetection of serum HBV DNA at levels 10-fold the LLOQ of the viral load after HBV DNA was undetectable.

4.2. Primary Endpoint(s) Analyses

The primary analysis will be based on the ES for analysis of Safety for each step: A, B or C.

4.2.1. Within groups assessment

- The percentage of participants/doses reporting each individual solicited administration site (any grade, grade 3 and above)
- and systemic (any grade, grade 3 and above, related, grade 3 and above related) symptoms during the 7-day (Day 1 to Day 7) follow-up period will be tabulated for each group with its exact 95% CI, for each dose and overall, per dose.

- The percentage of participants with at least one unsolicited AE within 30 days post each dose with its exact 95% CI will be tabulated by group and by MedDRA Primary SOC and PT. Similar tabulation will be done for grade 3 unsolicited AEs, for unsolicited AEs that resulted in a medically attended visit, for grade 3 and causally related unsolicited AEs and for unsolicited symptoms causally related to vaccination. The exact 95% CIs will be calculated assuming independence between doses. For fever, additional analyses will be performed by 0.5 °C increments.
- The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate System Organ Class (SOC)/PT. The percentage of patients/doses with unsolicited AEs within 30 days after any doses with its exact 95% CIs will be tabulated by group and by MedDRA SOC/PT. Similar tabulation will be done for grade 3 unsolicited AEs, for unsolicited AEs that resulted in a medically attended visit, for grade 3 and causally related unsolicited symptoms and for unsolicited AEs causally related to vaccination.
- For each group and for each hematology, biochemistry and urinalysis parameter, the percentage of patients having results below and/or above the normal laboratory ranges will be tabulated within 30 days after each vaccination (see Table 4 and Table 5 in the protocol).
- The maximum toxicity grading from Visit 1 (Day 1) to Visit 22 (Day 337) will be tabulated. Please refer to Appendix C in the protocol. Those laboratory parameters not included in the Appendix C will not be graded).
- The number of patients who experienced liver disease-related AEs (ALT flares, substantial bilirubin and/or INR change, hepatic decompensation, HBV virological breakthrough) up to Visit 22 (Day 337) will be reported.
- The number of patients who experienced any pIMDs up to Visit 22 (Day 337) will be reported.
- The number of patients who experienced any hematological AESIs up to Visit 22 (Day 337) will be reported.
- The number of patients who experienced at least one SAE up to Visit 22 (Day 337) will be reported.
- The percentage of patients/doses using concomitant medication/product (any medication/ product, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (Day 1 – Day 8) and during the 30-day follow-up period (Day 1 – Day 31) will be summarized per group for each dose and overall per dose.
- Occurrence of medically attended events (MAEs) up to six months after the last dose (Day 337, Visit 22).

Solicited Adverse Events

Solicited adverse events will be reported until day 7 using structured diaries. Missing or non-evaluable measurements will not be replaced.

The following local (injection-site) AEs will be solicited:

Pain at injection site
Redness at injection site
Swelling at injection site

The following general AEs will be solicited:

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Chills

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

In order to summarize the data, the maximum intensity of local injection site redness/swelling (in mm) and fever (in °C) will be categorized as follows:

Grading	Redness/swelling	Fever
0:	≤ 20 mm	< 38.0°C (100.4°F)
1:	> 20 - ≤ 50 mm	≥ 38.0°C (100.4°F) - ≤ 38.4°C (101.1°F)
2:	> 50 - ≤ 100 mm	≥ 38.5°C (101.2°F) - ≤ 38.9°C (102.0°F)
3:	> 100 mm	≥ 39.0°C (102.1°F)

Fever is defined as temperature ≥ 38.0°C / 100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.

Unsolicited Adverse Events

All the unsolicited adverse events occurring during 30 days after each vaccination, including the day of vaccination, and all medically attended adverse events, Potential Immune-Mediated disease, Liver disease-related adverse event, Hematological AESI, serious adverse events occurring at any time during the study will be recorded.

The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The unsolicited adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. Adverse events judged by the investigator as at least possibly related to study vaccine will be summarized by vaccine group, according to system organ class and preferred term within system organ class. When an unsolicited adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Only vaccine-emergent adverse events will be analysed, i.e., excluding those after a subject has given informed consent but before vaccination. The selection of unsolicited adverse events and the assignment to time intervals will be done by day of onset and not by days ongoing/persisting.

The analysis of unsolicited adverse events comprises the following categories:

- Any unsolicited adverse event.
- Causally related unsolicited adverse events.
- Grade 3 unsolicited adverse events
- Grade 3 causally related unsolicited adverse events.
- Serious adverse events (SAEs).
- Medically attended adverse events (MAEs).
- Potential Immune-Mediated disease (pIMDs)
- Liver disease related adverse events
- Haematological AESI
- Listing of AEs/SAEs leading to premature withdrawal from study or to interruption of vaccination will also be described in detail.

4.2.2. Sensitivity analyses

Not applicable.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Immunogenicity analysis

The primary immunogenicity analysis will be performed on the Per Protocol Set (PPS) for immunogenicity and complementary analyses will be performed on Exposed Set (ES).

4.3.1.1. Within groups assessment

For each group, at each time point that blood samples for immunogenicity are collected, and for each assay (unless specified otherwise):

- GMTs/ GMCs will be tabulated with exact 95% CIs and represented graphically.
- Number and percentage of patients above defined threshold will be tabulated with exact 95% CIs.
- Antibody titers/concentrations will be displayed using reverse cumulative curves.
- Number and percentage of patients of responders in terms of HBV-specific CD4+/CD8+ T-cells will be tabulated with exact 95% CIs.

Additional considerations

- The following parameters will be summarised by group using descriptive statistics (N, geometric mean [GM], min, Q1, median, Q3, max) at each time point during which blood samples are collected for CMI:
  - Frequency of HBcAg specific, HBsAg specific CD4+/CD8+ T cells CCI [redacted] identified as expressing at least 2 activation markers (among CD40L, 4-1BB, IL-2, TNFa, IFNg, IL-17, IL-13) including at least 1 cytokine (among IL-2, TNFa, IFNg, IL-17, IL-13).
  - Descriptive statistics of the cell-mediated immune response will be displayed graphically using boxplots (min, Q1, median, Q3, max), by group and timepoint.
- The percentage of subjects with at least a 2-fold, 4-fold, 6-fold, 8-fold, 10-fold increase post-vaccination as compared to pre-vaccination (Post over Pre) will be tabulated by timepoint and by group for,
- Number and percentage of HBc- and HBs- specific CD4+/CD8+ T-cell responders will be computed for the vaccine groups.
  - Cell-mediated immune response in terms of HBcAg specific, HBsAg specific CD4+/ CD8+ T cells frequencies expressing at least 2 activation markers (among CD40L, 4-1BB, IL-2, TNFa, IFNg, IL-17, IL-13) including at least 1 cytokine (among IL-2, TNFa, IFNg, IL-17, IL-13).
  - An analysis may be performed when CMI samples up to visit 22 (Day 337) are tested and results are available for Step A and Step B participants.
  - This analysis will be performed by the independent analysis center. However, some of the planned summaries may lead to inadvertent unblinding.
  - CCI [redacted] These graphs to be produced for Step A, B and C.

4.3.1.2. Sensitivity Analysis

A sensitivity analysis will be performed on the immunogenicity endpoints if deemed necessary. This analysis will include patients modified per protocol set for vaccination due to special circumstances mentioned in protocol.

4.3.2. Efficacy Analysis

- The primary efficacy analysis will be performed on the Per Protocol Set (PPS) for efficacy and complementary analyses will be performed on Exposed Set (ES).

4.3.2.1. Within group assessment

For each group, at each time point that blood samples are collected:

- qHBsAg GMCs will be tabulated with exact 95% CIs and represented graphically.
- qHBsAg concentrations will be displayed using reverse cumulative curves.
- qHBsAg loss and anti-HBs seroconversion rates at each post-vaccination time point will be tabulated with exact 95% CIs.
- The percentage of participants with 95% confidence intervals in each group who achieve Sustained Virological Response (SVR defined as HBsAg concentration <LLOQ and HBV DNA <LLOQ) for 24 weeks after the end of vaccination (Visit 22, Day 337) will be performed.
- The percentage of participants who achieve qHBsAg decrease (≥0.5 log decrease, ≥1-log decrease), and log-changes since baseline will be tabulated by group.
- The number and percentage of participants who experienced HBV DNA virologic breakthrough will be reported and time to onset will be summarised.
- The number and percentage of participants with HBsAg reversion and/or HBV DNA reversion will be tabulated. Time to reversion will be summarised. Individual post-vaccination versus pre-vaccination qHBsAg results will be plotted using scatter plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of qHBsAg concentrations at each post-vaccination time point over pre-vaccination will be tabulated with exact 95% CIs.,
- Kinetic graphs of patients for qHBsAg concentrations measured at each time point will be presented by group.

PoP

- In Step B and Step C, qHBsAg and HBsAg loss percentage of responders in the candidate study vaccines group will be computed with exact 80% CIs. PoP will be demonstrated if candidate study vaccine group from either Step B or Step C demonstrates the lower limit of the exact CI greater or equal to 15% at Day 337 (Visit 22).
- In Step B and Step C, 80% CIs of qHBsAg GMC ratios between groups receiving candidate study vaccine up to Visit 22 (Day 337) and placebo will be computed using an ANCOVA model on the logarithm 10 transformation of the concentrations. The ANCOVA model will include the vaccine group and country as fixed effects and the pre-vaccination concentration as covariate. Lower limit of the CI above 1 will also be considered as indicator of PoP.
  - For the PoP analysis, data obtained at Day 337 for the Group B1 will be compared to data obtained at Day 113 for the group B3, and similarly, data obtained at Day 337 for the Group C1 will be compared to data obtained at Day 113 for the group C2. At Day 337, Groups B1 and C1 will have received the four vaccines doses. At Day 113, Groups B3 and C2 will only have received

placebo (two doses). Although there is a difference of approximately 7.5 months between Day 113 and Day 337, it is not expected that qHBsAg decreases in patients receiving only NAs over that time period [Zoutendijk, 2011]. Therefore, measuring qHBsAg in the control group at Day 113 should provide similar results as if it was measured at Day 337.

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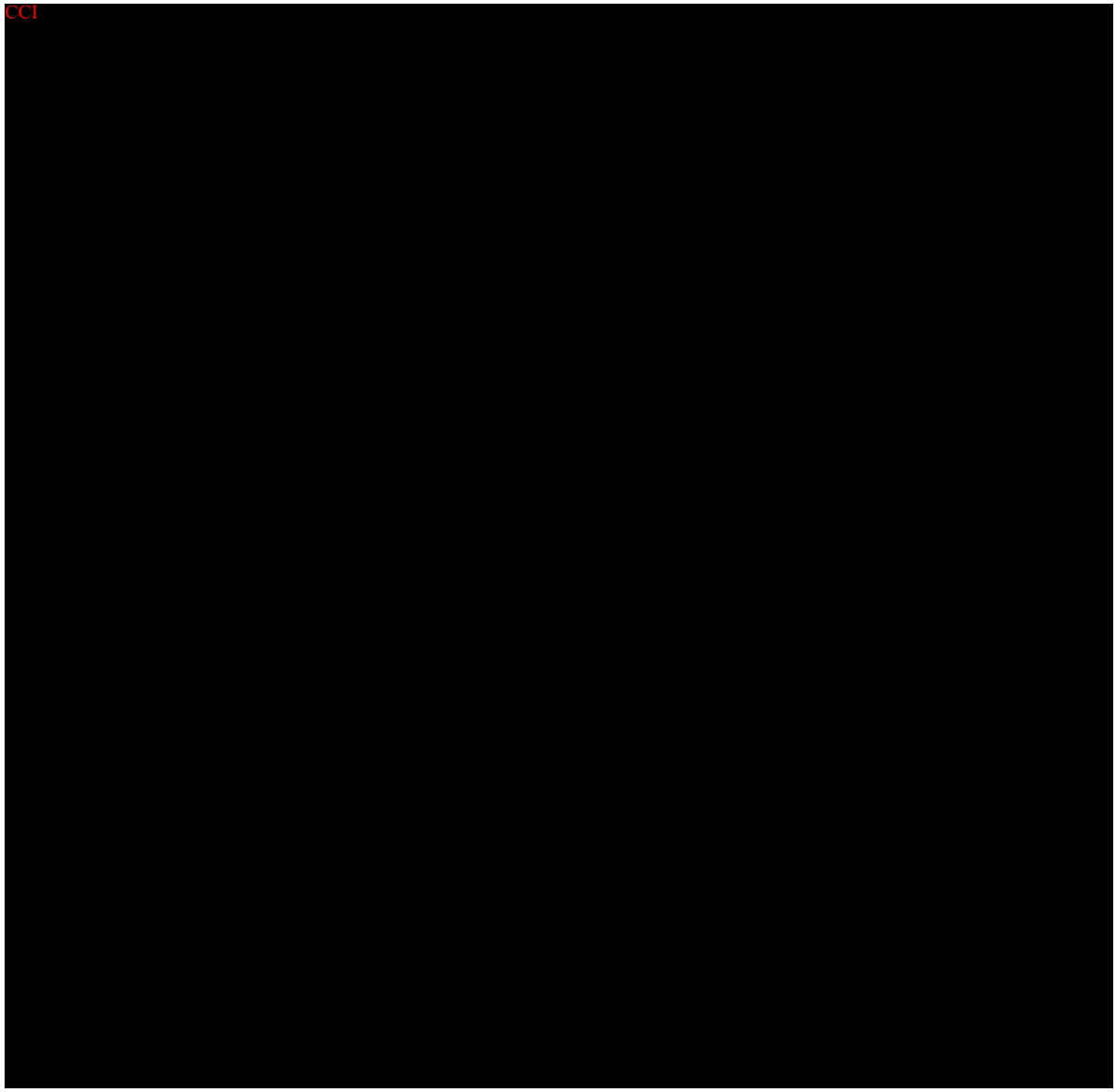

4.3.2.2. Sensitivity analysis

A sensitivity analysis will be performed POP endpoints for efficacy. This analysis will include patients in modified per protocol set for vaccination due to special circumstances mentioned in protocol.

4.3.2.3. Additional Considerations

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To avoid unblinding of individual participants,

- This analysis will be run by an independent analysis center to preserve blinding as much as possible. However, some of the planned summaries may lead to inadvertent unblinding.
- The primary analysis will be performed on the Exposed set and if, the percentage of vaccinated participants with results excluded from the per-protocol cohort is at least 15%, a secondary analysis will be performed on the Per Protocol Set (PPS).

4.3.3. Safety Analysis

The Secondary analysis will be based on the ES for analysis of Safety for each step A, B or C.

4.3.3.1. Within group assessment

- The number of patients who experienced at least one SAE during the entire study period will be reported. The number of patients who experienced at least one SAE causally related to an investigational vaccine throughout the study period will be reported.
- The number of patients who experienced any MAE during the entire study period will be reported.
- The number of patients who experienced any pIMDs during the entire study period will be reported.
- The number of patients who experienced liver disease-related AEs (ALT flares, substantial bilirubin and/or INR change, hepatic decompensation, HBV virological breakthrough) during the entire study period will be reported.
- The number and percentage of patients who experienced spontaneous local or general bleeding with thrombocytopenia (<50,000 platelets/mm^3) during the entire study period will be tabulated by group with exact 95% CIs.
- The number and percentage of patients who experienced anemia with Hb < 9.5 g/dl during the entire study period will be tabulated by group with exact 95% CIs.

- The number and percentage of patients with AEs and SAEs leading to withdrawal will be tabulated by group with exact 95% CIs.
- The number of patients who experienced pregnancy during the entire study period will be reported, with pregnancy outcome.
- For each group and for each hematology, biochemistry and urinalysis parameter, the percentage of patients having results below and/or above the normal laboratory ranges will be tabulated by each time point.

4.5. Safety Analyses

Safety analyses are described in Section 4.2.1.

4.5.1. COVID-19 Assessment and COVID-19 AEs

COVID-19 case assessments (confirmed, probable and suspected diagnosis) for participants with COVID-19 AEs will be summarized.

The number and percentage of participants with concomitant vaccination (COVID-19) before and during the study will be tabulated overall and per type of vaccine with exact 95% CI.

The number and percentage of patients who reported an AE related to COVID-19 infection will be tabulated with the following verbatim terms that should be used according to World Health Organization (WHO) definition.

- Suspected COVID-19 infection; or
- Probable COVID-19 infection; or
- Confirmed COVID-19 infection

4.6. Other Analyses

Not Applicable.

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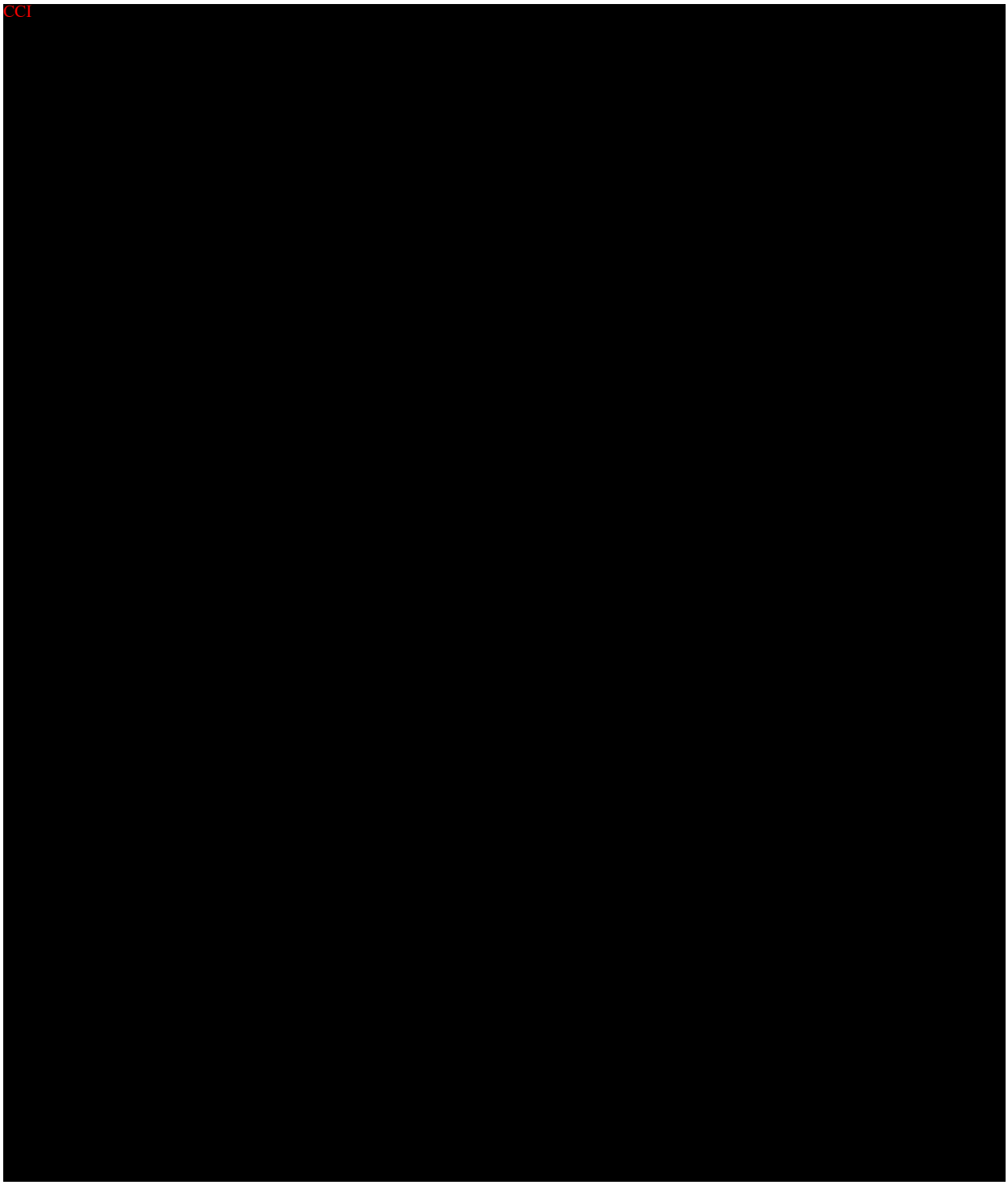

4.8. Final Analysis after Study Early Termination

The study is decided to be early terminated on 08 October 2024 after the analysis for safety, immunogenicity, and efficacy endpoints data up to 6 months post Dose 4 (Day 337). At this point, the GSK statistician is unblinded (i.e. has access to the individual patient treatment assignments).

The final analysis following the premature ending is planned on all available data up to data lock point. Safety analysis will be based on the Exposed Set, immunogenicity analysis will be based on Immunogenicity Set (mPPS-I), and efficacy analysis will be based on the Efficacy Set (mPPS-E). Complementary analyses for immunogenicity and efficacy endpoints will be performed on the Exposed Set. This final analysis will be documented in a statistical analysis package. Clinical study report will be written and made available to the investigators.

4.9. Changes to Protocol Defined Analyses

Changes or deviations to the originally planned statistical analysis specified in the protocol amendment 9 (Dated: [16-JUNE-2022]).

- Exposed set is considered as primary analysis set for the interim analysis of CMI and Efficacy to avoid inadvertent unblinding of the participants.
- For the interim efficacy and immunogenicity analysis no statistical report will be written. But will be documented in statistical analysis package (TFLS).

Changes or deviations to the originally planned statistical analysis specified in the protocol amendment 11 (Dated: [22-JUNE-2023]).

- Inclusion of modified per protocol set for efficacy and immunogenicity analysis.

Changes or deviations from the originally planned statistical analysis specified in the protocol amendment 11 are detailed below (Dated: [31-OCTOBER-2024]).

- The final analyses originally planned at Day 505 and Day 841 are cancelled due to the early termination of the study on 08 October 2024.
- The Efficacy Set (mPPS-E) and Immunogenicity Set (mPPS-I) are defined for final analysis after the study's early termination. Compared to the Per Protocol Set (PPS), the final analysis sets extended the maximum interval between subsequent vaccination up to 111 days. This is consistent with study procedures during special circumstances, based on the scientific rationale and defined in the protocol.

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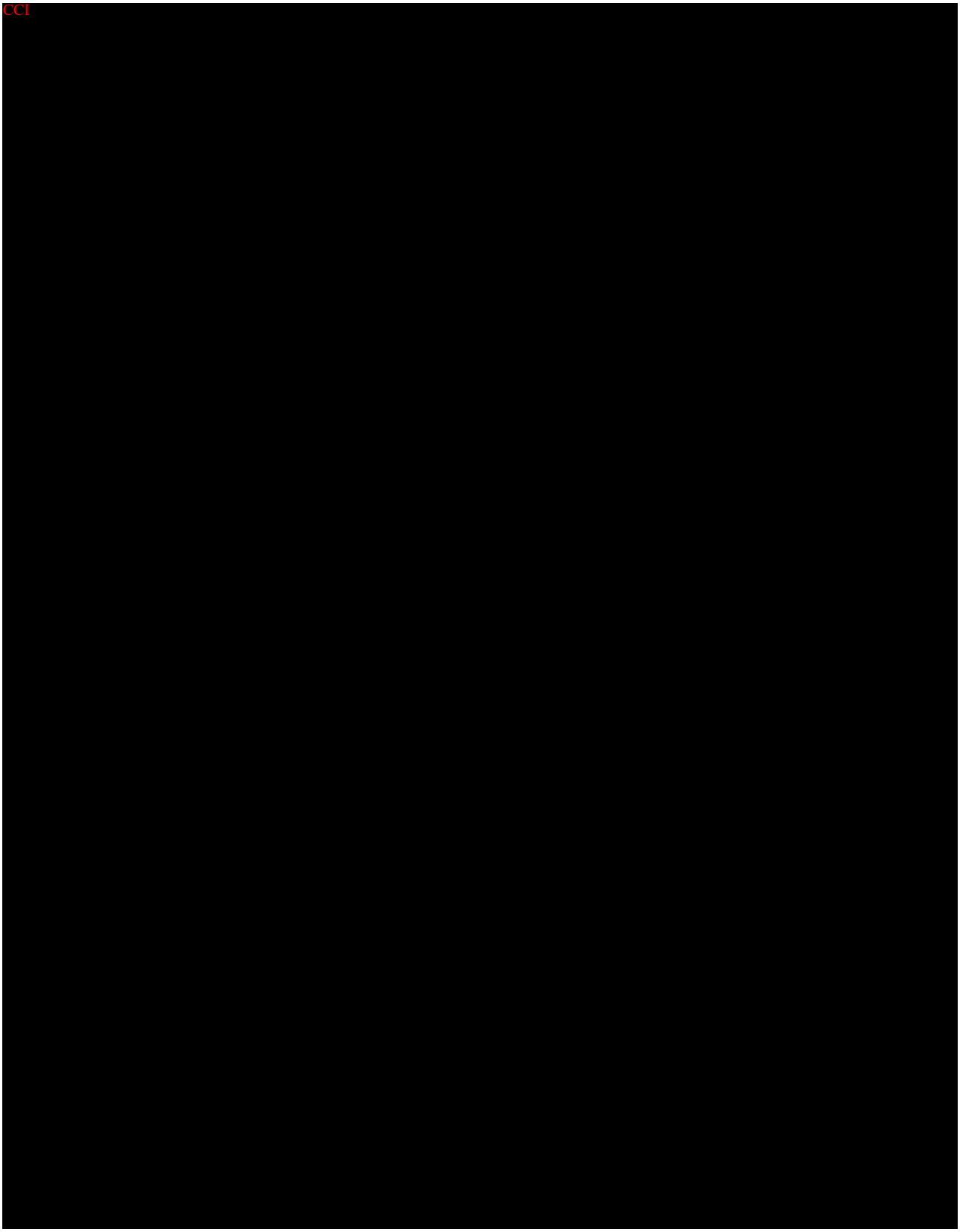

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6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Participant Disposition

The number of participants who withdraw from the study will be tabulated by group according to the reason for drop-out. This analysis will be based on the ES, the PPS for efficacy and immunogenicity sets (mPPS-E and mPPS-I).

6.1.2. Demographic and Baseline Characteristics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (BMI), pre-vaccination body temperature, qHBS will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maxima and minima of transformed height variables will be displayed with no decimals.

The maxima and minima of transformed weight variables will be displayed with no decimals with the exception of values are below 10kg where one decimal will be displayed.

Demographic characteristics by qHBs concentration will be summarized by group for Step B and Step C.

The maximum and minima of transformed body temperatures will be displayed with one decimal.

6.1.3. Protocol Deviations

The number of participants enrolled into the study as well as the number of participants excluded from per protocol set (PPS) analyses will be tabulated for the total population. This analysis, also broken down by study group, will be based on the ES.

The number of participants enrolled into the study as well as the number of participants excluded from per the ES will be tabulated for the total population. This will be based on all enrolled participants.

6.1.4. Subject exposure

The number and percentage of participants who received the Study vaccine and the control vaccine will be tabulated by group and by vaccine for the ES.

6.1.5. Concomitant Medications

Please refer section 4.2.1.

6.1.6. Concomitant Vaccinations

- A vaccine not foreseen by the study protocol administered during the period starting 14 days before each dose and ending 30 days after administration of the last vaccine(s) dose*, with the exception of annual influenza vaccine or pandemic influenza vaccine and COVID-19 vaccine (COVID-19 vaccines may be given at any time except within a 30-day period before or after each vaccine dose apart from COVID-19 mRNA based-vaccines that may be administered any time except for the period of 14 days before and 30 days after each study vaccine dose).

Note: If the type of COVID-19 vaccine is unknown, the allowed interval of 30 days before or after each study vaccine dose should be followed.

6.2. Appendix 2 Data Derivations Rule

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in section 6 (additional study-specific rules).

For the computation of the fold increase of the frequency, the results below the LLOQ of the assay will be replaced by the value of the 0.5*LLOQ except for CMI analyses.

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6.2.2. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a participant prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose administration, the relative dose will be derived from the additional information provided in the case report form (CRF) using the contents of the flag indicating if the event occurred before or after study dose. If 'after study dose' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before study dose' is selected, the relative dose for the event will be the dose prior to this one.

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6.2.3.2. Laboratory data

Clinical safety laboratory values will be summarized at each time-point of assessment, by study group.

Grades will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" see APPENDIX C in the study protocol. Those laboratory parameters not included on FDA Toxicity Grading Scale will not be graded.

6.2.3.3. Daily recording of solicited events

6.2.3.3.1. Studies with paper diaries

For studies using paper diaries which have questions in the CRF indicating the presence or absence of solicited events, the following rules are applicable:

- Denominators for the summary of administration site (or systemic) solicited events will be calculated using the number of participants who respond "Yes" or "No" to the question concerning the occurrence of administration site (or systemic) events.

- When a specific solicited event is marked as having not occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=N for the specified post-dose period for the event in question), all daily measurements will be imputed as Grade 0.
- When a specific solicited event is marked as having occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=Y for the specified post-dose period for the event in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited event summary tables.
- When the occurrence of a specific solicited event is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-dose period for the event in question) but the group of solicited events (administration site or systematic) is marked as having occurred (i.e. SDTM CE.CEOCCUR = Y), all missing daily recordings will be given imputed values to allow them to contribute to the 'any' rows but not to specific grade rows of the solicited event summary tables.
- The following table shows how participants contribute to each category for a specific solicited event over the Day X to Day Y post-dose period:

Solicited event category	Participants included in the calculation of the numerator
Any	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y or with the adverse event marked as present and at least one missing daily recording between Day X and Day Y
At least grade 1	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y
At least grade 2	All participants with at least one occurrence of the adverse event at grade 2 or grade 3 between Day X and Day Y
At least grade 3	All participants with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

6.2.4. Data derivation

6.2.4.1. Age at first dose in years

Age will be calculated as the number of years between the date of birth and the date of first vaccination.

In case of partial dates, the following 2 dates will be used as replacement dates:

- 15th of month, if the day is missing.
- 30th of June, if day and months are missing.

6.2.4.2. Age category at vaccination

As only the year of birth will be collected in the eCRF, there might be some discrepancies between the age computed using standard derivation rules and the age category used in SBIR for the minimization.

Therefore, for the analysis by age, the age categories will be determined according to the information entered in SBIR (add name of variable in SDTM), except for "≥65 YOA" category which will be obtained using the derived age because this category is not used in SBIR for minimization.

6.2.4.3. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = (Temperature (Fahrenheit) - 32) x 5/9

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6.2.4.6. Adjusted GMT or GMC ratios

When between-group GMT or GMC ratios are computed and adjusted for two-level categorical co-variables, these co-variables should be included as dummy continuous variables in the SAS procedure.

6.2.4.7. Onset day

The onset day for an event (e.g. AE, concomitant medication/vaccination) is the number of days between the last study vaccine dose and the start date of the event plus one day. This is 1 for an event occurring on the same day as a study dose (and reported as starting after study dose). If pre-exposure dates are involved then plus one day is not required.

6.2.4.8. Duration of events

The duration of an event with a start and end date will be the difference between the start and end date plus one day, i.e. an event that starts on 3 March 2018 and ends on 12 March 2018 has a duration of 10 days.

The duration of an event with a start and end date will be the difference between the start and end date, i.e. an event that starts on 3 March 2018 and ends on 04 March 2018 then event is considered to last at-least 48 hours (as worst case scenario).

The duration of solicited events will be calculated as the sum of the individual days plus one day with the adverse event reported at grade 1 or higher during the solicited event period.

6.2.4.9. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered as general events since the administration site flag is not included in the expedited adverse event CRF pages.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

6.2.4.10. Counting rules for occurrences of solicited events

When the occurrences of solicited adverse events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs. Also, in the case of co-administered study vaccines, an injection site reaction recorded for a subject following multiple vaccines will be counted as only one occurrence.

6.2.4.11. Counting rules for occurrence of unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

As per CDISC Vaccines Therapeutic Area guide, the solicited events which continue beyond the observation period are stored in the Adverse Events (AE) domain but they do not contribute to the summaries of unsolicited adverse events.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as ‘UNKNOWN’ when displayed in a statistical output.

6.2.5. Display of decimals

6.2.5.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal except for 100% in which case no decimal will be displayed.

6.2.5.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with two decimals.

6.2.5.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (BMI), pre-dose body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maximum and minimum of transformed body temperatures will be displayed with one decimal.

6.2.5.4. Serological summary statistics

The number of decimals used when displaying geometric mean titers (GMT) or concentrations (GMC) and their confidence limits is shown in the following table:

GMT or GMC value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMT or GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the one with the higher number of decimals). For example, if GMT or GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

GMT or GMC ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

7. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. Biometrika. 1934;26:404-13.

Zoutendijk R, Hansen BE, Van Vuuren AJ, Boucher CA, Janssen HL. Serum HBsAg decline during longterm potent nucleos(t)ide analogue therapy for chronic hepatitis B and prediction of HBsAg loss. J Infect Dis. 2011;204(3):415-8.