Protocol Amendment 11

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

NCT number: NCT03866187

Date of Document: 23-Jun-2023

Clinical Study Protocol

Sponsor:
GlaxoSmithKline Biologicals SA
Rue de l'Institut 89
1330 Rixensart, Belgium

Primary Study vaccines and numbers	• GlaxoSmithKline (GSK) Biologicals' Hepatitis B Virus (HBV) viral vectored vaccines and adjuvanted proteins vaccine (GSK3528869A) including: – Chimpanzee adenovirus HBV vaccine (ChAd155-hIi-HBV) – Modified Vaccinia Ankara HBV vaccine (MVA-HBV) – HBc-HBs/AS01$_{B-4}$
Other Study product	• Placebo
eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
EudraCT number	2017-001452-55
Date of protocol	Final Version 1: 15 November 2017
Date of protocol amendment	Amendment 1 Final: 22 May 2018 Amendment 2 Final: 17 December 2018 Amendment 3 Final: 6 August 2019 Amendment 4 Final: 29 April 2020 Amendment 5 Final: 20 May 2020 Amendment 6 Final: 16 March 2021 Amendment 7 Final: 30 July 2021 Amendment 8 Final: 8 November 2021 Amendment 9 Final: 16 June 2022 Amendment 10 Final: 23 September 2022 Amendment 11 Final: 22 June 2023
Title	Safety, efficacy, immunogenicity study of GSK Biologicals' HBV viral vector and adjuvanted proteins vaccine (GSK3528869A) in adult patients with chronic Hepatitis B infection.
Detailed Title	A first-time-in human (FTIH), Phase I/II, randomized, multi-centric, 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 co-administration of adjuvanted proteins therapeutic vaccine (GSK3528869A) in chronic Hepatitis B patients (18-65 years old) well controlled under nucleo(s)tide analogue (NA) therapy.

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
EudraCT number	2017-01452-55
Detailed Title	A first-time-in human (FTIH), Phase I/II, randomized, multi-centric, 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 co-administration of adjuvanted proteins therapeutic vaccine (GSK3528869A) in chronic Hepatitis B patients (18-65 years old) well controlled under nucleo(s)tide analogue (NA) therapy.
Co-ordinating authors (Amended: 22 June 2023)	PPD ***and*** PPD PPD**,** Scientific Writers, Modis for GSK Biologicals PPD, Scientific Writer
Contributing authors (Amended: 22 June 2023)	• PPD and PPD, Clinical ***Science*** Leads • PPD, PPD and PPD, Study Delivery Leads • PPD ***and*** PPD, Lead Statistician • PPD ***and*** PPD, ***Study*** Statistician • PPD and PPD, Clinical Laboratory Science Representatives, Clinical Readout Team Leaders • PPD and PPD, Laboratory Science Representatives, Laboratory Study Managers • PPD ***and*** PPD, Clinical Safety Representatives • PPD ***and*** PPD, Clinical Trial Supply Managers • PPD and PPD, Study Data Managers • PPD and PPD, Oversight Data Managers

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
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Detailed Title	A first-time-in human (FTIH), Phase I/II, randomized, multi-centric, 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 co-administration of adjuvanted proteins therapeutic vaccine (GSK3528869A) in chronic Hepatitis B patients (18-65 years old) well controlled under nucleo(s)tide analogue (NA) therapy.
Contributing authors (Contd.) (Amended: 22 June 2023)	• PPD ***and*** PPD, Global Regulatory Leads • PPD ***and*** PPD Global Patent Representatives • PPD and PPD Public Disclosure Representatives • PPD Clinical and R&D Project Leads ***(CPLs)***

GSK Biologicals' Protocol DS v 15.0

Protocol Amendment 11 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
EudraCT number	2017-001452-55
Date of protocol amendment	Amendment 11 Final: 22 June 2023
Detailed Title	A first-time-in human (FTIH), Phase I/II, randomized, multi-centric, 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 co-administration of adjuvanted proteins therapeutic vaccine (GSK3528869A) in chronic Hepatitis B patients (18-65 years old) well controlled under nucleo(s)tide analogue (NA) therapy.
Sponsor signatory (Amended: 22 June 2023)	Dietrich Bosse, MD Clinical and R&D Project Lead Therapeutic Hepatitis B (CHB-TI) vaccines, GlaxoSmithKline Biologicals, SA
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 11 Rationale

Amendment number:	Amendment 11

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Protocol Amendment 11 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' study vaccines and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the patient and/or the patient's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccines, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
EudraCT number	2017-001452-55
Date of protocol amendment	Amendment 11 Final: 22 June 2023
Detailed Title	A first-time-in human (FTIH), Phase I/II, randomized, multi-centric, 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 co-administration of adjuvanted proteins therapeutic vaccine (GSK3528869A) in chronic Hepatitis B patients (18-65 years old) well controlled under nucleo(s)tide analogue (NA) therapy.
Investigator name	_____
Signature	_____
Date	_____

For Germany only:

Leiter der klinischen Prüfung name, function and title	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

Sponsor

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

Sponsor Medical Expert for the Study

Refer to the local study contact information document.

Sponsor Study Monitor

Refer to the local study contact information document.

Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.4.2.

GSK Biologicals' Central Safety Physician On-Call Contact information for Emergency Unblinding

GSK Biologicals Central Safety Physician Phone contact: refer to protocol Section 5.3.1.

SYNOPSIS

Detailed Title	A first-time-in human (FTIH), Phase I/II, randomized, multi-centric, 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 co-administration of adjuvanted proteins therapeutic vaccine (GSK3528869A) in chronic Hepatitis B patients (18-65 years old) well controlled under nucleo(s)tide analogue (NA) therapy.
Indication	Chronic hepatitis B (CHB) infection
Rationale for the study and study design	• Rationale for the study: Treatment with GSK Biologicals' HBV therapeutic vaccines aims to restore immunity to HBV, leading to clearance of HBsAg or reduction of HBsAg concentration, in order to allow patients to safely discontinue NA therapy without virological or clinical relapse. • Rationale for the study design: This clinical dose-finding study will be conducted in one segment of the CHB patients that is at low risk of severe hepatitis exacerbation. The choice of the intramuscular route for each of the vaccines is based on clinical data obtained with similar type of vaccines when given intramuscularly in human and for which the safety, reactogenicity and immunogenicity profile was established. Two different doses of ChAd155-hIi-HBV ($5x10^9$ and $5x10^{10}$ vp) and MVA-HBV ($2x10^7$ and $2x10^8$ pfu]) will be assessed and were selected based on available clinical data with ChAd3- and MVA-based vectored vaccines using other antigens. Two different doses of HBc-HBs antigens will be assessed, containing 20-20, and 80-80 µg of HBc and HBs, respectively. The existing HBV vaccines containing 20 µg of HBsAg and up to 100 µg of HBs without or with HBcAg have been administered safely in clinical trials in CHB patients. • Rationale for the use of placebo: A PBS solution is included as a negative control (placebo) in a low number of patients in the study. The use of the placebo control and the single-blind, randomized study design will allow controlling for potential biases in the conduct of the study. Importantly, each patient including those in the control group will remain under NA treatment throughout the duration of the study.

Objectives

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.

Secondary

- To assess the immunogenicity 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.
- 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 a at least 10-fold decrease (i.e. 1-log difference) in qHBsAg or show HBsAg loss at Day 337 versus Day 1, or

  – There is 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 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.

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Study design

- Experimental design: FTIH, Phase I/II, single-blind, randomized, controlled, multi-centric, multi-country study with a staggered design and limited enrolment at the beginning of each step.
- 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:

Synopsis Table 1 Study groups, treatments and epochs foreseen in the study

Study group	Study treatment	Approximate Number of patients	Age (Min/Max)	Epoch 001 Screening phase	Epoch 002 Primary phase	Epoch 003 Follow-up phase
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	CCI	18 years – 65 years	●	●	●
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		18 years – 65 years	●	●	●
A3*	D1: PBS D57: PBS D113:PBS D169: PBS		18 years – 65 years	●	●	●*
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		18 years – 65 years	●	●	●
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		18 years – 65 years	●	●	●
B3	D1: PBS D57: PBS D113: ChAd155-hli-HBV $5x10^{10}$ vp D169: MVA-HBV 2x108 pfu		18 years – 65 years	●	●	●
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		18 years – 65 years	●	●	●
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		18 years – 65 years	●	●	●

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

- Control:
  - 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.
- Blinding:

Synopsis 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 for 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 for 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, blood collection specific to that study remains mandatory for Days 3 and 31.

† For patients in Step B and Step C, blood collection will be 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 for 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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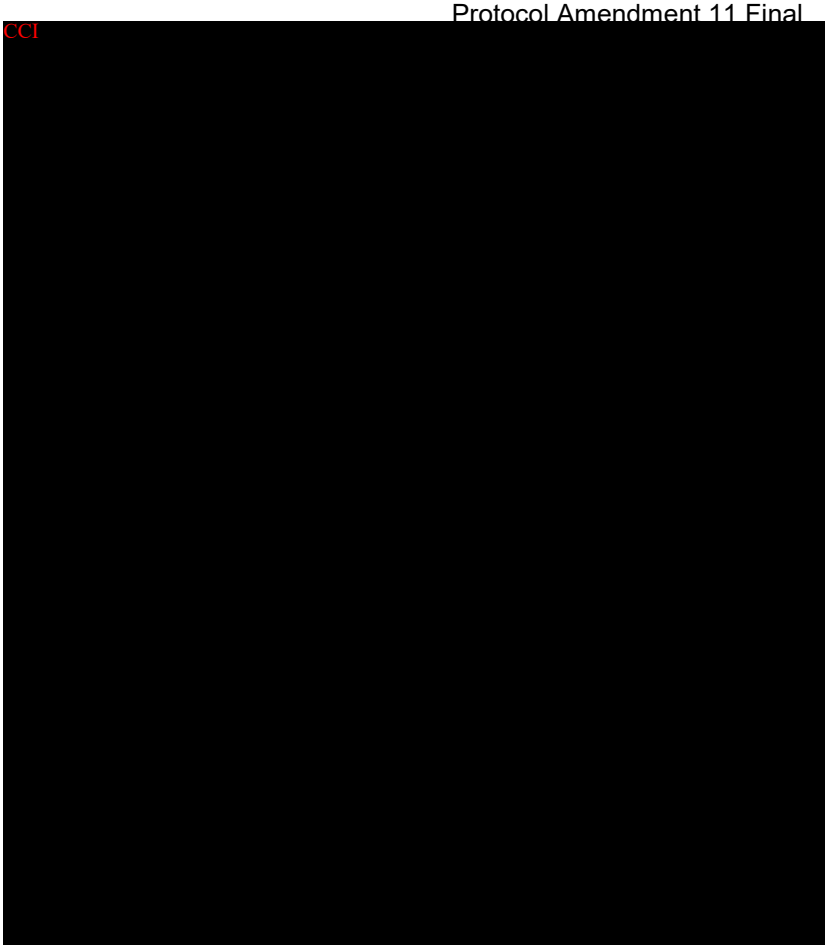

- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring: Internal Safety Review Committee (iSRC). An external expert with clinical expertise in hepatology will work together with the iSRC to review the safety data and contribute to the decision-making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

Number of patients

A total of approximately CCI patients are planned to be recruited in this study.

Endpoints

Primary

- 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 (Day 337, Visit 22).
- Occurrence of potential immune-mediated diseases (pIMDs) up to six months after the last dose (Day 337, Visit 22).
- Occurrence of liver-disease related AEs up to six months after the last dose (Day 337, Visit 22).
- Occurrence of hematological adverse events of special interest (AESIs) up to six months after the last dose (Day 337, Visit 22).
- Occurrence of medically attended events (MAEs) up to six months after the last dose (Day 337, Visit 22).

Secondary

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.

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.

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/mm3).
  - 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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TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF APPENDICES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AFP	α-Fetoprotein
ALEH	Asociación Latinoamericana para el Estudio del Hígado
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
APRI	Aspartate Transaminase to Platelets Ratio Index
AS	Adjuvant System
BMI	Body Mass Index
CBC	Complete Blood Count
cccDNA	Covalently Closed Circular Deoxyribonucleic Acid
CCLIA	Competitive Chemiluminescent Immunoassay
CDC	Centers for Disease Control
CFC	Cytokine Flow Cytometry
ChAd	Chimpanzee Adenovirus
CHB	Chronic Hepatitis B
CKD-EPI	Chronic Kidney Disease Epidemiologic Collaboration
CLIA	Chemiluminescent Immunoassay
CLS	Clinical Laboratory Sciences
CMI	Cell-Mediated Immunity
CMIA	Chemiluminescent Microparticle Immunoassay
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRDL	Clinical Research and Development Lead
CyTOF	Cytometry by Time of Flight
DNA	Deoxyribonucleic Acid
EASL	European Association for the Study of the Liver
eCRF	electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
EoS	End of Study
ES	Exposed Set
ETV	Entecavir
FDA	Food and Drug Administration, United States of America
FTIH	First-Time-In Human
GCP	Good Clinical Practice

GFR	Glomerular Filtration Rate
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titre
GSK	GlaxoSmithKline
HBc	Hepatitis B core protein
HBcrAg	Hepatitis B Core-Related Antigen
HBIg	Hepatitis B Immunoglobulin
HBpol	Hepatitis B Polymerase
HBs	Hepatitis B surface protein
HBsAb	Anti-HBs Antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
hCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
hIi	Human Invariant Chain
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HSV	Herpes Simplex Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Intracellular Cytokine Staining
IEC	Independent Ethics Committee
IFN	Interferon
IM	Intramuscular
INR	International Normalized Ratio
IRB	Institutional Review Board
iSRC	Internal Safety Review Committee
IU	International Unit
kPa	KiloPascal
LLOQ	Lower Limit Of Quantification
LSLV	Last Subject Last Visit
MACDP	Metropolitan Atlanta Congenital Defects Program
MAE	Medically Attended Event
MedDRA	Medical Dictionary for Regulatory Activities

METAVIR	Meta-Analysis of Histological Data in Viral Hepatitis
MHC	Major Histocompatibility Complex
mRNA	messenger Ribonucleic Acid
MVA	Modified Vaccinia Ankara
NA	Nucleo(s)tides Analogues
NHP	Non-Human Primates
PBMC	Peripheral Blood Mononuclear Cell
PCD	Primary Completion Date
PCR	Polymerase Chain Reaction
PegIFN	Pegylated Interferon
Pfu	Plaque Forming Unit
PID	Patient Identification Number
pIMD	Potential Immune-Mediated Disease
Pol	Polymerase
PoP	Proof of Principle
PP	Per protocol
PT	Preferred Term
qHBsAg	Quantitative Hepatitis B Surface Antigen
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBIR	Randomisation System on Internet
SD	Standard Deviation
SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SpA	Spondyloarthritis
SPM	Study Procedures Manual
SRT	Safety Review Team
TAF	Tenofovir alafenamide
TDF	Tenofovir Disoproxil Fumarate
TE	Transient Elastography
TTS	Thrombosis with Thrombocytopenia Syndrome
ULN	Upper Limit of Normal
vp	Virus Particle
VSMB	Vaccines Safety Monitoring Board
WHO	World Health Organisation

GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- current bilateral tubal ligation or occlusion,
- Combined estrogen and progesterone oral contraceptives,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- Contraceptive vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilisation prior to the female patient's entry into the study, and this male is the sole partner for that patient,

  The information on the male sterility can come from the site personnel's review of the patient's medical records; or interview with the patient on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and/or progesterone alone oral contraceptive.

Adequate contraception does not apply to patients of child bearing potential with same sex partners, or for patients who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) can therefore be any unfavourable 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 trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, 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 serious adverse event. In a single-blind study, the investigator and/or his staff are aware of the treatment assignment but the patient is not.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study: **(Synonym of End of Trial)**	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV
Epoch:	An epoch is a set of consecutive time points or a single time point from a single protocol. Epochs are defined to support a main purpose which is either to draw conclusions on patient participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the time points included in an epoch must be sufficient to fulfil the purpose of the epoch. Typical examples of epochs are screening, primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Sections 6.7.2 and 10.5 for details on criteria for evaluability).
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
Menopause / Post-menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A blood sample for simultaneous follicle-stimulating hormone and estradiol levels may be collected at the discretion of the investigator to confirm non-reproductive potential.
Patient:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine(s) or as a control.
Patient number:	A unique number identifying a patient, assigned to each patient consenting to participate in the study.
Pharmacogenomics:	The International Conference on Harmonization (ICH) E15 Guidance for Industry defines pharmacogenomics as Study of variation of DNA and RNA characteristics as related to drug or treatment response. Pharmacogenetics, which is a subset of pharmacogenomics, is “the study of variations in DNA sequence as related to drug response.” Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (*e.g.*, mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (pharmacokinetics, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research are not pharmacogenomics.

Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
Primary completion date:	The date that the final patient was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of patients, 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 treatment to patients in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the patient or an observer during a specified post-vaccination follow-up period.
Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/ product /placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
Treatment:	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 patient.
Treatment number:	A number identifying a treatment to a patient, according to treatment allocation.
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.

1. INTRODUCTION

1.1. Background

1.1.1. Medical Need

The burden of chronic Hepatitis B virus (HBV) infection constitutes a public health threat in many areas of the world. According to the WHO global hepatitis report [WHO, 2017], more than 250 million people are chronically infected with HBV. The prevalence of HBV infection varies in different parts of the world: more than 6% of the general population in Africa and Western Pacific regions but less than 1% of the general population in America. If left untreated, chronic HBV infection can lead to cirrhosis, hepatic decompensation and hepatocellular carcinoma. These long-term complications are life-threatening and accounted for 887 000 deaths.

Currently, there are two main treatment options for chronic hepatitis B (CHB) patients: either by pegylated interferon alpha (PegIFNα) or by nucleo(s)tide analogues (NA) [EASL, 2017]. PegIFNα aiming at induction of a long-term immune control with a finite duration treatment may achieve sustained off-treatment control, but durable virological response and hepatitis B surface antigen (HBsAg) loss is limited to a small proportion of patients. In addition, owing to its poor tolerability and long-term safety concerns, a significant number of patients are ineligible for this type of treatment.

NAs target HBV virion synthesis. The NAs approved in Europe for HBV treatment include entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) that are associated with high barrier against HBV resistance as well as lamivudine (LAM), adefovir dipivoxil (ADV) and telbivudine (TBV) that are associated with low barrier to HBV resistance. The main advantage of treatment with a potent NA with high barrier to resistance (*i.e.*, ETV, TDF, TAF) is its predictable high long-term antiviral efficacy leading to HBV DNA suppression in the vast majority of compliant patients as well as its favourable safety profile. The disadvantage of NA treatment is its long-term therapeutic regimen, because a NA does not usually achieve HBV eradication and NA discontinuation may lead to the HBV relapse [Kranidioti, 2015]. HBsAg loss representing a functional cure is now the gold standard treatment endpoint in CHB [Block, 2017; Cornberg, 2017], which however, is rarely achieved with NA treatment [Zoutendijk, 2011].

Despite the potent suppression of HBV replication in livers by a NA, the dysfunction of HBV-specific antiviral immunity persists in patients. Combinations of direct antivirals and restoration of immune responses may be needed for the sustainability of the functional cure.

1.1.2. Need for a new vaccination strategy

Previous therapeutic vaccines have induced very low levels of HBV-specific T cell response with minimal effects on viral suppression or HBV seroconversion events. Early effort on recombinant vaccines based on HBV surface and/or PreS antigens preliminarily induced antibody response but no HBV-specific CD8+ T-cell response, with no clinical or virological benefit [Jung, 2002; Vandepapelière, 2007]. A DNA vaccine expressing

HBV envelope failed to restore T cell response specific to HBsAg and HBcAg thus did not decrease the risk of relapse in patients after NA discontinuation [Fontaine, 2015]. With new delivery systems, a DNA vaccine (prime vaccine) and MVA viral vector vaccine (boost vaccine) encoding S, preS1/S2 showed no T cell induction or reduction in viremia suggesting HBV PreS and surface antigens alone are not sufficient to cure patients [Cavenaugh, 2011]. A lipopeptide vaccine targeting a CTL epitope derived from HBcAg was shown to initiate CTL activity but at a very low magnitude that failed in viral clearance [Heathcote, 1999]. More recently, vaccine strategies targeting multiple HBV antigens and new delivery systems have been investigated. A recombinant HBsAg/HBcAg vaccine led to a viral load decrease to a very low level (*i.e.* ~50 IU/ml) in only half of the patients [Al-Mahtab, 2013]. A DNA vaccine encoding S, preS1/S2, core, polymerase and X proteins with genetically adjuvanted IL-12 together with lamivudine induced a multi-specific T cell response and a >2 log10 decrease in viral load in half of the patients. However, changes in quantitative detection of HBsAg, loss of HBsAg or HBsAg seroconversion were not observed in any patients [Yang, 2012]. The GS-4774 vaccine, a yeast-based T cell vaccine expressing large S, core and X proteins of HBV did not provide significant reduction in HBsAg in virally-suppressed CHB patients. The vaccine was shown to elicit HBV-specific T cell response preliminarily to X- and core antigens but much weaker response to the S antigen [Lok, 2016].

GSK Biologicals' new vaccination strategy relies on a heterologous prime-boost approach with HBV viral vector vaccines (ChAd155-hIi-HBV followed by MVA-HBV) with sequential or co-administration of $AS01_{B\text{-}4}$-adjuvanted HBc-HBs proteins. The vaccines will be administered in patients with chronic HBV infection who are virally suppressed on NA therapy but not functionally cured. This strategy is based on the following observations:

- Adenovirus and MVA vectors are potent and technologically advanced CD8+ T-cell-inducing viral vectors [Folgori, 2006; Zaiss, 2010; Barnes, 2012; Sheehy, 2012; Cottingham, 2013]. Specifically, when a MVA vector is administered after adenovirus immunization, it has been shown to significantly boost the adenovirus-induced CD8+ T-cell responses [Swadling, 2014].
- Enhanced and sustained CD8+ T-cell responses were demonstrated in mice and non-human primates using an adenoviral vector-based vaccine encoding fusion of target antigen with the major histocompatibility complex (MHC) Class II CD74 invariant chain (hIi, genetic adjuvant) [Mikkelsen, 2011; Capone, 2014].
- Combining an adjuvant system such as AS01 to Malaria RTS, S antigen, HBsAg or Zoster glycoprotein E antigen was shown to dramatically enhance the antibody and CD4+ T-cell adaptive response to the targeted antigen, as the ability of AS01 to improve adaptive immune responses is linked to a transient stimulation of the innate immune system leading to the generation of high number of efficient Ag-presenting dendritic cells [Chlibek, 2013; Chlibek, 2014; Didierlaurent, 2014; Leroux-Roels, 2014; Leroux-Roels, 2016].
- Administration of viral vectored vaccines together with adjuvanted proteins may therefore induce a strong, multifunctional and complementary antigen-specific immune response [Omosa-Manyonyi, 2015].

A decrease in HBV-DNA load precedes the detection of HBV specific T-cell responses, both in patients resolving natural infections and in those displaying flare-ups of hepatitis associated with HBeAg seroconversion during chronic infection [Webster, 2004]. Reducing HBV DNA load by antiviral chemotherapy prior to starting therapeutic vaccination may, therefore, increase the responsiveness of HBV-specific T-cells to the vaccines [Michel, 2011; Boni, 2012].

Please refer to the current Investigator Brochure for information regarding the pre-clinical information of ChAd155-hIi-HBV, MVA-HBV and HBc-HBs/AS01$_{B-4}$.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

Treatment with GSK Biologicals' HBV therapeutic vaccines aims to restore immunity to HBV, as evidenced by clearance of HBsAg or reduction of HBsAg concentration, in order to allow patients to safely discontinue NA therapy without virological or clinical relapse [Chong, 2017; Lampertico, 2014].

Considering the current knowledge on HBV immunity, GSK Biologicals' vaccination strategy relies on the administration of three vaccines in heterologous prime-boost regimens: primed with ChAd155-hIi-HBV followed by a boost with MVA-HBV, with subsequent or co-administration of HBc-HBs/AS01$_{B-4}$.

The two viral vectored vaccines aim to induce an immune response ($CD8^+$ T-cells and, to a lesser extent, $CD4^+$ T-cells) to the core and surface antigens; the adjuvanted proteins aim to induce a robust $CD4^+$ T-cell and antibody response to the same core and surface antigens.

The aims of the study are as follows:

- **Phase I Dose-escalation safety lead-in** (Step A and Step B) aims to assess safety of a low dose (Step A) and a target dose (Step B) of the vaccine, both in a sequential regimen;
- **Phase II Regimen-finding** that assesses the target doses of the vaccines given in different regimens in Step B and Step C, aims:
  - To evaluate the safety profile of sequential regimen in Step B (with or without adjuvanted proteins i.e. group B1 and B3 respectively), adjuvanted proteins given alone (group B2) and co-administration regimens in Step C,
  - To evaluate whether one or more vaccine regimens tested will induce a decrease in serum HBsAg concentration (proof-of-principle [PoP]),
  - To evaluate the added value of the adjuvanted proteins on top of viral vector vaccines,

- To evaluate the best vaccination regimen for the administration of the adjuvanted proteins (i.e. either sequentially to or co-administered with the viral vectored vaccines),
- To evaluate the added value of 3 boost doses versus one boost dose of MVA-HBV co-administered with adjuvanted proteins (group C1 and C2),
- To assess the induction of HBV-specific CD8+ and CD4+ T-cell responses and antibody responses by different vaccine regimens.

1.2.2. Rationale for the study design

Study population: This first-time-in human (FTIH) study will be conducted in one segment of the CHB patients that is at low risk of severe hepatitis exacerbation: adult patients between 18 and 65 years of age, HBeAg-negative chronic HBV infection, with no cirrhosis or no advanced fibrosis, with HBV viral suppression and normal ALT on entecavir (ETV) or tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) treatment for at least 24 months.

It has shown that patients under long-term effective therapy with NA have a restored function of HBV-specific T-cells [Boni, 2012]. ETV, TDF and TAF are highly effective NAs with no or minimal resistance reported to date. Selecting patients well-controlled under these NA therapy may therefore optimize their response to the vaccines while minimizing the risk for viral reactivation due to appearance of drug-resistant mutant.

At Screening, liver fibrosis stage assessment (aiming to exclude patients with advanced fibrosis/cirrhosis) will rely on two different non-invasive approaches: a ‘‘biological’’ approach based on the quantification of biomarkers in serum samples and a ‘‘physical’’ approach based on the measurement of liver stiffness.

As per European Association for the Study of the Liver (EASL) and Asociación Latinoamericana para el Estudio del Hígado (ALEH) clinical practice guidelines for non-invasive tests for evaluation of liver disease severity and prognosis, FibroTest is one of the most widely used and validated patented tests in clinical practice due to its high applicability and good inter-laboratory reproducibility [EASL, 2015]. It is less accurate in detecting intermediate stages of fibrosis than cirrhosis. The performance is better for detecting cirrhosis than significant fibrosis. Serum biomarkers of fibrosis are well validated in patients with chronic viral hepatitis with more evidence for HCV than for HBV and HIV/HCV coinfection. Transient elastography (TE) FibroScan can be considered the non-invasive standard for the measurement of liver stiffness. It is well validated in viral hepatitis with performance equivalent in hepatitis B, hepatitis C and in HIV-HCV coinfection. It performs better for detection of cirrhosis than for detection of significant fibrosis and is a reliable method for the diagnosis of cirrhosis in patients with chronic liver diseases, that generally performs better at ruling out than ruling in cirrhosis (with negative predictive value higher than 90%).

Among the different available strategies, algorithms combining TE and serum biomarkers appear to be the most attractive and validated one [Leroy, 2016; Castéra, 2005]. In patients with viral hepatitis C, when TE and serum biomarkers results are in accordance,

the diagnostic accuracy is increased for detecting significant fibrosis but not for cirrhosis. In cases of unexplained discordance, a liver biopsy should be performed if the results would change the patient management. In a prospective study of chronic hepatitis C (CHC), a significant positive correlation was observed between liver stiffness as measured by FibroScan and fibrosis stages as determined by on biopsy [Ziol, 2005]. The distinctive cut-off values of 9.6 kiloPascal (kPa) and 14.5 kPa were considered in diagnosis of extensive fibrosis (METAVIR F3) and cirrhosis (METAVIR F4), respectively. In another prospective study in CHC patients, the performance of FibroScan was compared with FibroTest, aspartate transaminase to platelets ratio index (APRI) and liver biopsy [Castéra, 2005]. FibroScan and FibroTest have shown similar accuracy in estimating the liver fibrosis staging. The best performance was obtained by combining the FibroScan and FibroTest, The most discriminant cut-off value for advanced fibrosis (METAVIR F3) was determined as 9.5 kPa and 12.5 kPa for cirrhosis (METAVIR F4). In a meta-analysis of the FibroTest diagnostic value, it was found that FibroTest had a higher or similar prognostic value compared with biopsy in patients with CHB, CHC and alcoholic liver disease (ALD) [Halfon, 2008]. In another prospective study in patients with alcoholic liver disease, FibroTest has been shown to identify advanced liver fibrosis with high diagnostic accuracy [Thiele, 2018]. The cutoff score 0.58 ruled out advanced fibrosis with a negative predictive value (NPV) of 97%. In a Phase III study on the combination of several direct antiviral agents (DAAs) in treating genotype 3 chronic HCV infection with advanced liver disease, liver biopsy, Fibroscan and FibroTest plus APRI were used to define the liver fibrosis stage of the study population [Leroy, 2016]. Advanced fibrosis was defined as a METAVIR score of F3 or an Ishak score of 4 on liver biopsy, or a FibroScan ≥ 9.6 kPa but < 14.6 kPa, or a FibroTest score of 0.58-0.74 plus an APRI score above 1 but below 2. Cirrhosis was defined as a METAVIR score of F4 or an Ishak score > 4 on liver biopsy, a liver stiffness value ≥ 14.6 kPa, or a FibroTest result ≥ 0.75 plus APRI ≥ 2. Where different testing methods yielded conflicting results, biopsy data took precedence. If biopsy data were not available, a FibroScan result took precedence over the FibroTest/APRI result. In this study, we adopt both Fibroscan and FibroTest to rule out patients with advanced liver fibrosis or cirrhosis. Only patients with FibroScan < 9.6 kPa or FibroTest score < 0.59, will be included in this FTIH study.

Route of administration: The choice of the intramuscular route for ChAd155-hIi-HBV is based on the assumption that no co-infection of natural human Adenovirus could occur at this site. Furthermore, there is a large body of data from clinical trials in humans using replication defective Ad5- and Ad6-based HIV vaccines injected intramuscularly showing an excellent safety profile, no viral shedding, and high levels of immunogenicity. MVA-HBV will also be given by the intramuscular route following several studies on other MVA vector vaccines demonstrating similar immunogenicity but less local reactivity when MVA vectors were administered by the intramuscular compared to the subcutaneous route. Intramuscular vaccination with $AS01_B$-containing vaccines has been largely studied in the Company's Zoster program [Lal, 2015; Cunningham, 2016], Malaria program [Agnandji, 2011; Asante, 2011; Lusingu, 2010] and Tuberculosis program [Penn-Nicholson, 2015] with an acceptable safety profile.

Dose of each of the vaccines: Two different doses of ChAd155-hIi-HBV ($5x10^9$ and $5x10^{10}$ vp) and MVA-HBV ($2x10^7$ and $2x10^8$ pfu) will be assessed and were selected based on available clinical data with ChAd3- and MVA-based vectored vaccines using

other antigens. ChAd3 vector is closely related to ChAd155. In HCV clinical trials where ChAd3-NSmut was assessed at doses of $5x10^8$, $5x10^9$, $2.5x10^{10}$, $7.5x10^{10}$ vp in healthy adults and in patients with chronic HCV, each vaccine dose was well tolerated while a dose response was observed up to the $2.5x10^{10}$ dose [Barnes, 2012; Kelly, 2016]. Booster doses of HCV MVA-NSmut were administered at doses of $2x10^6$, $2x10^7$ or $2x10^8$ pfu in subjects primed with $2.5x10^{10}$ vp of ChAd3 NSmut: the $2x10^7$ and $2x10^8$ pfu doses were equally well tolerated and immunogenic [Swadling, 2016]. The clinical development of an Ebola vaccine candidate has used ChAd3 as a vector (ChAd3-EBO-Z). In this program, doses of $1x10^{10}$, $2.5x10^{10}$, $5x10^{10}$ and $1x10^{11}$ vp were evaluated in healthy adults [Tapia, 2016]. The vaccines were well tolerated and higher immune responses were associated with the highest dose.

Two different doses of HBc-HBs antigens will be assessed, containing 20-20, and 80-80 µg of HBc and HBs, respectively. The existing HBV vaccines containing 20 µg of HBsAg and up to 100 µg of HBs without or with HBcAg have been administered safely in clinical trials in CHB patients [Vandepapelière, 2007; Al-Mahtab, 2013]. Clinical data with other $AS01_B$-adjuvanted vaccines suggest vaccine containing lower antigen doses may perform as good as or better than those containing higher doses [Van Braeckel, 2011]. CCI [redacted] Such interference observed in mice may however not be deemed relevant to the administration of the vaccine in CHB patients [Al-Mahtab, 2013]. A vaccine containing equal concentrations of HBcAg and HBsAg was able to induce an immune response to both antigens.

Vaccine regimen: The two lead vaccine regimens tested in our study will be 1) a prime with ChAd155-hIi-HBV and boost with MVA-HBV, followed by two booster doses of adjuvanted proteins, and 2) a prime with ChAd155-hIi-HBV co-administered with adjuvanted proteins followed with three booster doses of MVA-HBV co-administered with adjuvanted proteins. The clinical study design includes also three active control groups consisting of 1) patients vaccinated with adjuvanted proteins only, and 2) patients primed with ChAd155-hIi-HBV and boosted with MVA-HBV only, and 3) patients primed with ChAd155-hIi-HBV co-administered with adjuvanted protein followed with one booster dose of MVA-HBV co-administered with adjuvanted protein. The interval of 8 weeks between doses is based on existing clinical data with other related vaccines.

Previous data generated at GSK showed that $AS01_B$-adjuvanted proteins induce strong antibody and antigen-specific $CD4^+$ T-cell responses but $CD8^+$ T-cell response after $AS01_B$-adjuvanted proteins is however weak [Leroux-Roels, 2010; Van Braeckel, 2011]. Therefore the co-administration or sequential administration of $AS01_B$-adjuvanted protein vaccine with the heterologous prime-boost with viral vector vaccines aims to complement the breadth of the immune response to the targeted antigens.

CCI [redacted]

CCI [redacted] Please refer to the Investigator Brochure for more information.

In a recent study on human immunodeficiency virus (HIV) vaccine, GSK has evaluated the prime-boost or co-administration of adenoviral vector (Ad35-GRIN) with adjuvanted proteins (F4co/AS01$_B$). The co-administration of the adjuvanted protein and the adenovirus vector was shown to be well tolerated and resulted in a strong, polyfunctional and complementary HIV-specific immune response in HIV-uninfected volunteers after two doses that was maintained up to one year post third dose. The regimen "priming with adjuvanted proteins followed by boosting with the viral vector" appeared to induce CD4$^+$ T-cells that were less polyfunctional than when the adenovectored vaccine was given as priming vaccine [Omosa-Manyonyi, 2015]. Based on these data, the FTIH study with therapeutic HBV vaccine will evaluate different vaccination schedules where HBc-HBs/AS01$_{B-4}$ is given either sequentially to or co-administered with the heterologous prime-boost with ChAd155-hIi-HBV and MVA-HBV.

1.2.3. Rationale for the use of placebo

A PBS solution is included as a negative control (placebo) in a low number of patients in the study. The use of the placebo control and the single-blind, randomized study design will allow controlling for potential biases in the conduct of the study.

Importantly, each patient including those in the control group will remain under NA treatment throughout the duration of the study.

1.3. Benefit : Risk Assessment

Approximately CCI [redacted] patients in this study will receive the investigational HBV viral vector and/or adjuvanted protein vaccines, whereas the other approximately CCI [redacted] patients will receive the placebo only.

Although clinical data on similar type of vaccines are available that are supportive to the use of each vaccine in the proposed vaccine regimen (see Sections 1.2.2 and 1.3.1), none of the investigational vaccines to be used in this study have been administered in humans yet prior the study start. Therefore, safety and efficacy of the proposed vaccine regimen are unknown until the data are generated.

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of the ChAd155-hIi-HBV, MVA-HBV and HBc-HBs/AS01$_{B-4}$ and for the data generated during the study.

The following section outlines the risk assessment and mitigation strategy for this study protocol.

1.3.1. Risk Assessment

1.3.1.1. Vaccination

Vaccination in general may lead to local reactions at injection site, such as pain, redness and swelling.

As with all injectable vaccines, immediate systemic allergic reactions to vaccination can occur. These are however very rare and are estimated to occur once per 450,000 vaccinations to once per 1,000,000 for vaccines which do not contain allergens such as gelatin or egg protein [Zent, 2002]. In order to be able to treat patients with an immediate systemic allergic reaction to vaccination, all patients will need to remain under observation at the study site for at least 60 minutes after vaccination. For the management of anaphylactic reactions, access to an emergency room or to a first aid kit will be available at the sites.

1.3.1.2. ChAd155-hIi-HBV and MVA-HBV

ChAd155-hIi-HBV has not previously been tested in humans. Adenoviral gene transfer vectors are known to induce thrombocytopenia when administered systemically (i.v.). CCI [redacted] In clinical development programs of other adenoviral vectors within the Company, a transient drop in thrombocyte counts and hemoglobin were noted following intramuscular administration, without clinical signs and restored over time. Given these observations, the risks of spontaneous bleeding due to thrombocytopenia and anemia were considered as potential risks for the ChAd155-hIi-HBV vaccine. With accumulation of safety data in clinical development programs of other adenoviral vectors within the Company, this risk has been redefined as “transient (non-clinically significant) decreases in hematologic parameters”. Safety provisions will be included in this FTIH study such as enrolling patients with normal hematology parameters and a broad safety hematology and biochemistry evaluation at each study visit.

CCI [redacted]

MVA is widely considered as the vaccinia virus strain of choice for clinical investigation because of its acceptable safety profile. Over 120,000 humans have been inoculated and successfully vaccinated against smallpox with MVA during the campaign for the eradication of smallpox in Germany in the 1970s, including elderly and immunocompromised persons. More recently, the use of MVA in recombinant vaccines have been tested in a number of clinical studies, including those for vaccines against HIV and HCV [Guerra, 2010; Currier, 2010; Earl, 2009; Habersetzer, 2009; Bain, 2009;

Fournillier, 2007]. The safety data obtained from previous trials using other MVA based vaccines have shown that they are generally well tolerated.

The heterologous prime-boost regimen with Chimpanzee adenoviral vector vaccine and MVA vector vaccines showed that the MVA vector vaccine was more reactogenic than the Chimpanzee adenoviral vector vaccine but was still well tolerated with the majority of AEs being mild in intensity [Swadling, 2014; Mensah, 2016; Green, 2015; Ewer, 2016].

CCI [redacted]

Two recent publications have shown that autoantibodies targeting the CLIP peptide (a region of the hIi) could be a biomarker for the early diagnosis of the autoimmune disease inflammatory spondyloarthritis (SpA) [Baerlecken, 2014; Baraliakos, 2014].

However, several arguments suggest the risk for vaccine-induced SpA or other potential immune mediated diseases (pIMDs) is minimal:

- A humanized anti-CD74 monoclonal antibody (milatuzumab) targeting cell surface expressed epitope of the molecule CD74 which is expressed on monocytes, macrophages, and B cells but not T-cells was assessed in patients with multiple myeloma or B-cell lymphoma. No spondyloarthritis cases were reported in these patients [Christian, 2015; Martin, 2015]. The anemia, lymphopenia, neutropenia, thrombocytopenia reported in these patients could be due to the patient's underlying disease as similar AE have been observed with other monoclonal antibody therapies. Single dose studies of milatuzumab in monkeys showed no adverse effects but did transiently decrease circulating B and T lymphocytes and natural killer cells [Kaufman, 2013; Christian, 2015; Martin, 2015; Stein, 2007].
- SpA therapy relies on non- steroidal anti-inflammatory drugs and anti-TNFα therapy, the latter being effective in approximately half of patients. TNFα is mostly produced by dendritic cells and monocytes. A B-cell-directed therapy (rituximab) was safely tested but ineffective in patients with SpA failing to respond to TNFα blockers. Altogether these data support that the mechanism for SpA pathogenesis involves MHC class I cells and not B-cells nor antibodies [Song, 2010; Bowness, 2015].
- CCI [redacted] (Please refer to IB for more information).

Nevertheless, the risk that the ChAd155-hIi-HBV vaccine induces an immune response against the hIi and a pIMD cannot be entirely ruled out. CCI [redacted]

1.3.1.3. HBc-HBs/AS01$_{B-4}$

The formulation with the AS01$_{B-4}$ adjuvant and the HBV antigens was selected for the HBV therapeutic program as it demonstrated the highest process robustness. To date, the AS01-containing vaccines have been largely studied in the Company's Zoster program [Lal, 2015; Cunningham, 2016; Leroux-Roels, 2012], Malaria program [Agnandji, 2011; Asante, 2011; Lusingu, 2010] and Tuberculosis program [Penn-Nicholson, 2015] with an acceptable safety profile.

The general concern that Adjuvant Systems could induce events of possible autoimmune etiology is considered a potential risk. In order to ensure adequate detection and follow-up of pIMDs, the occurrence of pIMDs will be duly monitored and reported for the entire study period.

1.3.1.4. Risks linked to the study population (*i.e.* chronically infected HBV patients)

During the natural course of the disease, viral clearance of HBV occurs through immunological mechanism that may be associated with hepatitis flares, and in some rare instances, it can lead to fulminant hepatic failure. Hepatic damage is possibly triggered by inefficient T-cell control and recruitment of inflammatory cells (macrophages) during the disease progress. When the HBV-specific $CD8^+$ T-cell response is unable to control virus replication, it may contribute to liver pathology, not only directly but also by causing the recruitment of non-virus-specific T-cells while, in the presence of an effective HBV-specific $CD8^+$ T-cell response, inhibition of virus replication can be independent of liver damage [Maini, 2000]. Importantly, cytokines can mediate viral clearance without direct hepatocyte killing [Phillips, 2010]. Also, several mechanisms are in place to control "exuberant" T-cell activation and protect from liver failure (IL-10, arginase, PD1 and other co-inhibitory pathways).

The proposed vaccination strategy aims to induce a robust response in terms of antibodies, $CD4^+$ and $CD8^+$ T-cells to the selected antigens: robust antibody response and $CD4^+$ T-cell response (but no $CD8^+$ T-cell response) have already been observed in previous studies in CHB patients and no life-threatening hepatitis flares were reported [Vandepapelière, 2007].

Several types of vaccines have been tested in CHB patients. These vaccines consisted of recombinant protein vaccines (with or without adjuvants), immuno-complexes HBs-anti-HBs, DNA/MVA prime-boost vaccination and yeast-based vaccine expressing recombinant proteins. To the Company's knowledge, no significant safety issues were reported in these trials but the vaccines were generally ineffective in controlling the virus. None of these vaccines was able to mount a de-novo robust and broad immune response targeting both the HBc and HBs antigens as well as the different segments of the immune system ($CD4^+$ T-cells, $CD8^+$ T-cells and antibodies) [Michel, 2015].

However, when similar viral vectored-based vaccines using HCV immunogens were tested in chronic HCV-infected patients, the safety profile was acceptable but the vaccine failed to induced virus-specific T-cell responses [Swadling, 2016].

Considering the risk of hepatic failure that may be triggered by vaccine-induced immune response, this FTIH will be conducted in CHB adult (18-65 years of age) patients at low

risk of hepatitis flares, *i.e.* in those patients under NA therapy since at least 24 months, well-controlled (HBV DNA suppressed and alanine transaminase [ALT] normalized within the past 24 months) and with no advanced liver fibrosis or cirrhosis of any stage.

In order to detect any potential safety issue, patients will be closely monitored for safety and testing will include liver chemistry and coagulation.

1.3.1.5. Risks linked to the collection of biospecimens in the study

Biospecimens to be collected in this study are blood samples, buccal swab***s*** and urine samples, which are commonly used in clinical diagnosis with generally few procedural complications. The volume of blood being taken during the course of the study is not expected to compromise patients' health. It is less than the safe limit in a clinical trial recommended by the WHO [Howie, 2011]. Therefore we do not anticipate adverse events as a consequence of blood sampling.

1.3.2. Benefit Assessment

Although vaccination strategy aims to induce an immune response that has been suggested to play an important role in the clearance of the HBV virus as evidenced by HBsAg loss, the patients receiving the investigational HBV therapeutic vaccines may not directly benefit from vaccination as the investigational vaccines have not been assessed yet and it is hence not known whether it will be truly effective against chronic HBV infection.

The patient's participation will benefit other patients in the future since information collected during this study will help in the evaluation of HBV therapeutic vaccines and other vaccines based on similar technology.

The vaccines and study tests will be provided free of costs to the patient.

1.3.3. Overall Benefit: Risk Conclusion

The investigational vaccine regimen aims to achieve functional cure of HBV infection as evidenced by HBsAg loss. This trial is a first-time-in-human study: the investigational HBV viral vector vaccines and adjuvanted protein vaccines have not been tested in human to date so information on vaccine safety and efficacy is not available. Clinical data with similar type of technology (ChAd and/or MVA prime-boost) but other immunogens (Malaria, Ebola, HCV, HIV) are available and did not raise major safety concerns. Clinical data with other $AS01_B$ adjuvanted vaccines, including with HBsAg are available and did not raise major safety concerns. Immune-mediated liver toxicity cannot be ruled out. Measures to minimize risk to patients participating in this study are included in the study protocol and holding rules are built in case of safety signals. In addition, the study will be followed up by an internal Safety Review Committee (iSRC) including also a hepatologist. The potential risks associated with the HBV viral vector and adjuvanted proteins vaccines are justified by the potential benefits to patients.

2. OBJECTIVES

2.1. Primary objective

- 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.

Refer to Section 10.1 for the definition of the primary endpoints.

2.2. Secondary objectives

- To assess the immunogenicity 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.
- 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 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.

Refer to Section 10.2 for the definition of the secondary endpoints.

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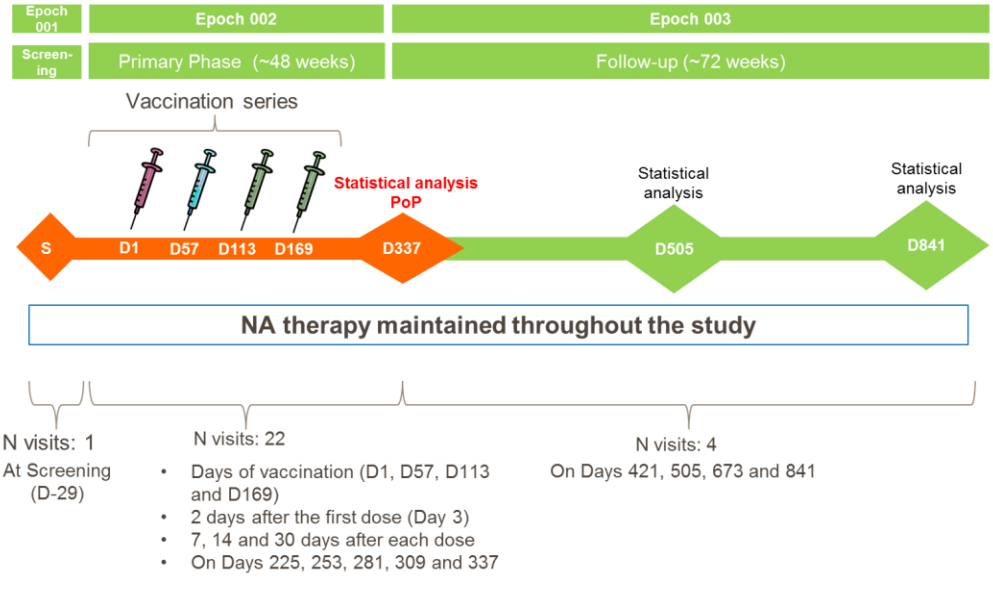
3. STUDY DESIGN OVERVIEW

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

During special circumstances (e.g., Coronavirus disease 2019 [COVID-19] pandemic), certain study procedures should be adapted to protect patient's welfare, and as far as possible ensure the potential benefit to the patient and promote data integrity (Section 5.6.18).

Figure 1 Study design



D: Day; N: Total number; NA: Nucleo(s)tides analogues; PoP: Proof-of-principle; S: Screening.
For information on the dose escalation, refer to Figure 4.
Refer to Section 5.6.18 for study procedures to be adapted during special circumstances.

D: Day; N: Approximate number of patients to be enrolled and vaccinated.
* Step A, B and C will be performed in a staggered manner. 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. Please, see Section 8.8.2 for more information.

- **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)

Refer to glossary of terms for the definition of PCD.

- **End of Study (EoS):** Last testing results released of samples collected at Visit 26.

Refer to glossary of terms for the definition of EoS.

- **Study groups:**

Table 1 Study groups, treatments and epochs foreseen in the study

Study group	Study treatment	Approximate Number of patients	Age (Min/Max)	Epoch 001 Screening phase	Epoch 002 Primary phase	Epoch 003 Follow-up phase
A1	D1: ChAd155-hIi-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	CCI	18 years – 65 years	●	●	●
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		18 years – 65 years	●	●	●
A3 *	D1: PBS D57: PBS D113:PBS D169: PBS		18 years – 65 years	●	●	● *
B1	D1: ChAd155-hIi-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		18 years – 65 years	●	●	●
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		18 years – 65 years	●	●	●
B3	D1: PBS D57: PBS D113: ChAd155-hIi-HBV $5x10^{10}$ vp D169: MVA-HBV 2x108 pfu		18 years – 65 years	●	●	●
C1	D1: ChAd155-hIi-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		18 years – 65 years	●	●	●
C2	D1: PBS D57: PBS D113: ChAd155-hIi-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		18 years – 65 years	●	●	●

For information on vaccines administered to each group, please refer to Table 20 and Table 21.
* 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:**
  - 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.

  For details on the staggered enrolment on, please see Section 8.8.2.

- **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 (see Table 4 and Table 5). In case of abnormal parameters, blood samples may be collected at additional unscheduled visits. For more information, see Section 8.5.3.

    * 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 (AFP) 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.

CCI [redacted]

- **Patient** input into study design: Due to the feedback from patients that the number of visits may be challenging, the study team is working with countries/sites to provide an option where patients may be offered home nursing visits according to local regulations. The home nursing providers will go to the patient's home, decreasing the number of times the patient must travel to the research site. Only selected visits will have the option to be performed as a home visit, these may include biological samples collection, patient's assessments and data collection. The full specifications of the home nursing services will be outlined in the SPM.
- **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. Refer to Section 8.8 for detailed description of holding rules and safety monitoring.
- CCI [redacted]
- 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.
- **Ancillary study**: To evaluate the shedding potential of the replication incompetent ChAd155-hIi-HBV vaccine, an ancillary study has been set-up and described in a separate study protocol TH HBV VV-031 HBS:001. This ancillary study will be performed on a subset of patients recruited in Step B. Biological samples (throat swab and urine samples) from these subjects will be collected at Visit***s*** 1, 2, 3, 4 and 5.

4. STUDY COHORT

4.1. Number of patients/centers

This will be a multi-centric, multi-country study.

The target is to enroll approximately CCI [redacted] eligible patients. Refer to Section 10.4 for the estimation of the sample size.

When target enrolment is reached, any additional eligible patient who has provided informed consent before the target was reached will be allowed to be enrolled into the study.

4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

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

- Patients who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the patient prior to performing any study specific procedure.
- A male or female between, and including, 18 and 65 years of age at the time of the first vaccination.
- Female patients of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as hysterectomy, bilateral ovariectomy or post-menopause.

  Please, refer to the glossary of terms for the definition of menopause.
- Female patients of childbearing potential may be enrolled in the study if the patient:
  - has practiced adequate contraception for 30 days prior to vaccination, and
  - has a negative pregnancy test at Screening, and
  - has agreed to continue adequate contraception from Screening until 12 weeks after completion of the vaccination series.

  Please refer to the glossary of terms for the definition of adequate contraception.
- Male patients
  - with documented bilateral vasectomy and resultant azoospermia, bilateral orchiectomy or azoospermia, or
  - who agree to practice abstinence from penile-vaginal intercourse (when this is their preferred and usual lifestyle) or use condoms from Screening until 12 weeks after completion of the vaccination series.
- CHB patient, under and adherent to treatment with a nucleos(t)ide analogue with high barrier to resistance (e.g. ETV, TDF, TAF) given as per approved label/dosage for at least 24 months.
- Documented medical history of HBeAg-negative CHB prior to onset of NA therapy (applicable to all patients in Step A and Step B and to some patients in Step C) or documented medical history of HBeAg-negative CHB over a period of at least 24 months prior screening (applicable to some patients in Step C only).
- Documented HBV viral suppression as per local clinical diagnosis within the previous 24 months AND at Screening test HBV DNA < 10 IU/mL. If no results are available, two Screening tests need to be performed at least 2 weeks apart. Small

fluctuations of HBV DNA (≤ 10 x lower limit of quantification (LLOQ); LLOQ defined by laboratory that performed testing) are allowed provided HBV DNA is < 10 IU/mL at Screening and was clearly not rising during the previous 24 months.

- Documented normal level of ALT as per local clinical diagnosis within the previous 24 months AND at Screening test ALT ≤ 48 U/L. Small fluctuations of ALT (≤ 1.5 X ULN) are allowed provided ALT ≤ 48 U/L at Screening. If no results are available, two Screening tests need to be performed at least 2 weeks apart. ULN are to be defined according to local laboratory reference range.
- No clinical diagnosis of cirrhosis (e.g. F4 by METAVIR scoring system or ≥ 6 by Ishak scoring system or FibroScan TE score > 12.5 kPa) within the previous 24 months.
- FibroScan TE score < 9.6 kPa and FibroTest score < 0.59 at Screening. A patient with one of these parameters out of range, but having the liver biopsy within 12 months before screening that showed F0-2 by METAVIR scoring system or stage 0-4 by Ishak scoring system, can be included.
- HBsAg concentration > 50 IU/ml and anti-HBs negative at Screening.
- Anti-HBc positive at Screening.
- HBeAg-negative at Screening.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the patient must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines during the period starting 30 days before the first dose of study vaccines (Day -29 to Day 1), or planned use during the study period.
- Any medical condition that in the judgment of the investigator would make intramuscular (IM) injection unsafe.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs (including but not limited to IFN) during the period starting six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone ≥ 10 mg/day or equivalent. Inhaled and topical steroids are allowed.
- Administration of immunoglobulins and/or any blood products during the period starting 3 months before the first dose of study vaccines or planned administration during the study period.
- Use of systemic cytotoxic agents, chronic antiviral agents or Chinese herbal medicines which, in the opinion of the investigator, may have activity against HBV

within the previous 6 months prior to randomization into this study. Antiviral treatment/prevention for influenza or herpes simplex virus (HSV) is allowed.

- Administration of adenovirus/adenovector-based or MVA-based vaccine within the last 12 months except for adenovirus/adenovector-based COVID-19 vaccines that could be administered up to 30 days prior to the first study vaccine dose (applicable for all patients except for the patients in France) OR Administration of adenovirus/adenovector-based or MVA-based vaccine within the last 12 months (applicable for the patients in France only).
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 14 days before each dose and ending 30 days after each dose of vaccines, with the exception of influenza vaccine that may be given at any time except within a 7-day period before or after each vaccine dose and COVID-19 vaccine that 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.
- Treatment with nephrotoxic drugs (e.g. aminoglycosides, amphotericin B, vancomycin, cidofovir, foscarnet, cis-platinum, pentamidine, etc.) or competitors of renal excretion (e.g. probenecid) within 2 months prior to Screening or the expectation that patient will receive any of these during the course of the study. TAF/TDF given as NA therapy is allowed.
- Concurrently participating in another clinical study, at any time during the study period, in which the patient has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Medical history of cirrhosis.
- Medical history of hepatic decompensation (e.g. ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, variceal bleeding, or hepatic encephalopathy).
- Planned for liver transplantation or previous liver transplantation.
- Personal or family (first degree) history of autoimmune disease.
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines.
- Evidence of HCV and hepatitis D Virus (HDV) infection. History of acute hepatitis A and acute hepatitis E is not an exclusion criterion.
- Suspicion of or confirmed HCC or any other liver cancer in medical history or at Screening:
- Suspicious foci at liver imaging exam.
- Elevated α-fetoprotein > 50 ng/ml.

- Documented evidence of other currently active cause of hepatitis (e.g. auto-immune hepatitis, primary biliary cirrhosis; primary sclerosing cholangitis, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease).
- Hematology and biochemistry parameters outside normal clinical range at Screening:

  Biochemistry:

  – Glomerular filtration rate (GFR) < 60 mL/min

  – Bilirubin > 27.5 µmol/L unless it is considered as clinically not significant by the Investigator or the diagnosis of Gilbert Syndrome has been established and confirmed by the Investigator

  – GGT > 65 U/L for males or GGT > 45 U/L for females unless it is considered as clinically not significant by the Investigator

  – ALT > 48 U/L

  – AST > 42 U/L unless it is considered as clinically not significant by the Investigator

  – ALP > 125 U/L unless it is considered as clinically not significant by the Investigator

  Hematology:

  – Hemoglobin < 12.0 g/dl (for females) or < 13.5 g/dl (for males) unless it is considered as clinically not significant by the Investigator

  – Red blood cell (RBC) count < 3.9 x 106 cells/mm3 (females) or < 4.4 x 106 cells/mm3 (males) unless it is considered as clinically not significant by the Investigator

  – White blood cell count (WBC) < 3,500 cells/mm3 or > 12,000 cells/mm3 unless it is considered as clinically not significant by the Investigator

  – Platelets < 140,000 cells/mm3

  – International Normalized Ratio (INR) > 1.32 (i.e. 1.1 x ULN)
- Known diabetes Type I.
- Body Mass Index (BMI) > 35 kg/m² at Screening.
- Any serious or active medical or psychiatric illnesses other than chronic hepatitis B which, in the opinion of the investigator, would interfere with patient treatment, assessment or compliance with the protocol. This would include any uncontrolled clinically significant renal, cardiac, pulmonary, vascular, neurogenic, digestive, metabolic (diabetes, thyroid disorders, adrenal disease), immunodeficiency disorders or cancer.
- History of or current drug abuse and/or excess of alcohol consumption as defined per local guidelines.
- HIV-positive patient.
- Pregnant or lactating female.

- Female planning to become pregnant or planning to discontinue contraceptive precautions in the period starting from the Screening Visit up to 12 weeks post-last vaccination visit.
- Fever and or acute minor illness (such as mild diarrhea, mild upper respiratory infection) may, be enrolled for Screening at the discretion of the investigator, provided that the condition is resolved at the time of vaccination.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for GCP, all applicable patient privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Patient informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed informed consent must be obtained from each patient prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Patient identification and randomization

5.2.1. Patient identification

Patient identification numbers (PIDs) will be assigned sequentially to the patients who have consented to participate in the study, according to the range of PIDs allocated to each study center.

5.2.2. Randomization of treatment

Allocation ratio: Step A: 1:1:1; Step B: 2:1:1; Step C: 2:1

Over-randomization:

☐ **No**

☒ **Yes, description:** At least 20% over-randomization

Subset:

☒ **No**

☐ **Yes, description:**

SBIR:

☐ **No**

☒ **Yes:** HBsAg concentration at Screening will be used as a minimization factor (<1000 IU/ml and ≥ 1000 IU/ml) for Step B and Step C randomization except for the patients needed for the first iSRC review in Step C.

Replacement randomized:

☒ **No**

☐ **Yes**

5.2.2.1. Treatment allocation to the patient

The treatment numbers will be allocated by component.

5.2.2.1.1. Study group and treatment number allocation

The target will be to enrol approximately [redacted] eligible patients, with possible 20% over-randomization. Randomization will be performed within each sequential step with the following randomization ratio: Step A: 1:1:1; Step B: 2:1:1; Step C: 2:1 (See Section 3 for more information on the groups).

Allocation of the patient to a study group at the investigator site will be performed using a randomization system on internet (SBIR). The randomization algorithm will use a

minimization procedure [White, 1978] accounting for HBsAg concentration (<1000 IU/ml and ≥ 1000 IU/ml) measured at Screening. The minimization procedure will be applied for patients enrolled in the steps B and C except for the patients needed for the first iSRC review in Step C to ensure to have not more than [redacted] patients in a treatment group as required for the iSRC evaluations.

After obtaining the signed and dated ICF from the patient and having Investigator checked the eligibility of the patient after screening procedures have been all completed, the site staff in charge of the vaccine administration will access SBIR. Upon receiving the patient identification number and HBsAg concentration, the randomization system will determine the study group and will provide the treatment number to be used for the first dose.

The first dose of the study vaccine can be administered only after the eligibility has been confirmed at Visit 1 (Please refer to Section 5.6.2). The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

5.2.2.1.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the patient identification number, and the system will provide a treatment number consistent with the allocated study group.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

5.3. Method of blinding

For this FTIH study, single-blinding will be used because there is a difference in the volume to be administered to patients in the different groups (0.1 ml or 0.5 ml) of Step A and because the products are to be stored at different temperature.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the patient and study (without any link to the treatment attributed to the patient) to each sample.

5.3.1. Emergency unblinding

Unblinding a participant's individual intervention number should occur ONLY in case of a medical emergency when knowledge of the intervention is essential for the clinical management or welfare of the participant.

The emergency unblinding process enables the investigator to have unrestricted, immediate and direct access to the participant's individual study intervention via SBIR, an automated Internet-based system.

As back up process, the investigator has the option of contacting a GSK Biologicals' Helpdesk (refer to the Table 3) if he/she needs help performing the unblinding (i.e. he/she cannot access the automated Internet-based system).

A non-investigator physician (e.g. physician from emergency room) or participant/care giver/family member may also request emergency unblinding either via the investigator (preferred option) or via the GSK Biologicals' Helpdesk (back up process).

Where applicable, the patient/participant card lists contact information for both the investigator and GSK Biologicals' Helpdesk.

Table 3 Contact information for emergency unblinding

GSK Helpdesk

Available 24/24 hours and 7/7 days

The Helpdesk is available by phone, fax and email

Phone (for countries where the toll-free number is not available): +32 2 656 68 04

Country	Toll-free number
Belgium, France, Germany, Spain, Taiwan	00 800 4344 1111
Hongkong	006 800 4344 1111
Thailand	001 800 4344 1111
United Kingdom	0800 056 7221

Fax: +32 2 401 25 75
E-mail: rix.ugrdehelpdesk@gsk.com

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the patients.

The burden of the study for the subject will be minimised as much as possible. For taking blood samples, three attempts at most should be performed. If the physician is not successful after the third attempt, he/she will make no further attempts. A local numbing cream or patch will also be offered at the discretion of the investigator prior to blood sampling, in order to minimise pain when blood samples are drawn.

Patients enrolled in this study will remain under NA therapy throughout the study. However, if a patient has experienced a drug-induced toxicity, the NA drug may be switched to another NA drug at the discretion of the Investigator.

For information on the holding rules applicable to this study, refer to Section 8.8.3. For information on safety evaluation by the iSRC, refer to Section 8.8.1.

5.5. Outline of study procedures (Amended: 22 June 2023)

For a detailed list of study procedures to be performed for all steps (A, B and C) during the primary phase and the follow-up phase, refer to Table 4 (Screening to Visit 17) and Table 5 (Visit 18 to Visit 26 and unscheduled visits). Intervals authorized between study visits are provided in Table 6.

For study procedures to be adapted during special circumstances, refer to Section 5.6.18.

Table 4 ***List of study procedures: Screening and primary phase (Screening Visit to Visit 17) (Amended: 22 June 2023)***

Epoch	Epoch 001	Epoch 002																
Study Phase	Screening	Primary Phase																
Type of contact	Screening Visit [t]	Visit 1	Visit 2 [q, s]	Visit 3 [s]	Visit 4 [s]	Visit 5 [q, s]	Visit 6 [^]	Visit 7 [s]	Visit 8 [s]	Visit 9 [q, s]	Visit 10 [^]	Visit 11 [s]	Visit 12 [s]	Visit 13 [q, s]	Visit 14 [^]	Visit 15 [s]	Visit 16 [s]	Visit 17 [q, s]
Time points	Day -29	Day 1	Day 3	Day 8	Day 15	Day 31	Day 57	Day 64	Day 71	Day 87	Day 113	Day 120	Day 127	Day 143	Day 169	Day 176	Day 183	Day 199
Sampling time point(s)	Screening	Pre	Post-Vacc 1					Post-Vacc 2				Post-Vacc 3				Post-Vacc 4		
Informed consent	●																	
Check inclusion/exclusion criteria	●	O																
Collect demographic data	●																	
Measure/record height and weight	●																	
Medical history	●																	
Hepatitis B history	●																	
12-lead electrocardiogram [n]	●	●					● [n]				● [n]				● [n]			
Liver ultrasound [j]	●																	
Transient elastography (FibroScan)	●																	
Physical examination/vital signs [m; n]	●	●	O	O	O	O	● [n]	O	O	O	● [n]	O	O	O	● [n]	O	O	O
Urine pregnancy test [a, n]	●	●					● [n]				● [n]				● [n]			
Screening conclusion	●																	
eCRF investigator's signature	●																	
Biospecimen sampling																		
Blood sampling for biochemistry (~3.5 ml) [b,g,k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood sampling for biochemistry (AFP) (~3.5 ml) [k]	●																	
Blood sampling for FibroTest (~8.5 ml) [k]	●																	
Blood sampling for hematological tests/CBC (~2.0 ml) [c, g,]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood sampling for hematological tests/INR (~4.5 ml) [c,g]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood sampling for autoimmune antibodies (~13.5 ml)	●																	
Blood sampling for HBV, HCV, HDV and HIV serology (~18.5 ml)	●																	
Blood sampling for qHBsAg (~3.5 ml)	●	●				●	●			●	●			●	●			●

Epoch	Epoch 001	Epoch 002																
Study Phase	Screening	Primary Phase																
Type of contact	Screening Visit [t]	Visit 1	Visit 2 [q, s]	Visit 3 [s]	Visit 4 [s]	Visit 5 [q, s]	Visit 6 [^]	Visit 7 [s]	Visit 8 [s]	Visit 9 [q, s]	Visit 10 [^]	Visit 11 [s]	Visit 12 [s]	Visit 13 [q, s]	Visit 14 [^]	Visit 15 [s]	Visit 16 [s]	Visit 17 [q, s]
Time points	Day -29	Day 1	Day 3	Day 8	Day 15	Day 31	Day 57	Day 64	Day 71	Day 87	Day 113	Day 120	Day 127	Day 143	Day 169	Day 176	Day 183	Day 199
Sampling time point(s)	Screening	Pre	Post-Vacc 1					Post-Vacc 2				Post-Vacc 3				Post-Vacc 4		
Blood sampling for HBV-DNA and new viral markers (~10 ml)	●					●	●			●	●			●	●			●
Blood sampling for CMI response (~20 ml) [d]		●			●		●	●	●		●		●		●		●	
Blood sampling for humoral response to HBV antigens (~3.5 ml) [e]		●			●				●		●		●				●	
CCI [redacted]																		
Blood sampling for serum repository (~3.5 ml)		●							●		●		●				●	
Urine sampling for urine chemistry (dipstick) [f]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
CCI [redacted]																		
Vaccines																		
Study group randomization [r]	O [r]	O [r]																
Treatment number allocation [n]		O					O [n]				O [n]				O [n]			
Pre-vaccination body temperature [n]		●					● [n]				● [n]				● [n]			
Check contraindications to vaccination [n]		O					O [n]				O [n]				O [n]			
Vaccine administration [n]		●					● [n]				● [n]				● [n]			
Recording of administered treatment number [n]		●					● [n]				● [n]				● [n]			
Safety assessment																		
Recording of concomitant medications/vaccinations [h]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Record intercurrent medical conditions leading to elimination from per-protocol [i]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Distribution of diary cards [n]		O					O [n]				O [n]				O [n]			
Return of diary cards			O	O				O				O				O		
Diary card transcription by investigator (or delegate)			●	●				●				●				●		

Epoch	Epoch 001	Epoch 002																
Study Phase	Screening	Primary Phase																
Type of contact	Screening Visit [t]	Visit 1	Visit 2 [q, s]	Visit 3 [s]	Visit 4 [s]	Visit 5 [q, s]	Visit 6 [^]	Visit 7 [s]	Visit 8 [s]	Visit 9 [q, s]	Visit 10 [^]	Visit 11 [s]	Visit 12 [s]	Visit 13 [q, s]	Visit 14 [^]	Visit 15 [s]	Visit 16 [s]	Visit 17 [q, s]
Time points	Day -29	Day 1	Day 3	Day 8	Day 15	Day 31	Day 57	Day 64	Day 71	Day 87	Day 113	Day 120	Day 127	Day 143	Day 169	Day 176	Day 183	Day 199
Sampling time point(s)	Screening	Pre	Post-Vacc 1					Post-Vacc 2				Post-Vacc 3				Post-Vacc 4		
Recording of solicited AEs (Days 1–7 post-vaccination) self-reported by the patient [n]		●	●	●			● [n]	●			● [n]	●			● [n]	●		
Recording of unsolicited AEs within 30 days post-vaccination (Day 1-30) [n, o]		●	●	●	●	●	● [n]	●	●	● [o]	●	●	● [o]	● [o]	●	●	●	● [o]
Recording of SAEs		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of MAEs		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of AESIs [v]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of AEs/SAEs leading to study withdrawal		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of pregnancy and pregnancy outcome		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

AE: Adverse events; AESI: Adverse event of special interest; AFP: alpha-fetoprotein; CBC: complete blood count; CMI: cell-mediated immunity; DNA: Deoxyribonucleic acid; eCRF: electronic Case Report Form GSK: GlaxoSmithKline; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; hIi: human invariant chain; INR: international normalized ratio; MAE: medically attended event; ml: milliliter; pIMDs: potential immune-mediated diseases; qHBsAg: quantitative hepatitis B surface antigen; SAE: serious adverse event; Vacc: vaccination.

● 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.

[^] If subsequent vaccination cannot be administered within an interval of 53 - 63 days due to special circumstances or any other reasons, please refer to Section 5.6.18.
Refer to Section 5.6.18 for study procedures to be adapted during special circumstances.

[a] Women of childbearing potential are to have a pregnancy test prior to study vaccination (either a blood or urine test, depending on local clinical requirement). For women of non-childbearing potential, the specific reason for not performing a pregnancy test needs to be documented in the eCRF (current tubal ligation, hysterectomy, ovariectomy, post-menopause or other).

[b] For biochemical tests to be performed, please refer to Table 10 and Table 15.

[c] For information about hematological tests to be performed, please refer to Table 10 and Table 15.

[d] Blood sampling for CMI response will be collected from patients in centres with access to the PBMC processing facilities. For information about CMI response assays to be performed, please refer to Table 13 and Table 19.

[e] For information about humoral response assays to be performed, please refer to Table 12 and Table 18

[f] For information about urinalysis tests to be performed, please refer to Table 10 and Table 15.
Routine urinalysis is done by dipstick. A microscopic examination and albumin to creatinine ratio (ACR) should be done (locally) if there is blood or protein reported from urine dipstick. If urine albumin and/or creatinine values are <LLOQ due to which the ACR cannot be calculated, it should be documented in the eCRF.
[g] Additional blood sampling for biochemical/hematological testing may need to be performed in case of abnormal lab parameters. For more information, please refer to Section 8.5.3.
[h] For more information please refer to Section 6.7.
[i] For more information, please refer to Section 6.8.
[j] If liver ultrasound is not possible, alternative liver imaging examination (*e.g.* magnetic resonance or computerized tomography) may be performed at the discretion on the investigator. If it is not possible to perform a liver ultrasound at screening, a routine ultrasound performed within 180 days prior to the vaccination visit 1, can be used for eligibility assessment. For Germany, please see the country-specific requirements in Section 12.
[k] Blood samples for creatinine**,** FibroTest and Liver kidney microsomal type 1 (LKM-1) autoantibody tests should be collected after a minimum 8 hour fast.
[l] CCI [redacted].
[m] At Screening, a physical examination should be performed based on the clinical history of the patient. Physical examination at each subsequent study visit will be performed only if the patient indicates during questioning and test result review that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate. At Screening and at each vaccination, vital signs (including systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest) should be collected. Collected information needs to be recorded in the eCRF.
[n] Procedure not applicable if vaccination could not be administered at that vaccination visit.
[o] Procedure not applicable if vaccination was not administered at preceding vaccination visit.
CCI [redacted]
[q] The minimum requirements at Visits 2, 5, 9, 13 and 17 are safety assessment including, but not limited to, recording of solicited symptoms, unsolicited AEs within 30 days post-vaccination, SAEs, MAEs, AESIs, SAEs related to study participation, or to a concurrent GSK medication/vaccine, AEs/SAEs leading to study withdrawal, pregnancy and pregnancy outcome, intercurrent medical conditions leading to elimination from per-protocol analyses and concomitant medications/vaccinations. The collection of data for safety assessment can be performed remotely (e.g. via phone contact). Other study procedures including biological samples collection and physical examination are optional at the discretion of the Investigator. However, efforts should be made for the patients needed for the first iSRC review in Step C to perform Visit 2 at the site to allow collection of biological samples for safety evaluation by iSRC. For patients participating to TH HBV VV-031 HBS:001 study, biological samples collection specific to that study remains mandatory for Visits 2 and 5.
[r] The randomization is performed after screening and prior Visit 1. All eligibility criteria should be confirmed before vaccination at Day 1 visit (i.e. Visit 1).
[s] In the sites/countries where a home nursing is possible according to local regulations, the patients may be offered the option to have a home visit. Only selected visits will have the option to be performed as a home visit, these may include biological samples collection, patients' assessments and data collection. The full specifications of the home nursing services will be outlined in the SPM.
[t] The screening window is extended from 90 days to 180 days except for CBC, INR, liver chemistry and HBV-DNA for which testing should be repeated if the interval between blood sampling at screening visit and the first dose vaccination at Visit 1 exceeds 90 days.
CCI [redacted]
[v] In case of a TTS event, an additional blood sample 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. For more information, please refer to Section 5.7.2**.**

*CCI
[redacted]).

Table 5 ***List of study procedures: primary phase (Visit 18 to Visit 22), follow-up phase (Visit 23 to Visit 26) and unscheduled visits (Amended: 22 June 2023)***

Epoch	Epoch 002					Epoch 003				
Study Phase	Primary Phase					Follow-up Phase				
Type of contact	Visit 18 [m]	Visit 19 [l, m]	Visit 20 [m]	Visit 21 [l, m]	Visit 22 [m]	Visit 23 [m]	Visit 24 [m]	Visit 25 [m]	Visit 26 [m]	Unscheduled visit
Time points	Day 225	Day 253	Day 281	Day 309	Day 337	Day 421	Day 505	Day 673	Day 841	
Sampling time point(s)	Post-Vacc 4									
Physical examination	O	O	O	O	O	O	O	O	O	O
Liver ultrasound [j, k]					●		●		●	
Transient elastography (FibroScan) [k]					●		●		●	
Biospecimen sampling										
Blood sampling for biochemistry (~3.5 ml) [a, h,i]	●	●	●	●	●	●	●	●	●	●
Blood sampling for biochemistry (AFP) (~3.5 ml) [i]					●		●		●	
Blood sampling for FibroTest (~8.5 ml) [i]					●		●		●	
Blood sampling for hematological tests/CBC (~2.0 ml) [b, h]	●	●	●	●	●	●	●	●	●	●
Blood sampling for hematological tests/INR (~4.5 ml) [b,h]	●	●	●	●	●	●	●	●	●	●
Blood sampling for qHBsAg (~3.5 ml)	●	●	●	●	●	●	●	●	●	
Blood sampling for HBV-DNA [n] and new viral markers (~10 ml)	●	●	●	●	●	●	●	●	●	● [n]
Blood sampling for CMI response (~20 ml) [c]					●		●		●	
Blood sampling for humoral response to HBV antigens (~3.5 ml) [d]					●		●		●	
Blood sampling for serum repository (~3.5 ml)					●		●		●	
Urine sampling for urine chemistry (dipstick) [e]	●	●	●	●	●					
Safety assessments										
Recording of concomitant medications/vaccinations [f]	●	●	●	●	●	●	●	●	●	●
Record intercurrent medical conditions leading to elimination from per-protocol [g]	●	●	●	●	●	●	●	●	●	●
Recording of SAEs	●	●	●	●	●	●	●	●	●	●
Recording of MAEs	●	●	●	●	●	●	●	●	●	●
Recording of AESIs[o]	●	●	●	●	●	●	●	●	●	●

Epoch	Epoch 002					Epoch 003				
Study Phase	Primary Phase					Follow-up Phase				
Type of contact	Visit 18 [m]	Visit 19 [l, m]	Visit 20 [m]	Visit 21 [l, m]	Visit 22 [m]	Visit 23 [m]	Visit 24 [m]	Visit 25 [m]	Visit 26 [m]	Unscheduled visit
Time points	Day 225	Day 253	Day 281	Day 309	Day 337	Day 421	Day 505	Day 673	Day 841	
Sampling time point(s)	Post-Vacc 4									
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●	●
Recording of AEs/SAEs leading to study withdrawal	●	●	●	●	●	●	●	●	●	●
Recording of pregnancy and pregnancy outcome	●	●	●	●	●	●	●	●	●	●
Conclusion										
eCRF investigator's signature					●				●	
Primary phase conclusion					●					
Study Conclusion									●	

AE: Adverse events; AESI: Adverse event of special interest; AFP: alpha-fetoprotein; CBC: complete blood count; CMI: cell-mediated immunity; DNA: Deoxyribonucleic acid; eCRF: electronic Case Report Form; GSK: GlaxoSmithKline; HBV: hepatitis B virus; INR: international normalized ratio; MAE: medically attended event; ml: milliliter; pIMDs: potential immune-mediated diseases; qHBsAg: quantitative hepatitis B surface antigen; SAE: serious adverse event; Vacc: vaccination.

Note: The double-line border following Visit 22 indicates the analyses which will be performed on all data (*i.e.* data that are as clean as possible) obtained up to Visit 22.

● 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.

Refer to Section 5.6.18 for study procedures to be adapted during special circumstances.

[a] For information about biochemical and biomarkers tests to be performed, please refer to Table 10 and Table 15. For information about virological tests to be performed, please refer to Table 11.

[b] For information about hematological tests to be performed, please refer to Table 10 and Table 15.

[c] For information about CMI response assays to be performed, please refer to Table 13 and Table 19.

[d] For information about humoral response assays to be performed, please refer to Table 12 and Table 18.

[e] For information about urinalysis tests to be performed, please refer to Table 10 and Table 15. ***Routine urinalysis is done by dipstick. A microscopic examination and albumin to creatinine ratio (ACR) should be done (locally) if there is blood or protein reported from urine dipstick. If urine albumin and/or creatinine values are <LLOQ due to which the ACR cannot be calculated, it should be documented in the eCRF.***

[f] For detailed information, please refer to Section 6.7.

[g] For detailed information, please refer to Section 6.8.

[h] Additional blood sampling for biochemical/hematological testing may need to be performed in case of abnormal lab parameters. For more information, please refer to Section 8.5.3.

[i] Blood samples for creatinine and FibroTest tests should be collected after a minimum 8 hour fast**.**

[j] If liver ultrasound is not possible, alternative liver imaging examination (*e.g.* magnetic resonance or computerized tomography) may be performed at the discretion on the investigator. If it is not possible to perform a liver ultrasound at screening, a routine ultrasound performed within 180 days prior to the vaccination visit 1, can be used for eligibility assessment. For Germany, please see the country-specific requirements in Section 12.

[k] If procedure has not been performed at the respective timepoints, it should be done at earliest convenience.

[l] For patients in Step A: the minimum requirements of Visits 19 and 21 are safety assessment including recording of solicited symptoms, unsolicited AEs within 30 days post-vaccination, SAEs, MAEs, AESIs, SAEs related to study participation, or to a concurrent GSK medication/vaccine, AEs/SAEs leading to study withdrawal, pregnancy and pregnancy outcome, intercurrent medical conditions leading to elimination from per-protocol analyses and concomitant medications/vaccinations. The safety assessment can be performed via telephone contact. Other study procedures including biological samples collection and physical examination are optional at the discretion of the Investigator. For patients in Step B and Step C, Visits 19 and 21 are cancelled.

[m] In the sites/countries where a home nursing is possible according to local regulations, the patients may be offered the option to have a home visit. Only selected visits will have the option to be performed as a home visit, these may include biological samples collection, patients' assessments and data collection. The full specifications of the home nursing services will be outlined in the SPM.

[n] Procedure to be performed in addition to the other procedures only if Unscheduled visit is planned in order to check for contraindication to the subsequent vaccination in case no biological samples have been collected since the previous vaccination visit due to special circumstances. Please refer to Section 5.6.18.

[o] In case of a TTS event, collection of an additional blood sample within 2 weeks of the diagnosis of the TTS for exploratory testing is optional. 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. For more information, please refer to Section 5.7.2.

Whenever possible, the investigator should arrange study visits within the interval described in Table 6.

Table 6 Intervals between study visits

Interval	Optimal length of interval [a]	Allowed interval [c]
Screening Phase		
Screening Visit (Day -29) → Visit 1 (Day 1)	30 days	15 – 180 days [e]
Primary Phase		
Visit 1 (Day 1) → Visit 2 (Day 3)	2 days	1 - 3 days
Visit 1 (Day 1) → Visit 3 (Day 8)	7 days	7 - 9 days
Visit 1 (Day 1) → Visit 4 (Day 15)	14 days	12 - 18 days
Visit 1 (Day 1) → Visit 5 (Day 31)	30 days	30 - 42 days
Visit 1 (Day 1) → Visit 6 (Day 57)	56 days	53 - 63 days [b, c, d]
Visit 6 (Day 57) → Visit 7 (Day 64)	7 days	7 - 9 days
Visit 6 (Day 57) → Visit 8 (Day 71)	14 days	12 - 18 days
Visit 6 (Day 57) → Visit 9 (Day 87)	30 days	30 - 42 days
Visit 6 (Day 57) → Visit 10 (Day 113)	56 days	53 - 63 days [b, c, d]
Visit 10 (Day 113) → Visit 11 (Day 120)	7 days	7 - 9 days
Visit 10 (Day 113) → Visit 12 (Day 127)	14 days	12 - 18 days
Visit 10 (Day 113) → Visit 13 (Day 143)	30 days	30 - 42 days
Visit 10 (Day 113) → Visit 14 (Day 169)	56 days	53 - 63 days [b, c, d]
Visit 14 (Day 169) → Visit 15 (Day 176)	7 days	7 - 9 days
Visit 14 (Day 169) → Visit 16 (Day 183)	14 days	12 - 18 days
Visit 14 (Day 169) → Visit 17 (Day 199)	30 days	30 - 42 days
Visit 14 (Day 169) → Visit 18 (Day 225)	56 days	56 - 60 days
Visit 14 (Day 169) → Visit 19 (Day 253)	84 days	77 - 90 days
Visit 14 (Day 169) → Visit 20 (Day 281)	112 days	105 - 118 days
Visit 14 (Day 169) → Visit 21 (Day 309)	140 days	133 - 146 days
Visit 14 (Day 169) → Visit 22 (Day 337)	168 days	147 - 188 days
Follow-up Phase		
Visit 14 (Day 169) → Visit 23 (Day 421)	252 days (36 weeks)	232 - 270 days
Visit 14 (Day 169) → Visit 24 (Day 505)	336 days (48 weeks)	312 - 360 days
Visit 14 (Day 169) → Visit 25 (Day 673)	504 days (72 weeks)	468 - 540 days
Visit 14 (Day 169) → Visit 26 (Day 841)	672 days (96 weeks)	620 - 720 days

[a]. Whenever possible the investigator should arrange study visits within this interval.
[b]. 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.
[c] In case of special circumstances, this interval between two subsequent doses can be extended up to 84 days.
[d] 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 (Please refer to section 5.6.18 and section 9.2.2).
[e] The screening window is extended from 90 days to 180 days except for CBC, INR, liver chemistry and HBV-DNA for which testing should be repeated if the interval between blood sampling at screening visit and the first dose vaccination at Visit 1 exceeds 90 days.

5.6. Detailed description of study procedures

5.6.1. Informed consent

The signed informed consent of the patient must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent.

5.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 at enrolment.

Eligibility criteria (Please refer to Sections 4.2 and 4.3) must be carefully assessed at the Screening visit and at the Visit 1.

Medical and medication history will be assessed as related to the inclusion/exclusion criteria listed in Sections 4.2 and 4.3.

At Screening, if a patient has hematological/biochemical parameters out of normal range which are expected to be temporary, a re-Screening visit may be scheduled during which blood sample collection for hematology/biochemistry will be repeated. Other screening procedures may be repeated if the investigator believes there is a reason to do so.

Eligible patients who fall out of the 180-day Screening window, a re-Screening should be performed to confirm eligibility, except for CBC, INR, liver chemistry and HBV-DNA for which testing should be repeated if the interval between blood sampling at screening visit and the first dose vaccination at Visit 1 exceeds 90 days.

Patients who failed to meet eligibility criteria under previous versions of the protocol may be re-screened to enter the study.

Upon completion of all Screening procedures (refer to Table 4), the investigator will review the inclusion/exclusion criteria for each patient. Patients meeting all eligibility criteria will be randomized in the study. Their Screening information will be recorded on the appropriate screen of eCRF.

5.6.3. Collect demographic data

Record demographic data such as year of birth, sex, race and ethnicity in the patient's eCRF.

5.6.4. Medical history

Obtain the patient's medical history by interview and/or review of the patient's medical records and record any pre-existing conditions or signs and/or symptoms present in a patient prior to the first study vaccination in the eCRF.

5.6.5. HBV disease history

- The following details on HBV disease history will be collected and recorded in the eCRF.
- Year of HBV detection,
- Suspected mode of infection (parenteral, perinatal, sexual, unknown),
- Previous history of acute Hepatitis B (Yes/ No/ Unknown. If yes, precise year),

- Previous clinical monitoring of Hepatitis B, if available,

  HBV DNA (concentration and date),

  ALT (serum ALT level and date),

  Liver fibrosis staging (method, date, result),
- Previous treatment of chronic Hepatitis B other than ETV, TDF or TAF (Yes/ No/ Unknown. If yes, drug name, route, start and end dates),
- History and ongoing treatment with high barrier to resistance NAs, e.g. ETV, TDF or TAF (drug name, route, start date and end date, if applicable),
- Genotype, if available.

5.6.6. Measure/record height and weight

Measure patient's height and weight and record in the patient's eCRF.

5.6.7. Physical examination

At Screening, perform a targeted physical examination based on the clinical history of the patient. Physical examination at each subsequent study visit will be performed only if the patient indicates during questioning and test result review that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate. Collected information needs to be recorded in the eCRF.

At Screening and at each vaccination, vital signs (including systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest) will be collected and 12-lead electrocardiogram (ECG) will be performed. Collected information needs to be recorded in the eCRF.

Routine clinical management of chronic HBV infection and if deemed necessary, a further targeted workup will be performed according to local medical practice.

Liver ultrasound and transient elastography (FibroScan) will be performed according to local medical practice. Collected information will be recorded in the eCRF. If liver ultrasound is not possible, alternative liver imaging examination (*e.g*. magnetic resonance or computerized tomography) may be performed at the discretion on the investigator. If it is not possible to perform a liver ultrasound at screening, a routine ultrasound performed within 180 days prior to the vaccination visit 1, can be used for eligibility assessment. For Germany, please see the country-specific requirements in Section 12.

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

5.6.8. Pregnancy test

Female patients of childbearing potential are to have a urine pregnancy test or a serum human chorionic gonadotrophin (hCG) test at Screening and prior to any study vaccine administration. The study vaccines may only be administered if the pregnancy test is negative.

Note: Pregnancy test must be performed even if the patient is menstruating at the time of the study visit.

5.6.9. Check contraindications to vaccination

Contraindications to vaccination must be checked at the beginning of each vaccination visit. Refer to Section 6.6 for more details.

5.6.10. Assess pre-vaccination body temperature

The oral body temperature of each patient needs to be measured prior to any study vaccine administration. If the patient has fever (fever is defined as temperature ≥38.0°C/100.4°F) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 6).

5.6.11. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 5.2.2. The number of each administered treatment must be recorded in the eCRF.

5.6.12. Biospecimen sampling

During the study, blood sampling will be performed on all patients, regardless of the study groups, for:

- Biochemistry (ALT, AST, ALP, GGT, Bilirubin and Creatinine): ~3.5 ml
- Biochemistry (AFP): ~3.5 ml,
- Biochemistry (FibroTest): ~8.5 ml,
- Complete blood count: ~2.0 ml,
- INR: ~4.5 ml,
- Autoimmune antibodies: ~13.5 ml,
- Viral serology (HBV, HCV, HDV and HIV): ~18.5 ml,
- qHBsAg: ~3.5 ml,
- HBV-DNA and new viral markers: ~10.0 ml,
- CMI response (only in patients from sites with access to PBMC processing facilities): ~20.0 ml,

- humoral response to HBV antigens: ~3.5 ml,
- CCI [redacted]
- Serum repository: ~3.5 ml.

Blood samples for creatinine, FibroTest and Liver kidney microsomal type 1 (LKM-1) autoantibody tests should be collected after a minimum 8 hour fast.

A maximum volume of blood to be drawn during the 2.5 year study period (from Screening to Day 841) from each patient from centres with access to PBMC processing facilities is approximately 883.5 mL and from each patient from centres with no access to PBMC processing facilities is approximately 643.5 mL. Among all visits, the highest volume of blood on a single visit will be approximately 64 mL (on Day -29) and the highest volume of blood over 8-week will be approximately 186 mL for patients from centres with access to PBMC processing facilities or 106 mL for patients from centres with no access to PBMC processing facilities (from Day 57 to Day 113), which are below the safe limits as recommended by the WHO [Howie, 2011].

- Urine samples (dipstick) will be collected for urine chemistry.

CCI [redacted]

For more information on the biological sampling to be performed at each study visit, please refer to Table 4 and Table 5.

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

Refer to Section 8.5.3 for the handling of abnormal hematology/biochemistry parameters.

5.6.13. Study Vaccines administration

- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly (IM) in the deltoid of the non-dominant arm. For patients receiving co-administrations of HBc-HBs/AS01B-4 with either MVA-HBV or ChAd155-hIi-HBV (patients randomized in the C1 or C2 group), one vaccine will be administered in the non-dominant deltoid, while the other vaccine will be administered in the dominant deltoid (refer to Section 6.3 for detailed description of the vaccines administration procedure).
- If the investigator or delegate determines that the patient's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 6).
- The patients will be observed closely for at least 60 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.14. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.7.

Intercurrent medical conditions that may lead to elimination of a patient from per-protocol analyses must be checked and recorded in the eCRF as described in Section 6.8.

5.6.15. Recording of AEs, SAEs, AESIs and pregnancies

- Refer to Section 8.3 for procedures for the investigator to record AEs, SAEs, AESI and pregnancies. Refer to Section 8.4 for guidelines and how to report SAEs, AESIs and pregnancies to GSK Biologicals.
- The patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- At each vaccination visit, diary cards will be provided to the patient. The patient will be instructed to measure and record body temperature, and any solicited local/general AEs on the day of vaccination and during the next 6 days. The patient will be instructed to return the completed diary card to the investigator at the next study visits.
- Collect and verify completed diary cards during discussion with the patient on Visit 2, Visit 3, Visit 7, Visit 11 and Visit 15.
- Any unreturned diary cards will be sought from the patient through telephone call(s) or any other convenient procedure.
- The investigator or delegate will transcribe the collected information into the eCRF in English.

5.6.16. Home nursing procedures

In the sites/countries where a home nursing is possible according to local regulations, the patients may be offered the option to have a home visit. Only selected visits will have the option to be performed as a home visit, these may include biological samples collection, patient assessments and data collection. The full specifications of the home nursing services will be outlined in the SPM.

5.6.17. Screening conclusion, primary phase conclusion and study conclusion

At the end of the Screening phase (Screening visit), at the end of the primary phase (Visit 22) and at the end of the study (Visit 26), the investigator will:

- Review data collected to ensure accuracy and completeness;
- Complete the Screening Conclusion/Primary Phase Conclusion/Study Conclusion screen, as applicable, in the eCRF.

5.6.18. Study procedures during special circumstances

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 applied. For the duration of such special circumstances, the following measures may be implemented for enrolled patients of the impacted countries or sites:

- Study visits may be replaced by a telephone call, other means of virtual contact or home visit, if appropriate to collect the safety information (AEs and concomitant medications/vaccinations), unless a patient presents symptoms or reports AEs that necessitate a site visit in Investigator's judgement.
- Diary cards may be transmitted from and to the site by electronic means and/or conventional mail.
- The screening activities and vaccine administration may be put on hold in line with specific local guidance or when deemed necessary by the Investigator or by Sponsor. Notification to Ethical Committees / Independent Review Boards and Competent Authorities should be made as appropriate. When it deems appropriate to resume the screening activities and vaccine administration, this can be done following notification to the Ethical Committees / Independent Review Boards and Competent Authorities and approvals as needed.
- Maximum interval between study vaccinations: If despite best efforts it is not possible to administer subsequent dose of study vaccine as defined in the protocol (see Table 6), a maximum dose interval of 111 days between two subsequent doses should be used. The maximum interval has been determined based on experience with Ebola ChAd-MVA prime-boost in Phase I study [Tapia, 2016]. In this study, MVA-BN-Filo booster vaccine given 11 – 16 weeks (79 - 111 days) after priming with ChAd3-EBO-

Z was well tolerated and immunogenic eliciting both anamnestic antibody responses and robust multifunctional CD4 and CD8 memory T-cell responses.

- Discontinuation from study vaccination: If a maximum interval of 111 days since previous vaccination is exceeded, vaccination should be discontinued.
- Adaptation of study visits when subsequent vaccination cannot be administered as defined in the protocol i.e. at interval of 53 – 63 days:
- If subsequent vaccination cannot be administered within an interval of 53 - 63 days, only the visits specified in Table 7 should be performed at least every 4 weeks after the previous vaccination to follow up on safety and laboratory parameters. For management of those visits, refer to Table 7. Data collected at those visits should be encoded using unscheduled visit form in eCRF until the vaccination is resumed within a maximum of 111 days interval from the previous vaccination.
- If subsequent vaccination can be administered within maximum interval of 111 days from the date of previous dose administration, the visit related to this vaccination should be performed and further visits should follow as defined in Table 4, Table 5 and Table 6. If no biological samples have been collected since the previous vaccination visit, an unscheduled should be performed, as defined in Table 5 to check for contraindications to the subsequent vaccination. Vaccination visit and subsequent visits should be encoded as regular visits in eCRF.
- If subsequent vaccination cannot be administered within maximum interval of 111 days from the date of previous dose administration, patient should discontinue study vaccination and management of follow up visits in the primary phase (Epoch 002) should be performed as indicated in Table 7 and described below:
  - For patients who discontinued vaccination after vaccination Dose 1, Visits 10, 12, 13, 14 and 17-22 should be performed, as defined in Table 4 and Table 5, for follow up on safety and laboratory parameters.
  - For patients who discontinued vaccination after vaccination Dose 2, Visits 14 and 17-22 should be performed, as defined in Table 4 and Table 5, for follow up on safety and laboratory parameters.
  - For patients who discontinued vaccination after vaccination Dose 3, Visits 18-22 should be performed, as defined in Table 5, for follow up on safety and laboratory parameters.

  Data collected at the above mentioned visits should be encoded as regular visits in eCRF.

  For all patients who discontinued study vaccination, the planned visits in the follow up phase (Epoch 003) should be performed as defined by protocol.

Biological samples may be collected at a different location* other than the study site or at patient's home, in line with applicable local guidance. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use. In case of anticipated delay or urgency in obtaining the biological sample result to follow safety parameters post-vaccination, the investigator is recommended to

collect an additional biological sample for local testing. If such sample is required, it is important that the sample for central testing is obtained at the same time.

- In case a Grade 3 laboratory parameter abnormality is detected, an unscheduled visit should be performed, per protocol planned as a site visit. However, Investigator should practice his/her medical judgement on the clinical relevance of any abnormality and manage this according to the local clinical practice and local guideline concerning the COVID-19. If the site visit restriction is in place, the Investigator should contact the concerned patient in a remote manner (e.g. phone contact or home visit, if appropriate) to collect the safety information. Whenever possible and in line with applicable local guidance, the Investigator should arrange the clinical and laboratory examination at a different location* other than the study site that is accessible for the concerned patient.

  * 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 should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.

Impact on the per protocol set for immunogenicity and efficacy will be determined on a case by case basis. Due to potential increase of the drop-out rate and potential administration of COVID-19 vaccines during study participation (outside of study procedures), to ensure sufficient number of evaluable patients:

- Allowed intervals between two subsequent vaccinations, that constitute criterion for per protocol set, has been extended from 53 - 63 days to 84 days;
- An increase of maximum 15% in sample size in Step B and in Step C can be anticipated.

Table 7 Study visits of Epoch 002 to be performed if subsequent vaccination cannot take place within allowed interval of 53 - 63 days from previous vaccination

Epoch	Epoch 002																		
Study Phase	Primary Phase																		
Type of contact	Visit 1	Visits 2-5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19 ^	Visit 20	Visit 21 ^	Visit 22
Time points	Day 1	Day 3 - Day 31	Day 57	Day 64	Day 71	Day 87	Day 113	Day 120	Day 127	Day 143	Day 169	Day 176	Day 183	Day 199	Day 225	Day 253	Day 281	Day 309	Day 337
Previous vaccination Dose																			
Dose 1	Dose 1	N	Un	C	C	Un	MV*	C	N	N	MV	C	C	N	N	N	N	N	N
Dose 2			Dose 2	N	N	N	Un	C	Un	Un	MV*	C	C	N	N	N	N	N	N
Dose 3							Dose 3	N	N	N	Un	C	C	Un	N*	N	N	N	N
Dose 4											Dose 4	N	N	N	N	N	N	N	N

N: Visit including procedures as defined for this visit in Table 4 and Table 5. Visit should be encoded as regular visit in eCRF.
Un: Visit performed in special circumstances (e.g. remotely, home visit) including as many procedures as possible as defined for this visit in Table 4. Visit should be encoded using Unscheduled visit form in eCRF.
C: Visit cancelled if subsequent vaccination was not yet administered
MV: Modified Visit applicable for patient who discontinued from study vaccination. This visit excludes vaccination-related procedures while maintaining all non vaccination-related procedures. For details, refer to Table 4. Visit should be encoded using vaccination visit form in eCRF.
* Discontinuation of study vaccination may apply, if interval of 111 days from the date of previous dose administration is exceeded. This should be determined based on the actual date of the previous dose administration.
^ For patients in Step B and Step C, Visits 19 and 21 are cancelled.
Note:
1. If the above visits are performed in special circumstances (e.g. remotely, home visit), as many procedures as possible should be done (refer to Table 4 and Table 5).
2. If subsequent vaccination can be administered within maximum interval of 111 days from the date of previous dose administration, the visit related to this vaccination should be performed and further visits should follow as defined in Table 4, Table 5 and Table 6. Vaccination and subsequent visits should be encoded as regular visits in eCRF.
3. If subsequent vaccination cannot be administered within a maximum interval of 111 days from the date of previous dose administration, patient should discontinue study vaccination and follow up visits should be performed as indicated above. The timepoints from vaccination Dose 1, Dose 2 and Dose 3 at which patient should be considered as discontinued from study vaccination are marked with * in the above table and should be determined based on the actual date of the previous dose administration.
4. Management of visits for patient who completed Dose 4 vaccination is shown for completeness

In view of the current medical need for COVID-19 vaccination, guidance/recommendations from National Authorities should apply first and foremost if/when existing.

Recommendations on spacing between COVID-19 vaccine and study vaccination based on type of COVID-19 vaccine are outlined in Table 8. Note that the interval between two subsequent study vaccine doses can be extended up to 84 days to accommodate COVID-19 vaccinations.

Table 8 Recommendations on spacing between COVID-19 vaccine and study vaccination by type of COVID-19 vaccine

COVID-19 vaccine	Prior study vaccination	During study vaccination	After study vaccination
mRNA based	14 days before first study vaccine dose	At least 14 days before or 30 days after study vaccination	30 days after last vaccine dose
Adenovector-based	30 days before first study vaccine dose (applicable for all patients except for the patients in France) OR 12 months before first study vaccine dose (applicable for the patients in France only).	At least 30 days before or after study vaccination	30 days after last vaccine dose
Protein-based adjuvanted	30 days before first study vaccine dose	At least 30 days before or after study vaccination	30 days after last vaccine dose
Other technologies	30 days before first study vaccine dose	At least 30 days before or after study vaccination	30 days after last vaccine dose

Whenever multiple types of COVID-19 vaccine are offered, a COVID-19 vaccine that is not adenovector-based may be considered as a better choice.

5.7. Biological sample handling and analysis

Please refer to the SPM for details on biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the patient but will be coded with the patient identification number (PID).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all patients will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual patient.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

Collected samples will be stored for a maximum of 20 years (counting from when the last patient performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the patient consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the patient from the per-protocol analysis (See Section 10.5 for the definition of cohorts to be analyzed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological samples

Table 9 Biological samples

Sample type	Component	Time point ***	Quantity	Unit	Cohort/subset
Blood	HBV, HCV, HDV and HIV serology	Screening	~18.5	ml	All patients
	Autoimmune antibodies *	Screening	~13.5	ml	
	Biochemistry (FibroTest) *	Screening, Visit 22, Visit 24 and Visit 26	~8.5	ml	
	Biochemistry (AFP) *	Screening, Visit 22, Visit 24 and Visit 26	~3.5	ml	
	Biochemistry (ALT, AST, ALP, GGT, Bilirubin and Creatinine) *	All visits	~3.5	ml	
	Hematology (CBC) **	All visits	~2.0	ml	
	Hematology (INR)	All visits	~4.5	ml	
	HBV-DNA and new viral markers	Screening, Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14 Visit 17, Visit 18, Visit 19, Visit 20, Visit 21, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26	~10	ml	
	qHBsAg	Screening, Visit 1, Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 19, Visit 20, Visit 21, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26	~3.5	ml	
	CMI response	Visit 1, Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16, Visit 22, Visit 24 and Visit 26	~20	ml	All patients from sites with access to PBMC processing facilities
	Humoral response to HBV antigens	Visit 1, Visit 4, Visit 8, Visit 10, Visit 12, Visit 16, Visit 22, Visit 24 and Visit 26	~3.5	ml	All patients
	CCI [redacted]				
	Serum repository	Visit 1, Visit 8, Visit 10, Visit 12, Visit 16, Visit 22, Visit 24 and Visit 26	~3.5	ml	
CCI [redacted]					
Urine	Urine chemistry	All visits up to Visit 22 included.	NA	NA	

* Blood samples for creatinine, FibroTest and LKM-1 autoantibodies tests should be collected after a minimum 8 hour fast.

** CBC includes erythrocytes, leukocytes, neutrophils, lymphocytes, eosinophils, basophils, monocytes, platelets, hemoglobin and hematocrit.

*** For all patients, biological samples collection at Visits 2, 5, 9, 13 and 17 are not mandatory and can be collected at the discretion of the Investigator.

For patients in Step B and Step C, biological samples collection is cancelled for Visits 19 and 21.
For patients participating in TH HBV VV-031 HBS:001 study, biological samples collection specific to that study remains mandatory for Visits 2 and 5.
† This buccal swab sampling is optional and will only be performed for patients who consented to have pharmacogenomics tests done on their samples.

CCI

A serum or plasma sample collected before the NA treatment, if the sample is available and if the patient consents, will be used for HBV genotyping.

In case of a TTS event, an additional blood sample (~3.5ml) should be collected within 2 weeks of the diagnosis of the TTS. 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. Additional blood sample collection for TTS event reported during the follow-up phase is optional. This serum sample (if available) as well as the samples collected for repository, as already specified in the protocol, will be used for exploratory testing and better understanding of the pathogenesis of TTS event. Since scientific knowledge on TTS pathology and biomarkers for TTS risks in relation to adenovector-based vaccines is evolving, this exploratory testing is not to guide TTS management and no assay details are specified in the protocol. This testing will be performed at a laboratory designated by GSK Biologicals.

5.7.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the address of the clinical laboratories used for sample analysis.

Hematology, biochemistry, autoimmune antibodies and urine chemistry assessments will be performed at GSK Biologicals or at a laboratory designated by GSK Biologicals using commercial tests (see Table 10).

Table 10 Hematology, biochemistry, autoimmune antibody and urine tests

System	Discipline	Component	Method	Scale	Laboratory
Whole blood	Hematology	Erythrocytes (Red Blood Cells)	As per Q² Solutions practice	Quantitative	Q² Solutions
		Leukocytes (White Blood Cells)		Quantitative	
		Neutrophils		Quantitative	
		Lymphocytes		Quantitative	
		Eosinophils		Quantitative	
		Basophils		Quantitative	
		Monocytes		Quantitative	
		Platelets		Quantitative	
		Hemoglobin		Quantitative	
		Hematocrit		Quantitative	
		Prothrombin Time International Normalised Ratio (INR)		Quantitative	
Serum	Biochemistry	Alanine Aminotransferase (ALT)		Quantitative	
		Aspartate Aminotransferase (AST)		Quantitative	
		Alkaline Phosphatase (ALP)		Quantitative	
		Gamma Glutamyl Transferase (GGT)		Quantitative	
		Total Bilirubin		Quantitative	
		Creatinine		Quantitative	
		Alpha-fetoprotein		Quantitative	
		FibroTest		Quantitative	
	Autoimmune antibodies	Antinuclear antibodies (ANAs)		Qualitative	
		Smooth muscle antibodies (SMAs)		Qualitative	
		Liver kidney microsomal 1 Ab.IgG (LKM-1)		Qualitative	
		Anti-liver cytosol 1 (anti LC1) antibodies		Quantitative	
Urine	Urine chemistry	Leukocytes, Blood, Proteins, Glucose, Ketones, Bilirubin, Urobilinogen, Nitrite, Specific gravity, pH	As per local practice	Semi-quantitative	On site

Serology and virology assays will be performed at laboratories designated by GSK Biologicals using commercial tests or tests to be developed at the lab (see Table 10).

Table 11 HBV, HCV, HDV and HIV serology and HBV virology assays

System	Discipline	Component	Method	Scale	Laboratory
Serum	HBV serology	Hepatitis B Virus.Surface Ab (Anti-HBs)[a]	CMIA	Qualitative	GSK Biologicals' laboratory or laboratory designated by GSK
		Hepatitis B Virus.Surface Ag (HBsAg)	CMIA	Quantitative	
		Hepatitis B Virus.e Ag (HBeAg)[a]	CLIA	Qualitative	Q² Solutions
		Hepatitis B Virus.Core Ab (Anti-HBc) [a]	CMIA	Qualitative	
		Hepatitis B Virus.e Ab (Anti-HBe)[a]	CCLIA	Qualitative	
	HCV serology	Hepatitis Virus C Ab (anti-HCV) [a]	CMIA	Qualitative	Q² Solutions
	HDV serology	Hepatitis Virus D Ab (Anti-HDV) [a]	ELISA	Qualitative	Q² Solutions
	HIV serology	Human Immunodeficiency Virus Ab (Anti-HIV) [a]	CMIA	Qualitative	Q² Solutions
	HBV virology	Hepatitis B Virus DNA (HBV DNA)	qPCR	Quantitative	DDL Diagnostic Laboratory
		HBV DNA whole sequencing[b]	Sequencing	N/A	

[a] This test will be performed at Screening only.
[b] This test will be performed in case of virological breakthrough.

The cut-off for HBV DNA measured by qPCR will be 10 IU/mL.

Antibody concentrations will be measured by immune-chemistry assays at GSK Biologicals' laboratory or designated laboratory using standardized procedures (see Table 12).

Table 12 Humoral Immunity (Antibody determination)

System	Component	Method	Components priority rank	Laboratory [a]
Serum	Hepatitis B Virus.Surface Ab	CLIA	1	GSK Biologicals' laboratory or laboratory designated by GSK
	Hepatitis B Virus Core Ab	ELISA	2	
	CCI [redacted]			

[a] GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. Refer to APPENDIX B for the laboratory addresses.

CMI assays will be performed in GSK Biologicals' laboratory or designated laboratory using standardized procedures (see Table 13).

Table 13 Cell-mediated Immunity

System	Component	Challenge	Method	Component priority rank	Laboratory[a]
PBMC	HBc-specific ($CD4^+/CD8^+$) T-cells	HBc peptide pool	CFC	1	GSK Biologicals' laboratory or laboratory designated by GSK
	HBs-specific ($CD4^+/CD8^+$) T-cells	HBs peptide pool	CFC	2	
	CCI				

[a] GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium.

CCI

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

5.7.4. Biological samples evaluation

5.7.4.1. Evaluation of hematology, biochemistry and urinalysis

Table 15 Evaluation of hematology, biochemistry and urinalysis

Sample type	Type of contact and time point **	Study group	Approximate No Patients	Component	Components priority rank
Hematology					
Blood	At Screening	All study groups		INR	NA
				CBC*	NA
	All time points	All study groups		INR	1
				CBC*	2
Biochemistry					
Serum	At Screening	All study groups		ALT, AST, GGT, ALP, Bilirubin, Creatinine	NA
				AFP	
				FibroTest	
	Visit 1 ~ Visit 26	All study groups		ALT, AST, GGT, ALP, Bilirubin, Creatinine	NA
	Visit 22, Visit 24 and Visit 26	All study groups		ALT, AST, GGT, ALP, Bilirubin, Creatinine	1
				FibroTest	2
				AFP	3

Sample type	Type of contact and time point **	Study group	Approximate No Patients	Component	Components priority rank
Urinalysis					
Urine	All time points up to Visit 22 included.	All study groups	CCI [redacted]	Leucocytes, Blood, Proteins, Glucose, Ketones, Bilirubin, Urobilinogen, Nitrite, Specific gravity, pH	NA

NA: not applicable
* CBC includes erythrocytes, leukocytes, neutrophils, lymphocytes, eosinophils, basophils, monocytes, platelets, hemoglobin and hematocrit.
** For all patients, biological samples collection at Visits 2, 5, 9, 13 and 17 are not mandatory and can be collected at the discretion of the Investigator.
For patients in Step B and Step C, biological samples collection is cancelled for Visits 19 and 21.
For patients participating in TH HBV VV-031 HBS:001 study, biological samples collection specific to that study remains mandatory for Visits 2 and 5.

5.7.4.2. Evaluation of serum HBV antigens

Table 16 Evaluation of serum HBV antigens

Sample type	Type of contact and time point *	Study group	No Patients	Component	Components priority rank
Serum	Screening, Visit 1, Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 19, Visit 20, Visit 21, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26	All study groups	CCI [redacted]	HBsAg	NA

CCI [redacted]

* For all patients, biological samples collection at Visits 5, 9, 13 and 17 are not mandatory and can be collected at the discretion of the Investigator.
For patients in Step B and Step C, biological samples collection is cancelled for Visits 19 and 21.
For patients participating in TH HBV VV-031 HBS:001 study, biological samples collection specific to that study remains mandatory for Visit 5.

5.7.4.3. Evaluation of molecular biology

Table 17 Evaluation of molecular biology

Sample type	Type of contact and time point *	Study group	No Patients	Component	Components priority rank
Serum	Screening, Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 19, Visit 20, Visit 21, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26	All study groups	CCI	HBV DNA	1
CCI	CCI			CCI	

* For all patients, biological samples collection at Visits 5, 9, 13 and 17 are not mandatory and can be collected at the discretion of the Investigator.
For patients in Step B and Step C, biological samples collection is cancelled for Visits 19 and 21.
For patients participating in TH HBV VV-031 HBS:001 study, biological samples collection specific to that study remains mandatory for Visit 5.

CCI

5.7.4.4. Evaluation of immunogenicity

Table 18 Evaluation of humoral immunogenicity

Sample type	Type of contact and time point	Sub groups	No. patients	Component	Components priority rank
Blood for humoral response	Visit 1, Visit 4, Visit 8, Visit 10, Visit 12, Visit 16, Visit 22, Visit 24 and Visit 26	All study groups	CCI	Anti-HBc	2
				Anti-HBs Ig total	1
	CCI				
CCI					

Table 19 Evaluation of cell-mediated immunogenicity

Sample type	Type of contact and time point	Sub groups	No. patients [b]	Component	Components priority rank
Blood for CMI response	Visit 1, Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16, Visit 22, Visit 24 and Visit 26	All study groups	CCI	HBc-specific ($CD4^+$/$CD8^+$) T-cells	1
				HBs-specific ($CD4^+$/$CD8^+$) T-cells	2
	CCI				

[a] CCI

[b] Patients from the sites with access to PBMC processing facilities

CCI

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In case of insufficient blood sample volume to perform all assays, the samples will be analyzed according to priority ranking provided in Table 18 and Table 19.

CCI

6. STUDY VACCINES AND ADMINISTRATION

6.1. Description of study vaccines

All candidate vaccines/products to be used have been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccines are described in separate Quality Assurance documents (*e.g.* release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines are labelled and packed according to applicable regulatory requirements.

Table 20 Study vaccines

Treatment name	Product	Formulation	Presentation	Volume of product to be administered	Total treatment volume to be administered	Number of doses
ChAd155-hli-HBV 5x10^{9} vp [a]	ChAd155-hli-HBV	CCI		0.05 ml	0.1 ml	1 (Step A: Group A1)
	NaCl			0.05 ml		
ChAd155-hli-HBV 5x10^{10} vp	ChAd155-hli-HBV			0.5 ml	0.5 ml	1 (Step B: Groups B1 and B3; Step C: all groups)
MVA-HBV 2x10^{7} pfu [b]	MVA-HBV			0.05 ml	0.1 ml	1 (Step A, Group A1)
	NaCl			0.05 ml		
MVA-HBV 2x10^{8} pfu	MVA-HBV			0.5 ml	0.5 ml	1 (Step B: Groups B1 and B3. Step C: Group C2)
						3 (Step C: Group C1)
HBc-HBs/AS01$_{B-4}$ 20-20	HBc-HBs			NA	0.5 ml	2 (Step A: Group A1)
	AS01B-4			0.5 ml		4 (Step A: Group A2)
HBc-HBs/AS01$_{B-4}$ 80-80	HBc-HBs			NA	0.5 ml	2 (Step B:Group B1)
						3 (Step C:Group C2)
	AS01B-4			0.5 ml		4 (Step B: Group B2. Step C: Group C1)
Placebo (Formulation buffer S9B (PBS))	Formulation buffer S9b			0.5 ml	0.5 ml	4 (Step A: Group A3. Step C: Group C2)
						2 (Step B: Group B3)

CCI [redacted]

6.2. Storage and handling of study vaccines

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor. Refer to the Module on Clinical Trial Supplies in the SPM for more details on temperature excursion ranges of the study vaccines.

6.3. Dosage and administration of study vaccines

Table 21 Dosage and administration

Type of contact and time point	Study group	Treatment name	Volume to be administered	Route	Site	Side[a]
Step A						
Visit 1 (D1)	A1	ChAd155-hli-HBV $5x10^9$ vp	0.1 ml	IM	Deltoid	Non-dominant
	A2	HBc-HBs/AS01$_{B-4}$ 20-20	0.5 ml			
	A3	Placebo (Formulation buffer S9B (PBS))	0.5 ml			
Visit 6 (D57)	A1	MVA-HBV $2x10^7$ pfu	0.1 ml	IM	Deltoid	Non-dominant
	A2	HBc-HBs/AS01$_{B-4}$ 20-20	0.5 ml			
	A3	Placebo (Formulation buffer S9B (PBS))	0.5 ml			
Visit 10 (D113) and Visit 14 (D169)	A1	HBc-HBs/AS01$_{B-4}$ 20-20	0.5 ml	IM	Deltoid	Non-dominant
	A2	HBc-HBs/AS01$_{B-4}$ 20-20	0.5 ml			
	A3	Placebo (Formulation buffer S9B (PBS))	0.5 ml			
Step B						
Visit 1 (D1)	B1	ChAd155-hli-HBV $5x10^{10}$ vp	0.5 ml	IM	Deltoid	Non-dominant
	B2	HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml			
	B3	Placebo (Formulation buffer S9B (PBS))	0.5 ml			
Visit 6 (D57)	B1	MVA-HBV $2x10^8$ pfu	0.5 ml	IM	Deltoid	Non-dominant
	B2	HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml			
	B3	Placebo (Formulation buffer S9B (PBS))	0.5 ml			
Visit 10 (D113)	B1	HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml	IM	Deltoid	Non-dominant
	B2	HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml			
	B3	ChAd155-hli-HBV $5x10^{10}$ vp	0.5 ml			
Visit 14 (D169)	B1	HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml	IM	Deltoid	Non-dominant
	B2	HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml			
	B3	MVA-HBV $2x10^8$ pfu	0.5 ml			
Step C						
Visit 1 (D1)	C1	ChAd155-hli-HBV $5x10^{10}$ vp	0.5 ml	IM	Deltoid	Dominant
		HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml			Non Dominant
	C2	Placebo (Formulation buffer S9B (PBS))	0.5 ml			Dominant

Type of contact and time point	Study group	Treatment name	Volume to be administered	Route	Site	Side[a]
		Placebo (Formulation buffer S9B (PBS))	0.5 ml			Non Dominant
Visit 6 (D57)	C1	MVA-HBV 2x10^8 pfu	0.5 ml	IM	Deltoid	Dominant
		HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml			Non Dominant
	C2	Placebo (Formulation buffer S9B (PBS))	0.5 ml			Dominant
		Placebo (Formulation buffer S9B (PBS))	0.5 ml			Non Dominant
Visit 10 (D113)	C1	MVA-HBV 2x10^8 pfu	0.5 ml	IM	Deltoid	Dominant
		HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml			Non-Dominant
	C2	ChAd155-hli-HBV 5x10^{10} vp	0.5 ml			Dominant
		HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml			Non-Dominant
Visit 14 (D169)	C1	MVA-HBV 2x10^8 pfu	0.5 ml	IM	Deltoid	Dominant
		HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml			Non-Dominant
	C2	MVA-HBV 2x10^8 pfu	0.5 ml			Dominant
		HBc-HBs/AS01$_{B-4}$ 80-80	0.5 ml			Non-Dominant

6.4. Minimizing environmental contamination with genetically modified organisms

Each product will be used in accordance with the applicable genetically modified organism (GMO) regulations.

To minimize release of the recombinant vectored vaccine virus into the environment, each vaccine is produced under good manufacturing practice (GMP) conditions with the handling of live material in appropriate laboratory facilities. This is to ensure that any release of modified organism is contained, inactivated and incinerated, using single use equipment as much as possible, to avoid release of modified genetic material into the environment.

After each vaccination, the injection site will be covered with a dressing in order to absorb any virus that may leak out through the needle track. The dressing will be removed only after 30 minutes and will be disposed as GMO waste in accordance with the applicable guidelines/standard operating procedures at the investigator's site.

6.5. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of patients (including over-randomization when applicable), at least 30% additional vaccine doses will be supplied to replace those that are unusable.

6.6. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of the study vaccine. If any of these events occur during the study, the patient must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.5).

- Anaphylaxis following the administration of vaccines,
- Pregnancy (see Section 8.2.1),
- Confirmed ALT flares (ALT > 8 x ULN),
- Confirmed ALT flares (ALT > 5 x ULN) for more than 2 weeks,
- Confirmed ALT flares (ALT > 3 x ULN) and liver-related substantial biochemical changes (i.e. INR > 1.5 or bilirubin > 2 x ULN),
- Confirmed ALT flares (ALT > 3 x ULN) with the appearance of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia.

  Note: At Laboratory Q^2 Solutions, The ULN for ALT is 48 U/L, ULN for bilirubin is 22 µmol/L. In case the test is performed locally, the reference range of the local laboratory should be used.
- Hepatic decompensation.
- HBV-DNA breakthrough.
- Spontaneous local or general bleeding AND thrombocytes < 50000/mm3.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Any other significant condition which, in the opinion of the investigator, would preclude further administration of the study vaccine.
- Occurrence of a pIMD that, in the opinion of the investigator, exposes the patient to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine(s). Refer to Section 8.1.5.3 for the definition of pIMDs.
- Discontinuation of NA therapy

The following events constitute contraindications to administration of the study vaccines at that point in time; if any of these events occur at the time scheduled for vaccination, the patient may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or the patient may be withdrawn at the discretion of the investigator (see Section 8.5).

- Acute disease and/or fever at the time of vaccination.
  - 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.
  - Patients with a minor illness (such as mild diarrhoea, mild upper respiratory infection) can be administered all vaccines/products.

6.7. Concomitant medications/products and concomitant vaccinations

At each study visit, the investigator or delegate should question the patient about any medications/products taken and vaccinations received by the patient.

6.7.1. Recording of concomitant medications/products and concomitant vaccinations

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

- All concomitant medications/products, except vitamins and dietary supplements, administered during a 30-day follow-up (i.e. day of vaccination and 29 subsequent days).
- Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccines and ending at the last study visit (Day -29 to Day 841).
- Any COVID-19 vaccine administered in the period starting 12 months prior to the vaccination visit 1 and ending at the last study visit**.**
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [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.
- Any concomitant medications/products/vaccines listed in Section 6.7.2.
- Any concomitant medications/products/vaccines relevant to a SAE/AESI to be reported as per protocol or administered at any time during the study period for the treatment of a SAE/AESI. In addition, concomitant medications relevant to SAEs and AESIs need to be recorded on the expedited Adverse Event report.
- Nucleos(t)ide analogues with high barrier to resistance (e.g. ETV, TDF, TAF). that the patient takes to control chronic hepatitis B.

6.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a patient from per-protocol analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the patient from the study but may determine a patient's evaluability in the per-protocol analysis. See Section 10.5 for cohorts to be analyzed.

- 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.
- 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.

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if, necessary for that vaccine provided it is licensed and used according to its Product Information.
- Immunoglobulins and/or any blood products administered within 30 days before the blood sampling.

6.8. Intercurrent medical conditions that may lead to elimination of a patient from per-protocol analyses

At each study visit subsequent the vaccination visit, it must be verified if the patient has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

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.

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each patient will be instructed to contact the investigator immediately should they/the patient manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable 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.

Examples of an AE include:

- 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 study vaccines administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccines or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine(s)/product(s) administration.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (*i.e*. invasive procedures, modification of patient's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- 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.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.

- Pre-existing conditions or signs and/or symptoms present in a patient prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF.

8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,

  Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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.

- Requires hospitalisation or prolongation of existing hospitalisation,

  Note: In general, hospitalisation signifies that the patient has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

  Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

- Results in disability/incapacity, OR

  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, diarrhoea, 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.

- Is a congenital anomaly/birth defect in the offspring of a study patient.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also 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 or convulsions that do not result in hospitalisation.

8.1.3. Solicited adverse events

8.1.3.1. Solicited local (injection-site) adverse events

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

Table 22 Solicited local adverse events

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

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 23 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Chills

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

Note: Patients will be instructed to measure and record the body temperature in the evening. Should additional temperature measurements be performed at other times of day, patients will be instructed to record the highest temperature in the diary card. The preferred location for measuring temperature in this study is the oral cavity.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (*e.g*. clinical chemistry, hematology, urinalysis) or other abnormal assessments (*e.g*. physical examination) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 8.1.2). 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. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

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

8.1.5. Adverse events of special interest (AESIs)

8.1.5.1. Liver disease-related adverse events

Liver-disease-related (LDR) adverse events are defined as adverse events related to the underlying chronic HBV infection and characterized by one or more of the following [Lok, 2003]:

ALT flares

- Elevation of ALT > 3 X ULN:
  - Mild: > 3-5 X ULN
  - Moderate: > 5-10 X ULN
  - Severe: > 10 X ULN

ALT flares with other substantial biochemical changes

- Bilirubin ≥ 2 X ULN
- And/or INR > 1.5

Note: At Laboratory Q^2 Solutions, the ULN for ALT is 48 U/L, ULN for bilirubin is 22 µmol/L. In case the test is performed locally, the reference range of the local laboratory should be used.

Hepatic decompensation

- Occurrence of one or more of the following events: ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, variceal bleeding, or hepatic encephalopathy.

HBV-DNA breakthrough

- 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.

In case of liver disease-related AE (as defined above), patient will be queried for possible medication/herbal substance that may have altered these parameters, as well as for the followings signs/symptoms: appearance or worsening of fatigue, nausea, vomiting, abdominal pain, jaundice, fever.

8.1.5.2. Hematological adverse events of special interest

- Spontaneous local or general bleeding with thrombocytes < 50,000 platelets/mm^3,
- Anemia with hemoglobin < 9.5 g/dl.

8.1.5.2.1. Thrombosis with Thrombocytopenia Syndrome (Amended: 22 June 2023)

Recently, following COVID-19 vaccines, thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed very rarely following vaccination with adenovector-based COVID-19 vaccines. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases had a fatal outcome. ***The majority of these cases occurred within the first two weeks following adenovector-based COVID-19 vaccination and mostly in women under 60 years of age (applicable for all patients except for the patients in Belgium). OR*** The majority of these cases occurred within the first three weeks following adenovector-based COVID-19 vaccination and mostly in individuals under 60 years of age ***(applicable for the patients in Belgium only).***

Currently available data are insufficient to either disprove or confirm that TTS is a class effect for adenovector-based vaccines. As of May 2021, no TTS event has been reported in any GSK studies using adenovector-based vaccines. However, as a precautionary measure, safety information related to occurrence of TTS will be collected in this study and additional blood sample will be asked from a patient reporting TTS.

Individuals diagnosed with thrombocytopenia during the entire vaccination phase (from dose 1 till 1 month post-last dose) and follow-up phase should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis during the entire vaccination phase (from dose 1 till 1 month post-last dose) and follow-up phase should be evaluated for thrombocytopenia. For diagnostic algorithm and clinical management of TTS, clinical guidelines and local recommendations should be followed. For case definition of TTS, please refer to the Brighton Collaboration Case Definition provided in APPENDIX E.

In case a confirmed TTS event is reported during this study, patients will be queried for additional information which will be documented in the eCRF by the investigator and an additional blood sample should be collected within 2 weeks of the diagnosis of the TTS for exploratory testing and better understanding of the pathogenesis. Additional blood sample collection for TTS event reported during the follow-up phase is optional. Since scientific knowledge on TTS pathology and biomarkers for TTS risks in relation to adenovector-based vaccines is evolving, this exploratory testing is not to guide TTS management and no assay details are specified in the protocol.

8.1.5.3. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 24.

However, the investigator will exercise his/her medical and scientific judgement in deciding 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.

Table 24 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy). Optic neuritis. Multiple sclerosis. Transverse myelitis. Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. Demyelinating peripheral neuropathies including: Chronic inflammatory demyelinating polyneuropathy, Multifocal motor neuropathy Polyneuropathies associated with monoclonal gammopathy. Narcolepsy.	Systemic lupus erythematosus and associated conditions Systemic scleroderma (Systemic sclerosis), including: Diffuse Scleroderma CREST syndrome Idiopathic inflammatory myopathies, including: Dermatomyositis Polymyositis Anti-synthetase syndrome. Rheumatoid Arthritis and associated conditions including: Juvenile Idiopathic Arthritis Still's disease. Polymyalgia rheumatica. Spondyloarthropathies, including: Ankylosing Spondylitis, Reactive Arthritis (Reiter's Syndrome), Undifferentiated Spondyloarthritis, Psoriatic Arthritis, Enteropathic arthritis. Relapsing Polychondritis. Mixed Connective Tissue disorder. Gout.	Psoriasis. Vitiligo. Erythema nodosum. Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis). Lichen planus. Sweet's syndrome. Localised Scleroderma (Morphoea).
Vasculitis	**Blood disorders**	**Others**
Large vessels vasculitis including: Giant Cell Arteritis (Temporal Arteritis), Takayasu's Arteritis. Medium sized and/or small vessels vasculitis including: Polyarteritis nodosa, Kawasaki's disease, Microscopic Polyangiitis, Wegener's Granulomatosis (granulomatosis with polyangiitis), Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis), Buerger's disease (thromboangiitis obliterans), Necrotizing vasculitis (cutaneous or systemic), anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura (IgA vasculitis),	Autoimmune hemolytic anemia. Autoimmune thrombocytopenia. Antiphospholipid syndrome. Pernicious anemia. Autoimmune aplastic anemia. Autoimmune neutropenia. Autoimmune pancytopenia.	Autoimmune glomerulonephritis including: IgA nephropathy, Glomerulonephritis rapidly progressive, Membranous glomerulonephritis, Membranoproliferative glomerulonephritis, Mesangioproliferative glomerulonephritis. Tubulointerstitial nephritis and uveitis syndrome. Ocular autoimmune diseases including: Autoimmune uveitis Autoimmune retinitis. Autoimmune myocarditis. Sarcoidosis. Stevens-Johnson syndrome. Sjögren's syndrome. Alopecia areata.

Vasculitis	Blood disorders	Others
Behcet's syndrome, Leukocytoclastic vasculitis.		Idiopathic pulmonary fibrosis. Goodpasture syndrome. Raynaud's phenomenon.
Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
Autoimmune hepatitis. Primary biliary cirrhosis. Primary sclerosing cholangitis. Autoimmune cholangitis.	Inflammatory Bowel disease, including: Crohn's disease, Ulcerative colitis, Microscopic colitis, Ulcerative proctitis. Celiac disease. Autoimmune pancreatitis.	Autoimmune thyroiditis (Hashimoto thyroiditis). Grave's or Basedow's disease. Diabetes mellitus type I. Addison's disease. Polyglandular autoimmune syndrome. Autoimmune hypophysitis.

When there is enough evidence to make any of the above diagnoses, 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) and PT codes corresponding to the above diagnoses will be available to investigators at study start.

8.1.6. COVID-19

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). When reporting an AE (serious or non-serious as defined in Section 8.1.2) related to COVID-19 infection, the following verbatim terms should be used according to World Health Organisation (WHO) definition (Please refer to APPENDIX D):

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

Information pertaining to COVID-19 infection should be entered in the dedicated eCRF page.

8.2. Events or outcomes not qualifying as adverse events or serious adverse events

8.2.1. Pregnancy

Female patients who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccines but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a 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 Sections 8.4.1 and 8.4.3:

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

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (*i.e.* death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per CDC MACDP guidelines) identified in the offspring of a study patient (either during pregnancy, at birth or later) regardless of whether the foetus 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 vaccines will be reported to GSK Biologicals as described in Section 8.4.3. 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.

8.3. Detecting and recording adverse events, serious adverse events and pregnancies

8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

All AEs starting within 30 days following administration of each dose of study vaccine(s) (*i.e.* day of vaccination and 29 subsequent days) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccines and will end at study conclusion. See Section 8.4 for instructions on reporting of SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (*i.e.* protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the patient consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccines and will end at study conclusion. See section 8.4 for instructions on reporting of pregnancies.

The time period for collecting and recording of AESIs (liver disease-related AEs, hematological AESIs and pIMDs) will begin at the first receipt of study vaccines and will end at study conclusion. See section 8.4 for instructions on reporting of pIMDs.

An overview of the protocol-required reporting periods for AEs, SAEs, pIMDs, liver disease-related AEs, hematological AESIs and pregnancies is given in Table 25.

Table 25 Reporting periods for collecting safety information

Event	Screening	V1 D1 Vacc1	D7 End of 7-day FU	D30 End of 30-day FU	V6 D57 Vacc2	D63 End of 7-day FU	D86 End of 30-day FU	V10 D113 Vacc3	D119 End of 7-day FU	D142 End of 30-day FU	V14 D169 Vacc4	D175 End of 7-day FU	D198 End of 30-day FU	V24 D505	V25 D673	V26 D841
Solicited local and general AEs																
Unsolicited AEs																
SAEs																
SAEs related to study participation or concurrent GSK medication/ vaccine																
MAE																
Pregnancies																
pIMDs*																

Event	Screening	V1 D1 Vacc1	D7 End of 7-day FU	D30 End of 30-day FU	V6 D57 Vacc2	D63 End of 7-day FU	D86 End of 30-day FU	V10 D113 Vacc3	D119 End of 7-day FU	D142 End of 30-day FU	V14 D169 Vacc4	D175 End of 7-day FU	D198 End of 30-day FU	V24 D505	V25 D673	V26 D841
Liver disease-related adverse event*																
Hematological AESI*																
AEs/SAEs leading to study withdrawal																

AEs: adverse events; AESI: adverse events of special interest; D: Day; FU: follow-up; GSK: GlaxoSmithKline; MAE: medically attended event; pIMDs: potential immune-mediated diseases; SAEs: serious adverse events; SC: study conclusion; V: visit; Vacc: vaccination.
The double-bordered lines indicate timings of vaccine administration
*For information on AESIs (*i.e.* pIMDs, liver disease-related adverse event and hematological AESIs), please refer to Section 8.1.5.

8.3.2. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 25. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a patient has been discharged from the study, and he/she considers the event reasonably related to the study vaccines, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.3.3. Evaluation of adverse events and serious adverse events

8.3.3.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the patient should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine(s) or since the previous visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (*e.g.* hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the patient's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

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 and not the individual signs/symptoms.

8.3.3.2. Assessment of adverse events

8.3.3.2.1. Assessment of intensity

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

Table 26 Intensity scales for solicited symptoms

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Headache	0	Normal
	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
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Chills	0	Normal
	1	Mild: Chills that is easily tolerated
	2	Moderate: Chills that interferes with normal activity
	3	Severe: Chills that prevents normal activity
Myalgia	0	Normal
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity

*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.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

Grade 0	≤ 20 mm
Grade 1	> 20 mm to ≤ 50 mm
Grade 2	> 50 mm to ≤ 100 mm
Grade 3	> 100 mm

Fever will be scored as follows:

	Celsius	Fahrenheit
Grade 1	38.0 to 38.4°C	100.4 to 101.1°F
Grade 2	38.5 to 38.9°C	101.2 to 102.0°F
Grade 3	≥ 39°C	≥ 102.1°F

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 judgement.

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

1 (mild)	=	An AE which is easily tolerated by the patient, 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. Such an AE would, 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 a 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 8.1.2.

8.3.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between study vaccines and the occurrence of each AE/SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE could be causally related to a specific vaccine/product administered (*i.e.* investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine(s)/product(s) cannot be determined the investigator should indicate the AE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccines will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the study vaccine(s)?

YES : There is a reasonable possibility that the study vaccine(s) contributed to the AE.

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

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order 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 vaccines, if applicable.
- Erroneous administration.
- Other cause (specify).

8.3.3.3. 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).

8.3.3.4. Medically attended visits

For each solicited and unsolicited symptom the patient experiences, the patient will be asked if he/she received medical attention defined as hospitalisation, 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.

8.4. Reporting of serious adverse events, pregnancies, and other events

8.4.1. Prompt reporting of serious adverse events, pregnancies, and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 27, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 27, once the investigator becomes aware of the pregnancy.

AESIs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 27, once the investigator determines that the event meets the protocol definition of an AESI.

Table 27 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

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	2 weeks*	electronic pregnancy report	2 weeks*	electronic pregnancy report
AESIs	24 hours**‡	electronic Expedited Adverse Events Report	24 hours**	electronic Expedited Adverse Events Report

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

8.4.2. Contact information for reporting serious adverse events, pregnancies and AESIs (liver disease-related AEs, hematological AESIs and pIMDs)

Study Contact for Reporting SAEs, AESIs and pregnancies
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs, AESIs and pregnancies
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: ogm28723@gsk.com

8.4.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study patient, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

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

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the SPONSOR INFORMATION) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.4.4. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a patient is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

8.4.5. Reporting of AESIs to GSK Biologicals

Once an AESI is diagnosed (serious or non-serious) in a study patient, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows to specify that the event is an AESI and whether it is serious or non-serious. The report will always be completed as thoroughly as possible with all available details of the

event. For pIMDs, this will be done in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding an AESI, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the AESI causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the AESI.

Refer to Section 8.4.3.1 for back-up system in case the electronic reporting system does not work.

8.4.6. Updating of SAE, pregnancy, and AESI information after removal of write access to the patient's eCRF

When additional SAE, pregnancy, or AESI information is received after removal of the write access to the patient's eCRF, 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 the SPONSOR INFORMATION) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 27.

8.4.7. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the study vaccines and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.5. Follow-up of adverse events, serious adverse events, pregnancies, AESIs and handling of abnormal parameters

8.5.1. Follow-up of adverse events and serious adverse events

8.5.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each patient and provide additional relevant information on the patient's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 27).

All SAEs and AESIs (serious or non-serious) documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last visit of the patient.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

8.5.1.2. Follow-up after the patient is discharged from the study

The investigator will follow patients:

- with SAEs, serious or non-serious AESIs, or patients withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the patient is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper/ electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a patient dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

8.5.2. Follow-up of pregnancies

Pregnant patients 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 Biologicals using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

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

8.5.3. Handling of abnormal biochemistry and hematology parameters

Throughout the study period, in case of ALT > 3 X ULN, every attempt should be made to have the patient return to the study site as soon as possible to:

- Repeat the biochemistry and hematology tests on newly collected blood samples, preferably within 48-72 hours, to confirm the abnormalities and to determine if they are increasing or decreasing. If deemed necessary, the retests could be performed locally, at the discretion of the investigator. The normal laboratory ranges of the local laboratory and the results should be recorded in the eCRF.
- enquire details of the signs/symptoms, e.g. appearance or worsening of fatigue, nausea, vomiting, abdominal pain, jaundice, fever.
- If the liver biochemistry parameter abnormality is confirmed or symptoms persist, the patient should be under appropriate monitoring, at the discretion of the investigator, which may include but not limited to:
- Repeat the tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the patient is asymptomatic,
- Obtain a more detailed history of symptoms and concurrent diseases,
- Query for possible exposure to medication/herbal substance or environmental chemical agents or alcohol use or special diets that may have altered these parameters,
- Perform additional clinical examinations and/or testing as appropriate to identify the possible cause of the abnormal parameters.

Patients with other hematology/biochemistry parameters of Grade 3 and above have to repeat the relevant tests at least once a week until returned to normal or Grade 1 values.

During the primary phase,

- Patients with confirmed ALT > 384 U/L (i.e. > 8 X ULN) (repeated testing preferably within 48-72 hours) will be withdrawn from vaccination. If the result is not confirmed, tests will be repeated until ALT level decreases to < 72 U/L (*i.e.* < 1.5 X ULN). Patients with ALT < 72 U/L (*i.e.* < 1.5 X ULN) will be eligible for the next vaccine administration.
- Patients with confirmed ALT > 241 U/L (i.e. > 5 X ULN) (repeated testing preferably within 48-72 hours) that persists for 2 weeks will be withdrawn from vaccination. If the result is not confirmed, tests will be repeated until ALT level decreases to < 72 U/L (*i.e.* < 1.5 X ULN). Patients with ALT < 72 U/L (*i.e.* < 1.5 X ULN) will be eligible for the next vaccine administration.
- Patients with confirmed ALT > 144 U/L (i.e. > 3 X ULN) and INR > 1.5 (repeated testing preferably within 48-72 hours) will be withdrawn from vaccination. If the result is not confirmed, tests will be repeated until ALT level decreases to < 72 U/L (*i.e.* < 1.5 X ULN) and INR decreases to < 1.2. Patients with ALT < 72 U/L (*i.e.* < 1.5 X ULN) and INR < 1.2 will be eligible for the next vaccine administration.

- Patients with confirmed ALT > 144 U/L (*i.e.* > 3 X ULN) and bilirubin > 44 µmol/L (> 2 X ULN) (repeated testing preferably within 48-72 hours) will be withdrawn from vaccination. If the result is not confirmed, tests will be repeated until ALT level decreases to < 72 U/L (*i.e.* < 1.5 X ULN) and bilirubin level decreases to < 22 µmol /L (*i.e.* < 1 X ULN). Patients with ALT < 72 U/L (*i.e.* < 1.5 X ULN) and bilirubin < 22 µmol/L (*i.e.* < 1 X ULN) will be eligible for the next vaccine administration.

The interval between the two vaccine doses may then be extended to up to maximum 12 weeks.

8.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE / AESI should be recorded in Expedited Adverse Event Report of the patient's eCRF (refer to Section 6.7).

8.7. Subject card

Study patients must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each patient. In an emergency situation this card serves to inform the responsible attending physician that the patient is in a clinical study and that relevant information may be obtained by contacting the investigator.

Patients must be instructed to keep subject cards in their possession at all times during the study duration.

8.8. Holding rules and safety monitoring

8.8.1. Internal Safety Review Committee (iSRC)

This study will be overseen by an iSRC operating under a charter. Core members of the iSRC will include a GSK Biologicals' safety physician, a hepatologist, a Clinical Research and Development Lead, and a biostatistician who are not otherwise involved in the conduct of the Therapeutic HBV studies. The iSRC will conduct the safety review using unblinded data.

The iSRC will determine whether any of the predefined study holding rules (see Section 8.8.3) are met or whether there is any other safety signal during the planned iSRC evaluation (see Section 8.8.2). In addition to the planned iSRC evaluation, *ad hoc* iSRC reviews can be triggered in case any safety concern is observed.

An external (non-GSK) expert with 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.

If no safety signal is observed, the favourable outcome of the safety evaluation authorising the investigator to proceed with vaccination of patients will be documented and provided in writing to the investigators.

If a holding rule is met, the study will be put on hold. All vaccinations will cease immediately, but all other procedures relating to safety, immunology, efficacy and disease monitoring will continue. Following an internal review, Company 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. If following this internal safety review, the Sponsor deems it appropriate to restart the enrolment, this can be done following approval of a substantial amendment by the regulatory authorities.

8.8.2. Details on the staggered vaccination and dose escalation

The study will be conducted following a staggered design overseen by the iSRC (see Figure 4).

Within each Step (see Figure 3):

- A maximum of CCI patients per group (e.g. CCI will first be randomized for vaccination and followed for 2 days. When all these patients have completed Visit 2 (*i.e.* 2-day post Dose 1), iSRC will review all the available safety data. If the iSRC considers it appropriate to continue, the randomization of the remaining patients in each group can start. If ≥CCI patients randomized at the same study site on the same day, these patients should be vaccinated sequentially with at least 60 minutes apart to allow monitoring of any acute event, such as anaphylactic reaction.
- Prior to the administration of the Dose 2, Dose 3 and Dose 4 to the first patient, a favorable outcome of the iSRC evaluation of data up to 30 days after Dose 1, Dose 2 and Dose 3, respectively, should be available.

CCI

iSRC: internal Safety Review Committee; p-v: post-vaccination.
For the second dose vaccination, there will be at least 8 days apart between the time the initially recruited patients (i.e. CCI complete administration of Dose 2 and the remaining patients within each step start receiving Dose 2. This will allow a completion of 7-day safety follow up of Dose 2 by initially recruited patients before dosing of Dose 2 to the remaining patients.

Dose-escalation between steps will be done as follows (See Figure 4):

- Step A (low dose of each vaccine): Approximately CCI patients will be randomised for vaccination in Step A. When all these patients have completed Visit 8 (*i*.e. 14-day post Dose 2), the iSRC will review all the available safety data. If the iSRC considers it appropriate to continue the study, Step B treatment randomization and administration can start. Note that safety assessment of at least CCI patients in Step A with available data up to Visit 8 i.e. 14 days post-vaccination Dose 2, may be considered sufficient prior moving to Step B, if approved by local authorities. Refer to Section 8.8.3.2 for considerations to conclude Step A with CCI patients instead of CCI patients initially planned.
- Step B (prime-boost with ChAd155-hIi-HBV and MVA-HBV and sequential administration with HBc-HBs/AS01$_{B-4}$): Approximately CCI patients from Step B will first be randomised for vaccination. When they have completed Visit 8 (*i.e*. 14-day post Dose 2), the iSRC will review all the available safety data. If the iSRC considers it appropriate to continue the study, the treatment randomisation and administration to the remaining patients in Step B can start.
- Step C (prime-boost with ChAd155-hIi-HBV and MVA-HBV and co-administration with HBc-HBs/AS01B-4): After Step B enrolment is complete, Step C treatment randomization and administration can start.
- Prior to initiating the randomization for each step, the study team will review the number of subjects available for that step.

8.8.3. Holding rules

8.8.3.1. Holding rules definitions and monitoring

The following safety holding rules (Table 28) will be checked by iSRC during each safety evaluation. Meeting any of these holding rules during the primary phase will trigger a hold of vaccination in the clinical study, irrespective of the number of patients enrolled and/or the timing of the event relative to vaccination.

- **Holding rules 1, 2 and 3** will be assessed by the iSRC during the safety evaluation.
- **Holding rules 1 and 3** will also be monitored by the investigator on a continuous basis irrespective of the number of patients enrolled. If an investigator detects one of the holding rules mentioned above, he/she will immediately put the enrolment or the vaccination on hold and he/she will immediately inform the Sponsor and enter the data in the eCRF. It is the Sponsor's responsibility to put the enrolment or the vaccination on hold at all sites.

Table 28 Holding rules

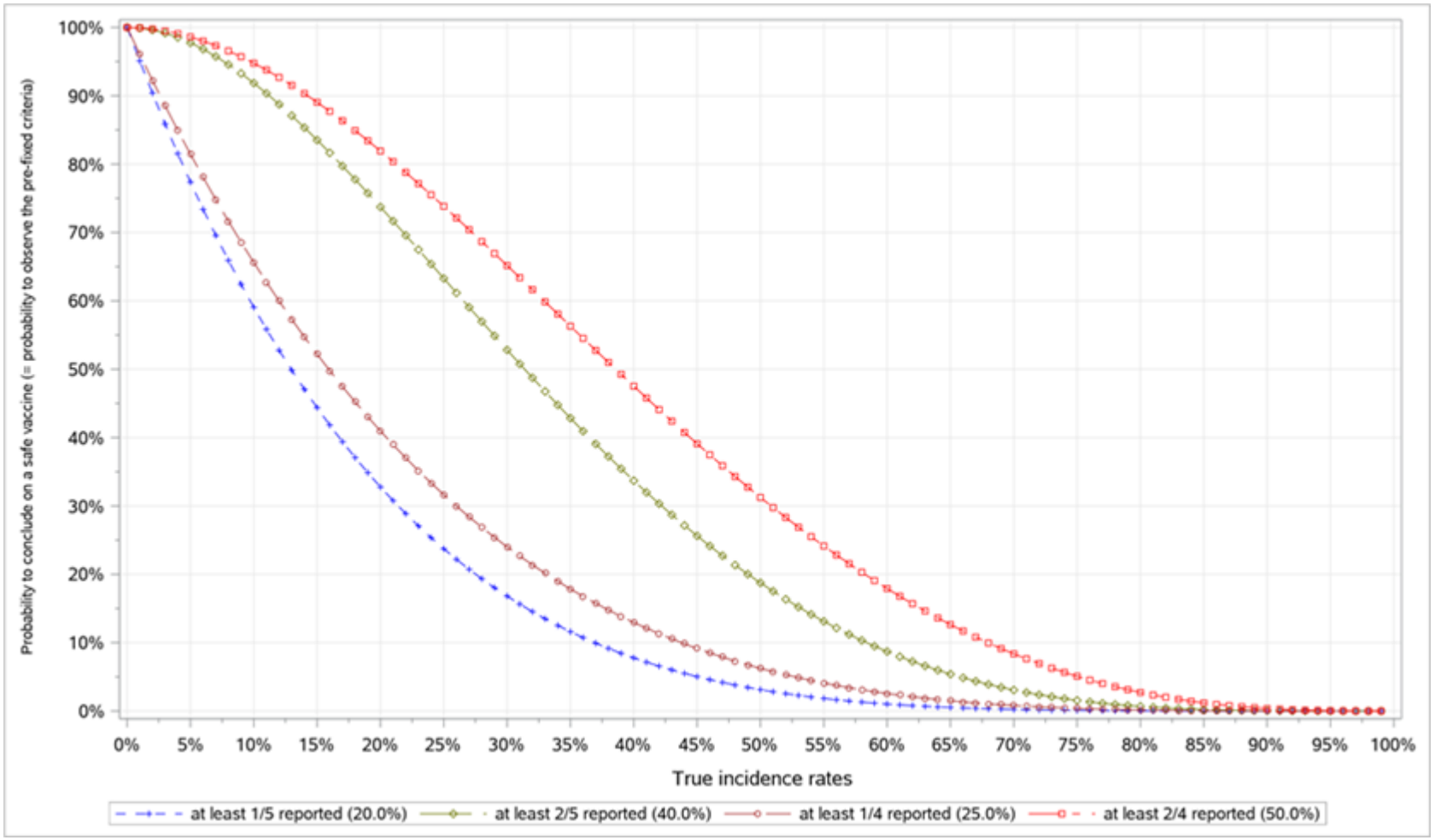
Holding Rule	Event	Number of patients
1a	Death or any life-threatening SAE	≥ 1
1b	Any SAE that is considered as related to the vaccine in an investigational group	≥ 1
1c	Any withdrawal from the study (by investigator or patient request) following a Grade 3 AE that cannot reasonably be attributed to a cause other than vaccination	≥ 1
1d	Any local or general solicited AE leading to hospitalization, or fever > 40°C (104°F) that cannot reasonably be attributed to a cause other than vaccination, or necrosis at the injection site, within the 7-day (days 1-7) post-vaccination period	≥ 1
2a	Any Grade 3 solicited local AE (lasting 48h or more) in an investigational group, within the 7-day (day 1-7) post-vaccination period	At least 25% AND ≥ 2 in a vaccine group
2b	Any Grade 3 solicited general AE (lasting 48h or more) in an investigational group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (day 1-7) post-vaccination period	At least 25% AND ≥ 2 in a vaccine group
2c	Any Grade 3 unsolicited AE in an investigational group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (day 1-7) post-vaccination period or Any Grade 3 abnormality in pre-specified hematological or biochemical laboratory parameters in an investigational group within the 7-day (day 1-7) post-vaccination period	At least 25% AND ≥ 2 in a vaccine group
3a	Any acute exacerbation or severe hepatitis flare (intermittent elevation of ALT to more than 10 times the ULN) *	≥ 1
3b	Any acute exacerbation or moderate hepatitis flare for more than 2 weeks (intermittent elevation of ALT to > 5 to < 10 X ULN) *	≥ 1
3c	Any ALT flare (ALT > 3XULN) with other substantial liver biochemical change defined as an increase in serum bilirubin to ≥2 x ULN and/or international normalized ratio (INR) >1.5 *	≥ 1
3d	Any hepatic decompensation defined as the occurrence of 1 or more of the following events: ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, variceal bleeding, or hepatic encephalopathy	≥ 1
3e	Any reactivation of chronic hepatitis B as characterized by HBV-DNA breakthrough accompanied with 1 or more of the following: ALT elevation to > 3 X ULN, substantial biochemical changes, or hepatic decompensation as defined above	≥ 1
3f	Any AE related to spontaneous local or general bleeding AND Thrombocytopenia < 50,000/mm^3	≥ 1

* The abnormal value should be confirmed by an additional testing preferably within 48-72 hours; if no additional value is available within one week, the initial value will be considered as confirmed. ULN for ALT = 48 U/L (Q^2 Solutions Laboratory); ULN for bilirubin = 22 µmol/L (Q^2 Solutions Laboratory). In case the test is repeated locally, the reference range of the local laboratory should be used and recorded.

8.8.3.2. Risk assessment for the holding rules

Figure 5 presents the probability of not meeting defined holding rule for CCI patients per study group.

Figure 5 Safety holding rules with associated probabilities



The above Figure 5 illustrates that, with CCI patients in a group:

- **For holding rules 1 and 3, using a cut-off of CCI**, there is around 90% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 35% and around 60% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 10%.
- **For holding rule 2, using a cut-off of CCI** there is only around 60% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 35% and around 90% chance that the holding rule is not met in a vaccine group if the corresponding event has true incidence rate of 10%.
- **For holding rules 1 and 3, using a cut-off of CCI** there is around 82% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 35% and around 66% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 10%.
- **For holding rule 2, using a cut-off of CCI,** there is around 44% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 35% and around 95% chance that the holding rule is not met in a vaccine group if the corresponding event has true incidence rate of 10%.

Table 29 provides the impact on the probability of detecting holding rule with CCI patients as compared to CCI patients :

- There is a decrease in sensitivity of detecting a holding rule event, meaning that there is 5% to 7% decrease in probability of detecting a holding rule event in CCI patient among 4 patients as compared to CCI patients and 3% to 14% decrease in probability of detecting a holding rule in CCI patients among CCI patients as compared to CCI patients.
- If the study had continued to vaccinate CCI patients in Step A CCI patients per group), considering the incidence rates of 25% [95%CI: 0.63;80.59] observed in CCI patients CCI patients per group), the probability to have an event meeting a holding rule criterion will be below 50% [49%=Upper limit of 1-sided 67% CI] with 67% of confidence.
- No AEs meeting holding rule events were reported up to 14 days post-vaccination Dose 2. Therefore, if the study had continued to enrol up to CCI patients, the additional safety data are very unlikely to change the observed safety profile.

Table 29 Probability of meeting holding rule with CCI patients

True Incidence rates	Probability of meeting holding rule CCI			
10%	41%	34%	8%	5%
15%	56%	48%	16%	11%
20%	67%	59%	26%	18%
25%	76%	68%	37%	26%
30%	83%	76%	47%	35%
35%	89%	82%	57%	44%
40%	92%	87%	66%	52%

By Data lock point of 24 April 2020, CCI patients received at least one dose of study treatment in Step A. Among them CCI patients completed the study treatment and CCI patients received at least 2 doses of study treatment. To date, no safety concerns were raised and no holding rule was met as confirmed by iSRC based on the safety review. Refer to IB Edition 4 Supplement for details.

Considering that no events that could trigger a holding rule were reported up to 14 days post-vaccination Dose 2, if the study had to continue to enrol up to CCI patients in Step A, the additional safety data would be very unlikely to change the observed safety profile. The likelihood of detection of holding rule based on CCI patients among CCI patients versus CCI patients per group (i.e. CCI patients versus CCI patients in total in Step A) has been thoroughly evaluated.

Therefore it is proposed that safety assessment of at least CCI patients in Step A with available data up to Visit 8 i.e. 14 days post-vaccination Dose 2, may be considered sufficient prior moving to Step B.

For sites that participate in Step A, this will be implemented, when approved by local authorities. For sites that do not participate in Step A, safety assessment of Step A patients only or assessment of cumulative data of Step A and first patients in Step B will be considered prior starting the Step B, depending on the country feedback.

Figure 6 presents the probability of not meeting defined holding rule for CCI patients per study group.

The above Figure 6 illustrates that, with CCI patients in a group:

- **For holding rules 1 and 3, using a cut-off of CCI**, there is around 88% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 10% and around 45% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 5%.
- **For holding rule 2, using a cut-off of CCI,** there is around 90% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 20% and around 10% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 20%.
- **For holding rule 2, using a cut-off of CCI,** there is around 70% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 30% and there is around 96% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 10%.

The above Figure 7 illustrates that, with CCI patients in a group:

- **For holding rules 1 and 3, using a cut-off of CCI,** there is around 90% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 5% and around 10% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 5%.

- **For holding rule 2, using a cut-off of** CCI , there is around 90% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 10% and around 10% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 10%.
- **For holding rule 2, using a cut-off of** CCI **,** there is around 90% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 35% and there is around 99% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 10%.

9. PATIENT COMPLETION AND WITHDRAWAL

9.1. Patient completion

A patient who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

9.2. Patient withdrawal

Patients withdrawn after randomization will not be replaced.

9.2.1. Patient withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any patient who did not come back for the concluding visit foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the patient will be used for the analysis.

A patient is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this patient from the date of withdrawal/last contact.

Investigators will make an attempt to contact those patients who do not return for scheduled visits or follow-up. Specific actions to be taken by the Investigator to re-establish the contact with the patient may include up to 3 telephone calls and/or emails and a certified letter to the last known address.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a patient from the study was made by the patient himself/herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Solicited adverse event

- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Sponsor study termination.
- Other (specify).

*In case a patient is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the patient in the eCRF.

Patients who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from patients who are withdrawn for other reasons. Investigators will follow patients who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.5.1.2).

9.2.2. Patient withdrawal from study vaccines

A 'withdrawal' from the study vaccines refers to any patient who does not receive the complete treatment, *i.e.* when no further planned dose is administered from the date of withdrawal. A patient withdrawn from the study vaccines may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol. For the purpose of this study, all study procedures except study vaccines administration, its related procedures (treatment number allocation, etc.) remain applicable to the patients.

If vaccination cannot be administered within a maximum of 111 days between subsequent vaccinations (refer to Table 6), patient should discontinue study vaccination and management of follow up visits in the primary phase (Epoch 002) should be performed as described below and in Section 5.6.18:

- For patients who discontinued vaccination after vaccination Dose 1, Visits 10, 12, 13, 14 and 17-22 should be performed, as defined in Table 4 and Table 5, for follow up on safety and laboratory parameters.
- For patients who discontinued vaccination after vaccination Dose 2, Visits 14 and 17-22 should be performed, as defined in Table 4 and Table 5, for follow up on safety and laboratory parameters.
- For patients who discontinued vaccination after vaccination Dose 3, Visits 18-22 should be performed, as defined in Table 5, for follow up on safety and laboratory parameters.
- For all patients who discontinued study vaccination, the planned visits in the follow up phase (Epoch 003) should be performed as defined in Table 5.

Information relative to premature discontinuation of the study vaccines will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the patient himself/herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Solicited adverse event
- Not willing to be vaccinated
- Other (specify).

9.3. Screening and baseline failures

A patient is considered to be a Screening failure if the patient signs the ICF, but withdraws before randomization to study treatment. The following information will be collected for Screening failures:

- Informed consent
- Inclusion/exclusion criteria
- Demographic data
- Medical history
- Physical examination
- Blood samples for Screening tests
- SAEs related to study participation, to concomitant use of GSK products or any fatal SAEs
- Screening failure details

10. STATISTICAL METHODS

10.1. Primary endpoints

- Occurrence of 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 SAEs up to six months after the last dose (Day 337, Visit 22).
- Occurrence of pIMDs up to six months after the last dose (Day 337, Visit 22).
- Occurrence of liver-disease related AEs up to six months after the last dose (Day 337, Visit 22).
- Occurrence of hematological AESIs up to six months after the last dose (Day 337, Visit 22).
- Occurrence of medically attended events (MAEs) up to six months after the last dose (Day 337, Visit 22).

10.2. Secondary endpoints

Immunogenicity

Immunogenicity with respect to HBV components of the viral vectored vaccines and adjuvanted proteins vaccines, at predefined time points (see Table 4 and Table 5).

- 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.

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.

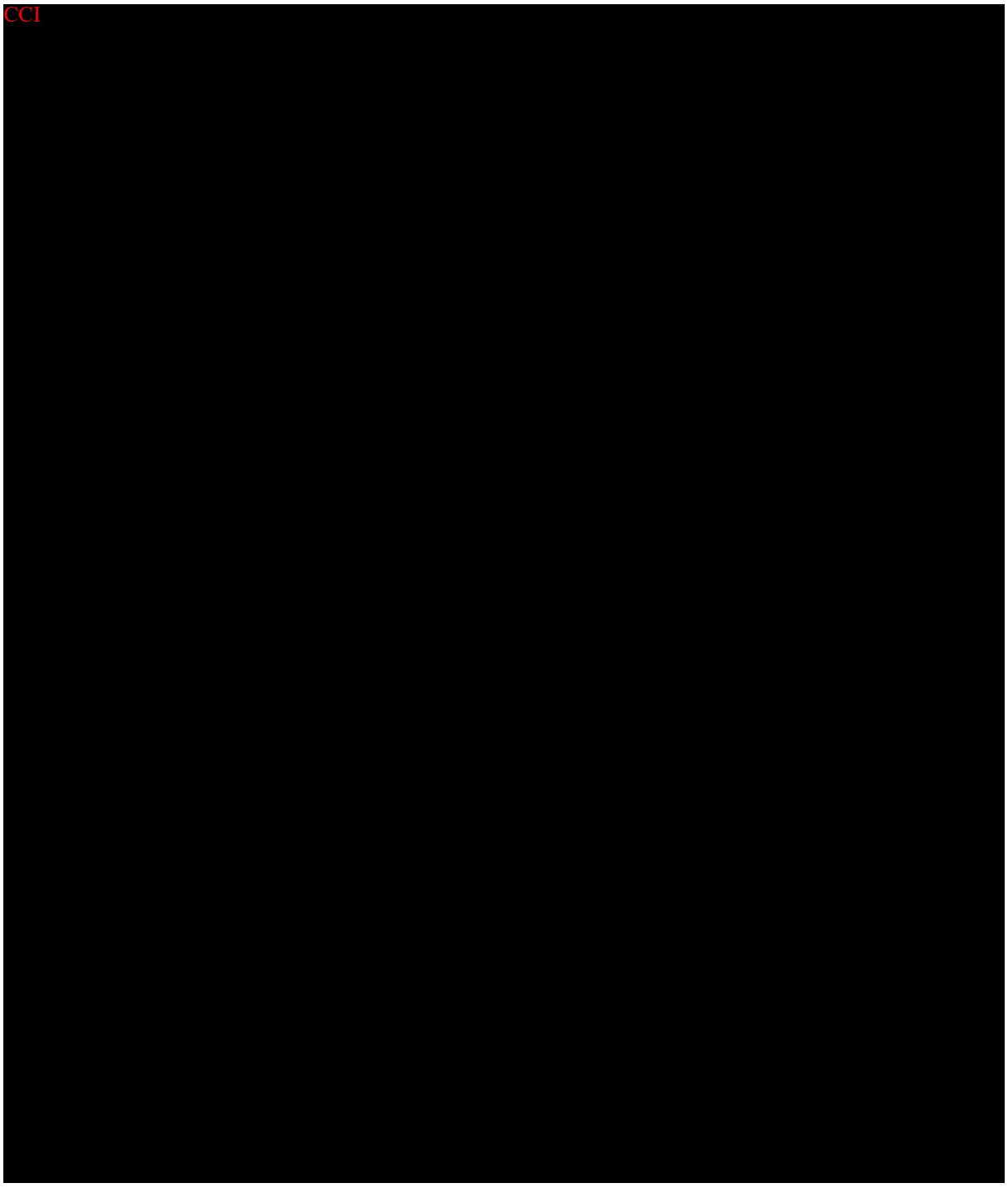
Safety

- 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/mm3),
  - 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.

CCI



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11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, public disclosure requirements and publications must be fulfilled.

11.1. electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, patient initials will not be collected nor transmitted to GSK. Patient data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst other items, the:

- Data are authentic, accurate, and complete.
- Safety and rights of patients are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (*e.g.* audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format

other than hard copy (*e.g.* microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures, otherwise, the minimum retention period will default to 25 years after completion of the study report.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available clinical trial registers and publication policy

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary PCD and to have secondary endpoint disclosed at latest 12 months after the LSLV as described in the protocol.

As per EU regulation, summaries of the results of GSK interventional studies (phase I-IV) in adult population conducted in at least one EU member state will be posted on publicly available EMA registers within 12 months of EoS (as defined in the protocol) in the concerned EU member state. However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

11.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals 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 patients, as appropriate.

11.7. Data Sharing

Under the framework of the SHARE initiative, results of GSK studies may be combined with non- GSK studies, to investigate further about the study product(s) and other product(s), and /or the disease/condition under investigation and related diseases and conditions.

11.8. Pharmacogenomics

By United States federal regulation, annual reports must include relevant pharmacogenomics results experiment. Refer to the US Guidance for industry "Pharmacogenomic data submissions" for more information on the process and format for submission of such data.

12. COUNTRY SPECIFIC REQUIREMENTS

12.1. Germany

Explanatory statement concerning Gender Distribution (Article 7, paragraph 2 (12) of the German GCP ORDER).

For this TH HBV VV-001 study, there is no intention to conduct specific analyses investigating the relationship between gender and the safety, immunogenicity and efficacy of the investigational HBV vaccines. Recruitment will include both males and females. To not expose pregnant women and their foetuses/children to an early-phase investigational vaccine, females enrolled in this trial will either be of non-childbearing potential (*i.e.*, hysterectomy, bilateral ovariectomy or be premenarchal or postmenopausal), or if she is of childbearing potential, she must have a negative pregnancy test at the Screening and practice adequate contraception from Screening until 12 weeks after completion of the vaccine series (Refer to the study protocol, Section 4.2 "Inclusion criteria" and Section 4.3 "Exclusion criteria"). The recruitment will be closed to females who are pregnant or lactating. Similarly, patients becoming or deciding to become pregnant during the study must stop the subsequent dose of vaccination.

According to the Hepatitis B annual epidemiological report by European Centre for Disease Prevention and Control, male-to-female ratio of acute or chronic hepatitis B was 1.5 to 1 [European Centre for Disease Prevention and Control, 2016]. In Germany, the prevalence of acute or chronic HBV infection (as evident by anti-HBc positive and HBsAg positive) among men was 0.5% (0.2–1.1) and among women was 0.2% (0.1–0.4); the relatively high prevalence among men as compared to women was statistically not significant [Poethko-Müller, 2013]. With respect to the nucleot(s)ide treatment, there is no gender differences in the safety outcomes or efficacy [Summary of product characteristics for Entecavir; Prescribing information for Tenofovir disoproxil fumarate].

Liver ultrasound

In case liver ultrasound is not possible, another imaging method may be used at the discretion of the investigator. However, study related application of radioactive substances or ionizing radiation (including X-rays) needs approval by Federal Office for Radiation Protection according § 23 StrlSchV respectively § 28a RöV.

Remote Source Data Verification (rSDV) during exceptional situations in Germany

Frequent instream monitoring of safety data by the central study team at GSK is required for this study. Instream review of study data items and processes should be considered during exceptional situations/circumstances, such as with pandemics like COVID-19, focusing on key data points, patient assessments and processes that are critical to ensure the rights, safety and well-being of study participants and the integrity of the study and data. Prior to any rSDV activity a written agreement by the Investigator will be obtained. The agreement includes the extent and the method of rSDV activities. Monitoring Plan and Study-Specific Risk Register will be updated to include rSDV activities and clinical research associates (CRAs) will be guided for the conduct of rSDV.

Option 1 Transfer of redacted Source Documentation

Process for transfer and review of redacted source documentation provided by the site:

- The CRA instructs study site on the source data needed for the remote SDV activities.
- The CRA instructs site staff they must pseudonymize the requested documentation, do a quality check that anonymized (redacted) areas cannot be read, and then delivers the documentation to the CRA in an encrypted form of communication (the site should have a documented process).
- The minimum requirements regarding quality of the copies will be agreed with the site upfront:
  - For the scanning of paper documents resolution will be a minimum of 300 dots per inch (dpi).
  - For the scanning of photographs and images resolution will be 600 dots per inch (dpi) minimum.
  - Colour scanners must be able to produce copies that match the original.
  - A4 format as final size without loss of information.

  - Documents will be saved as portable document format (PDF).
  - In order to maintain quality standards, a captured image will not be subjected to non-uniform scaling (i.e. sizing) or re-sampling to a lower resolution.

- Redacted source document scans will be sent to the CRA via email using one of the following secure options:

a. Transport Layer Security (TLS) connection:

TLS connections are intended to support significant mail flow between GSK and external partners in a secure manner.

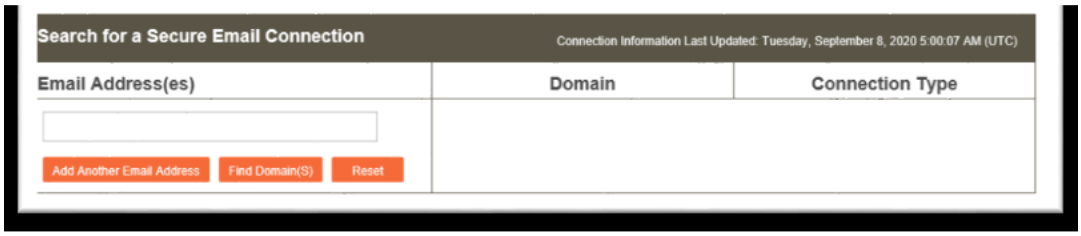
b. GSK Secure

In cases where only a handful of users are communicating or the volume of emails is low, the use of GSK secure, the GSK ad-hoc message encryption solution is recommended.

c. Password protected PDF attachment

  - A password protected scan (PDF) will be attached to an email. The password to open the attachment will be sent in a separate email.

- The CRA may use the secure email website to assess whether the sites email address is secure (i.e. encrypted).



- Prior to starting remote SDV the CRA ensures that the provided documents are complete and do not contain any Personal Information (PI).
  - In case the CRA detects any PI that has not been redacted, the CRA informs the study site and deletes the files (incl. the Recycle bin).
  - A Data Breach must be reported Data Breach Web Report Form.
- Use of an external PC screen is recommended. The CRA will not generate any copies from the source data received.
- Source data verification/review will be conducted according to the process outlined in the GSK Monitoring SOP.
- After completion of SDV activities, the CRA deletes all copies/images of subject data received from the site. This includes the deletion of the recycle bin and any temporary files.
- A statement confirming that all documents were destroyed will be provided by the CRA via email to the site.
- Details of what was monitored remotely will be documented in the appropriate section of the Monitoring Visit Report (MVR).

Option 2 – Review of Subject Source Documentation remotely

Process for use of Webcams, WebEx, MS Teams for viewing subject source remotely:

- The CRA ensures that the site personnel sharing information with GSK has authority to do so.
- Remote SDV activities will be performed exclusively by the assigned site monitor.
- Prior to conducting any remote SDV activities the CRA ensures that a written informed consent, covering the proposed SDV activities, has been signed by the study patient.
- For CRAs using GSK laptops, only use GSK approved video conferencing tools (e.g. MS Teams or GSK WebEx). Live image transmission is fully encrypted and protected for authorised user. By using these systems, it will be assured that data will be viewed only but not transmitted/stored.
- For functional service provider (FSP)/Local contract research organisation (CRO) CRAs not using GSK laptops, only MS Teams via RAA (Remote Access Application) may be used for meetings between the CRA and the site. WebEx is not permitted from non-GSK laptops. Other tools like FaceTime, WhatsApp or Zoom are not permitted since they do not have sufficient encryption features. GSK does not have enterprise contract/privacy agreement with these providers.
- Prior to the remote monitoring visit, the CRA instructs study site on the specific data needed for the remote SDV.
- Source data verification will be conducted according to the process outlined in the Monitoring SOP.
- The use of a headset is required, do not use computer audio.
- The CRA does not capture screens or take pictures of screens to ensure we are not transferring content outside of clinical sites.
- WebEx or Teams do not store or have access to any data, GSK staff is not allowed to make or store any screenshots or save any data which has been shared.
- Details of what was monitored remotely will be documented in the appropriate section of the MVR.

In case of technical malfunctions or if the security of the transmission is no longer ensured, we will pause rSDV activities. GSK Issue Management Procedures will be initiated.

12.2. France

This section includes requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information applicable to the study.

1. Concerning the « SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA»

- The following vulnerable subject populations will be excluded: minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.
- A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code law L.1121-8-1). (exception for a participant to a non-interventional study if authorised by the Ethics Committee). It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:
  - is either affiliated to or beneficiary of a social security category;
  - has got an authorisation by the Ethics Committee.

2. Concerning the "STATISTICAL CONSIDERATIONS AND DATA ANALYSES" and specially in the "SAMPLE SIZE ASSUMPTIONS"

   The expected number of subjects to be recruited in France is declared to the French regulatory authority.

3. Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

- In section "Regulatory and Ethical Considerations, including the Informed Consent Process"
  - Concerning the process for informing the subject and/or his/her legally authorized representative, the following text is added:

  French Patient Informed Consent Form is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent in triplicate (quadriplicate for minor subject). It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee and the maintenance of confidentiality of the returned consent form by GlaxoSmithKline France.

  - Concerning the process for obtaining subject informed consent:

  When a research involving human being is carried out on a minor / on an adult in the care of a "tutelle" guardian, consent is given by their legal representative and, if the committee mentioned in article L. 1123-1 considers that the research in question, because of the seriousness of the restraints or the specificity of the medical acts involved, entails a serious risk of affecting their private life or the integrity of their body, consent is given by the family council if it has been instated, or by the judge of "tutelle" guardians.

  When research involving human being is carried out on an adult in the care of a "curatelle" guardian, consent is given by the subject assisted by his guardian. However, if the adult in the care of a "curatelle" guardian is invited to participate in research which the committee mentioned in article L. 1123-1 considers, because of the seriousness of the restraints or the specificity of the medical acts involved, to entail a serious risk of affecting their private life or the integrity of their body, the matter is submitted to the judge of guardians who decides whether the adult is

capable of giving her/his consent. In the case of incapacity, the judge will decide whether or not to authorise the research involving human being.

– Concerning the management of the Patient Informed Consent Forms, the following text is added:

The first copy of the Patient Informed Consent Form is kept by the investigator. The second copy is kept by the Medical Director of GlaxoSmithKline France and the last copy(ies) is(are) given to the subject or their legally authorized representative(s).

The second copy of all the consent forms will be collected by the Clinical Research Assistant (CRA) under the Investigator's control, and placed in a sealed envelope bearing only:

– the study number,

– the identification of the Centre: name of the principal investigator and centre number,

– the number of informed consents,

– the date,

– and the principal investigator's signature.

Then, the CRA hands the sealed envelope over to the Medical Director, for confidential recording, under the responsibility of the Medical Director.

- NOTIFICATION TO THE HOSPITAL DIRECTOR

  In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

- INFORMATION TO THE HOSPITAL PHARMACIST

  In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

4. Concerning the " DATA MANAGEMENT " the following text is added:

- Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GlaxoSmithKline data bases by GlaxoSmithKline Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Data Protection French Law n° 78-17 of 6th January 1978, each of these people

aforesaid has a right of access, correction and opposition on their own data through GlaxoSmithKline Laboratory (Clinical Operations Department).

- DEMOGRAPHIC DATA

  In accordance with the Data Protection French Law n° 78-17 of 6th January 1978 – article 8, the ethnic origin can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- TESTING OF BIOLOGICAL SAMPLES

  In accordance with the French Public Health Code law – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

5. Monitoring visits

   The Health Institution and the Investigator agree to receive on a regular basis a Clinical Research Assistant (CRA) of GLAXOSMITHKLINE or of a service provider designated by GLAXOSMITHKLINE. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GLAXOSMITHKLINE or from a service provider designated by GLAXOSMITHKLINE. In addition, the Health Institution and the Investigator agree that the CRA or the service provider designated by GLAXOSMITHKLINE have direct access to all the data concerning the Study (test results, medical record, etc …). This consultation of the information by GLAXOSMITHKLINE is required to validate the data registered in the electronic Case Report Form (eCRF), in particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

6. Data entry into the eCRF

   The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's electronic Case Report Form (eCRF) use here below:

   The Health Institution and the Investigator undertake:

- That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the electronic Case Report Form (eCRF) of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.
- That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.
- That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.
- To keep the IT Equipment and/or access codes in a safe and secure place and to authorize only the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.

- To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.
- To return at the end of the Study the IT Equipment and/or access codes to GLAXOSMITHKLINE or to any company designated by GLAXOSMITHKLINE and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

7. CTR publication

   It is expressly specified that GLAXOSMITHKLINE and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GLAXOSMITHKLINE GROUP named Clinical Trial Registered (CTR) including the registration of all the clinical trials conducted by the GLAXOSMITHKLINE Group and this before or after the publication of such results by any other process.

8. Data Protection French Law of 6th January 1978 (CNIL)

   In accordance with the Data Protection French Law of 6 January 1978, computer files used by GLAXOSMITHKLINE to monitor and to follow the implementation and the progress of the Study are declared with CNIL by GLAXOSMITHKLINE. The Investigator has regarding the processing data related to her/him a right of access, of rectification and of opposition with GLAXOSMITHKLINE in accordance with the legal provisions. This information can be transferred or be accessed to other entities of GLAXOSMITHKLINE Group, what the Investigator agrees by the signature of the present Protocol.

9. Investigational Product Accountability, Reconciliation, and Destruction

   In specific situations (if the site has 1- an approval from the French Regulatory Agency (ANSM) and 2- a GSK written endorsement letter) where institutional practices dictate that the site disposes of and/or destroys IP prior to allowing the "monitor' to verify and document IP accountability, the following applies:

   "During the conduct of the Study, Investigational Product (IP) will be destroyed by the Institution prior to a GlaxoSmithKline "monitor" conducting final investigational product accountability. Institution agrees that such destruction will comply with Institution's investigational product accountability procedures and will provide GlaxoSmithKline with investigational product accountability logs and supporting documentation to verify adherence to 'Bonnes Pratiques Cliniques' (decision dated on the 24th of November 2006).

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APPENDIX A LABORATORY ASSAYS

1. Anti-HBs Ig tot (CLIA) - ADVIA Centaur anti-HBs2 (Siemens Healthcare)

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 HBs Ag (ad and ay) is labelled 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 exist 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 et ay are two different subtypes of S antigen

2. Anti-HBc

Not yet developed

CCI

4. qHBsAg – HBsAg assay (Abbott)

The Abbott HBsAg assay is a two-step immunoassay using chemiluminescent paramagnetic microparticles (CMIA) technology for the quantitative determination of HBsAg. In the first step, sample is mixed with microparticles coated with anti-HBs; antibody-antigen will form if HBsAg is present in the sample. In the second step, acridium-labeled anti-HBs conjugate is added. A direct relationship exists between the amount of HBsAg present in the sample and the RLU detected by the system.

5. qHBsAg – HBsAg assay (Abbott) with pre-treatment

Immune complexes (Ag-Ab complexes) can be present in the sample. Those immune complexes can interfere with the HBsAg dosage. In order to avoid this interference, sample is pre-treated with a chaotropic agent that dissolves the immune complexes. After this pre-treatment, sample is used as described in the previous section.

CCI

[redacted]

7. HBV DNA assay

Cobas® HBV assay for use on the Cobas 4800 System (ROCHE) or equivalent will be used for the detection and the quantification of HBV DNA in serum.

It is an in vitro nucleic acid amplification test for the quantitation of hepatitis B virus DNA in human EDTA plasma or serum of HBV-infected individuals. This test is intended for use as an aid in the management of patients with chronic HBV infection undergoing anti-viral therapy. The test can be used to measure HBV DNA levels at baseline and during treatment to aid in assessing response to treatment.

Primers and probe target the highly conserved pre-core and core regions of the HBV genome. The test covers all known HBV genotypes (A-H) and the HBV viral load is reported as IU/ml.

This assay, commercialized by ROCHE, is CE-approved. Performance characteristics of the assay were evaluated by the manufacturer and are summarized into the kit package insert.

CCI

[redacted]

CCI [redacted]

11. CFC Assay

This assay is applied to measure the frequency of antigen-specific T-lymphocytes in peripheral blood. Blood samples are collected by venipuncture and PBMCs are prepared by certified laboratories by centrifugation onto a Lymphoprep™ cushion within 24 hours following collection. PBMC suspensions are stored in liquid nitrogen until analysis. To measure T-cell responses elicited by the vaccine candidate, samples are thawed and cultured overnight in the presence of costimulatory antibodies (anti-CD28 and anti-CD49d) without stimulation (background control) or with peptide pools (15mer overlapping by 11) covering the sequence of the relevant antigens (HBs, HBc, CCI [redacted]. Cells are then immunostained for surface phenotypic markers (CD4 and CD8), permeabilized and then immunostained for CD3 and activation markers (the costimulatory molecules CD40L and 4-1BB and the cytokines IL-2, IFN-γ, TNF-α, IL-13, IL-17). Analysis is performed by multiparametric flow cytometry, and the results are expressed after background subtraction as frequencies of antigen specific $CD4^+$ (or $CD8^+$) T-cells producing various combinations of the activation markers assessed per million $CD4^+$ (or $CD8^+$) T-cells.

APPENDIX B CLINICAL LABORATORIES

Table 34 GSK Biologicals' laboratories

CCI

[redacted]

Table 35 Outsourced laboratories

CCI

[redacted]

APPENDIX C TOXICITY GRADING FOR HEMATOLOGY, BIOCHEMISTRY AND URINALYSIS PARAMETERS

Component	Grade 1	Grade 2	Grade 3	Grade 4
Hematology				
Hemoglobin (g/dl) male	13.5 - 12.5	12.4 - 10.5	10.4 - 8.5	< 8.5
Hemoglobin change from baseline male (g/dl)	< 1.5	1.6 - 2	2.1 - 5	> 5
Hemoglobin (g/dl) female	12 -11	10.9 - 9.5	9.4 - 8	< 8
Hemoglobin change from baseline female (g/dl)	< 1.5	1.6 - 2	2.1 - 5	> 5
WBC (cell/mm^3) increase	10,800 - 15,000	15,001 - 20,000	20,001 - 25,000	> 25,000
WBC (cell/mm^3) decrease	3,500 - 2,500	2,499 - 1,500	1,499 - 1,000	< 1,000
Lymphocyte (cell/mm^3) decrease	1,000 - 750	749 - 500	499 - 250	< 250
Neutrophils (cell/mm^3) decrease	2,000 - 1,500	1,499 - 1,000	999 - 500	< 500
Eosinophils (cell/mm^3)	650 - 1,500	1,501 - 5,000	> 5,000	hypereosinophilic syndrome
Platelet (cell/mm^3) decrease	140,000 - 125,000	124,000 - 100,000	99,000 - 25,000	< 25,000
INR increase	1.1 - < 1.5 x ULN	1.5 - < 2.0 x ULN	2.0 - 3.0 x ULN	> 3.0 x ULN
Biochemistry				
ALT (increase by factor)	1.1 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
AST (increase by factor)	1.1 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
ALP (increase by factor)	1.1 - 2.0 x ULN	2.1 - 3 x ULN	3.1 - 10 x ULN	> 10 x ULN
Total Bilirubin, if LFT normal (increase by factor)	1.1 - 1.5 x ULN	1.6 - 2 x ULN	2.1 - 3.0 x ULN	> 3 x ULN
Total Bilirubin, if LFT abnormal (increase by factor)	1.1 - 1.25 x ULN	1.26 - 1.5 x ULN	1.51 - 1.75 x ULN	> 1.75 x ULN
GGT (increase by factor)	> 1.25 - 2.5 x ULN	> 2.5 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Creatinin (increase by factor)	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 2.5 x ULN	> 2.5 x ULN or dialysis required
Urinalysis*				
Protein	trace	1 +	2 +	> 2+
Glucose	trace	1 +	2 +	> 2+
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 -1 0	11 - 50	> 50 and/or gross blood	hospitalized for packed red blood cell (PRBC) transfusion

* For urinalysis the primary testing method used in the clinical trials is urine dipstick. This method of testing does not allow for precise conversion of the results of blood in urine into FDA grading. Therefore blood in urine results are reported based on dipstick scale (small + refers to ≥ 25 ery/µL, moderate ++ refers to ≥ 80 ery/µL, large +++ refers to ≥ 200 ery/µL).

APPENDIX D CASE DEFINITION FOR COVID-19 CORONAVIRUS INFECTION

WHO Case Definition (Version: March 20, 2020):

- **Suspected case**
  - A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR
  - A patient with any acute respiratory illness AND having been in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset; OR
  - A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

- **Probable case**
  - A suspect case for whom testing for the COVID-19 virus is inconclusive (inconclusive being the result of the test reported by the laboratory); OR
  - A suspect case for whom testing could not be performed for any reason.

- **Confirmed case**
  - A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

  A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:
  - Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
  - Direct physical contact with a probable or confirmed case;
  - Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR
  - Other situations as indicated by local risk assessments.

  Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

APPENDIX E UPDATED BRIGHTON COLLABORATION CASE DEFINITION FOR THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME (TTS)

(The current interim case definition, v10.16.4 dated 11 November 2021 is provided below. Please refer to https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-interim-case-definition/ for the most updated version of the case definition.)

Beginning in February, 2021, multiple European countries (e.g., Austria, Denmark, Norway, Germany, UK) and Australia have reported cases of thrombosis with thrombocytopenia syndrome (TTS) in persons who received the Astra-Zeneca (AZ) COVID-19 vaccine (1-3, 10) and more recently in the US with the Janssen vaccine (11). In May 2021, a draft interim case definition was proposed by the Brighton Collaboration. Since that time, understanding of this condition and its relationship to vaccines has evolved. Recent work by Andreas Greinacher and others now allow revision of the original case definition and level of certainty algorithm [Greinacher, 2022]. The goal of this case definition is to facilitate harmonized studies of this outcome. This supplements guidelines published by WHO provided information on case identification for treatment.

The Case Definition (CD) Level of Certainty (LOC) is determined based on a series of clinical conditions defined below.

Condition A: ☐ Platelet count <150 X 10^9/L and of new onset with no known recent exposure to heparin (within the last 30 days)

Condition B1: ☐ Presence of thrombosis/thromboembolism confirmed by ≥ 1 of the following (Check all that apply below)

☐ Imaging Study

- Ultrasound – Doppler
- CT scan – contrast / angiography
- Magnetic resonance venography or arteriography
- Echocardiogram
- Perfusion V/Q scan
- Conventional angiography / digital subtraction angiography

☐ Surgical procedure – that confirmed presence of a thrombus (e.g. thrombectomy)

☐ Pathologic examination – including biopsy or autopsy

Condition B2: ☐ Severe and persistent headache onset ≥5d post vaccination with elevated D-DIMER >8x ULN (Upper limits of normal)

Condition C: ☐ Clinical presentation suggests one of the specific clinical syndromes below? (Check the most appropriate) NOTE: the italicized signs/symptoms in brackets after each are suggestive of the syndrome but not an exhaustive list; some of them should be present. Diagnosis of the syndrome by a clinical specialist is also acceptable

☐ Cerebral venous sinus thrombosis / other Cerebral venous thrombosis (new onset of unexplained headache, often severe, typically persisting; focal cerebral dysfunction; encephalopathy; seizure; blurred vision; double vision)

☐ Deep vein thrombosis (new onset swelling usually but not always in lower extremities; localized swelling accompanied by pain [may be crampy in nature] and tenderness; reddened/discoloured/warm skin; pitting edema)

☐ Pulmonary thromboembolism (sudden onset: shortness of breath[at rest or on exertion], pleuritic chest pain [sudden, intense, sharp, stabbing or burning in nature, made worse by breathing/coughing/sneezing/laughing], cough +/- hemoptysis), tachypnea, tachycardia, arrhythmia, cyanosis, hypotension)

☐ Intra-abdominal thrombosis. (abdominal pain [may be out of proportion to physical exam findings], bloating, nausea, vomiting, diarrhea, bloody stools, ascites, hepatomegaly if hepatic vein location)

☐ Ischemic Stroke (sudden onset of focal neurologic deficits such as difficulty with speech [dysphasia or dysarthria], hemiparesis, ataxic gait abnormal eye movements, facial paresis)

☐ Myocardial infarction (chest pain [often crushing in nature], shortness of breath, arrhythmias, cyanosis, sudden death)

☐ Arterial Thrombosis

Condition D: ☐ One or more of these imaging or lab findings supportive of the diagnosis of thrombosis / thromboembolism? (Check all that apply)

☐ Echocardiogram or doppler ultrasound

☐ Computed tomography without contrast or MRI

☐ D-dimer (Elevated above upper limit of normal for age)

Condition E: ☐ At least one of these Lab findings that are strongly supportive of the diagnosis of platelet-activating antibody mediated thrombosis? (Check all that apply)

☐ D-dimer > 4 times ULN for age

☐ Positive anti-platelet factor 4 (PF4) assay: specific anti-PF4 ELISA (note: rapid tests are insensitive for these antibodies) or functional test with addition of PF4

TTS Case Definition Level of Certainty Determination

If yes to (A and B1) or yes to (A and B2): then is Level 1

If no to (B1 and B2)_and_[If yes to A plus yes to (C and E)] then is level 1

If no to (B1 and B2)_and_[If yes to A plus yes to (C and D)] then is level 2

If no to (B1 and B2)_and_[If yes to A plus [(yes to C) and (no to D and E)] then is level 3If there is insufficient information to determine the conditions needed to a level of certainty of 1, 2 or 3 then the level of certainty is level 4

If there is sufficient information to determine the conditions A, B, C, D, and E but the aggregate of the conditions do not meet the LOC 1, 2, or 3 then the LOC is Level 5; Not a Case of TTS.

APPENDIX F AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
Amendment number:	1
Amendment date:	22 May 2018
Co-ordinating author:	PPD, *Scientific Writer (XPE Pharma & Science for GSK Biologicals)*

Rationale/background for changes:

CCI

[redacted]

List of changes

On the cover page, the list of contributing authors has been updated with 4 new contributors:

- PPD ***and*** PPD, *Study Delivery Leads*
- PPD ***and*** PPD, *Clinical Safety Representatives*
- PPD ***and*** PPD *Oversight Data Managers*
- PPD ***and*** PPD, *Clinical and Epidemiology Project Leads*

In Section 5.5 Outline of study procedures, Table 3 has been updated:

Table 3 List of study procedures: Screening and primary phase (Screening Visit to Visit 17)

Type of contact	Screening Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17
Physical examination/***vital signs*** [m]	•	•	*O*	*O*	*O*	*O*	•	*O*	*O*	*O*	•	*O*	*O*	*O*	•	*O*	*O*	*O*

[m] At Screening, a physical examination should be performed based on the clinical history of the patient. Physical examination at each subsequent study visit will be performed only if the patient indicates during questioning and test result review that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate. At Screening and at each vaccination, vital signs (including

systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest) should be collected. Collected information needs to be recorded in the eCRF.

In Section 8.3.3.2.1 Assessment of intensity, additional information on intensity grading of local redness/swelling and fever has been provided:

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

Grade 0	***≤ 20 mm***
Grade 1	***> 20 mm to ≤ 50 mm***
Grade 2	***> 50 mm to ≤ 100 mm***
Grade 3	***> 100 mm***

***Fever will be scored as follows*:**

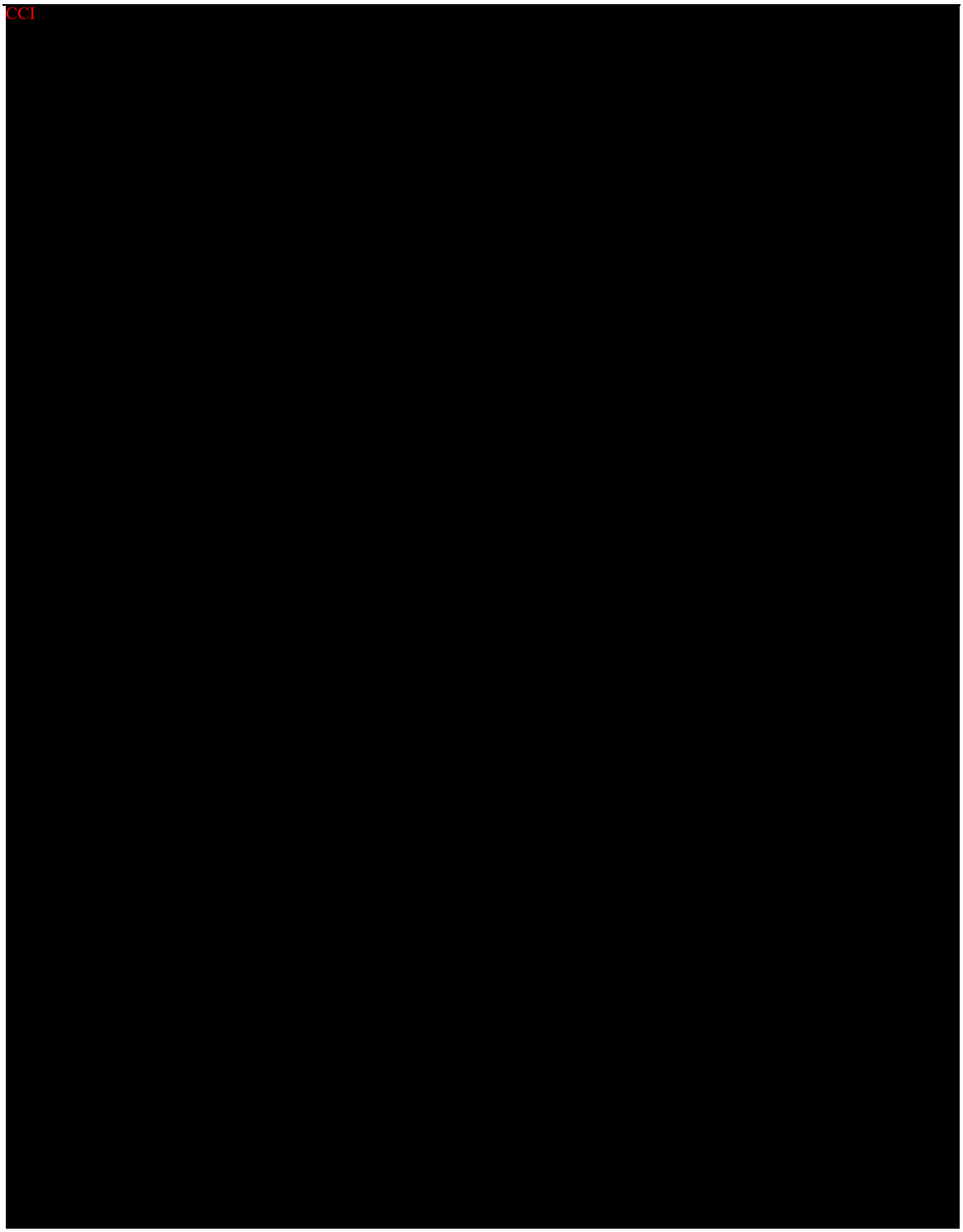
	Celsius	***Fahrenheit***
Grade 1	***38.0 to 38.4°C***	***100.4 to 101.1°F***
Grade 2	***38.5 to 38.9°C***	***101.2 to 102.0°F***
Grade 3	***≥ 39°C***	***≥ 102.1°F***

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
Amendment number:	2
Amendment date:	17 December 2018
Co-ordinating author:	PPD, *Scientific Writer (XPE Pharma & Science for GSK Biologicals)*
Rationale/background for changes:	

CCI

[redacted]

CCI



List of changes

On the cover page, the list of contributing authors has been updated:

- PPD ***and*** PPD, Clinical Research Development Lead***s***
- PPD ***and*** PPD, *Clinical Laboratory Science Representative**s**, Clinical Readout Team Leader**s***
- PPD ***and*** PPD, Laboratory Science Representative***s***, Laboratory Study Manager***s***
- PPD ***and*** PPD, Clinical Trial Supply Manager***s***,

In the Synopsis and in Section 1.2.2, 'immunogens' has been changed to 'antigens' for clarity.

Two different doses of ChAd155-hIi-HBV ($5x10^9$ and $5x10^{10}$ vp) and MVA-HBV ($2x10^7$ and $2x10^8$ pfu) will be assessed and were selected based on available clinical data with ChAd3- and MVA-based vectored vaccines using other ***antigens***.

In the Synopsis and in Section 2.2, the secondary objective related to the proof-of-principle has been clarified. The Table 26 was edited accordingly.

2) ~~If t~~***T***here is ~~at least~~ a 10-fold difference in mean ~~q~~HBsAg ***concentration*** between a vaccine group at Day 337 and the respective control group ~~(i.e. a lower limit of the 80% CI of the GMC concentration ratio > 1)~~ ***(i.e. the criterion is to observe a point estimate of at least 10-fold decrease between the groups with statistical significance, i.e., 80% CI on the ratio not including 1)***.

Table 26 Power to demonstrate a defined fold-decrease (i.e. log-difference) between two groups with CCI and CCI evaluable patients per group respectively, SD varying from 0.5 to 0.9 – one-sided alpha = 10%

***True fold* decrease**	**N per group**	**SD**	**Power**
1-log decrease (*i.e.*10-fold decrease)	CCI	0.5	100%
		0.9	97%

CCI

In the Synopsis and in Section 3, the control groups have been clarified:

- Control:
  - ~~***Group B2***~~
  - ~~***Group B3***~~
  - ~~***Group C2***~~

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.

CCI [redacted]

In the Synopsis and Section 3, an error in the timepoints for collecting blood samples for serum repository has been corrected. This is now aligned with Table 3 and Table 4:

- Blood samples for serum repository will be collected on Day 1, ~~75, 121, 136, 195, 361, 541~~ ***71, 113, 127, 183, 337, 505 and 841***.

CCI [redacted]

In the Synopsis and in Section 10.2, one secondary endpoint was adapted to be aligned with the laboratory assays:

Frequency of HBc- and HBs- specific $CD4^+$ T-cells and $CD8^+$ T-cells***;*** $CD4^+$ T-cells responder, $CD8^+$ T-cells responder~~, number of $CD4^+$ T-cells per million cells, $CD8^+$ T-cells per million cells.~~

CCI [redacted]

CCI [redacted]

The list of abbreviations has been updated:

APRI	***Aspartate Transaminase to Platelets Ratio Index***
CCLIA	***Competitive Chemiluminescent Immunoassay***
CFC	***Cytokine Flow Cytometry***
CKD-EPI	***Chronic Kidney Disease Epidemiologic Collaboration***
CLIA	***Chemiluminescent Immunoassay***
CMI	Cell-Mediated ~~Immunogenicity~~ ***Immunity***
CMIA	***Chemiluminescent Microparticle Immunoassay***
ELISA	***Enzyme Linked Immunosorbent Assay***
ES	***Exposed Set***
kPa	***KiloPascal***
METAVIR	***Meta-Analysis of Histological Data in Viral Hepatitis***
PCR	***Polymerase Chain Reaction***
Pfu	***Plaque Forming Unit***
~~**TVC**~~	~~Total Vaccinated Cohort~~

In the Glossary of Terms, the definition of menopause and post-menopause has been clarified:

Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. ~~A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.~~

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A blood sample for simultaneous follicle-stimulating hormone and estradiol levels may be collected at the discretion of the investigator to confirm non-reproductive potential.

In Section 1.1.2, clarification has been provided:

GSK Biologicals' new vaccination strategy relies on a ***heterologous*** prime-boost approach with HBV viral vector vaccines (ChAd155-hIi-HBV followed by MVA-HBV) with sequential or co-administration of $AS01_{B-4}$-adjuvanted HBc-HBs proteins.

In Section 1.2.2, justification on the cut-off of FibroTest and Fibroscan for the inclusion criteria has been provided:

Among the different available strategies, algorithms combining TE and serum biomarkers appear to be the most attractive and validated one [Leroy, 2016; Castéra, 2005]. In patients with viral hepatitis C, when TE and serum biomarkers results are in accordance, the diagnostic accuracy is increased for detecting significant fibrosis but not for cirrhosis. In cases of unexplained discordance, a liver biopsy should be performed if the results would change the patient management. ~~In this FTIH, such strategy will be adopted to exclude CHB patients with significant fibrosis and cirrhosis.~~ ***In a prospective study of chronic hepatitis C (CHC), a significant positive correlation was observed between liver stiffness as measured by FibroScan and fibrosis stages as determined by on biopsy [Ziol, 2005]. The distinctive cut-off values of 9.6 kiloPascal (kPa) and 14.5 kPa in diagnosis of extensive fibrosis (METAVIR F3) and cirrhosis (METAVIR F4), respectively. In another prospective study in CHC patients, the performance of FibroScan was compared with FibroTest, aspartate transaminase to platelets ratio index (APRI) and liver biopsy [Castéra, 2005]. FibroScan and FibroTest have shown similar accuracy in estimating the liver fibrosis staging. The best performance was obtained by combining the FibroScan and FibroTest, The most discriminant cut-off value for advanced fibrosis (METAVIR F3) were determined as 9.5 kPa and 12.5 kPa for cirrhosis (METAVIR F4). In a meta-analysis of the FibroTest diagnostic value, it was found that FibroTest had a higher or similar prognostic value compared with biopsy in patients with CHB, CHC and alcoholic liver disease (ALD) [Halfon, 2008]. In another prospective study in patients with alcoholic liver disease, FibroTest has been show to identify advanced liver fibrosis with high diagnostic accuracy [Thiele, 2018]. The cutoff score 0.58 ruled out advanced fibrosis with an negative predictive value (NPV) of 97%. In a Phase III study on the combination of several direct antiviral agents (DAAs) in treating genotype 3 chronic HCV infection with advanced liver disease, liver biopsy, Fibroscan and FibroTest plus APRI were used to define the liver fibrosis stage of the study population [Leroy, 2016]. Advanced fibrosis was defined as a METAVIR score of F3 or an Ishak score of 4 on liver biopsy, or a FibroScan ≥ 9.6 kPa but <14.6 kPa, or a FibroTest score of 0.58-0.74 plus an APRI score above 1 but below 2. Cirrhosis was defined as a METAVIR score of F4 or an Ishak score > 4 on liver biopsy, a liver stiffness value ≥14.6 kPa, or a FibroTest result ≥ 0.75 plus APRI ≥ 2. Where different testing methods yielded conflicting results, biopsy data took precedence. If biopsy data were not available, a FibroScan result took precedence over the FibroTest/APRI result. In this study, we adopt both Fibroscan and FibroTest to rule out patients with advanced liver fibrosis or cirrhosis. Only patients with FibroScan < 9.6 kPa or FibroTest score < 0.59, will be included in this FTIH study.***

In Section 1.2.2, an error has been corrected:

Route of administration: The choice of the intramuscular route for ChAd155-hIi-HBV is based on the assumption that no co-infection of natural human Adenovirus could occur at this site. Furthermore, there is a large body of data from clinical trials in humans using replication defective Ad5- and Ad6-based HIV vaccines injected intramuscularly showing an excellent safety profile, no viral shedding, and high levels of immunogenicity. MVA-~~NSmut~~***HBV*** will also be given by the intramuscular route following several studies ***on other MVA vector vaccines*** demonstrating similar immunogenicity but less local reactivity when MVA vectors were administered by the intramuscular compared to the subcutaneous route.

CCI [redacted]

The ChAd155-hIi-HBV includes a DNA sequence coding for CD74, also called the invariant chain (hIi). Since hIi is a self-antigen expressed throughout the immune system by B cells, activated T-cells, dendritic cells, monocytes and macrophages and widely expressed in the thymus, ~~it should be well tolerated~~ ***immune tolerance to this antigen should be well established.***

Single dose studies of milatuzumab in monkeys showed no adverse effects but did ***transiently*** decrease circulating B and T lymphocytes and natural killer cells [Kaufman, 2013; Christian, 2015; Martin 2015; Stein, 2007].

Nevertheless, the risk that the ChAd155-hIi-HBV vaccine induces an immune response against the hIi and a pIMD cannot be entirely ruled out. CCI [redacted]

In Section 3, information related to the ancillary TH HBV VV-031 HBS:001 study, where shedding of ChAd1555-hIi-HBV will be assessed, has been added:

- CCI [redacted]
- ***Ancillary study: To evaluate the shedding potential of the replication incompetent ChAd155-hIi-HBV vaccine, an ancillary study has been set-up and described in a separate study protocol TH HBV VV-031 HBS:001. This ancillary study will be performed on a subset of patients recruited in Step B. Biological samples (throat swab and urine samples) from these subjects will be collected at Visit 1, 2, 3, 4 and 5.***

In Section 4.2:

The authorized ALT level at screening has been clarified:

- Documented normal level of ALT as per local clinical diagnosis for at least 24 months AND at Screening test ALT ***≤ 48 U/L*** ~~< ULN~~. Small fluctuations of ALT (≤ 1.5 X ULN) are allowed provided ALT ≤ ~~<~~ 48 U/L at Screening. If no results are available, two Screening tests need to be performed at least 2 weeks apart. ULN are to be defined according to local laboratory reference range.

The inclusion criterion related to previous diagnosis of advanced liver fibrosis and cirrhosis has been clarified according to the definition provided in Section 1.2.2:

- No clinical diagnosis of advanced liver fibrosis and cirrhosis ***(F3 or F4 by METAVIR scoring system or ≥ 4 by Ishak scoring system)*** within the previous 24 months.

In Section 4.3, the exclusion criteria related to the use of immunosuppressants and to the documented evidence of other active cause of hepatitis have been updated:

- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs (including but not limited to IFN) during the period starting six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone ≥ ***10*** ~~20~~ mg/day or equivalent. Inhaled and topical steroids are allowed.
- Documented evidence of other currently active cause of hepatitis (e.g. auto-immune hepatitis ~~as per Screening test~~, primary biliary cirrhosis; primary sclerosing cholangitis, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease).

In Section 5.2.2 and 5.2.2.1.1, the minimization procedure has been clarified:

Section 5.2.2:

SBIR: ☐ **No**

☒ **Yes:** HbsAg concentration at Screening will be used as a minimization factor (<1000 IU/ml and ≥ 1000 IU/ml) ***for Step B and Step C randomization.***

Section 5.2.2.1.1:

Allocation of the patient to a study group at the investigator site will be performed using a randomization system on internet (SBIR). The randomization algorithm will use a minimization procedure ***[White, 1978]*** accounting for HbsAg concentration ***(<1000 IU/ml and ≥ 1000 IU/ml) measured*** at Screening***. The minimization procedure will be applied for patients enrolled in the steps B and C.***

After obtaining the signed and dated ICF from the patient and having checked the eligibility of the patient, the site staff in charge of the vaccine administration will access SBIR. Upon ***receiving*** the patient identification number ***and HbsAg concentration***, the randomization system will determine the study group and will provide the treatment number to be used for the first dose.

In Table 6 (Section 5.7.2) and Table 11 (Section 5.7.4.1), the hematological components to be tested as part of CBC have been clarified in the footnotes.

(CBC) includes erythrocytes, leukocytes, neutrophils, lymphocytes, eosinophils, basophils, monocytes, platelets, hemoglobin and hematocrit.

In Table 3:

- Four timepoints for the procedure "Recording of unsolicited AEs" have been added on Days 31, 87, 143 and 199.
- Four timepoints for the procedure "Recording of solicited AEs" have been added on Days 8, 64, 120 and 176.
- Two timepoints for the procedure "Blood sampling for CMI response" have been changed from Days 120 and 176 to Days 127 and 183.
- CCI [redacted]
- The blood volume to be collected for HBV, HCV, HDV and HIV serology has been changed to 18,5 ml.
- The blood volume to be collected for measurement of autoimmune antibodies has been changed to 13,5 ml.
- The symbol "~" has been added before each volume to be collected. This change was also made on Table 4.

Table 3 List of study procedures: Screening and primary phase (Screening Visit to Visit 17)

Type of contact	Screening Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17
Time points	**Day -29**	**Day 1**	**Day 3**	**Day 8**	**Day 15**	**Day 31**	**Day 57**	**Day 64**	**Day 71**	**Day 87**	**Day 113**	**Day 120**	**Day 127**	**Day 143**	**Day 169**	**Day 176**	**Day 183**	**Day 199**
Sampling time point(s)	**Screening**	**Pre**	**Post-Vacc 1**					**Post-Vacc 2**				**Post-Vacc 3**				**Post-Vacc 4**		
Biospecimen sampling																		
Blood sampling for biochemistry (~3.5 ml) [b,g,k]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Blood sampling for biochemistry (AFP) (~3.5 ml) [k]	•																	
Blood sampling for FibroTest (~8.5 ml) [k]	•																	

Type of contact	Screening Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17
Time points	**Day -29**	**Day 1**	**Day 3**	**Day 8**	**Day 15**	**Day 31**	**Day 57**	**Day 64**	**Day 71**	**Day 87**	**Day 113**	**Day 120**	**Day 127**	**Day 143**	**Day 169**	**Day 176**	**Day 183**	**Day 199**
Sampling time point(s)	**Screening**	**Pre**	**Post-Vacc 1**					**Post-Vacc 2**				**Post-Vacc 3**				**Post-Vacc 4**		
Biospecimen sampling																		
Blood sampling for hematological tests/CBC (~2.0 ml) [c,g]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood sampling for hematological tests/INR (~4.5 ml) [c,g]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood sampling for autoimmune antibodies (~***13.5*** ~~8.5~~ ml)	●																	
Blood sampling for HBV, HCV, HDV and HIV serology (~***1***8.5 ml)	●																	
Blood sampling for qHBsAg (~3.5 ml)	●	●				●	●			●	●			●	●			●
Blood sampling for HBV-DNA and new viral markers (~10 ml)	●					●	●			●	●			●	●			●
Blood sampling for CMI response (~20 ml) [d]		●			●		●	●	●		●	●	●		●	●	●	
Blood sampling for humoral response to HBV antigens (~3.5 ml) [e]		●			●				●		●		●				●	
CCI [redacted]																		
Blood sampling for serum repository (~3.5 ml)		●							●		●		●				●	

Type of contact	Screening Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17
Time points	**Day -29**	**Day 1**	**Day 3**	**Day 8**	**Day 15**	**Day 31**	**Day 57**	**Day 64**	**Day 71**	**Day 87**	**Day 113**	**Day 120**	**Day 127**	**Day 143**	**Day 169**	**Day 176**	**Day 183**	**Day 199**
Sampling time point(s)	**Screening**	**Pre**	**Post-Vacc 1**					**Post-Vacc 2**				**Post-Vacc 3**				**Post-Vacc 4**		
Biospecimen sampling																		
Safety assessment																		
Recording of unsolicited AEs within 30 days post-vaccination (Day 1-30)		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of solicited AEs (Days 1-7 post-vaccination) self-reported by the patient		●	●	●			●	●			●	●			●	●		

Table 4 List of study procedures: primary phase (Visit 18 to Visit 22), follow-up phase (Visit 23 to Visit 26) and unscheduled visits

Type of contact	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	Visit 26	Unscheduled visit
Time points	**Day 225**	**Day 253**	**Day 281**	**Day 309**	**Day 337**	**Day 421**	**Day 505**	**Day 673**	**Day 841**	
Sampling time point(s)	**Post-Vacc 4**									
Biospecimen sampling										
Blood sampling for biochemistry (~3.5 ml) [a, h,i]	●	●	●	●	●	●	●	●	●	●
Blood sampling for biochemistry (AFP) (~3.5 ml) [i]					●		●		●	
Blood sampling for FibroTest (~8.5 ml) [i]					●		●		●	
Blood sampling for hematological tests/CBC (~2.0 ml) [b, h]	●	●	●	●	●	●	●	●	●	●
Blood sampling for hematological tests/INR (~4.5 ml) [b,h]	●	●	●	●	●	●	●	●	●	●
Blood sampling for qHBsAg (~3.5 ml)	●	●	●	●	●	●	●	●	●	
Blood sampling for HBV-DNA and new viral markers (~10 ml)	●	●	●	●	●	●	●	●	●	
Blood sampling for CMI response (~20 ml) [c]					●		●		●	
Blood sampling for humoral response to HBV antigens (~3.5 ml) [d]					●		●		●	
Blood sampling for serum repository (~3.5 ml)					●		●		●	
Urine sampling for urine chemistry (dipstick) [e]	●	●	●	●	●					

Table 4 List of study procedures: primary phase (Visit 18 to Visit 22), follow-up phase (Visit 23 to Visit 26) and unscheduled visits

Type of contact	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	Visit 26	Unscheduled visit
Time points	Day 225	Day 253	Day 281	Day 309	Day 337	Day 421	Day 505	Day 673	Day 841	
Sampling time point(s)	Post-Vacc 4									

In Section 5.6.5, information on the high barrier to resistance treatment to be collected has been clarified:

- ***History and ongoing*** ~~Current~~ treatment with ***high barrier to resistance Nas, e.g.*** ETV, TDF or TAF (drug name, route, start date and end date, if applicable),

In Section 5.6.12, the blood volumes to be collected for the measurement of autoimmunes antibodies and for viral serology have been changed to 13.5 ml and 18.5 ml, respectively. The total volume of blood across the full study period, the highest volume per visit and the highest volume over a 8-week period have been adapted.

- Autoimmune antibodies: ~~8.5~~***13.5*** ml,
- Viral serology (HBV, HCV, HDV and HIV): ~~8.5~~***18.5*** ml,

The volume of blood to be collected from each patient during the 2.5 year study period (from Screening to Day 841) is approximately ***883.5*** ~~875.5~~ ml. Among all visits, the highest volume of blood on a single visit will be approximately ***64*** ~~51~~ ml ***(on Day -29)*** and the highest volume of blood over 8-week will be approximately ***186*** ~~145~~ ml ***(from Day 57 to Day 113)***, which are below the safe limits as recommended by the WHO [Howie, 2011].

In Table 6 (Section 5.7.2),

- Two timepoints for the blood sampling for CMI response have been changed from Days Visit 11 and Visit 15 to Visit 12 and Visit 16.
- CCI [redacted]
- The blood volume to be collected for HBV, HCV, HDV and HIV serology has been changed to 18,5 ml.
- The blood volume to be collected for measurement of autoimmune antibodies has been changed to 13,5 ml.
- The symbol "~" has been added before each volume to be collected.

Table 6 Biological samples

Sample type	Component	Time point	Quantity	Unit	Cohort/subset
Blood	HBV, HCV, HDV and HIV serology	Screening	~~8.5~~***18.5***	ml	All patients
	Autoimmune antibodies	Screening	~~8.5~~***13.5***	ml	
	Biochemistry (FibroTest) *	Screening, Visit 22, Visit 24 and Visit 26	~8.5	ml	
	Biochemistry (AFP) *	Screening, Visit 22, Visit 24 and Visit 26	~3.5	ml	
	Biochemistry (ALT, AST, ALP, GGT, Bilirubin and Creatinine) *	All visits	~3.5	ml	
	Hematology (CBC) **	All visits	~2.0	ml	
	Hematology (INR)	All visits	~4.5	ml	
	HBV-DNA and new viral markers	Screening, Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14 Visit 17, Visit 18, Visit 19, Visit 20, Visit 21, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26	~10	ml	
	qHBsAg	Screening, Visit 1, Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 19, Visit 20, Visit 21, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26	~3.5	ml	
	CMI response	Visit 1, Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, ~~Visit 11~~, ***Visit 12,*** Visit 14, ~~Visit 15~~, ***Visit 16***, Visit 22, Visit 24 and Visit 26	~20	ml	
	Humoral response to HBV antigens	Visit 1, Visit 4, Visit 8, Visit 10, Visit 12, Visit 16, Visit 22, Visit 24 and Visit 26	~3.5	ml	
	CCI				
	Serum repository	Visit 1, Visit 8, Visit 10, Visit 12, Visit 16, Visit 22, Visit 24 and Visit 26	~3.5	ml	
CCI					
Urine	Urine chemistry	All visits up to Visit 22 included.	NA	NA	

Information in Table 7, Table 8, Table 9 and Table 10 has been presented so that it is now aligned with internal standards:

Hematology, biochemistry***, autoimmune antibodies*** and urine chemistry assessments will be performed at GSK Biologicals or at a laboratory designated by GSK Biologicals using commercial tests (see Table 7).

Table 7 Hematology, biochemistry, autoimmune antibody and urine tests

System	Discipline	Component	Method	Scale	Laboratory
Whole blood	Hematology	~~CBC~~***Erythrocytes (Red Blood Cells)***	As per Q² Solutions practice	***Quantitative***	Q² Solutions
		Leukocytes (White Blood Cells)		***Quantitative***	
		Neutrophils		***Quantitative***	
		Lymphocytes		***Quantitative***	
		Eosinophils		***Quantitative***	
		Basophils		***Quantitative***	
		Monocytes		***Quantitative***	
		Platelets		***Quantitative***	
		Hemoglobin		***Quantitative***	
		Hematocrit		***Quantitative***	
		~~INR~~ ***Prothrombin Time International Normalised Ratio (INR)***		***Quantitative***	
Serum	Biochemistry	~~ALT, AST, ALP, GGT, Bilirubin and Creatinine~~ ***Alanine Aminotransferase (ALT)***		***Quantitative***	
		Aspartate Aminotransferase (AST)		***Quantitative***	
		Alkaline Phosphatase (ALP)		***Quantitative***	
		Gamma Glutamyl Transferase (GGT)		***Quantitative***	
		Total Bilirubin		***Quantitative***	
		Creatinine		***Quantitative***	
		~~AFP~~ ***Alpha-fetoprotein***		Quantitative	
		FibroTest		Quantitative	
	Autoimmune antibodies	Antinuclear antibodies (ANAs)		Qualitative	
		Smooth-muscle antibodies (SMAs)		Qualitative	
		Liver-kidney microsomal ~~type~~ 1 ***Ab.IgG*** (LKM-1)		Qualitative	
		Anti-liver cytosol 1 (anti LC1) antibodies		Quantitative	

Table 8 HBV, HCV, HDV and HIV serology and HBV virology assays

System	Discipline	Component	Method	~~Kit/ manufacturer~~	~~Unit~~	~~Cut-off~~	Scale	Laboratory
Serum	HBV serology	Hepatitis B Virus.Surface Ab ***(Anti-HBs)*** [a]	***CMIA***	~~Alinity anti-HBs (Abbott)~~	~~mIU/mL~~	~~10~~	Ordinal	CEVAC
		Hepatitis B Virus.Surface Ag (qHBsAg)	~~Architect HbsAg assay~~ ***CMIA***	~~N/A~~	~~IU/ml~~	~~0.05~~ [e]	Quantitative	
		Hepatitis B Virus.e Ag (HbeAg)[a]	~~As per Q[2] Solutions practice~~ ***CLIA***	~~N/A~~	~~N/A~~	~~0.8~~	Qualitative	Q^2 Solutions
		Hepatitis B Virus.Core Ab ***(Angi-HBc)*** [a]	~~As per Q[2] Solutions practice~~ ***CMIA***	~~N/A~~	~~N/A~~	~~0.5~~	Qualitative	
		Hepatitis B Virus.e Ab (Anti-Hbe)[a]	~~As per Q[2] Solutions practice~~ ***CCLIA***	~~N/A~~	~~N/A~~	~~0.8~~	Qualitative	
	HCV serology	***Hepatitis Virus C Ab*** (Anti-HCV) [a]	~~As per Q[2] Solutions practice~~ ***CMIA***	~~N/A~~	~~N/A~~	~~0.8~~	Qualitative	Q^2 Solutions
	HDV serology	***Hepatitis Virus D Ab*** (Anti-HDV)[a]	~~As per Q[2] Solutions practice~~ ***ELISA***	~~N/A~~	~~N/A~~	~~0.9~~	Qualitative	Q^2 Solutions
	HIV serology	***Human Immunodeficiency Virus Ab*** (Anti-HIV) [a]	~~As per Q[2] Solutions practice~~ ***CMIA***	~~N/A~~	~~N/A~~	~~1~~ ~~N/A~~	Qualitative	Q^2 Solutions
	HBV virology	***Hepatitis B Virus DNA*** (HBV DNA)	***QPCR*** ~~Cobas® HBV assay~~	~~N/A~~	~~IU/mL~~	~~10~~	Quantitative	DDL Diagnostic Laboratory
		HBV DNA whole sequencing[b]	Sequencing	~~N/A~~	~~N/A~~	~~N/A~~	N/A	

[a] This test will be performed at Screening only.

[b] This test will be performed in case of virological breakthrough.

~~[e] This cut-off will be used at Screening. For other time points, the cut-off might change based on supplementary validation experiments.~~

The cut-off for HBV DNA measured by qPCR will be 10 IU/mL.

Table 9 Humoral Immunity (Antibody determination)

System	Component	Method	~~Kit / Manufacturer~~	~~Unit~~[a]	~~Cut-off~~[a]	Laboratory [ba]
Serum	~~Anti-HBs Ig tot~~ ***Hepatitis B Virus.Surface Ab***	CLIA	~~ADVIA Centaur anti-HBs2 (Siemens Healthcare)~~	~~mIU/ml~~	~~6.2~~	GSK Biologicals' laboratory or laboratory designated by GSK
	~~Anti-HBc~~ ***Hepatitis B Virus Core Ab***	To be developed [dc]	~~TBD~~	~~TBD~~	~~TBD~~	
	CCI [redacted]					

~~[a] Assay cut-off and unit might be subject to change during the course of the study (e.g. in case of requalification, revalidation or standardization). In this case, this will be documented in the clinical report.~~

~~[ba]~~ GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium or Marburg, Germany. Refer to APPENDIX B for the laboratory addresses.

~~[bc]~~ Exploratory test that will be performed depending on availability of assays and scientific relevance.

~~[cd]~~ This assay will be developed in the course of the study.

Table 10 Cell mediated immunity

System	Component	Challenge	Method	~~Unit~~	Laboratory[a]
PBMC	(HBs-specific ($CD4^+$/$CD8^+$) T-cells)	HBs peptide pool	***CFC*** ~~ICS~~	~~Events per million T-cells~~	GSK Biologicals' laboratory or laboratory designated by GSK
	HBc-specific ($CD4^+$/$CD8^+$) T-cells	HBc peptide pool	***CFC*** ~~ICS~~	~~Events per million T-cells~~	
	CCI [redacted]				

In Section 5.7.3, corrections have been made:

CCI [redacted]

In Table 12, timepoints for evaluating HbsAg CCI [redacted] have been adapted and the priority ranks were deleted:

Table 12 Evaluation of serum HBV antigens

Sample type	Type of contact and time point	Study group	No Patients	Component	Components priority rank
Serum	***Screening,*** Visit 1, Visit 5, Visit 6, Visit 9, Visit 10, Visit 13, Visit 14, Visit 17, Visit 18, Visit 19, Visit 20, Visit 21, Visit 22, Visit 23, Visit 24, Visit 25 and Visit 26	All study groups	CCI [redacted]	HbsAg	1
CCI [redacted]					
CCI [redacted]					

Table 14 Evaluation of humoral immunogenicity

Type of contact and time point	Sub groups	No. patients	Component	Components priority rank
Visit 1, Visit 4, Visit 8, Visit 10, Visit 12, Visit 16, Visit 22, Visit 24 and Visit 26	All study groups	CCI	Anti-HBc	2
			Anti-HBs Ig total	1
CCI				

In Table 15:

- Two timepoints for the blood sampling for CMI response have been changed from Days Visit 11 and Visit 15 to Visit 12 and Visit 16.
- CCI

Table 15 Evaluation of cell-mediated immunogenicity

Type of contact and time point	Sub groups	No. patients	Component	Components priority rank
Visit 1, Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, Visit ~~11~~***12***, Visit 14, Visit ~~15~~***16***, Visit 22, Visit 24 and Visit 26	All study groups	CCI	HBc-specific ICS ($CD4^+/CD8^+$) T-cells	1
			HBs-specific ICS ($CD4^+/CD8^+$) T-cells	2
CCI				

CCI

In Section 6.4, the wording related to disposal of the dressing has been adapted:

After each vaccination, the injection site will be covered with a dressing in order to absorb any virus that may leak out through the needle track. The dressing will be removed only after 30 minutes and will be disposed as GMO waste~~ by autoclaving or~~ in accordance with the applicable guidelines/standard operating procedures at the investigator's site.

In Section 6.7.1, Nas with high barrier to resistance have been added to the list of concomitant medications to be recorded:

- ***Nucleos(t)ide analogues with high barrier to resistance (e.g. ETV, TDF, TAF) that the patient takes to control chronic hepatitis B.***

In Section 6.7.2, the daily dose of prednisone that may lead to elimination from the per-protocol analyses has been changed from 20 mg to 10 mg:

- 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 ≥ ~~20~~ ***10*** mg/day or equivalent. Inhaled and topical steroids are allowed.

In Section 8.5.3, a mistake in the ALT level has been corrected:

- Patients with confirmed ALT within 144 - ~~239~~ ***240*** U/L (*i.e.* > 3 to ≤~~<~~ 5 X ULN) and INR > 1.5 (repeated testing preferably within 48-72 hours) will be withdrawn from vaccination. If the result is not confirmed, tests will be repeated until ALT level decreases to < 72 U/L (*i.e.* < 1.5 X ULN) and INR decreases to < 1.15. Patients with ALT < 72 U/L (*i.e.* < 1.5 X ULN) and INR < 1.15 will be eligible for the next vaccine administration.

In Section 8.8.2, a footnote has been added to Figure 3 to provide additional information on the staggered enrolment.

For the second dose vaccination, there will be at least 8 days apart between the initially recruited subjects (i.e. CCI ***and the remaining subjects within in each step***

In Section 8.8.3.2, the wording related to the risk assessment for holding rules has been clarified:

Figure 5 and Figure 6 present the probability of not meeting defined holding rule for CCI CCI patients per study group, respectively.

The above Figure 5 illustrates that, with CCI patients in a group:

- **For holding rules *1 and 3*, using a cut-off of** CCI, there is around 90% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 35% and around 60% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 10%.
- **For holding rule *2*, using a cut-off of** CCI**,** there is only around 60% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 35% and around 90% chance that the holding rule is not met in a vaccine group if the corresponding event has true incidence rate of 10%.

The above Figure 6 illustrates that, with CCI patients in a group:

- **For holding rules *1 and 3*, using a cut-off of** CCI, there is around 88% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 10% and around 45% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 5%.

- **For holding rules ~~2~~, using a cut-off of CCI, there is around 90% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 20% and around 10% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 20%.
- **For holding rules ~~2~~, using a cut-off of CCI, there is around 70% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 30% and ***there is around 96% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 10%.*** ~~Around 30% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 30%.~~

The above Figure 7 illustrates that, with CCI patients in a group:

- **For holding rules *1 and 3*, using a cut-off of CCI, there is around 90% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 5% and around 10% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 5%.
- **For holding rules ~~2~~, using a cut-off of CCI, there is around 90% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 10% and around 10% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 10%.
- **For holding rule *2*, using a cut-off of CCI, there is around 90% chance that the holding rule is met in a vaccine group if the corresponding event has a true incidence rate of 35% and ***there is around 99% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 10%.*** ~~Around 10% chance that the holding rule is not met in a vaccine group if the corresponding event has a true incidence rate of 35%.~~

In Section 10.5.1, 10.5.2, 10.8 and 10.9, the naming of the cohort has been aligned with CDISC requirements (i.e. TVC was changed to Exposed Set [ES] and ATP was changed to Per Protocol Set [PPS]).

Section 10.5.1:

10.5.1 ***Exposed Set*** ~~Total vaccinated cohort~~

The ~~Total vaccinated cohort~~ ***Exposed set*** (~~TVC~~***ES***) will include all patients with study vaccine administration documented:

- A **safety/reactogenicity** analysis based on the ~~TVC~~ ***ES*** will include all patients who received at least one vaccine dose.
- An **efficacy/immunogenicity** analysis based on ~~TVC~~ ***ES*** will include all vaccinated patients for whom efficacy/immunogenicity data are available.

The ~~TVC~~ ***ES*** analysis will be performed per treatment actually administered at Dose 1.

Section 10.5.2:

The per-protocol cohort for efficacy/immunogenicity will include all evaluable patients, *i.e.*, those who were included in the ~~TVC~~ ***ES*** and:

Section 10.8:

The analysis will be performed the same way for each step A, B or C. The primary analysis will be performed on the per-protocol cohort for efficacy/immunogenicity and if, in any study group, the percentage of vaccinated patients with serological results excluded from the per-protocol cohort is at least 15%, a second analysis will be performed on the ~~TVC~~ ***ES***.

Section 10.9:

The analysis will be performed the same way for each step A, B or C including patients from the ~~TVC~~ ***ES***.

In Section 10.6, the sentence related to cut-off presentation was deleted for alignment with changes in Table 8 and 9:

- Immunogenicity
  - ~~The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3.~~
  - A seronegative patient is a patient whose titre is below the cut-off value.

In Section 10.8.1, statistical analysis of CMI has been added:

- ***CMI results will be presented by group using descriptive statistics (N, geometric mean [GM], min, Q1, median, Q3, max).***

In Section 10.8.1, the possibility to perform additional statistical analyses has been mentioned:

If sufficient patients are available for the analysis, additional descriptive analysis may be performed by categories of baseline HbsAg concentration and HBV genotype.

In Section 10.9.1, the wording related to 2 safety analyses has been corrected/adapted:

- The number of patients who experienced **FibroScan TE score ≥ *9.6* ~~8.1~~ kPa and FibroTest score ≥ 0.59** at Day 337, 505 and 841 will be reported.
- The number of patients who ***developed hepatocellular carcinoma*** ~~experienced~~ ~~**liver mass** on liver imaging examination and/or **α-fetoprotein > 50 mg/ml**~~ at Day 337, 505 and 841 will be reported.

In Section 12 Country specific requirements, a new subsection for France (Section 12.2) has been added:

Section 12.2. France

This section includes requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information applicable to the study.

1. ***Concerning the « SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA»***

- ***The following vulnerable subject populations will be excluded: minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.***
- ***A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code law L.1121-8-1). (exception for a participant to a non-interventional study if authorised by the Ethics Committee). It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:***
  - ***is either affiliated to or beneficiary of a social security category;***
  - ***has got an authorisation by the Ethics Committee.***

2. ***Concerning the "STATISTICAL CONSIDERATIONS AND DATA ANALYSES" and specially in the "SAMPLE SIZE ASSUMPTIONS"***

The expected number of subjects to be recruited in France is declared to the French regulatory authority.

3. ***Concerning the "STUDY GOVERNANCE CONSIDERATIONS"***

- ***In section "Regulatory and Ethical Considerations, including the Informed Consent Process"***
  - ***Concerning the process for informing the subject and/or his/her legally authorized representative, the following text is added:***

  French Patient Informed Consent Form is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent in triplicate (quadriplicate for minor subject). It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee and the maintenance of confidentiality of the returned consent form by GlaxoSmithKline France.

  - ***Concerning the process for obtaining subject informed consent:***

  When a research involving human being is carried out on a minor / on an adult in the care of a "tutelle" guardian, consent is given by their legal representative and, if the committee mentioned in article L. 1123-1 considers that the research in question, because of the seriousness of the restraints or the specificity of the medical acts involved, entails a serious risk of affecting their private life or the integrity of their body, consent is given by the family council if it has been instated, or by the judge of "tutelle" guardians.

When research involving human being is carried out on an adult in the care of a "curatelle" guardian, consent is given by the subject assisted by his guardian. However, if the adult in the care of a "curatelle" guardian is invited to participate in research which the committee mentioned in article L. 1123-1 considers, because of the seriousness of the restraints or the specificity of the medical acts involved, to entail a serious risk of affecting their private life or the integrity of their body, the matter is submitted to the judge of guardians who decides whether the adult is capable of giving her/his consent. In the case of incapacity, the judge will decide whether or not to authorise the research involving human being.

- ***Concerning the management of the Patient Informed Consent Forms, the following text is added:***

The first copy of the Patient Informed Consent Form is kept by the investigator. The second copy is kept by the Medical Director of GlaxoSmithKline France and the last copy(ies) is(are) given to the subject or their legally authorized representative(s).

The second copy of all the consent forms will be collected by the Clinical Research Assistant (CRA) under the Investigator's control, and placed in a sealed envelope bearing only:

- ***the study number,***
- ***the identification of the Centre: name of the principal investigator and centre number,***
- ***the number of informed consents,***
- ***the date,***
- ***and the principal investigator's signature.***

Then, the CRA hands the sealed envelope over to the Medical Director, for confidential recording, under the responsibility of the Medical Director.

- ***NOTIFICATION TO THE HOSPITAL DIRECTOR***

In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

- ***INFORMATION TO THE HOSPITAL PHARMACIST***

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

4. Concerning the " DATA MANAGEMENT " the following text is added:

- ***Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GlaxoSmithKline data bases by GlaxoSmithKline Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Data Protection French Law n° 78-17 of 6th January 1978, each of these people aforesaid has a right of access, correction and opposition on their own data through GlaxoSmithKline Laboratory (Clinical Operations Department).***
- ***DEMOGRAPHIC DATA***

In accordance with the Data Protection French Law n° 78-17 of 6th January 1978 – article 8, the ethnic origin can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- ***TESTING OF BIOLOGICAL SAMPLES***

In accordance with the French Public Health Code law – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

5. Monitoring visits

The Health Institution and the Investigator agree to receive on a regular basis a Clinical Research Assistant (CRA) of GLAXOSMITHKLINE or of a service provider designated by GLAXOSMITHKLINE. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GLAXOSMITHKLINE or from a service provider designated by GLAXOSMITHKLINE. In addition, the Health Institution and the Investigator agree that the CRA or the service provider designated by GLAXOSMITHKLINE have direct access to all the data concerning the Study (test results, medical record, etc …). This consultation of the information by GLAXOSMITHKLINE is required to validate the data registered in the electronic Case Report Form (eCRF), in particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

6. Data entry into the eCRF

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's electronic Case Report Form (eCRF) use here below:

The Health Institution and the Investigator undertake:

- ***That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the***

electronic Case Report Form (eCRF) of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.

- ***That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.***
- ***That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.***
- ***To keep the IT Equipment and/or access codes in a safe and secure place and to authorize only the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.***
- ***To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.***
- ***To return at the end of the Study the IT Equipment and/or access codes to GLAXOSMITHKLINE or to any company designated by GLAXOSMITHKLINE and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.***

7. CTR publication

It is expressly specified that GLAXOSMITHKLINE and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GLAXOSMITHKLINE GROUP named Clinical Trial Registred (CTR) including the registration of all the clinical trials conducted by the GLAXOSMITHKLINE Group and this before or after the publication of such results by any other process.

8. Data Protection French Law of 6th January 1978 (CNIL)

In accordance with the Data Protection French Law of 6 January 1978, computer files used by GLAXOSMITHKLINE to monitor and to follow the implementation and the progress of the Study are declared with CNIL by GLAXOSMITHKLINE. The Investigator has regarding the processing data related to her/him a right of access, of rectification and of opposition with GLAXOSMITHKLINE in accordance with the legal provisions. This information can be transferred or be accessed to other entities of GLAXOSMITHKLINE Group, what the Investigator agrees by the signature of the present Protocol.

9. Investigational Product Accountability, Reconciliation, and Destruction

In specific situations (if the site has 1- an approval from the French Regulatory Agency (ANSM) and 2- a GSK written endorsement letter) where institutional practices dictate that the site disposes of and/or destroys IP prior to allowing the "monitor' to verify and document IP accountability, the following applies:

"During the conduct of the Study, Investigational Product (IP) will be destroyed by the Institution prior to a GlaxoSmithKline "monitor" conducting final investigational product accountability. Institution agrees that such destruction will comply with Institution's investigational product accountability procedures and will provide GlaxoSmithKline with investigational product accountability logs and supporting documentation to verify adherence to 'Bonnes Pratiques Cliniques' (decision dated on the 24th of November 2006).

In Section 13, references have been added:

Halfon P, Munteanu M & Poynard T. FibroTest-ActiTest as a non-invasive marker of liver fibrosis. Gastroenterol Clin Biol. 2008;32(6 Suppl 1):22-39.

Thiele M, Madsen BS, Hansen JF, et al. Accuracy of the enhanced liver fibrosis test vs FibroTest, elastography, and indirect markers in detection of advanced fibrosis in patients with alcoholic liver disease. Gastroenterology. 2018;154(5):1369-1379.

White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer. 1978;37:849-857.

Ziol M, Handra-Luca A, Kettaneh A, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology. 2005;41:48-54.

In Appendix A Laboratory assays:

- Mentions of "Architect" assay were removed. The Abbott platform to be used for measurement of HbsAg may either be the "Architect" or the "Alinity". Referring to the "Abbott" platform covers both options.
- Mention of the 'Lumipulse G' assay has been removed.
- Description of the CFC assay has been added.

4. qHBsAg – ~~Architect~~ HbsAg assay (Abbott)

The ~~architect~~ ***Abbott*** HbsAg assay is a two-step immunoassay using chemiluminescent paramagnetic microparticles (CMIA) technology for the quantitative determination of HbsAg. In the first step, sample is mixed with microparticles coated with anti-HBs; antibody-antigen will form if HbsAg is present in the sample. In the second step, acridium-labeled anti-HBs conjugate is added. A direct relationship exists between the amount of HbsAg present in the sample and the RLU detected by the system.

5. qHBsAg – ~~Architect~~ HbsAg assay (Abbott) with pre-treatment

Immune complexes (Ag-Ab complexes) can be present in the sample. Those immune complexes can interfere with the HbsAg dosage. In order to avoid this interference, sample is pre-treated with ~~Sodium Thiocyanate (NaSCN),~~ a chaotropic agent that dissolves the immune complexes. After this pre-treatment, sample is used as described in the previous section.

6. CCI [redacted]

11. CFC Assay

This assay is applied to measure the frequency of antigen-specific T-lymphocytes in peripheral blood. Blood samples are collected by venipuncture and PBMCs are prepared by certified laboratories by centrifugation onto a Lymphoprep™ cushion within 24 hours following collection. PBMC suspensions are stored in liquid nitrogen until analysis. To measure T-cell responses elicited by the vaccine candidate, samples are thawed and cultured overnight in the presence of costimulatory antibodies (anti-CD28 and anti-CD49d) without stimulation (background control) or with peptide pools (15mer overlapping by 11) covering the sequence of the relevant antigens (HBs, HBc, CCI [redacted] ***Cells are then immunostained for surface phenotypic markers (CD4 and CD8), permeabilized and then immunostained for CD3 and activation markers (the costimulatory molecules CD40L and 4-1BB and the cytokines IL-2, IFN-γ, TNF-α, IL-13, IL-17). Analysis is performed by multiparametric flow cytometry, and the results are expressed after background subtraction as frequencies of antigen specific CD4+ (or CD8+) T-cells producing various combinations of the activation markers assessed per million CD4+ (or CD8+) T-cells.***

In Appendix C Toxicity grading for hematology and biochemistry parameters, an error has been corrected:

Platelet (cell/mm^3) decrease	~~14,000~~***140,000*** - 125,000	124,000 - 100,000	99,000 - 25,000	< 25,000

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
Amendment number:	3
Amendment date:	6 August 2019
Co-ordinating author:	PPD, *Scientific Writer (Modis for GSK Biologicals)*

CCI

[redacted]

List of changes

On the cover page, the list of contributors has been updated:

- PPD ***and*** PPD, *Clinical Safety Representatives*
- PPD ***and*** PPD, *Study Data Managers*
- PPD ***and*** PPD, *Public Disclosure Representatives*

On the Sponsor Information page, information related to contact details for emergency unblinding have been added:

1. **GSK Biologicals' Central Safety Physician On-Call Contact information for Emergency Unblinding**

GSK Biologicals Central Safety Physician Phone contact: refer to protocol Section 5.3.1.

In the list of abbreviations, he following abbreviations were removed because not used in the text:

~~**Th1**~~	~~T-helper Type 1~~
~~**UPR**~~	~~Unfolded Protein Reponse~~

In Section 1.3.1.4, minor edits was made for alignment with the changes in the eligibility criteria:

Considering the risk of hepatic failure that may be triggered by vaccine-induced immune response, this FTIH will be conducted in CHB adult (18-65 years of age) patients at low risk of hepatitis flares, i.e. in those patients under NA therapy since at least 24 months, well-controlled (HBV DNA suppressed and alanine transaminase [ALT] normalized ***within the past*** ~~since at least~~ 24 months) and with no advanced liver fibrosis or cirrhosis of any stage.

In Section 3 and in the Synopsis, correction regarding blinding in Epoch 001 (Screening) was made:

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

In Section 3 and in the Synopsis, the following clarification has been provided:

Safety monitoring: Internal Safety Review Committee (iSRC). ***An external expert with 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***.

In Section 4.2, the following inclusion criterion was modified:

- Documented HBV viral suppression as per local clinical diagnosis ~~for at least~~ ***within the previous*** 24 months AND at Screening test HBV DNA < 10 IU/ml. If no results are available, two Screening tests need to be performed at least 2 weeks apart. Small fluctuations of HBV DNA (≤ 100 IU/ml) are allowed provided HBV DNA is < 10 IU/ml at Screening and was clearly not rising during the previous 24 months.
- Documented normal level of ALT as per local clinical diagnosis ~~for at least~~ ***within the previous*** 24 months AND at Screening test ALT ≤ 48 U/L. Small fluctuations of ALT (≤ 1.5 X ULN) are allowed provided ALT ≤ 48 U/L at Screening. If no results are available, two Screening tests need to be performed at least 2 weeks apart. ULN are to be defined according to local laboratory reference range.

- No clinical diagnosis of ~~advanced liver fibrosis and~~ cirrhosis (e.g. ~~F3 or~~ F4 by METAVIR scoring system or ≥ 6 by Ishak scoring system) within the previous 24 months.

In Section 4.3, the following eligibility criteria were modified:

- Medical history of ~~advanced fibrosis and~~ cirrhosis.
- Suspicion of or confirmed HCC or any other liver cancer in medical history or at Screening:
  - Elevated α-fetoprotein > 50 ~~mg~~ ***ng***/ml.
- Hematology and biochemistry parameters outside normal clinical range at Screening:

  Hematology:

  - Hemoglobin < 12.0 g/dl (for females) or < 13.~~8~~***5*** g/dl (for males)

  INR > ~~1.15~~ ***1.2***
- Body Mass Index (BMI) > ~~30~~ ***35*** kg/m² at Screening.

A new section (Section 5.3.1) on emergency unblinding was added:

Unblinding a participant's individual intervention number should occur ONLY in case of a medical emergency when knowledge of the intervention is essential for the clinical management or welfare of the participant.

The emergency unblinding process enables the investigator to have unrestricted, immediate and direct access to the participant's individual study intervention via SBIR, an automated Internet-based system.

As back up process, the investigator has the option of contacting a GSK Biologicals' Helpdesk (refer to the Table 3) if he/she needs help performing the unblinding (i.e. he/she cannot access the automated Internet-based system).

A non-investigator physician (e.g. physician from emergency room) or participant/care giver/family member may also request emergency unblinding either via the investigator (preferred option) or via the GSK Biologicals' Helpdesk (back up process).

Where applicable, the patient/participant card lists contact information for both the investigator and GSK Biologicals' Helpdesk.

Table 3 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email Phone: +32.2.656.68.04 Fax: +32.2.401.25.75 E-mail: rix.ugrdehelpdesk@gsk.com

In Section 8.5.3, abnormal parameters related to INR have been adapted to reflect the changes in eligibility criteria:

- Patients with confirmed ALT within 144 - 240 U/L (*i.e.* > 3 to ≤ 5 X ULN) and INR > 1.5 (repeated testing preferably within 48-72 hours) will be withdrawn from vaccination. If the result is not confirmed, tests will be repeated until ALT level decreases to < 72 U/L (*i.e.* < 1.5 X ULN) and INR decreases to < ~~1.15~~ ***1.2***. Patients with ALT < 72 U/L (*i.e.* < 1.5 X ULN) and INR < ~~1.15~~ ***1.2*** will be eligible for the next vaccine administration.

In Section 8.8.1, the following paragraph has been added:

An external (non-GSK) expert with 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.

In Section 10.11.1, the following clarification was made:

Stepwise safety analyses for iSRC review will be done as described in Section 8.8.1. These analyses will be performed by project independent statistician in order to keep GSK study team blinded ***as much as possible until*** ~~up to~~ the end of the defined step procedures.

In Appendix C, the lab value for toxicity grading of eosinophils was corrected (typo error) and a footnote related to blood in urine analysis was added:

Eosinophils (cell/mm^3)	~~600~~ ***650*** - 1,500	1,501 - 5,000	> 5,000	hypereosinophilic syndrome
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 -1 0	11 - 50	> 50 and/or gross blood	hospitalized for packed red blood cell (PRBC) transfusion

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
Amendment number:	4
Amendment date:	29 April 2020
Co-ordinating author:	PPD , Scientific Writer (Modis for GSK Biologicals)

CCI

[redacted]

CCI [redacted]

List of changes

On the cover page, the list of contributors has been updated:

- PPD ***and*** PPD, Scientific Writer***s***, Modis for GSK Biologicals

On the cover page, the list of contributors has been updated:

- PPD ***and*** PPD, *Clinical Research Development Leads*
- PPD ***and*** PPD***,*** *Study Delivery Leads*
- PPD***, Bio-Statistician***
- PPD and PPD, *Clinical Trial Supply Managers*
- PPD, and PPD, *Study Data Manager**s***
- PPD and PPD*, Public Disclosure Representative**s***

In the list of abbreviations, the following abbreviation was added because its use in the text:

COVID-19	***Coronavirus Disease 2019***
SARS-CoV-2	***Severe Acute Respiratory Syndrome Coronavirus 2***
WHO	***World Health Organisation***

In section 2.2, a typo has been corrected.

> 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 ~~a~~ at least 10-fold decrease (*i.e.* 1-log difference) in qHBsAg or show HbsAg loss at Day 337 versus Day 1, or

In Section 3, the following text and cross-reference to the new section (Section 5.6.17) was added to provide flexibility to certain study procedures during special circumstances, such as COVID-19 pandemic:

During special circumstances (e.g., Coronavirus disease [COVID-19] pandemic), certain study procedures should be adapted to protect patient's welfare, and as far as possible ensure the potential benefit to the patient and promote data integrity (Section 5.6.17).

In Section 3, a cross-reference to the new section (Section 5.6.17) was added to Figure 1 to provide flexibility to certain study procedures during special circumstances, such as COVID-19 pandemic:

Refer to Section 5.6.17 for study procedures to be adapted during special circumstances.

In Section 5.5, a cross-reference to the new section (Section 5.6.17) was added to provide flexibility to certain study procedures during special circumstances, such as COVID-19 pandemic:

For study procedures to be adapted during special circumstances, refer to Section 5.6.17.

In Section 5.5, a cross-reference to the new section (Section 5.6.17) was added to Tables 4-5 to provide flexibility to certain study procedures during special circumstances, such as COVID-19 pandemic:

Refer to Section 5.6.17 for study procedures to be adapted during special circumstances.

In Section 5.5, a cross-reference to the new section (Section 5.6.17) was added to Tables 4 for the management of study visits if subsequent vaccination cannot be administered within an interval of 56- 60 days due to special circumstances:

If subsequent vaccination cannot be administered within an interval of 56 - 60 days due to special circumstances, please refer Section 5.6.17.)

In Section 5.5, footnotes “n” and “o” were added to Tables 4 for procedures that are not applicable in case vaccination was not administered at vaccination visit or at preceding vaccination visit:

[n] Procedure not applicable if vaccination could not be administered at that vaccination visit.

[o] Procedure not applicable if vaccination was not administered at preceding vaccination visit.

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k If procedure has not been performed at the respective timepoints, it should be done at earliest convenience.

In Section 5.5, footnote "c" and cross-reference to the new section (Section 5.6.17) were added to Table 6 to provide additional criteria to be considered during special circumstances, such as COVID-19 pandemic:

In case of special circumstances, this interval between two subsequent doses can be extended up to 84 days. If more than 84 days elapsed from administration of the previous vaccine dose, study vaccination should continue provided that maximum interval of 111 days between doses is respected.

In Section 5.6.17, added new, to provide guidance on adapting study procedures during special circumstances, such as COVID-19 pandemic:

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 applied. For the duration of such special circumstances, the following measures may be implemented for enrolled patients of the impacted countries or sites:

- ***Study visits may be replaced by a telephone call, other means of virtual contact or home visit, if appropriate to collect the safety information (AEs and concomitant medications/vaccinations), unless a patient presents symptoms or reports AEs that necessitate a site visit in Investigator's judgement.***
- ***Diary cards may be transmitted from and to the site by electronic means and/or conventional mail.***
- ***The screening activities and vaccine administration may be put on hold in line with specific local guidance or when deemed necessary by the Investigator or by Sponsor. Notification to Ethical Committees / Independent Review Boards and Competent Authorities should be made as appropriate. When it deems appropriate to resume the screening activities and vaccine administration, this can be done following notification to the Ethical Committees / Independent Review Boards and Competent Authorities and approvals as needed.***
- ***Maximum interval between study vaccinations: If despite best efforts it is not possible to administer subsequent dose of study vaccine as defined in the protocol (see Table 6), a maximum dose interval of 111 days between two subsequent doses should be used. The maximum interval has been determined based on experience with Ebola ChAd-MVA prime-boost in Phase I study [Tapia, 2016]. In this study, MVA-BN-Filo booster vaccine given 11 – 16 weeks (79 - 111 days) after priming with ChAd3-EBO-Z was well tolerated and immunogenic eliciting both anamnestic antibody responses and robust multifunctional CD4 and CD8 memory T-cell responses.***
- ***Discontinuation from study vaccination: If a maximum interval of 111 days since previous vaccination is exceeded, vaccination should be discontinued.***
- ***Adaptation of study visits when subsequent vaccination cannot be administered as defined in the protocol i.e. at interval of 56 – 60 days:***
- ***If subsequent vaccination cannot be administered within an interval of 56 - 60 days, only the visits specified in Table 7 should be performed at least every 4 weeks after the previous vaccination to follow up on safety and laboratory***

parameters. For management of those visits, refer to Table 7. Data collected at those visits should be encoded using unscheduled visit form in eCRF until the vaccination is resumed within a maximum of 111 days interval from the previous vaccination.

- ***If subsequent vaccination can be administered within maximum interval of 111 days from the date of previous dose administration, the visit related to this vaccination should be performed and further visits should follow as defined in Table 4, Table 5 and Table 6. Vaccination visit and subsequent visits should be encoded as regular visits in eCRF.***
- ***If subsequent vaccination cannot be administered within maximum interval of 111 days from the date of previous dose administration, patient should discontinue study vaccination and management of follow up visits in the primary phase (Epoch 002) should be performed as indicated in Table 7 and described below:***

  For patients who discontinued vaccination after vaccination Dose 1, Visits 10, 12, 13, 14 and 17-22 should be performed for follow up on safety and laboratory parameters.

  For patients who discontinued vaccination after vaccination Dose 2, Visits 14 and 17-22 should be performed for follow up on safety and laboratory parameters.

  For patients who discontinued vaccination after vaccination Dose 3, Visits 18-22 should be performed for follow up on safety and laboratoryparameters.

  Data collected at the above mentioned visits should be encoded as regular visits in eCRF.

  For all patients who discontinued study vaccination, the planned visits in the follow up phase (Epoch 003) should be performed as defined by protocol.
- ***Biological samples may be collected at a different location* other than the study site or at patient's home, in line with applicable local guidance. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.***
- ***In case a Grade 3 laboratory parameter abnormality is detected, an unscheduled visit should be performed, per protocol planned as a site visit. However, Investigator should practice his/her medical judgement on the clinical relevance of any abnormality and manage this according to the local clinical practice and local guideline concerning the COVID-19. If the site visit restriction is in place, the Investigator should contact the concerned patient in a remote manner (e.g. phone contact or home visit, if appropriate) to collect the safety information. Whenever possible and in line with applicable local guidance, the Investigator should arrange the clinical and laboratory examination at a different location* other than the study site that is accessible for the concerned patient.***

  **** 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 should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.

Impact on the per protocol set for immunogenicity and efficacy will be determined on a case by case basis. Due to potential increase of the drop-out rate, to ensure sufficient number of evaluable patients:

- ***Allowed intervals between two subsequent vaccinations, that constitute criterion for per protocol set, has been extended from 56 - 60 days to 84 days;***
- ***An increase of maximum 15% in sample size in Step B and in Step C can be anticipated.***

Table 7 Study visits of Epoch 002 to be performed if subsequent vaccination cannot take place within allowed interval of 56 - 60 days from previous vaccination

Epoch	Epoch 002																		
Study Phase	Primary Phase																		
Type of contact	Visit 1	Visits 2-5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22
Time points	Day 1	Day 3 - Day 31	Day 57	Day 64	Day 71	Day 87	Day 113	Day 120	Day 127	Day 143	Day 169	Day 176	Day 183	Day 199	Day 225	Day 253	Day 281	Day 309	Day 337
Previous vaccination Dose																			
Dose 1	Dose 1	N	Un	C	C	Un	MV*	C	N	N	MV	C	C	N	N	N	N	N	N
Dose 2			Dose 2	N	N	N	Un	C	Un	Un	MV*	C	C	N	N	N	N	N	N
Dose 3							Dose 3	N	N	N	Un	C	C	Un	N*	N	N	N	N
Dose 4											Dose 4	N	N	N	N	N	N	N	N

N: Visit including procedures as defined for this visit in Table 4. Visit should be encoded as regular visit in eCRF.
Un: Visit performed in special circumstances (e.g. remotely, home visit) including as many procedures as possible as defined for this visit in Table 4. Visit should be encoded using Unscheduled visit form in eCRF.
C: Visit cancelled if subsequent vaccination was not yet administered.
MV: Modified Visit applicable for patient who discontinued from study vaccination. This visit excludes vaccination-related procedures while maintaining all non vaccination-related procedures. For details, refer to Table 4. Visit should be encoded using vaccination visit form in eCRF.
**** Discontinuation of study vaccination may apply, if interval of 111 days from the date of previous dose administration is exceeded. This should be determined based on the actual date of the previous dose administration.***
Note:
1. If the above visits are performed in special circumstances (e.g. remotely, home visit), as many procedures as possible should be done (refer to Table 4 and Table 5).
2. If subsequent vaccination can be administered within maximum interval of 111 days from the date of previous dose administration, the visit related to this vaccination should be performed and further visits

should follow as defined in Table 4, Table 5 and Table 6. Vaccination and subsequent visits should be encoded as regular visits in eCRF.
3. If subsequent vaccination cannot be administered within a maximum interval of 111 days from the date of previous dose administration, patient should discontinue study vaccination and follow up visits should be performed as indicated above. The timepoints from vaccination Dose 1, Dose 2 and Dose 3 at which patient should be considered as discontinued from study vaccination are marked with * in the above table and should be determined based on the actual date of the previous dose administration.
4. Management of visits for patient who completed Dose 4 vaccination is shown for completeness.

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[redacted]

In Section 8.1.6, added new, to include COVID cases in the safety reporting:

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). When reporting an AE (serious or non-serious as defined in Section 8.1.2) related to COVID-19 infection, the following verbatim terms should be used according to World Health Organisation (WHO) definition (Please refer to APPENDIX D):

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

Information pertaining to COVID-19 infection should be entered in the dedicated eCRF page.

In Section 9.2.2, a typo was corrected and a cross-reference was added the new section (Section 5.6.17) for management of study visits in patients who discontinued study vaccination due special circumstances:

A 'withdrawal' from the study vaccines refers to any patient who does not receive the complete treatment, *i.e.* when no further planned dose is administered from the date of withdrawal. A patient withdrawn from the study vaccines may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol. For the purpose of this study, all study procedures* except~~ing~~ study vaccines administration, its related procedures (treatment number allocation, etc.) remain applicable to the patients.

**** For management of study visits in patients who discontinued study vaccination due special circumstances, refer to Section 5.6.17.***

In Section 10.4.1, cross-reference was added to the new section (Section 5.6.17) for additional sample size considerations due to impact of special circumstances:

**** Refer to Section 5.6.17 for sample size considerations that may be adapted due to impact of special circumstances.***

In Appendix D, added new, to provide case definition for COVID-19 infection:

WHO Case Definition (Version: March 20, 2020):

- ***Suspected case***
  - ***A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR***
  - ***A patient with any acute respiratory illness AND having been in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset; OR***
  - ***A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.***
- ***Probable case***
  - ***A suspect case for whom testing for the COVID-19 virus is inconclusive (inconclusive being the result of the test reported by the laboratory); OR***
  - ***A suspect case for whom testing could not be performed for any reason.***
- ***Confirmed case***
  - ***A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.***

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

- ***Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;***
- ***Direct physical contact with a probable or confirmed case;***
- ***Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR***
- ***Other situations as indicated by local risk assessments.***

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
Amendment number:	5
Amendment date:	20 May 2020
Co-ordinating author:	PPD , Scientific Writer (Modis for GSK Biologicals)

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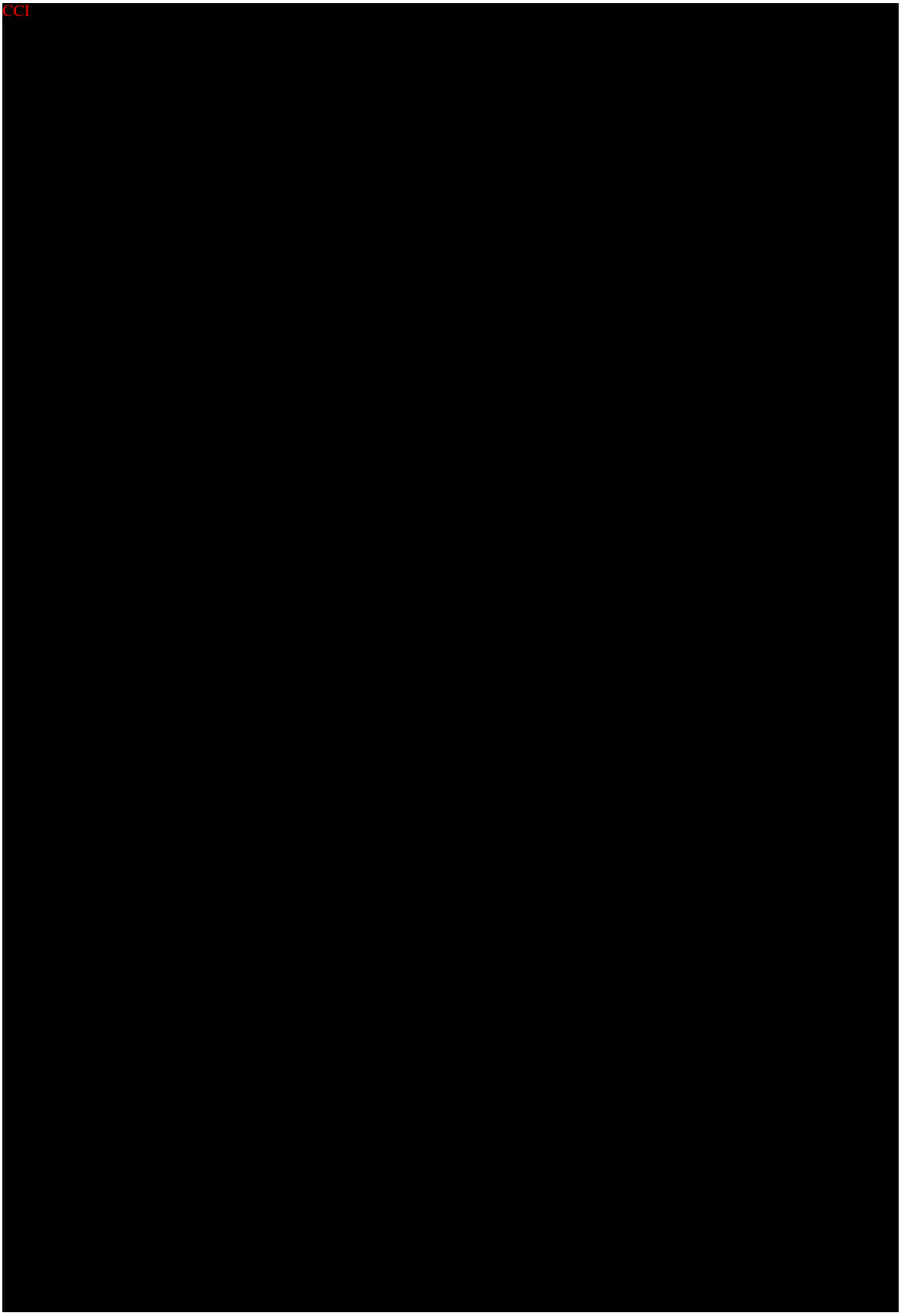

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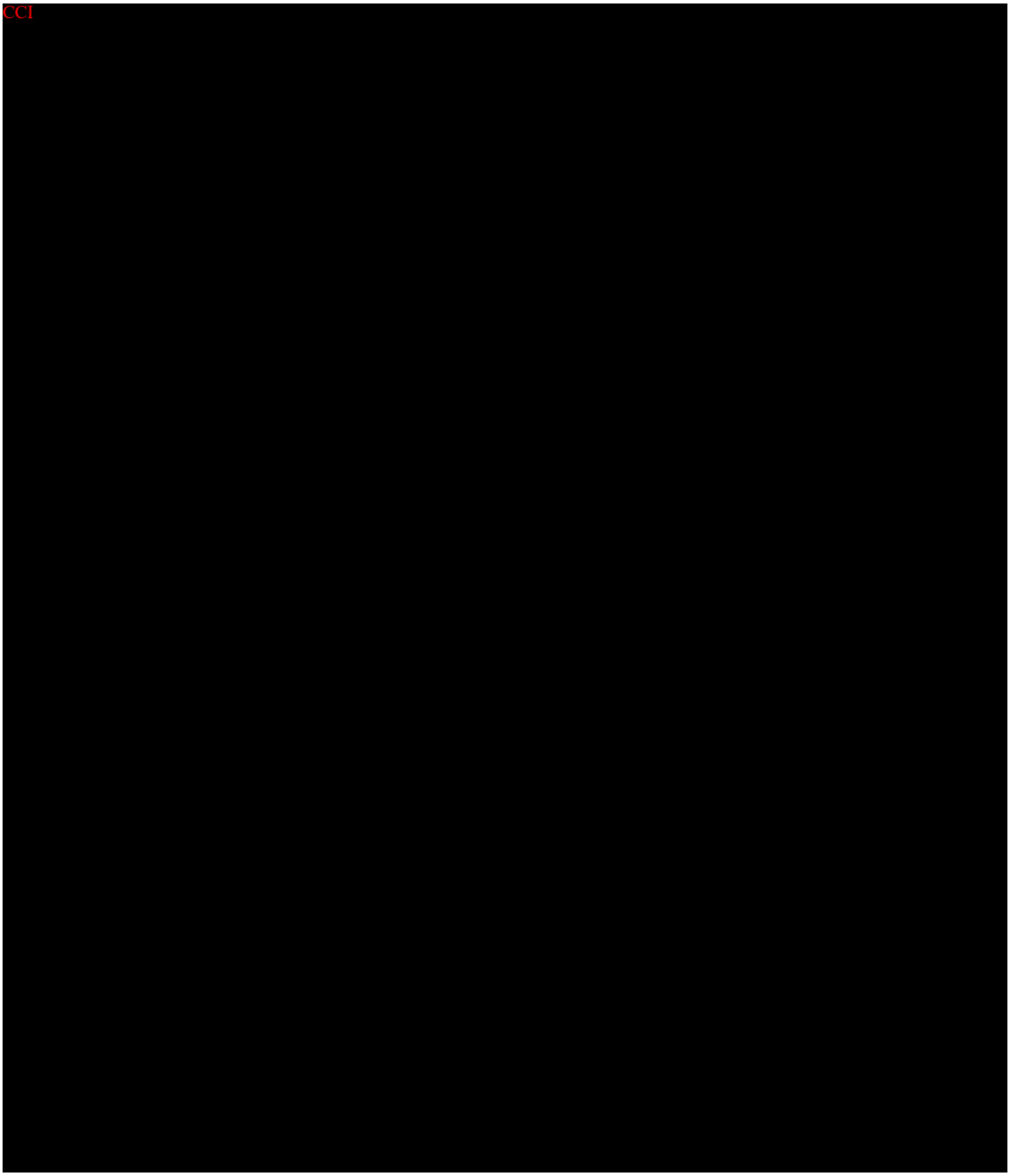

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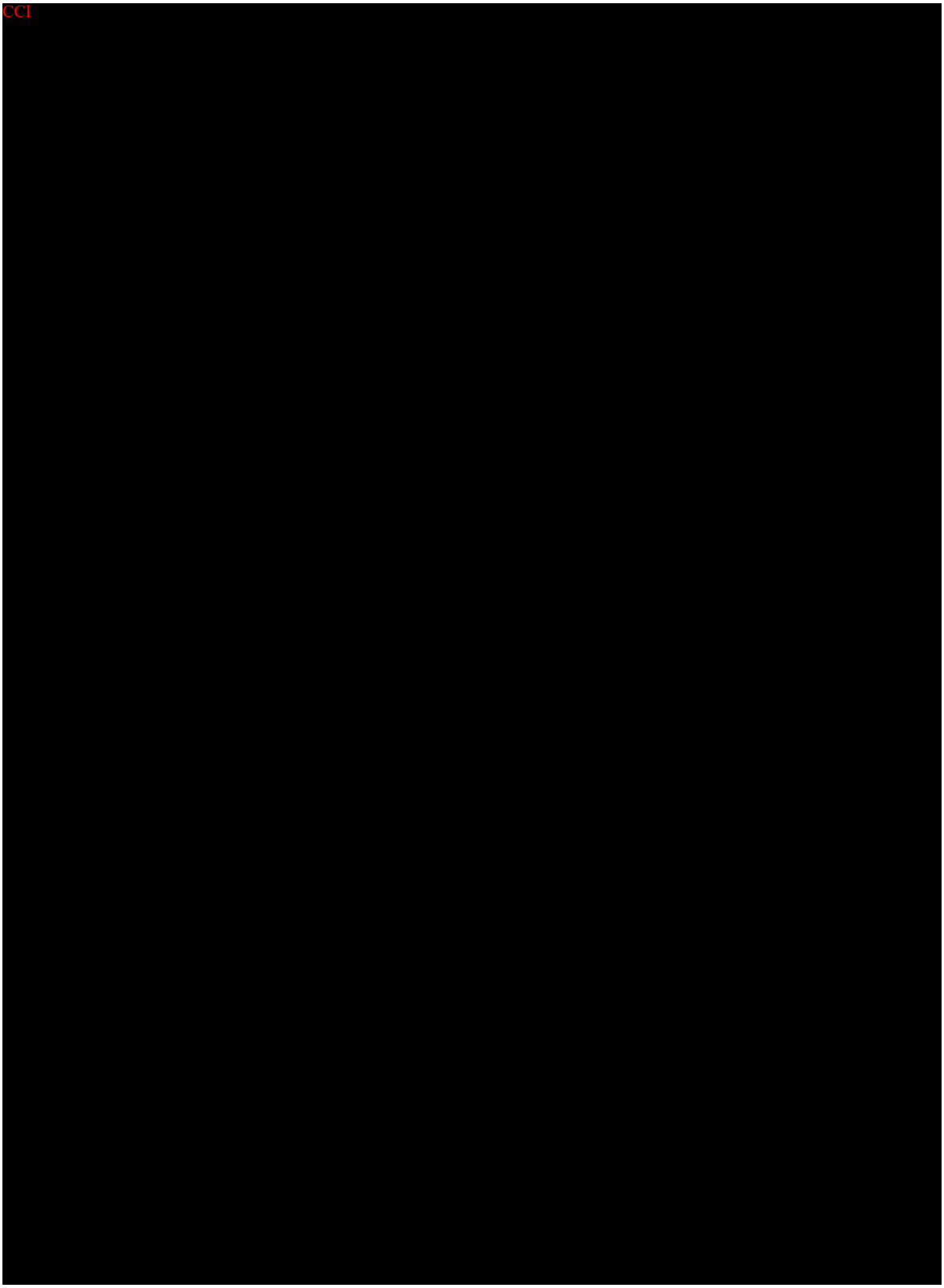
[redacted]

CCI



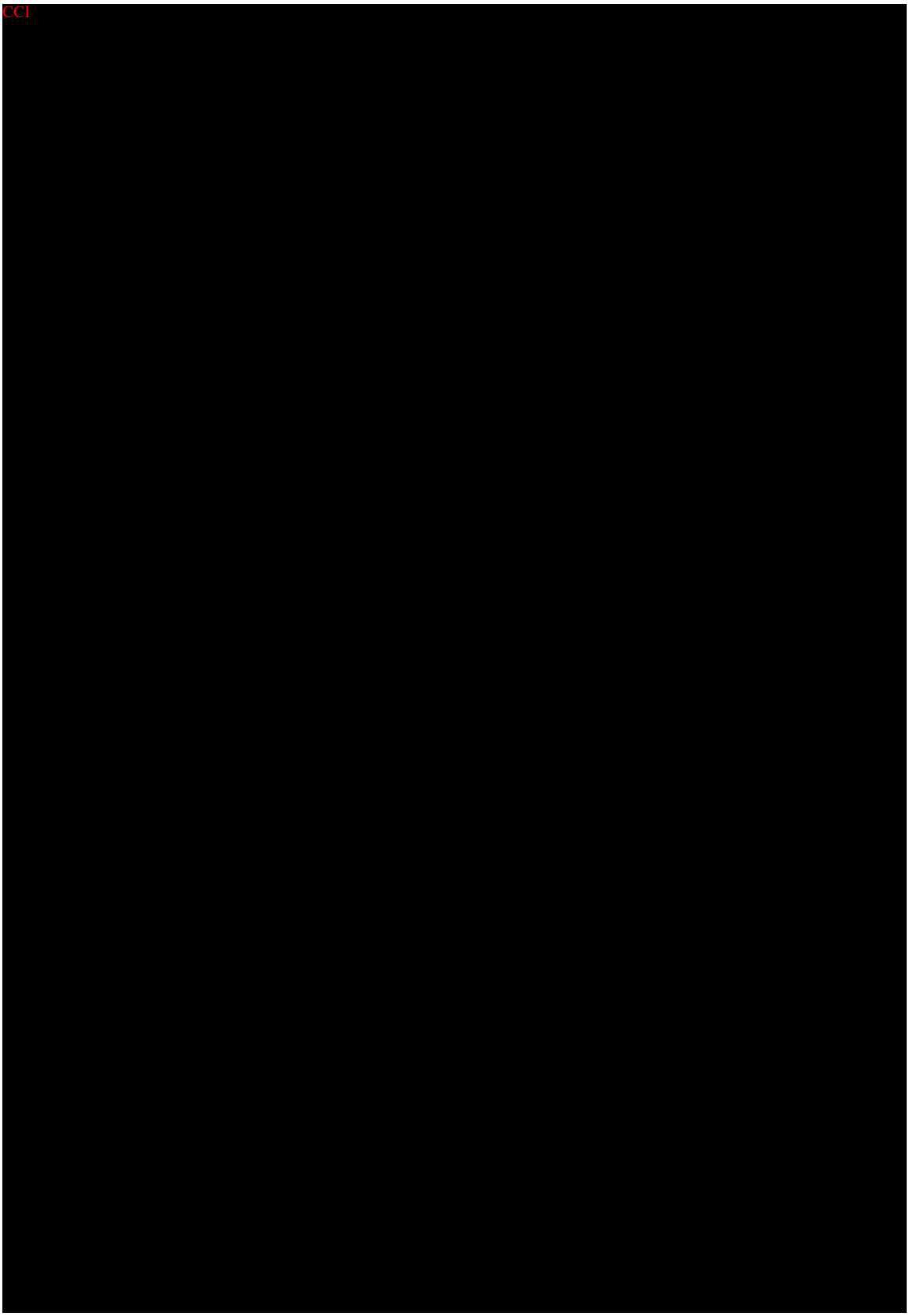
CCI

[redacted]

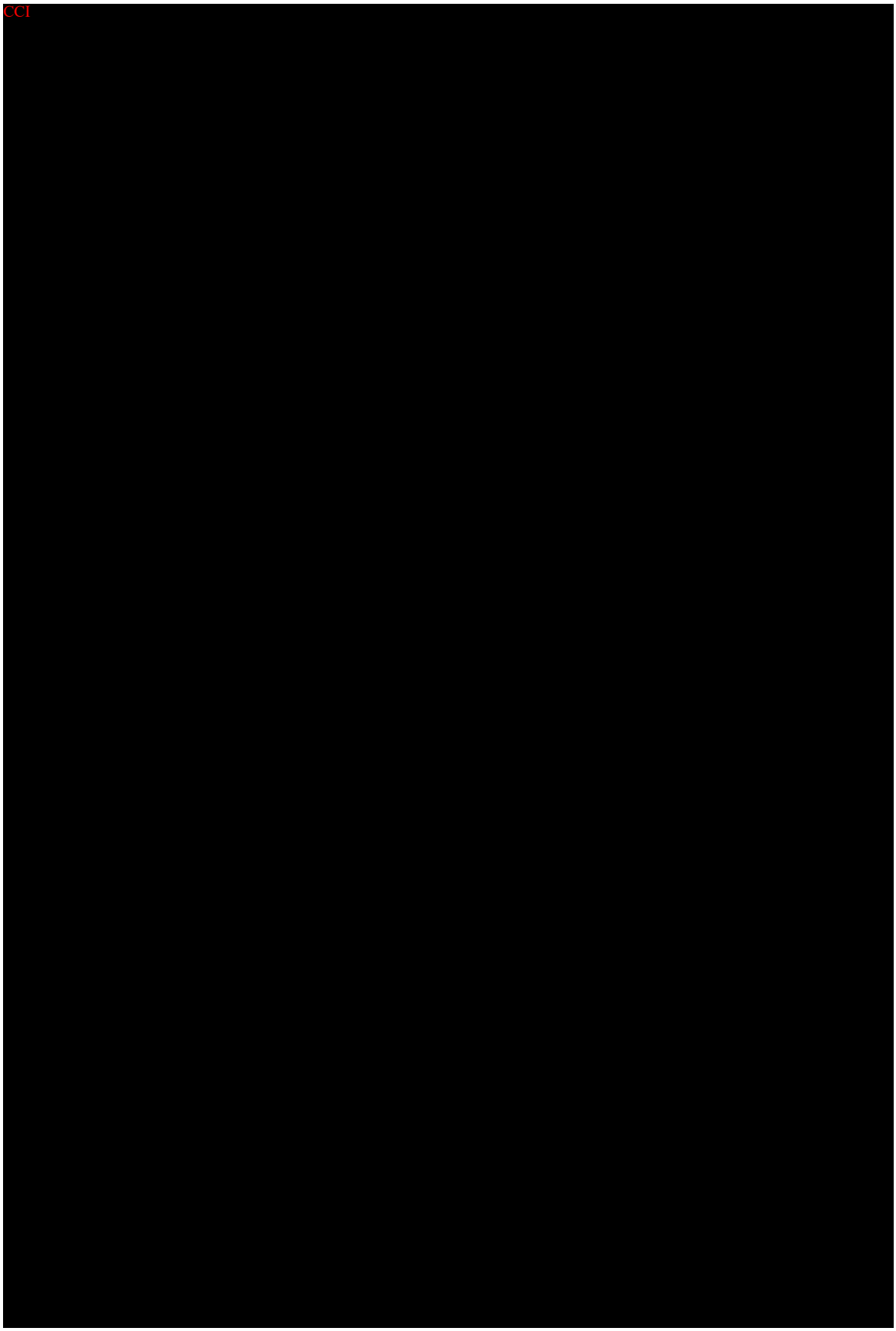
CCI

[redacted]

CCI



CCI



CCI [redacted]

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
Amendment number:	6
Amendment date:	16 March 2021
Co-ordinating author:	PPD, Scientific Writer
Rationale/background for changes:	

CCI [redacted]

CCI

[redacted]

List of changes
On the cover page, the names of co-ordinating author and contributing authors have been updated: • PPD , ***Scientific Writer***

- PPD
  Clinical Laboratory Science Representatives, Clinical Readout Team Leaders.
- PPD
  Study Data Managers
- PPD, Global Regulatory Lead***s***

The following note has been added in the sponsor signatory approval page:

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

List of abbreviations: The following abbreviation was added:

mRNA	***messenger Ribonucleic Acid***

In section 4.3, the following exclusion criteria have been updated:

- Administration of adenovirus/adenovector-based or MVA-based vaccine within the last 12 months ***except for adenovirus/adenovector-based COVID-19 vaccines that could be administered up to 30 day prior to the first study vaccine dose***.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 14 days before each dose and ending 30 days after each dose of vaccines, with the exception of influenza vaccine that may be given at any time except within a 7-day period before or after each vaccine dose ***and COVID-19 vaccine that 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.

In Section 5.2.2, the following wording has been added for SBIR:

SBIR:

☐ **No**

☒ **Yes:** hBsAg concentration at Screening will be used as a minimization factor (<1000 IU/ml and ≥ 1000 IU/ml) for Step B and Step C randomization ***except for the patients needed for the first iSRC review in Step C***

In Section 5.2.2.1.1, the following wording has been added:

Allocation of the patient to a study group at the investigator site will be performed using a randomization system on internet (SBIR). The randomization algorithm will use a minimization procedure [White, 1978] accounting for hBsAg concentration

(<1000 IU/ml and ≥ 1000 IU/ml) measured at Screening. The minimization procedure will be applied for patients enrolled in the steps B and C ***except for the patients needed for the first iSRC review in Step C to ensure to have not more than [CCI] patients in a treatment group as required for the iSRC evaluations.***

In Table 3, for Belgium, France Germany, Hongkong, Spain, Taiwan and Thailand, prefix numbers for contact information for emergency blinding have been added. The list of toll free numbers are presented in a tabular format.

GSK Helpdesk

Available 24/24 hours and 7/7 days

The Helpdesk is available by phone, fax and email

Phone: +32 2 656 68 04

Country	*Toll-free number*
Belgium, France, Germany, Spain, Taiwan	***00 800 4344 1111***
Hongkong	***006 800 4344 1111***
Thailand	***001 800 4344 1111***
United Kingdom	***0800 056 7221***

Fax: +32 2 401 25 75
E-mail: rix.ugrdehelpdesk@gsk.com

In Table 4, Table 5 and Section 5.6.7, the wording related to liver ultrasound has been updated:

- If liver ultrasound is not possible, alternative liver imaging examination (e.g. magnetic resonance or computerized tomography) may be performed at the discretion on the investigator. ***If it is not possible to perform a liver ultrasound at screening, a routine ultrasound performed within 180 days prior to the vaccination visit 1, can be used for eligibility assessment.*** For Germany, please see the country-specific requirements in Section 12.

In Table 4, the following footnote has been updated:

[q] The minimum requirements at Visits 2, 5, 9, 13 and 17 are safety assessment including, but not limited to, recording of solicited symptoms, unsolicited AEs within 30 days post-vaccination, SAEs, MAEs, AESIs, SAEs related to study participation, or to a concurrent GSK medication/vaccine, AEs/SAEs leading to study withdrawal, pregnancy and pregnancy outcome, intercurrent medical conditions leading to elimination from per-protocol analyses and concomitant medications/vaccinations. The collection of data for safety assessment can be performed remotely (e.g. via phone contact). Other study procedures including biological samples collection and physical examination are optional at the discretion of the Investigator. ***However, efforts should be made for the patients needed for the first iSRC review in Step C to perform Visit 2 at the site to allow collection of biological samples for safety evaluation by iSRC.*** For

patients participating to TH HBV VV-031 HBS:001 study, biological samples collection specific to that study remains mandatory for Visits 2 and 5.

In Table 4, Section 5.6.12, Table 9, Table 14, wording related to obtaining an additional buccal swab sample has been added.

In the event of DNA extraction failure, a replacement buccal swab sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

In Section 5.6.18, the following points are updated:

- Biological samples may be collected at a different location* other than the study site or at patient's home, in line with applicable local guidance. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use. ***In case of anticipated delay or urgency in obtaining the biological sample result to follow safety parameters post-vaccination, the investigator is recommended to collect an additional biological sample for local testing. If such sample is required, it is important that the sample for central testing is obtained at the same time.***
- Impact on the per protocol set for immunogenicity and efficacy will be determined on a case by case basis. Due to potential increase of the drop-out rate ***and potential administration of COVID-19 vaccines during study participation (outside of study procedures)***, to ensure sufficient number of evaluable patients:
  - Allowed intervals between two subsequent vaccinations, that constitute criterion for per protocol set, has been extended from 53 - 63 days to 84 days;
  - An increase of maximum 15% in sample size in Step B and in Step C can be anticipated.

A table summarizing the recommendations on spacing between COVID-19 vaccine and study vaccination based on type of COVID-19 vaccine has been added.

Recommendations on spacing between COVID-19 vaccine and study vaccination based on type of COVID-19 vaccine are outlined in Table 8. Note that the interval between two subsequent study vaccine doses can be extended up to 84 days to accommodate COVID-19 vaccinations

Table 8 Recommendations on spacing between COVID-19 vaccine and study vaccination by type of COVID-19 vaccine

COVID-19 vaccine	*Prior study vaccination*	*During study vaccination*	*After study vaccination*
mRNA based	*14 days before first study vaccine dose*	*At least 14 days before or 30 days after study vaccination*	*30 days after last vaccine dose*
Adenovector-based	*30 days before first study vaccine dose*	*At least 30 days before or after study vaccination*	*30 days after last vaccine dose*

Protein-based adjuvanted	***30 days before first study vaccine dose***	***At least 30 days before or after study vaccination***	***30 days after last vaccine dose***
Other technologies	***30 days before first study vaccine dose***	***At least 30 days before or after study vaccination***	***30 days after last vaccine dose***

In Table 12 and Table 13, priority ranking for humoral immunity and cell-mediated immunity component testing has been added, respectively.

Table 12: Humoral Immunity (antibody determination)

System	Component	Method	*Components priority rank*	Laboratory [a]
Serum	Hepatitis B Virus.Surface Ab	CLIA	***1***	GSK Biologicals' laboratory or laboratory designated by GSK
	Hepatitis B Virus Core Ab	To be developed [b]	***2***	
	CCI			

Table 13: Cell-mediated immunity

System	Component	Challenge	Method	*Component priority rank*	Laboratory[a]
PBMC	HBc-specific ($CD4^+/CD8^+$) T-cells	HBc peptide pool	CFC	***1***	GSK Biologicals' laboratory or laboratory designated by GSK
	HBs-specific ($CD4^+/CD8^+$) T-cells	HBs peptide pool	CFC	***2***	
	CCI				

In Section 6.7.1, the following point has been added:

- ***Any COVID-19 vaccine administered in the period starting 12 months prior to the vaccination visit 1 and ending at the last study visit***.

In Section 6.7.2, the following points have been updated:

- 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.

  In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if, necessary for that vaccine provided it is licensed and used according to its ***Product***

Information ~~Summary of Product Characteristics (SmPC) or Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained~~

In section 8.8.2, 'i.e.' has been changed to 'e.g.'

A maximum of CCI patients per group (~~i.e.~~ ***e.g***. N=6 in Step A; CCI will first be randomized for vaccination and followed for 2 days. When all these patients have completed Visit 2 (*i.e*. 2-day post Dose 1), iSRC will review all the available safety data. If the iSRC considers it appropriate to continue, the randomization of the remaining patients in each group can start. If ≥CCI patients randomized at the same study site on the same day, these patients should be vaccinated sequentially with at least 60 minutes apart to allow monitoring of any acute event, such as anaphylactic reaction.

In section 10.4.2, the following was updated:

- An interim analysis may be performed when CMI samples 14 days post-vaccination Dose 2 are tested and results are available for ***as many patients as possible but*** at least CCI patients ***vaccinated*** in Step B ***and available data of all patients in Step A***. Considering that CCI% patients may be eliminated from analysis set, the aim is to have ~~approximately~~ ***at least*** CCI evaluable patients of ***Step B*** CCI patients in group B1, CCI patients in group B2 and group B3)

In section 10.11.1, the following was updated:

- An interim analysis may be performed when CMI samples up to 14 days post-vaccination Dose 2 (Day 71) are tested and results are available for ***as many patients as possible but at least*** ~~approximately~~ CCI patients vaccinated in Step B ***and available data of all patients in Step A***. There will be no statistical adjustment done as this analysis is not related to confirmatory objective of the study. This analysis will be documented in a statistical report.

CCI

CCI [redacted]

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
Amendment number:	7
Amendment date:	30 July 2021
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

CCI [redacted]

CCI

[redacted]

CCI [redacted]

List of changes

- Throughout the document, the phase of the study was changed from Phase I to Phase I***/II***.
- On the cover page, the names of contributing authors have been updated:
  - PPD [redacted] Study Delivery Leads
  - PPD [redacted], Laboratory Science Representatives, Laboratory Study Managers
  - PPD [redacted], Public Disclosure Representatives

List of abbreviations: The following abbreviations were added:

CRA	***Clinical Research Associate***
TTS	***Thrombosis with Thrombocytopenia Syndrome***

In synopsis and Section 3, the following wording has been added under sampling schedule:

- CCI [redacted]
- ***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.***

In Section 1.2.1, the following wordings were modified:

The aims of the study are as follows~~This study aims~~:

- ***Phase I Dose-escalation safety lead-in (Step A and Step B) aims to assess safety of a low dose (Step A) and a target dose (Step B) of the vaccine, both in a sequential regimen;***
- ***Phase II Regimen-finding that assesses the target doses of the vaccines given in different regimens in Step B and Step C, aims:***
  - To evaluate the safety profile of ***sequential regimen in Step B (with or without adjuvanted proteins i.e. group B1 and B3 respectively), adjuvanted proteins given alone (group B2) and co-administration regimens in Step C*** ~~the vaccines in adult patients with hBeAg negative chronic HBV infection and with no advanced liver fibrosis or cirrhosis who are virally suppressed on NA treatment for at least 24months. As this is a Phase I study, patients will remain under NA therapy throughout the study~~,
  - To evaluate whether one or more vaccine regimens tested will induce a decrease in serum hBsAg concentration (proof-of-principle [PoP]),
  - To evaluate the added value of the adjuvanted proteins on top of viral vector vaccines,
  - To evaluate the best vaccination regimen for the administration of the adjuvanted proteins (i.e. either sequentially to or co-administered with the viral vectored vaccines),
  - To evaluate the added value of 3 boost doses versus one boost dose of MVA-HBV co-administered with adjuvanted proteins ***(group C1 and C2),***
  - To assess the induction of HBV-specific CD8+ and CD4+ T-cell responses and antibody responses by different vaccine regimens.

In Table 4, the following footnote related to TTS has been added:

- ***In case of a TTS event, an additional blood sample 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. For more information, please refer to Section 5.7.2.***

In Table 5, the following footnote related to TTS has been added:

- ***In case of a TTS event, collection of an additional blood sample within 2 weeks of the diagnosis of the TTS for exploratory testing is optional. 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. For more information, please refer to Section 5.7.2.***

In Section 5.6.18, additional wordings related to COVID-19 vaccines were added:

In view of the current medical need for COVID-19 vaccination, guidance/recommendations from National Authorities should apply first and foremost if/when existing.

Recommendations on spacing between COVID-19 vaccine and study vaccination based on type of COVID-19 vaccine are outlined in Table 8. Note that the interval between two subsequent study vaccine doses can be extended up to 84 days to accommodate COVID-19 vaccinations.

Table 8 Recommendations on spacing between COVID-19 vaccine and study vaccination by type of COVID-19 vaccine

COVID-19 vaccine	Prior study vaccination	During study vaccination	After study vaccination
mRNA based	14 days before first study vaccine dose	At least 14 days before or 30 days after study vaccination	30 days after last vaccine dose
Adenovector-based	30 days before first study vaccine dose	At least 30 days before or after study vaccination	30 days after last vaccine dose
Protein-based adjuvanted	30 days before first study vaccine dose	At least 30 days before or after study vaccination	30 days after last vaccine dose
Other technologies	30 days before first study vaccine dose	At least 30 days before or after study vaccination	30 days after last vaccine dose

Whenever multiple types of COVID-19 vaccine are offered, a COVID-19 vaccine that is not adenovector-based may be considered as a better choice.

In Table 9, the following footnote and text was updated:

- CCI [redacted]

In Section 5.7.2., the following wording related to TTS has been added:

- ***In case of a TTS event, an additional blood sample (~3.5ml) should be collected within 2 weeks of the diagnosis of the TTS. 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. Additional blood sample collection for TTS event reported during the follow-up phase is optional. This serum sample (if available) as well as the samples collected for repository, as already specified in the protocol, will be used for exploratory testing and better understanding of the pathogenesis of TTS event. Since scientific knowledge on TTS pathology and biomarkers for TTS risks in relation to adenovector-based vaccines is evolving, this exploratory testing is not to guide TTS management and no assay details are specified in the protocol. This testing will be performed at a laboratory designated by GSK Biologicals.***

In Table 12, the following assay details were added and the footnote was modified:

System	Component	Method	Components priority rank	Laboratory [a]
Serum	Hepatitis B Virus.Surface Ab	CLIA	1	GSK Biologicals' laboratory or laboratory designated by GSK
	Hepatitis B Virus Core Ab	~~To be developed~~ [b] ***ELISA***	2	
	CCI [redacted]			

	Chimpanzee Adenovirus Type 155 Ab	Seroneutralizing assay	4	

[a] GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium ~~or Marburg, Germany~~. Refer to APPENDIX B for the laboratory address.
[b] ~~This assay will be developed in the course of the study.~~

In Table 13, the following footnote was modified:

[a] GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium ~~or Marburg, Germany~~.

In Table 18 and Table 19, the following footnote was added:

CCI

[redacted]

Under Section 8.1.5.2, a sub-section related to TTS has been added:

Recently, following COVID-19 vaccines, thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed very rarely following vaccination with adenovector-based COVID-19 vaccines. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases had a fatal outcome. The majority of these cases occurred within the first two weeks following adenovector-based COVID-19 vaccination and mostly in women under 60 years of age.

Currently available data are insufficient to either disprove or confirm that TTS is a class effect for adenovector-based vaccines. As of May 2021, no TTS event has been reported in any GSK studies using adenovector-based vaccines. However, as a precautionary measure, safety information related to occurrence of TTS will be collected in this study and additional blood sample will be asked from a patient reporting TTS.

Individuals diagnosed with thrombocytopenia during the entire vaccination phase (from dose 1 till 1 month post-last dose) and follow-up phase should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis during the entire vaccination phase (from dose 1 till 1 month post-last dose) and follow-up phase should be evaluated for thrombocytopenia. For diagnostic algorithm and clinical management of TTS, clinical guidelines and local

recommendations should be followed. For case definition of TTS, please refer to the Brighton Collaboration Case Definition provided in Appendix E.

In case a confirmed TTS event is reported during this study, patients will be queried for additional information which will be documented in the eCRF by the investigator and an additional blood sample should be collected within 2 weeks of the diagnosis of the TTS for exploratory testing and better understanding of the pathogenesis. Additional blood sample collection for TTS event reported during the follow-up phase is optional. Since scientific knowledge on TTS pathology and biomarkers for TTS risks in relation to adenovector-based vaccines is evolving, this exploratory testing is not to guide TTS management and no assay details are specified in the protocol.

In Section 10.3, the following text was modified:

CCI [redacted]

In Section 10.4.2, the following wording was added:

Subsequent interim analyses on CMI samples 14 days post-vaccination Dose 2 may be performed for all patients in Step B and all patients in Step C (as many patients as possible in case of visit delay).

In Section 10.11.1, the following wordings were updated:

The sequence of analyses will be managed the same way in each defined step:

- Stepwise safety analyses for iSRC review will be done as described in Section 8.8. These analyses will be performed by project independent statistician in order to keep GSK study team blinded as much as possible until the end of the defined step procedures.

CCI [redacted]

- An interim analysis may be performed when CMI samples up to 14 days post-vaccination Dose 2 (Day 71) are tested and results are available for
  - as many patients as possible but at least CCI [redacted] patients vaccinated in Step B and available data of all patients in Step A. There will be no statistical adjustment done as this analysis is not related to confirmatory objective of the study. This analysis will be documented in a statistical report.
  - ***all patients in Step B* and,***
  - ***all patients in Step C****
- ****In case of visit delay, analysis may be performed for as many patients as possible with data available at the time of the analysis. Analysis for remaining patients will be performed at the time of the next analysis.***
- An interim analysis will be performed when core efficacy data up to 6 months post Dose 4 (Day 337) of all patients in Step B will be available. There will be no

statistical adjustment done as the analysis will be performed on the final data. This analysis will be documented in a statistical report. ***Clinical study report may be written if deemed necessary for regulatory consultation.***

- A final analysis of safety/immunogenicity/efficacy endpoints will be performed when all safety/reactogenicity and core assays data up to 6 months post Dose 4 (Day 337) are cleaned and available. At this point, the project GSK statistician will be unblinded (*i.e.* will have access to the individual patient treatment assignments), but no individual listings will be provided in order to keep the individual blinding. This analysis will be documented in a statistical report. ***Clinical study report may be written if deemed necessary for regulatory consultation.***

In section 12, the following country specific wording for Germany was added:

Remote Source Data Verification (rSDV) during exceptional situations in Germany

Frequent instream monitoring of safety data by the central study team at GSK is required for this study. Instream review of study data items and processes should be considered during exceptional situations/circumstances, such as with pandemics like COVID-19, focusing on key data points, patient assessments and processes that are critical to ensure the rights, safety and well-being of study participants and the integrity of the study and data. Prior to any rSDV activity a written agreement by the Investigator will be obtained. The agreement includes the extent and the method of rSDV activities. Monitoring Plan and Study-Specific Risk Register will be updated to include rSDV activities and clinical research associates (CRAs) will be guided for the conduct of rSDV.

Option 1 Transfer of redacted Source Documentation

Process for transfer and review of redacted source documentation provided by the site:

- ***The CRA instructs study site on the source data needed for the remote SDV activities.***
- ***The CRA instructs site staff they must pseudonymize the requested documentation, do a quality check that anonymized (redacted) areas cannot be read, and then delivers the documentation to the CRA in an encrypted form of communication (the site should have a documented process).***
- ***The minimum requirements regarding quality of the copies will be agreed with the site upfront:***
  - ***For the scanning of paper documents resolution will be a minimum of 300 dots per inch (dpi).***
  - ***For the scanning of photographs and images resolution will be 600 dots per inch (dpi) minimum.***
  - ***Colour scanners must be able to produce copies that match the original.***

- *A4 format as final size without loss of information.*
- *Documents will be saved as portable document format (PDF).*
- *In order to maintain quality standards, a captured image will not be subjected to non-uniform scaling (i.e. sizing) or re-sampling to a lower resolution.*

- *Redacted source document scans will be sent to the CRA via email using one of the following secure options:*

d. Transport Layer Security (TLS) connection:

TLS connections are intended to support significant mail flow between GSK and external partners in a secure manner.

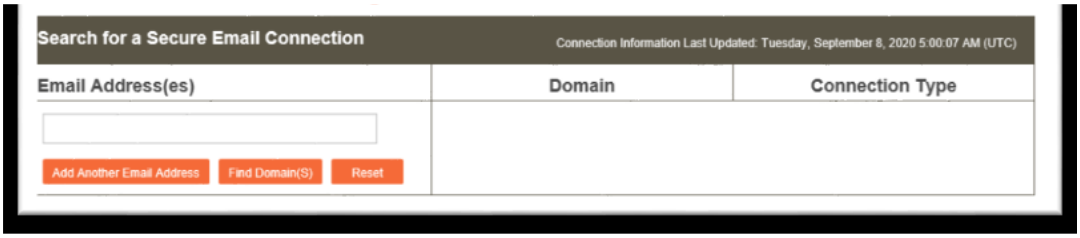
e. GSK Secure

In cases where only a handful of users are communicating or the volume of emails is low, the use of GSK secure, the GSK ad-hoc message encryption solution is recommended.

f. Password protected PDF attachment

- *A password protected scan (PDF) will be attached to an email. The password to open the attachment will be sent in a separate email.*

- *The CRA may use the secure email website to assess whether the sites email address is secure (i.e. encrypted).*



- *Prior to starting remote SDV the CRA ensures that the provided documents are complete and do not contain any Personal Information (PI).*
  - *In case the CRA detects any PI that has not been redacted, the CRA informs the study site and deletes the files (incl. the Recycle bin).*
  - *A Data Breach must be reported Data Breach Web Report Form.*
- *Use of an external PC screen is recommended. The CRA will not generate any copies from the source data received.*
- *Source data verification/review will be conducted according to the process outlined in the GSK Monitoring SOP.*
- *After completion of SDV activities, the CRA deletes all copies/images of subject data received from the site. This includes the deletion of the recycle bin and any temporary files.*

- ***A statement confirming that all documents were destroyed will be provided by the CRA via email to the site.***
- ***Details of what was monitored remotely will be documented in the appropriate section of the Monitoring Visit Report (MVR).***

Option 2 – Review of Subject Source Documentation remotely

Process for use of Webcams, WebEx, MS Teams for viewing subject source remotely:

- ***The CRA ensures that the site personnel sharing information with GSK has authority to do so.***
- ***Remote SDV activities will be performed exclusively by the assigned site monitor.***
- ***Prior to conducting any remote SDV activities the CRA ensures that a written informed consent, covering the proposed SDV activities, has been signed by the study patient.***
- ***For CRAs using GSK laptops, only use GSK approved video conferencing tools (e.g. MS Teams or GSK WebEx). Live image transmission is fully encrypted and protected for authorised user. By using these systems, it will be assured that data will be viewed only but not transmitted/stored.***
- ***For functional service provider (FSP)/Local contract research organisation (CRO) CRAs not using GSK laptops, only MS Teams via RAA (Remote Access Application) may be used for meetings between the CRA and the site. WebEx is not permitted from non-GSK laptops. Other tools like FaceTime, WhatsApp or Zoom are not permitted since they do not have sufficient encryption features. GSK does not have enterprise contract/privacy agreement with these providers.***
- ***Prior to the remote monitoring visit, the CRA instructs study site on the specific data needed for the remote SDV.***
- ***Source data verification will be conducted according to the process outlined in the Monitoring SOP.***
- ***The use of a headset is required, do not use computer audio.***
- ***The CRA does not capture screens or take pictures of screens to ensure we are not transferring content outside of clinical sites.***
- ***WebEx or Teams do not store or have access to any data, GSK staff is not allowed to make or store any screenshots or save any data which has been shared.***
- ***Details of what was monitored remotely will be documented in the appropriate section of the MVR.***

In case of technical malfunctions or if the security of the transmission is no longer ensured, we will pause rSDV activities. GSK Issue Management Procedures will be initiated.

In Table 33, the following was modified:

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart – Belgium
GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium
~~GSK Biological's Clinical Laboratory Sciences, Marburg~~	~~GSK Vaccines GmbH~~ ~~Emil-von-Behring-Str. 76~~ ~~35041 Marburg~~ ~~Deutschland/ Germany~~

In Table 34, the following was modified:

Laboratory	Address
CEVAC - University of Gent	***Corneel Heymanslaan 10*** ***9000 Gent*** ~~De Pintelaan, 185 Gent~~ Belgium

Brighton collaboration case definition is added in Appendix E.

Since at least mid-February 2021, multiple European countries (e.g., Austria, Denmark, Norway, Germany, UK) and Australia have reported cases of thrombosis with thrombocytopenia syndrome (TTS) in persons who received the Astra-Zeneca (AZ) COVID-19 vaccine [Greinacher, 2021; Schultz, 2021; ATAGI, 2021; Scully, 2021] and more recently in the US with the Janssen vaccine [Cines, 2021]. There is currently no standard case definition (CD) for TTS accepted for use by all countries. On 3 April 2021, the British Society of Haematology published its Updated Guidance on Management Version 1.0 with CD for possible, probable, and definite cases of TTS [British Society of Haematology, 2021]. This document is oriented towards identification and treatment of cases rather than being designed for epidemiologic studies, especially initial case finding, however. Therefore, there is an urgent need for the latter a draft of which is included in 4 below.

Since its inception in 1999, the Brighton Collaboration has sought to advance the science of vaccine safety by developing standard CD for adverse events following immunizations (AEFI's) [Bonhoeffer, 2002]. To date, >60 CD's have been developed, such as fever, seizure, anaphylaxis, intussusception, narcolepsy, etc. Individual CD for thrombosis [Draft Brighton Collaboration Case Definition of Thrombosis and Thromboembolism, 2021] and for thrombocytopenia [Wise, 2007] have also been developed.

- ***Based on this experience, we propose a two-step process (see proposed process below) to develop both:***
  - ***A "draft interim case definition" to facilitate identifying a cohort of individuals with this clinical entity (see interim/working CD for TTS below for process; interim case definition thrombosis thrombocytopenia syndrome version 16 below for draft); who could then be studied using a common study protocol and assessment tools.***

- ***While others have called this new syndrome Vaccine-induced immune thrombotic thrombocytopenia (VITT) [Greinacher, 2021; Schultz, 2021]; this assumes a causal mechanism. We have elected to use 'TTS' [ATAGI, 2021] for this initial case finding purpose.***
- ***To this end, vaccination with a SARS-2-CoV vaccine would not be required to enter this cohort but clearly vaccine exposure information would be collected on these individuals along with other variables and laboratory tests that have yet to be fullyidentified (see final CD below).***

– ***A final Brighton case definition (see final CD below)***

- ***When new clinical syndromes or diseases are first identified, standard CD are needed for both clinical (e.g., appropriate diagnosis, treatment) and public health (e.g. epidemiologic studies, and data harmonization) purposes. This is especially true for rare events where any misclassification will hinder scientific progress. The process for developing a final standard CD for a new illness usually takes some time requiring serial improvements of working or interim CD as full knowledge accumulates. The US CDC CD for what came to be called Acquired Immuno-Deficiency Syndrome (AIDS) for example was initially developed in 1981 and revised in 1985, 1987, and 1993 [British Society of Haematology, 2021]. The Chinese CD for COVID-19 changed seven times from 15 January 2020 to 30 March 2020 [Bonhoeffer, 2002].***
- ***The Brighton CD's are usually tiered into three levels of available evidence, level one (high), level two (medium), and level three (low). This gradient in evidence might be acquired from clinical trials (high) or routine passive surveillance (low); or alternatively, tertiary referral hospital (high) vs. basic rural clinic (low). We try generally to avoid use of the terms Definite, Probable, Possible in this context as these terms are also commonly used for the strength of causal link (see below), but are making an exception here as they are more concise and meaningful than not using them.***
- ***Because Brighton's overall interest is in accurate understanding of whether the vaccine exposure causes the AEFI or not; and because most AEFI's lack a unique clinical or laboratory marker to establish a causal link, the only way of demonstrating this causal link is by showing that vaccinated persons have a higher rate of the AEFI than unvaccinated persons in an unbiased manner (either from clinical trials or epidemiologic studies). Process-wise, the data for this rate comparison is usually best attained by first finding all possible cases of the specific AEFI or adverse event of special interest (AESI), then separately ascertaining their vaccine exposure status in a blinded manner, before linking the two. As Brighton CD are designed to find all possible cases of meaning the CD in an unbiased manner relative to vaccine exposure, they do not include vaccine exposure as part of the CD.***

<u>Proposed process:</u>

- ***For <u>interim/working CD for TTS</u>: We initially proposed identifying a small number (e.g. 3) haematologists familiar with the recent cases of TTS in***

UK/Europe to join a similar number of Brighton Thrombosis CD WG members. In practice, however, we found it too challenging to get busy clinicians together across multiple time zones in a hurry on short notice. Alternatively, we used a pre-organized meeting of the International Network of Special Immunization Services (INSIS) on this topic on 6 April 2021 (and subsequent days via email) to draft the interim version and are now sharing it for broad peer review. We hope to finalize the interim CD within 1-2 weeks. Our initial focus is on cases with both thrombocytopenia and thrombosis. We recognize that it is possible that some individuals may experience either thrombosis or thrombocytopenia alone, but evaluation of this will be done separately.

- ***For a <u>final CD</u>: we will:***
  - ***review as complete a description as possible of identified TTS cases;***
  - ***create a list of variables we wish to collect on them; we are merging questionnaires from UK, EMA, Canada, and others and will then develop a consensus document based upon peer review.***
  - ***organize and distribute the work to collect this information on each possible TTS case in a timely manner. For this process, we can create a distributed database file, merging all the de-identified data from each country, protecting confidentiality yet allowing for needed analyses.***
  - ***analyse the data to refine the Working CD with the goal of developing a formal final Brighton CD as swiftly as possible.***

Note: While this interim case definition focuses on identifying cases that have both thrombocytopenia and thrombosis, it is possible that patients with this condition are part of a spectrum which may include thrombocytopenia alone as well as patients with thrombosis without thrombocytopenia. The existing Brighton CD can be used to identify and classify those patients for further study. The US CDC has elected to prioritize previously identified manifestations including CVST and splanchnic vein thrombosis for signal evaluation [Shimabukuro, 2021]. However, here we have purposely used a broader definition to allow definition of what might be a broader spectrum of disease. In addition, in this revision we have attempted to address how heparin exposure should be addressed in identifying cases. Since exposure to heparin can cause heparin induced thrombocytopenia thrombosis (HITT) syndrome which clinically is similar to TTS, there was a consensus that cases should be stratified as to whether they had been exposed to heparin within 100 days of onset of their symptoms. We have therefore introduced levels 1-H, 2-H and 3-H for cases with heparin exposure in that time window. This heparin exposure could occur either before or after any vaccine exposure, if any.

<u>Interim Case Definition Thrombosis Thrombocytopenia Syndrome version 16</u>

Any patient presenting with both acute venous or arterial thrombosis and new onset thrombocytopenia [Wise, 2007] (as confirmed by both the Brighton Case Definitions for thrombocytopenia and thrombosis [Draft Brighton Collaboration Case Definition

of Thrombosis and Thromboembolism, 2021; Wise, 2007][1]. The Brighton Collaboration case definition for thrombocytopenia [Wise, 2007] requires a platelet count of less than 150 000/ µl.[2] Either one of the two Thrombocytopenia levels of certainty, Level 1 or Level 2, is sufficient to satisfy the condition of Thrombocytopenia for the TTS case definition.

- ***The Brighton Collaboration case definition for thrombosis [Draft Brighton Collaboration Case Definition of Thrombosis and Thromboembolism, 2021] is still undergoing final review. Currently the criteria for meeting the definition with level one certainty require confirmation by imaging, surgical, or pathology findings as specified below. Level two and three criteria are for a probable and possible case, respectively. The case definitions for probable and possible cases support case screening, identification, and inclusion from countries that may not have access to more sophisticated diagnostic studies.***
- ***TTS cases will be classified regarding level of certainty based upon the Brighton level of certainty achieved for thrombosis.***
- ***Cases will also be stratified as to whether the individual has had recent 1exposure to heparin.***

<u>Level 1</u> BC Thrombosis Thrombocytopenia Syndrome Case Criteria

A platelet count of less than 150 000/ µl of new onset without history of receipt of heparin within 100 days[3]

AND

Imaging study, surgical, or pathology findings consistent with thrombosis/thromboembolism

- ***Imaging studies include any of the following, depending on the location of the lesion[4]***
  - ***Ultrasound – Doppler***

---

[1] ***Note: Anti-PF-4 antibodies have been included in clinical case definitions designed to identify patients for treatment. Since our goal here is to provide an interim case definition to further our understanding of the syndrome via epidemiologic studies, these tests have not been included is the interim case definition, but this information will be collected on the cases identified.***

[2] ***For level one of the thrombocytopenia definition, either a blood smear to rule out platelet clumping or symptomatology in terms of bleeding is required. However, since with the TTS syndrome, the clinical manifestation is thrombosis and not bleeding and all cases will have thrombosis to meet the TTS definition, the requirement for a blood smear has been eliminated here.***

[3] ***No heparin within the last 100 days. Please see references for choice of this interval***

[4] ***Imaging will depend on location and whether venous or arterial thrombosis is present. With venogram for venous thrombosis and head CT or CT angiogram or MRI/MRI angiogram for arterial lesions.***

- *Computed Tomography (CT scan) – contrast/angiography*
- *Magnetic resonance venography (MRV) or arteriography (MRA)*
- *Echocardiogram*
- *Perfusion V/Q scan*
- *Conventional angiography/Digital subtraction angiography*

OR

- ***Procedure that confirms the presence of a thrombus (e.g. Thrombectomy)***

OR

- ***Pathology consistent with thrombosis/thromboembolism including biopsy or autopsy***

Most appropriate imaging test depends on the location of the lesion. Any of the tests listed may be used as available based on radiologist/expert interpretation.

Beyond the presence of thrombocytopenia, additional abnormal laboratory clotting study results are not required for confirmation as they can be normal in presence of thrombotic/thromboembolic events. When present, they can be supportive of the diagnosis, including:

- ***D-dimer elevated above the upper limit of normal for age***
- ***Shortened PT, PTT– below the lower limit of normal for age***

<u>Level 1-H</u> BC Thrombosis Thrombocytopenia Syndrome Case Criteria is the same as Level 1 except that the case has a history of heparin exposure within 100 days of symptom onset.

<u>Level 2</u> BC Thrombosis Thrombocytopenia Syndrome Criteria (modified) - Probable Case

- ***a platelet count of less than 150 000/ µl of new onset without recent history of receiving heparin within 100 days***

AND

A Clinical Presentation Consistent with Thrombosis or Thromboembolism Event, including

- ***Specific clinical syndromes including any of the following***
  - ***Deep vein thrombosis (DVT) – symptoms will depend on the location of the thrombosis, for example: swelling, pain, redness, or warmth of an extremity; headache, visual disturbance, seizures for sinus vein thrombosis; abdominal pain for intraabdominal thrombosis***

- *Pulmonary thromboembolism (PE) - sudden onset shortness of breath, pleuritic chest pain, sudden death/pulseless electrical activity arrest [Wells criteria for scoring –based on clinical findings]*
- *Stroke*
- *Myocardial infarction*
- *Arterial thrombosis*

AND

- ***Supporting Imaging or laboratory (D-dimer) findings suggestive but not definitive of thrombosis/thromboembolism including any of the following***
  - *Chest radiograph*
  - *Echocardiogram*
  - *Computed tomography without contrast*

  OR
  - *D-dimer - elevated above the upper limit of normal for age*

<u>Level 2-H</u> BC Thrombosis Thrombocytopenia Syndrome Case Criteria is the same as Level 2 except that the case has a history of heparin exposure within 100 days of symptom onset.

<u>Level 3</u> BC Thrombosis Criteria- Possible Case (Modified)

- ***a platelet count of less than 150 000/ µl of new onset without recent history of receiving heparin within 100 days.***

AND

Clinical Presentation Consistent with Thrombosis or Thromboembolism Event, including any of the following

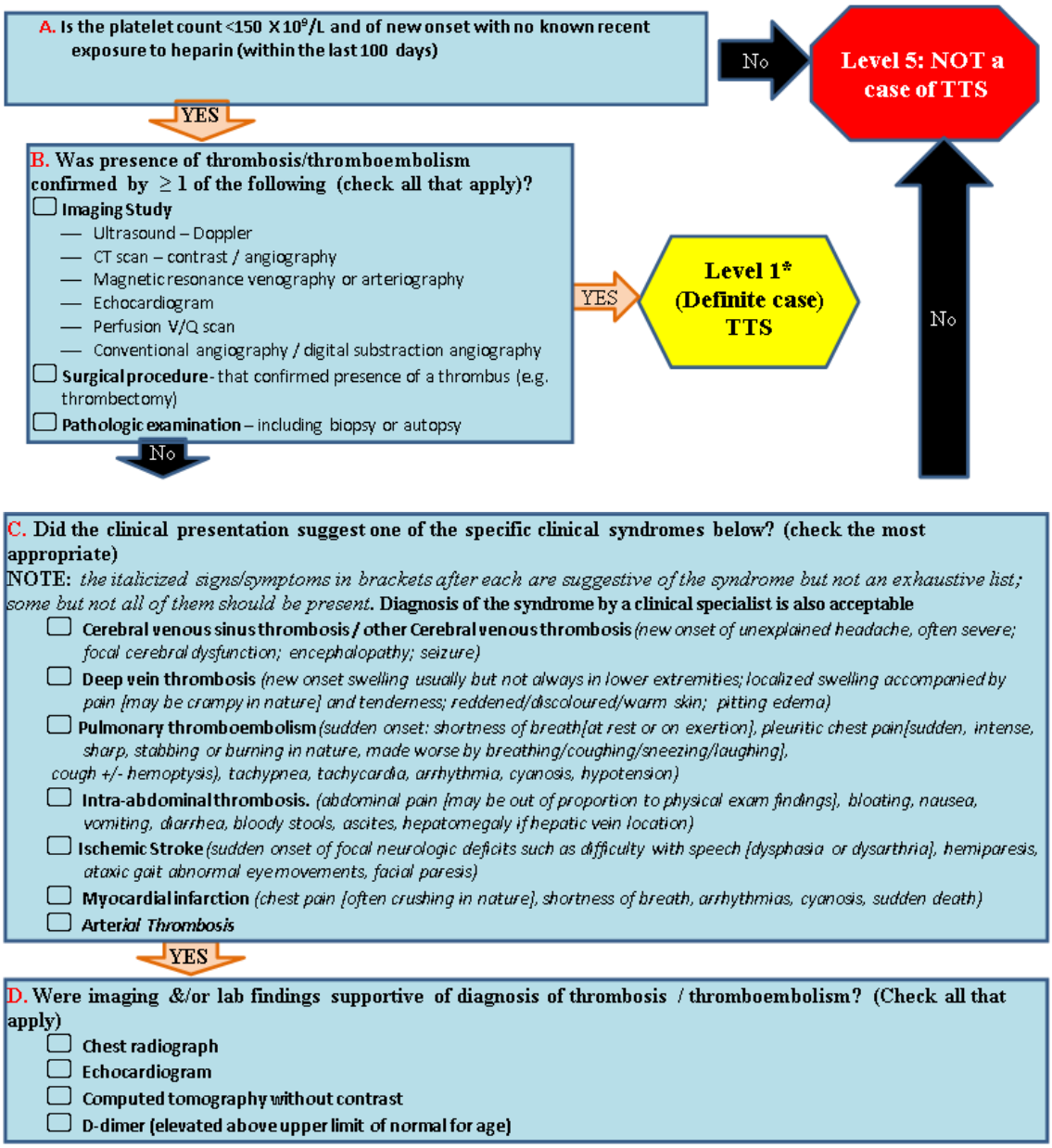
Specific clinical syndromes (see full list in the flow diagram below):

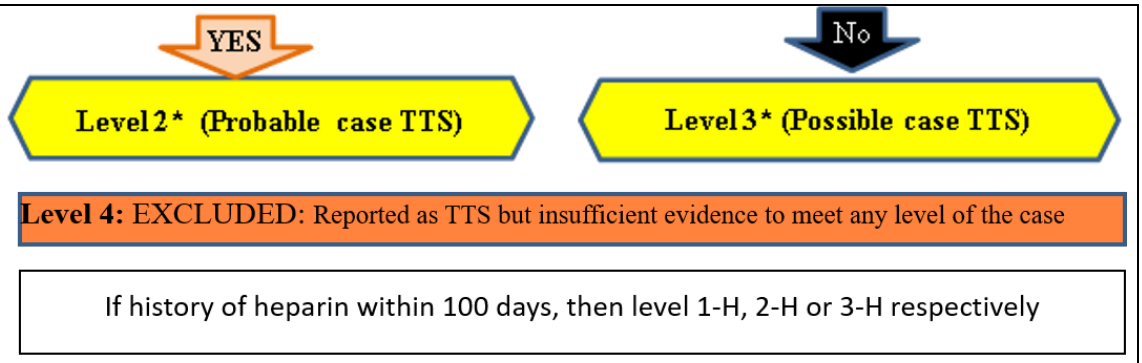
- ***Deep vein thrombosis (DVT) – symptoms will depend on the location of the thrombosis, for example: swelling, pain, redness, or warmth of an extremity; headache, visual disturbance, seizures for sinus vein thrombosis; abdominal pain for intraabdominal thrombosis.***
- ***Pulmonary thromboembolism (PE) - sudden onset shortness of breath, pleuritic chest pain, sudden death/pulseless electrical activity arrest (Wells criteria for scoring –based on clinical findings)***
- ***Stroke***
- ***Myocardial infarction***

- ***Arterial thrombosis***

<u>Level 3-H</u> BC Thrombosis Thrombocytopenia Syndrome Case Criteria is the same as Level 3 except that the case has a history of heparin exposure within 100 days of symptom onset.

Figure 8: Decision tree algorithm for case-finding of Thrombocytopenia Thrombosis Syndrome (TTS)





Acknowledgement

We thank in advance the voluntary contributions of all the colleagues who make developmentof Brighton Collaboration CDs possible. We hope to post a list such contributors for TTS CD when ready.

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eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
Amendment number:	8
Amendment date:	8 November 2021
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

CCI

[redacted]

List of changes

On the cover page, the names of contributing authors have been updated:

- PPD, Clinical Safety Representatives.
- PPD, Study Data Managers.

In Section 4.3, the following exclusion criterion has been modified.

- Administration of adenovirus/adenovector-based or MVA-based vaccine within the last 12 months except for adenovirus/adenovector-based COVID-19 vaccines that could be administered up to 30 days prior to the first study vaccine dose ***(applicable for all patients except for the patients in France) OR Administration of adenovirus/adenovector-based or MVA-based vaccine within the last 12 months (applicable for the patients in France only)***.

In Table 8, the following wording has been added for adenovector-based vaccines

COVID-19 vaccine	Prior study vaccination	During study vaccination	After study vaccination
mRNA based	14 days before first study vaccine dose	At least 14 days before or 30 days after study vaccination	30 days after last vaccine dose
Adenovector-based	30 days before first study vaccine dose ***(applicable for all patients except for the patients in France) OR 12 months before first study vaccine dose (applicable for the patients in France only).***	At least 30 days before or after study vaccination	30 days after last vaccine dose

Protein-based adjuvanted	30 days before first study vaccine dose	At least 30 days before or after study vaccination	30 days after last vaccine dose
Other technologies	30 days before first study vaccine dose	At least 30 days before or after study vaccination	30 days after last vaccine dose

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
Amendment number:	9
Amendment date:	16 June 2022
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

CCI

[redacted]

List of changes

On the cover page, the names of contributing authors have been updated:

- PPD Clinical Safety Representatives
- PPD, Study Data Managers
- PPD, Global Regulatory Leads
- PPD Public Disclosure Representatives.

In Sponsor signatory approval page, the sponsor details were updated:

Dorota Borys, MD
Clinical and Epidemiology R&D Project Lead
Therapeutic Hepatitis ***B (CHB-TI)*** and Pneumococcal vaccines,
GlaxoSmithKline Biologicals, SA

In Synopsis and Section 2.2, the following was modified in the secondary objectives:

- 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.
- To assess the efficacy ~~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.

CCI

[redacted]

In synopsis and Section 10.1, the Day and Visit details were added in the primary endpoints:

- Occurrence of serious adverse events (SAEs) up to six months after the last dose ***(Day 337, Visit 22)***.
- Occurrence of potential immune-mediated diseases (pIMDs) up to six months after the last dose ***(Day 337, Visit 22)***.
- Occurrence of liver-disease related AEs up to six months after the last dose ***(Day 337, Visit 22)***.
- Occurrence of hematological adverse events of special interest (AESIs) up to six months after the last dose (***Day 337, Visit 22)***.
- Occurrence of medically attended events (MAEs) up to six months after the last dose (***Day 337, Visit 22).***

CCI [redacted]

The following abbreviation was added in the list of abbreviations:

Pol	***Polymerase***

In Section 1.3, the following wordings were added:

Although clinical data on similar type of vaccines are available that are supportive to the use of each vaccine in the proposed vaccine regimen (see Sections 1.2.2 and 1.3.1), none of the investigational vaccines ***to be*** used in this study have been administered in humans yet ***prior the study start***. Therefore, safety and efficacy of the proposed vaccine regimen are unknown ***until the data are generated***.

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of the ChAd155-hIi-HBV, MVA-HBV and HBc-HBs/AS01$_{B-4}$ ***and for the data generated during the study***.

In Section 4.2, the following inclusion criterion was updated:

- Documented medical history of hBeAg-negative CHB prior to onset of NA therapy ***(applicable to all patients in Step A and Step B and to some patients in Step C) or documented medical history of hBeAg-negative CHB over a period of at least 24 months prior screening (applicable to some patients in Step C only).***

In Table 3, the following was added:

The Helpdesk is available by phone, fax and email
Phone ***(for countries where the toll-free number is not available)***: +32 2 656 68 04

CCI [redacted]

CCI [redacted]

In Table 11, laboratory details were updated

System	Discipline	Component	Method	Scale	Laboratory
Serum	HBV serology	Hepatitis B Virus.Surface Ab (Anti-HBs)[a]	CMIA	Qualitative	***GSK Biologicals' laboratory or laboratory designated by GSK***
		Hepatitis B Virus.Surface Ag (HBsAg)	CMIA	Quantitative	
		Hepatitis B Virus.e Ag (HBeAg)[a]	CLIA	Qualitative	Q^2 Solutions
		Hepatitis B Virus.Core Ab (Anti-HBc) [a]	CMIA	Qualitative	
		Hepatitis B Virus.e Ab (Anti-HBe)[a]	CCLIA	Qualitative	
		HBV DNA whole sequencing[b]	Sequencing	N/A	

In Table 13, Pol-specific details were added:

System	Component	Challenge	Method	Component priority rank	Laboratory[a]
PBMC	HBc-specific ($CD4^+/CD8^+$) T-cells	HBc peptide pool	CFC	1	GSK Biologicals' laboratory or laboratory designated by GSK
	HBs-specific ($CD4^+/CD8^+$) T-cells	HBs peptide pool	CFC	2	
	CCI [redacted]				

CCI [redacted]

In Table 19,

Sample type	Type of contact and time point	Sub groups	No. patients [b]	Component	Components priority rank
Blood for CMI response	Visit 1, Visit 4, Visit 6, Visit 7, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16, Visit 22, Visit 24 and Visit 26	All study groups	CCI	HBc-specific ($CD4^+$/$CD8^+$) T-cells	1
				HBs-specific ($CD4^+$/$CD8^+$) T-cells	2
	CCI				3
					4
					5

CCI [redacted]

In Section 8.4.2, the email address for GSK Biologicals Clinical Safety & Pharmacovigilance was updated:
Email address: ***ogm28723@gsk.com*** ~~Rix.CT-safety-vac@gsk.com~~

In Section 10.4.1, the following wording was added:

Endpoint 1 - "HBsAg loss percentage of responders in one group"

A sample of size of CCI [redacted] evaluable patients in the ~~vaccine~~ ***investigational*** group, with a one-sided alpha level of 10% will allow to conclude, with a power of at least 70% on a vaccine effect (*i.e.* at least 15% of responders, meaning a lower limit of the 80% CI of at least 15%) when having 30% responders in the vaccine group. ***Table 30 below provides the power to demonstrate at least 1-log decrease for a range of true response rates and sample sizes.***

Table 30: Power to demonstrate at least a 1-log decrease (i.e. 10-fold decrease) in qHBsAg or shows HBsAg loss at Day 337 versus Day 1

	True response rate	CCI [redacted]		
Power to demonstrate 80% CI LL >=15%	20%	23.9	16.4	14.8
	25%	48.5	31.3	24.3
	30%	71.8	48.4	35.2
	35%	87.6	64.8	46.7
	40%	95.6	78.2	58.0
Power to demonstrate 80% CI LL >=10%	15%	28.9	17.7	7.3
	20%	57.2	35.1	14.8
	25%	79.7	53.8	24.3
	30%	92.3	70.3	35.2
	35%	97.6	82.7	46.7
	40%	99.4	90.9	58.0

N = Number of evaluable patients
PASS – Test for one proportion using exact test

Table 32: Power to demonstrate a defined fold-decrease (*i.e.* log-difference) between two groups with CCI [redacted] evaluable patients per group respectively, SD varying from 0.5 to 0.9 – one-sided alpha = 10%

True-fold decrease	N per group	SD	Power
1-log decrease (*i.e.*10-fold decrease)	CCI [redacted]	0.5	100%
		0.9	97%
0.7-log decrease (*i.e.* 5-fold decrease)		0.5	100%
		0.9	88%
0.5-log decrease (i.e.3.2-fold decrease)		0.5	97%
		0.9	68%
1-log decrease (i.e.10-fold decrease)		***0.5***	***99.8%***
		0.9	***86.3%***
0.7-log decrease (i.e. 5-fold decrease)		***0.5***	***95.6%***
		0.9	***65.0%***

0.5-log decrease (i.e.3.2-fold decrease)	CCI [redacted]	***0.5***	***80.4%***
		0.9	***46.9%***

PASS – Two-Sample T-Test Power Analysis – H1: Mean < Mean Control

- ***An interim analysis may be performed on all available efficacy data, when at least approximately 50% of the patients (i.e.CCI patients i.e CCI evaluable patients in the B1 treatment group and CCI evaluable patients in the control group) in Step B have completed Visit 17 (Day 199) and data are available for the analysis.***
- ***If deemed necessary for the internal decision making, an additional interim analysis may be performed on all available efficacy data, when at least approximately 50% of the patients (i.e.CCI patients) in Step C have completed Visit 17 (Day 199) and data are available for the analysis.***

Otherwise mentioned, for all the planned analysis with CI, a 95% CI will be computed.

In Section 10.4.2, the following text and table were modified:

First interim analysis may be performed when CMI samples 14 days post-vaccination Dose 2 are tested and results are available for as many patients as possible but at least CCI patients vaccinated in Step B and available data of all patients in Step A. Considering that CCI% patients may be eliminated from analysis set, the aim is to have at least CCI evaluable patients of Step B CCI patients in group B1 CCI patients in group B2 and group B3).

Table 33: Exact 80% CI around observed percentage of CMI responders, considering ***a range of*** CCI evaluable patients

CCI [redacted]		**Observed percentage of CMI responders**	**Exact 80% CI (%)**
		20.0%	[5.5-45.0]
		30.0%	[11.6-55.2]
		40.0%	[18.8-64.6]
		50.0%	[26.7-73.3]
		60.0%	[35.4-81.2]
		70.0%	[44.8-88.4]
		80.0%	[55.0-94.5]
		90.0%	[66.3-99.0]
		20.0%	***[9.0-36.0]***
		30.0%	***[16.6-46.7]***
		40.0%	***[24.9-56.7]***
		50.0%	***[33.8-66.2]***
		60.0%	***[43.3-75.1]***
		70.0%	***[53.3-83.4]***
		80.0%	***[63.9-91.0]***
		90.0%	***[75.5-97.3]***
		20.0%	***[10.9-32.5]***
		30.0%	***[19.0-43.2]***
		40.0%	***[27.7-53.3]***
		50.0%	***[37.0-63.0]***
		60.0%	***[46.7-72.3]***
		70.0%	***[56.8-81.0]***

CCI [redacted]		***80.0%***	***[67.5-89.1]***
		90.0%	***[79.1-96.3]***

Subsequent interim analyses on CMI samples 14 days post-vaccination Dose 2 ***and 14 days post-vaccination dose 4*** may be performed for all patients in Step B and all patients in Step C (as many patients as possible in case of visit delay).

In Section 10.8.1, the following was added:

- ***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 (defined at 1-log increase from nadir in HBV DNA or HBV DNA becoming quantifiable after being below the LLOQ) 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.***
- Number and percentage of HBc-, HBs- CCI [redacted] specific CD4+/CD8+ T-cell responders will be computed ~~for the vaccine~~ ***by*** groups~~.~~

If sufficient patients are available for the analysis, efficacy analysis may be performed by categories of baseline HBsAg concentration, HBV genotype and subset of patients of this study meeting the eligibility criteria of the study TH HBV ASO-001.

The SAP will include a more technical and detailed description of the statistical analyses.

PoP

- In step B and step C, 80% CIs of qHBsAg GMC ratios between groups receiving candidate study vaccine at six months post last vaccine dose ***(Day 337, Visit 22)*** 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 titer as covariate. Lower limit of the CI above 1 will also be considered as indicator of PoP.

Exploratory group comparisons

- Additional exploratory group comparisons will be performed to evaluate the added value of the adjuvanted proteins on the top of viral vectored vaccines and to evaluate the best vaccination regimen for the administration of the adjuvanted proteins (i.e. either sequentially to or co-administered with the viral vectored vaccines).

- The qHBsAg GMC ratio between groups at six months post last vaccine dose ***(Day 337, Visit 22)*** 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 titer as covariate.
- The difference between the groups in percentage of patients with at least a 10-fold decrease (i.e. 1-log difference) in qHBsAg or HBsAg loss at Day 337 versus Day 1 will be computed with CIs.

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

If sufficient patients are available for the analysis, additional descriptive analysis may be performed by categories of baseline HBsAg concentration, HBV genotype ***and history of HBeAg-negative CHB (documented prior to onset of NA therapy or over a period of at least 24 months prior screening).***

The SAP will include a more technical and detailed description of the statistical analyses.

In Section 10.11.1, the following points were added:

- ***An interim analysis may be performed when CMI samples up to 14 days post-vaccination Dose 4 (Day 183) are tested and results are available for***
  - ***all patients in Step B* and,***
  - ***all patients in Step C****
  - ****In case of visit delay, analysis may be performed for as many patients as possible with data available at the time of the analysis. Analysis for remaining patients will be performed at the time of the next analysis.***
- ***An interim analysis may be performed on available efficacy data, when at least 50% of the patients CCI patients) in Step B have completed Visit 17 (Day 199) and efficacy data are available for the analysis. This analysis will be documented in a statistical report.***
- ***If deemed necessary for internal decision making, an interim analysis may be performed on available efficacy data, when at least approximately 50% of the patients (i.e. CCI patients) in Step C have completed Visit 17 (Day 199) and efficacy data are available for the analysis. This analysis will be documented in a statistical report.***
- A final analysis of follow-up for safety/immunogenicity/efficacy will be performed when all data up to Day 841 are cleaned and available. ***This analysis may be performed for combined Step A and Step B and separately for Step C.*** Individual listings will be provided at this stage. This analysis will be documented in a statistical report.

An integrated clinical study report containing all data will be written and made available to the investigators.

All the interim analyses will be performed by project independent statistician in order to keep GSK central study team blinded as much as possible.

In Section 13, the following reference was added:

Greinacher A, Langer F, Makris M, et al. Vaccine-induced immune thrombotic thrombocytopenia (VITT): Update on diagnosis and management considering different resources. J Thromb Haemost. 2022;20(1):149-156.

CCI [redacted]

This assay is applied to measure the frequency of antigen-specific T-lymphocytes in peripheral blood. Blood samples are collected by venipuncture and PBMCs are prepared by certified laboratories by centrifugation onto a Lymphoprep™ cushion within 24 hours following collection. PBMC suspensions are stored in liquid nitrogen until analysis. To measure T-cell responses elicited by the vaccine candidate, samples are thawed and cultured overnight in the presence of costimulatory antibodies (anti-CD28 and anti-CD49d) without stimulation (background control) or with peptide pools (15mer overlapping by 11) covering the sequence of the relevant antigens (HBs, HBc, CCI [redacted] Cells are then immunostained for surface phenotypic markers (CD4 and CD8), permeabilized and then immunostained for CD3 and activation markers (the costimulatory molecules CD40L and 4-1BB and the cytokines IL-2, IFN-γ, TNF-α, IL-13, IL-17). Analysis is performed by multiparametric flow cytometry, and the results are expressed after background subtraction as frequencies of antigen specific $CD4^+$ (or $CD8^+$) T-cells producing various combinations of the activation markers assessed per million $CD4^+$ (or $CD8^+$) T-cells.

In Table 35, the following was deleted:

~~CEVAC - University of Gent~~	~~Corneel Heymanslaan 10 9000 Gent Belgium~~

In Appendix C, the heading was modified and the following footnote was added:

Appendix C: Toxicity Grading For Hematology, Biochemistry and ***Urinalysis*** Parameters

**** For urinanalysis the primary testing method used in the clinical trials is urine dipstick. This method of testing does not allow for precise conversion of the results of blood in urine into FDA grading. Therefore blood in urine results are reported based on dipstick scale (small + refers to ≥ 25 ery/µL, moderate ++ refers to ≥ 80 ery/µL, large +++ refers to ≥ 200 ery/µL).***

In Appendix E, the case definition for Brighton Collaboration has been updated:

(The current interim case definition, v10.16.4 dated 11 November 2021 is provided below. Please refer to https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-interim-case-definition/ for the most updated version of the case definition.)

Beginning in February, 2021, multiple European countries (e.g., Austria, Denmark, Norway, Germany, UK) and Australia have reported cases of thrombosis with thrombocytopenia syndrome (TTS) in persons who received the Astra-Zeneca (AZ) COVID-19 vaccine (1-3, 10) and more recently in the US with the Janssen vaccine (11). In May 2021, a draft interim case definition was proposed by the Brighton Collaboration. Since that time, understanding of this condition and its relationship to vaccines has evolved. Recent work by Andreas Greinacher and others now allow revision of the original case definition and level of certainty algorithm [Greinacher, 2022]. The goal of this case definition is to facilitate harmonized studies of this outcome. This supplements guidelines published by WHO provided information on case identification for treatment.

The Case Definition (CD) Level of Certainty (LOC) is determined based on a series of clinical conditions defined below.

Condition A: ☐ Platelet count <150 X 10^9/L and of new onset with no known recent exposure to heparin (within the last 30 days)

Condition B1: ☐ Presence of thrombosis/thromboembolism confirmed by ≥ 1 of the following (Check all that apply below)

☐Imaging Study

- ***Ultrasound – Doppler***
- ***CT scan – contrast / angiography***
- ***Magnetic resonance venography or arteriography***
- ***Echocardiogram***
- ***Perfusion V/Q scan***
- ***Conventional angiography / digital subtraction angiography***

☐ Surgical procedure - that confirmed presence of a thrombus (e.g. thrombectomy)

☐ Pathologic examination – including biopsy or autopsy

Condition B2: ☐ Severe and persistent headache onset ≥5d post vaccination with elevated D-DIMER >8x ULN (Upper limits of normal)

Condition C: ☐ Clinical presentation suggests one of the specific clinical syndromes below? (Check the most appropriate) NOTE: the italicized signs/symptoms in brackets after each are suggestive of the syndrome but not an exhaustive list; some

of them should be present. Diagnosis of the syndrome by a clinical specialist is also acceptable

☐ Cerebral venous sinus thrombosis / other Cerebral venous thrombosis (new onset of unexplained headache, often severe, typically persisting; focal cerebral dysfunction; encephalopathy; seizure; blurred vision; double vision)

☐ Deep vein thrombosis (new onset swelling usually but not always in lower extremities; localized swelling accompanied by pain [may be crampy in nature] and tenderness; reddened/discoloured/warm skin; pitting edema)

☐ Pulmonary thromboembolism (sudden onset: shortness of breath[at rest or on exertion], pleuritic chest pain [sudden, intense, sharp, stabbing or burning in nature, made worse by breathing/coughing/sneezing/laughing], cough +/- hemoptysis), tachypnea, tachycardia, arrhythmia, cyanosis, hypotension)

☐ Intra-abdominal thrombosis. (abdominal pain [may be out of proportion to physical exam findings], bloating, nausea, vomiting, diarrhea, bloody stools, ascites, hepatomegaly if hepatic vein location)

☐ Ischemic Stroke (sudden onset of focal neurologic deficits such as difficulty with speech [dysphasia or dysarthria], hemiparesis, ataxic gait abnormal eye movements, facial paresis)

☐ Myocardial infarction (chest pain [often crushing in nature], shortness of breath, arrhythmias, cyanosis, sudden death)

☐ Arterial Thrombosis

Condition D: ☐ One or more of these imaging or lab findings supportive of the diagnosis of thrombosis / thromboembolism? (Check all that apply)

☐ Echocardiogram or doppler ultrasound

☐ Computed tomography without contrast or MRI

☐ D-dimer (Elevated above upper limit of normal for age)

Condition E: ☐ At least one of these Lab findings that are strongly supportive of the diagnosis of platelet-activating antibody mediated thrombosis? (Check all that apply)

☐ D-dimer > 4 times ULN for age

☐ Positive anti-platelet factor 4 (PF4) assay: specific anti-PF4 ELISA (note: rapid tests are insensitive for these antibodies) or functional test with addition of PF4

TTS Case Definition Level of Certainty Determination

If yes to (A and B1) or yes to (A and B2): then is Level 1

If no to (B1 and B2)_and_[If yes to A plus yes to (C and E)] then is level 1

If no to (B1 and B2)_and_[If yes to A plus yes to (C and D)] then is level 2

If no to (B1 and B2)_and_[If yes to A plus [(yes to C) and (no to D and E)] then is level 3If there is insufficient information to determine the conditions needed to a level of certainty of 1, 2 or 3 then the level of certainty is level 4

If there is sufficient information to determine the conditions A, B, C, D, and E but the aggregate of the conditions do not meet the LOC 1, 2, or 3 then the LOC is Level 5; Not a Case of TTS.

~~Since at least mid-February 2021, multiple European countries (e.g., Austria, Denmark, Norway, Germany, UK) and Australia have reported cases of thrombosis with thrombocytopenia syndrome (TTS) in persons who received the Astra-Zeneca (AZ) COVID-19 vaccine [Greinacher, 2021; Schultz, 2021; ATAGI, 2021; Scully, 2021] and more recently in the US with the Janssen vaccine [Cines, 2021]. There is currently no standard case definition (CD) for TTS accepted for use by all countries. On 3 April 2021, the British Society of Haematology published its Updated Guidance on Management Version 1.0 with CD for possible, probable, and definite cases of TTS [British Society of Haematology, 2021]. This document is oriented towards identification and treatment of cases rather than being designed for epidemiologic studies, especially initial case finding, however. Therefore, there is an urgent need for the latter a draft of which is included in 4 below.~~

~~Since its inception in 1999, the Brighton Collaboration has sought to advance the science of vaccine safety by developing standard CD for adverse events following immunizations (AEFI's) [Bonhoeffer, 2002]. To date, >60 CD's have been developed, such as fever, seizure, anaphylaxis, intussusception, narcolepsy, etc. Individual CD for thrombosis [Draft Brighton Collaboration Case Definition of Thrombosis and Thromboembolism, 2021] and for thrombocytopenia [Wise, 2007] have also been developed.~~

- ~~Based on this experience, we propose a two-step process (see proposed process below) to develop both:~~
- ~~A "draft interim case definition" to facilitate identifying a cohort of individuals with this clinical entity (see interim/working CD for TTS below for process; interim case definition thrombosis thrombocytopenia syndrome version 16 below for draft); who could then be studied using a common study protocol and assessment tools.~~
- ~~While others have called this new syndrome Vaccine-induced immune thrombotic thrombocytopenia (VITT) [Greinacher, 2021; Schultz, 2021]; this assumes a causal mechanism. We have elected to use 'TTS' [ATAGI, 2021] for this initial case finding purpose.~~

- ~~To this end, vaccination with a SARS-2-CoV vaccine would not be required to enter this cohort but clearly vaccine exposure information would be collected on these individuals along with other variables and laboratory tests that have yet to be fullyidentified (see final CD below).~~
- ~~A final Brighton case definition (see final CD below)~~
- ~~When new clinical syndromes or diseases are first identified, standard CD are needed for both clinical (e.g., appropriate diagnosis, treatment) and public health (e.g. epidemiologic studies, and data harmonization) purposes. This is especially true for rare events where any misclassification will hinder scientific progress. The process for developing a final standard CD for a new illness usually takes some time requiring serial improvements of working or interim CD as full knowledge accumulates. The US CDC CD for what came to be called Acquired Immuno-Deficiency Syndrome (AIDS) for example was initially developed in 1981 and revised in 1985, 1987, and 1993 [British Society of Haematology, 2021]. The Chinese CD for COVID-19 changed seven times from 15 January 2020 to 30 March 2020 [Bonhoeffer, 2002].~~
- ~~The Brighton CD's are usually tiered into three levels of available evidence, level one (high), level two (medium), and level three (low). This gradient in evidence might be acquired from clinical trials (high) or routine passive surveillance (low); or alternatively, tertiary referral hospital (high) vs. basic rural clinic (low). We try generally to avoid use of the terms Definite, Probable, Possible in this context as these terms are also commonly used for the strength of causal link (see below), but are making an exception here as they are more concise and meaningful than not using them.~~
- ~~Because Brighton's overall interest is in accurate understanding of whether the vaccine exposure causes the AEFI or not; and because most AEFI's lack a unique clinical or laboratory marker to establish a causal link, the only way of demonstrating this causal link is by showing that vaccinated persons have a higher rate of the AEFI than unvaccinated persons in an unbiased manner (either from clinical trials or epidemiologic studies). Process-wise, the data for this rate comparison is usually best attained by first finding all possible cases of the specific AEFI or adverse event of special interest (AESI), then separately ascertaining their vaccine exposure status in a blinded manner, before linking the two. As Brighton CD are designed to find all possible cases of meaning the CD in an unbiased manner relative to vaccine exposure, they do not include vaccine exposure as part of the CD.~~

~~Proposed process:~~

- ~~For interim/working CD for TTS: We initially proposed identifying a small number (e.g. 3) haematologists familiar with the recent cases of TTS in UK/Europe to join a similar number of Brighton Thrombosis CD WG members. In practice, however, we found it too challenging to get busy clinicians together across multiple time zones in a hurry on short notice. Alternatively, we used a pre-organized meeting of the International Network of Special Immunization Services (INSIS) on this topic on 6 April 2021 (and subsequent days via email) to draft the interim version and~~

are now sharing it for broad peer review. We hope to finalize the interim CD within 1-2 weeks. Our initial focus is on cases with both thrombocytopenia and thrombosis. We recognize that it is possible that some individuals may experience either thrombosis or thrombocytopenia alone, but evaluation of this will be done separately.

- For a final CD: we will:
- review as complete a description as possible of identified TTS cases;
- create a list of variables we wish to collect on them; we are merging questionnaires from UK, EMA, Canada, and others and will then develop a consensus document based upon peer review.
- organize and distribute the work to collect this information on each possible TTS case in a timely manner. For this process, we can create a distributed database file, merging all the de-identified data from each country, protecting confidentiality yet allowing for needed analyses.
- analyse the data to refine the Working CD with the goal of developing a formal final Brighton CD as swiftly as possible.

Note: While this interim case definition focuses on identifying cases that have both thrombocytopenia and thrombosis, it is possible that patients with this condition are part of a spectrum which may include thrombocytopenia alone as well as patients with thrombosis without thrombocytopenia. The existing Brighton CD can be used to identify and classify those patients for further study. The US CDC has elected to prioritize previously identified manifestations including CVST and splanchnic vein thrombosis for signal evaluation [Shimabukuro, 2021]. However, here we have purposely used a broader definition to allow definition of what might be a broader spectrum of disease. In addition, in this revision we have attempted to address how heparin exposure should be addressed in identifying cases. Since exposure to heparin can cause heparin induced thrombocytopenia thrombosis (HITT) syndrome which clinically is similar to TTS, there was a consensus that cases should be stratified as to whether they had been exposed to heparin within 100 days of onset of their symptoms. We have therefore introduced levels 1-H, 2-H and 3-H for cases with heparin exposure in that time window. This heparin exposure could occur either before or after any vaccine exposure, if any.

Interim Case Definition Thrombosis Thrombocytopenia Syndrome version 16

Any patient presenting with both acute venous or arterial thrombosis and new onset thrombocytopenia [Wise, 2007] (as confirmed by both the Brighton Case Definitions for thrombocytopenia and thrombosis [Draft Brighton Collaboration Case Definition of Thrombosis and Thromboembolism, 2021; Wise, 2007][5]. The Brighton Collaboration

[5] Note: Anti-PF-4 antibodies have been included in clinical case definitions designed to identify patients for treatment. Since our goal here is to provide an interim case definition to further our understanding of

~~case definition for thrombocytopenia [Wise, 2007] requires a platelet count of less than 150 000/ µl.[6] Either one of the two Thrombocytopenia levels of certainty, Level 1 or Level 2, is sufficient to satisfy the condition of Thrombocytopenia for the TTS case definition.~~

- ~~The Brighton Collaboration case definition for thrombosis [Draft Brighton Collaboration Case Definition of Thrombosis and Thromboembolism, 2021] is still undergoing final review. Currently the criteria for meeting the definition with level one certainty require confirmation by imaging, surgical, or pathology findings as specified below. Level two and three criteria are for a probable and possible case, respectively. The case definitions for probable and possible cases support case screening, identification, and inclusion from countries that may not have access to more sophisticated diagnostic studies.~~
- ~~TTS cases will be classified regarding level of certainty based upon the Brighton level of certainty achieved for thrombosis.~~
- ~~Cases will also be stratified as to whether the individual has had recent 1exposure to heparin.~~

~~Level 1 BC Thrombosis Thrombocytopenia Syndrome Case Criteria~~

~~A platelet count of less than 150 000/ µl of new onset without history of receipt of heparin within 100 days[7]~~

~~AND~~

~~Imaging study, surgical, or pathology findings consistent with thrombosis/thromboembolism~~

- ~~Imaging studies include any of the following, depending on the location of the lesion[8]~~
- ~~Ultrasound – Doppler~~
- ~~Computed Tomography (CT scan) – contrast/angiography~~
- ~~Magnetic resonance venography (MRV) or arteriography (MRA)~~

~~the syndrome via epidemiologic studies, these tests have not been included is the interim case definition, but this information will be collected on the cases identified.~~

~~[6] For level one of the thrombocytopenia definition, either a blood smear to rule out platelet clumping or symptomatology in terms of bleeding is required. However, since with the TTS syndrome, the clinical manifestation is thrombosis and not bleeding and all cases will have thrombosis to meet the TTS definition, the requirement for a blood smear has been eliminated here.~~

~~[7] No heparin within the last 100 days. Please see references for choice of this interval~~

~~[8] Imaging will depend on location and whether venous or arterial thrombosis is present. With venogram for venous thrombosis and head CT or CT angiogram or MRI/MRI angiogram for arterial lesions.~~

- ~~Echocardiogram~~
- ~~Perfusion V/Q scan~~
- ~~Conventional angiography/Digital subtraction angiography~~

~~OR~~

- ~~Procedure that confirms the presence of a thrombus (e.g. Thrombectomy)~~

~~OR~~

- ~~Pathology consistent with thrombosis/thromboembolism including biopsy or autopsy~~

~~Most appropriate imaging test depends on the location of the lesion. Any of the tests listed may be used as available based on radiologist/expert interpretation.~~

~~Beyond the presence of thrombocytopenia, additional abnormal laboratory clotting study results are not required for confirmation as they can be normal in presence of thrombotic/thromboembolic events. When present, they can be supportive of the diagnosis, including:~~

- ~~D-dimer elevated above the upper limit of normal for age~~
- ~~Shortened PT, PTT - below the lower limit of normal for age~~

~~Level 1-H BC Thrombosis Thrombocytopenia Syndrome Case Criteria is the same as Level 1 except that the case has a history of heparin exposure within 100 days of symptom onset.~~

~~Level 2 BC Thrombosis Thrombocytopenia Syndrome Criteria (modified) - Probable Case~~

- ~~a platelet count of less than 150 000/ µl of new onset without recent history of receiving heparin within 100 days~~

~~AND~~

~~A Clinical Presentation Consistent with Thrombosis or Thromboembolism Event, including~~

- ~~Specific clinical syndromes including any of the following~~
- ~~Deep vein thrombosis (DVT) - symptoms will depend on the location of the thrombosis, for example: swelling, pain, redness, or warmth of an extremity; headache, visual disturbance, seizures for sinus vein thrombosis; abdominal pain for intraabdominal thrombosis~~
- ~~Pulmonary thromboembolism (PE) - sudden onset shortness of breath, pleuritic chest pain, sudden death/pulseless electrical activity arrest [Wells criteria for scoring - based on clinical findings]~~
- ~~Stroke~~

- ~~Myocardial infarction~~
- ~~Arterial thrombosis~~

~~AND~~

- ~~Supporting Imaging or laboratory (D-dimer) findings suggestive but not definitive of thrombosis/thromboembolism including any of the following~~

- ~~Chest radiograph~~
- ~~Echocardiogram~~
- ~~Computed tomography without contrast~~

~~OR~~

- ~~D-dimer - elevated above the upper limit of normal for age~~

~~Level 2-H BC Thrombosis Thrombocytopenia Syndrome Case Criteria is the same as Level 2 except that the case has a history of heparin exposure within 100 days of symptom onset.~~

~~Level 3 BC Thrombosis Criteria- Possible Case (Modified)~~

- ~~a platelet count of less than 150 000/ µl of new onset without recent history of receiving heparin within 100 days.~~

~~AND~~

~~Clinical Presentation Consistent with Thrombosis or Thromboembolism Event, including any of the following~~

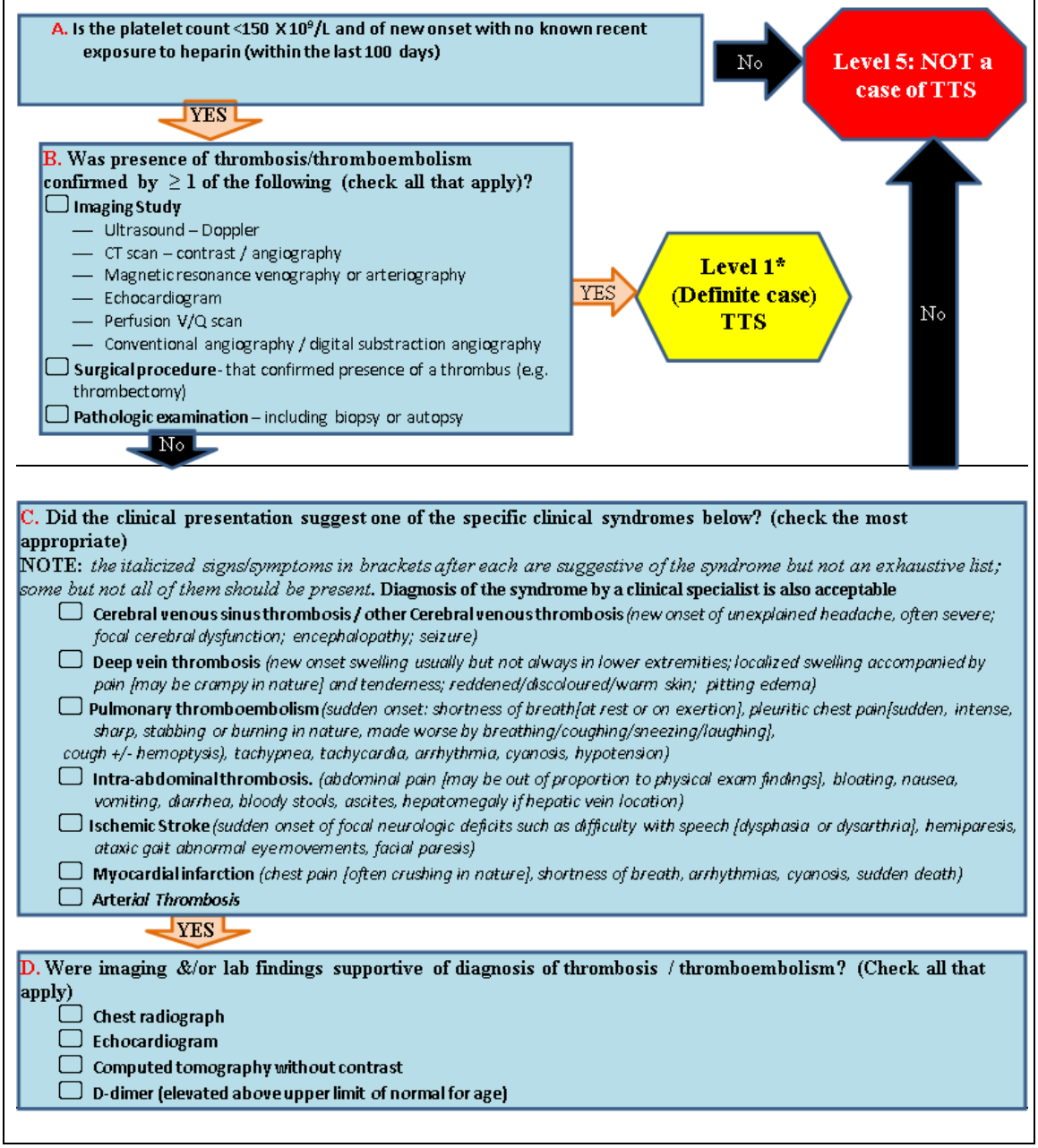
~~Specific clinical syndromes (see full list in the flow diagram below):~~

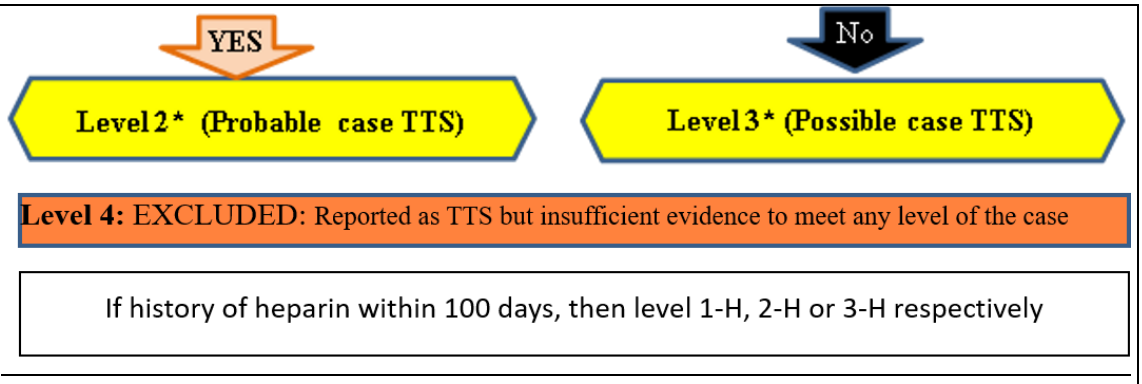
- ~~Deep vein thrombosis (DVT) – symptoms will depend on the location of the thrombosis, for example: swelling, pain, redness, or warmth of an extremity; headache, visual disturbance, seizures for sinus vein thrombosis; abdominal pain for intraabdominal thrombosis.~~

- ~~Pulmonary thromboembolism (PE) – sudden onset shortness of breath, pleuritic chest pain, sudden death/pulseless electrical activity arrest (Wells criteria for scoring – based on clinical findings)~~
- ~~Stroke~~
- ~~Myocardial infarction~~
- ~~Arterial thrombosis~~

~~Level 3-H BC Thrombosis Thrombocytopenia Syndrome Case Criteria is the same as Level 3 except that the case has a history of heparin exposure within 100 days of symptom onset.~~

~~Figure 8 Decision tree algorithm for case-finding of Thrombocytopenia Thrombosis Syndrome (TTS)~~





~~Acknowledgement~~

~~We thank in advance the voluntary contributions of all the colleagues who make developmentof Brighton Collaboration CDs possible. We hope to post a list such contributors for TTS CD when ready.~~

~~References~~

~~ATAGI statement on AstraZeneca vaccine in response to new vaccine safety concerns. https://www.health.gov.au/news/atagi-statement-on-astrazeneca-vaccine-in-response-to-new- vaccine- safety-concerns (accessed Apr. 10, 2021).~~

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~~Wise RP, Bonhoeffer J, Beeler J, Donato H, Downie P, Matthews D, et al; Brighton Collaboration Thrombocytopenia Working Group. Thrombocytopenia: case definition and guidelines for collection,analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5717-24. https://doi.org/10.1016/j.vaccine.2007.02.067. Epub 2007 Mar 12. PMID: 17493712.~~

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
Amendment number:	10
Amendment date:	23 September 2022
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

CCI

[redacted]

List of changes

On the cover page, the names of contributing authors have been updated:

- PPD, Laboratory Science Representatives, Laboratory Study Managers
- PPD, Clinical and Epidemiology R&D Project Leads

In Sponsor signatory approval page, the sponsor details were updated

Dietrich Bosse, MD

~~Dorota Borys, MD~~

Clinical and Epidemiology R&D Project Lead
Therapeutic Hepatitis B (CHB-TI) ~~and Pneumococcal~~ vaccines,
GlaxoSmithKline Biologicals, SA

In Section 8.1.5.2.1, the following wording was modified:

Recently, following COVID-19 vaccines, thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed very rarely following vaccination with adenovector-based COVID-19 vaccines. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases had a fatal outcome. The majority of these cases occurred within the first ~~two~~ ***three*** weeks following adenovector-based COVID-19 vaccination and mostly in ~~women~~ ***individuals*** under 60 years of age.

In Appendix E, the title was updated:

Updated Brighton Collaboration Case Definition ***for Thrombosis with Thrombocytopenia Syndrome (TTS).***

eTrack study number and Abbreviated Title	204852 (TH HBV VV-001)
Amendment number:	11
Amendment date:	22 June 2023
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

CCI

[redacted]

List of changes:

On the cover page, the names of co-ordinating and contributing authors have been updated:

- PPD Scientific Writers, Modis for GSK Biologicals
- PPD, Scientific Writer
- PPD, Clinical ~~Research Development~~ ***Science*** Leads
- PPD, Lead Statistician
- PPD, ~~Bio-~~***Study*** Statistician
- PPD, Clinical Laboratory Science Representatives, Clinical Readout Team Leaders
- PPD, Clinical Safety Representatives
- PPD Clinical Trial Supply Managers
- PPD Global Regulatory Leads
- PPD, Global Patent Representatives
- PPD, Clinical and ~~Epidemiology~~ R&D Project Leads ***(CPLs)***

In Sponsor signatory approval page, the following details were updated

Dietrich Bosse, MD

Clinical and ~~Epidemiology~~ R&D Project Lead

Therapeutic Hepatitis B (CHB-TI) vaccines, GlaxoSmithKline Biologicals, SA

In Section 5.5., the following footnote has been added for the list of procedures table 4 and 5:

In Table 4:

AE: Adverse events; AESI: Adverse event of special interest; AFP: alpha-fetoprotein; CBC: complete blood count; CMI: cell-mediated immunity; DNA: Deoxyribonucleic acid; eCRF: electronic Case Report Form GSK: GlaxoSmithKline; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; hli: human invariant chain; INR: international normalized ratio; MAE: medically attended event; ml: milliliter; pIMDs: potential immune-mediated diseases; qHBsAg: quantitative hepatitis B surface antigen; SAE: serious adverse event; Vacc: vaccination.
● 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.
[^] If subsequent vaccination cannot be administered within an interval of 53 - 63 days due to special circumstances or any other reasons, please refer to Section 5.6.18.
Refer to Section 5.6.18 for study procedures to be adapted during special circumstances.
[a] Women of childbearing potential are to have a pregnancy test prior to study vaccination (either a blood or urine test, depending on local clinical requirement). For women of non-childbearing potential, the specific reason for not performing a pregnancy test needs to be documented in the eCRF (current tubal ligation, hysterectomy, ovariectomy, post-menopause or other).
[b] For biochemical tests to be performed, please refer to Table 10 and Table 15.
[c] For information about hematological tests to be performed, please refer to Table 10 and Table 15.
[d] Blood sampling for CMI response will be collected from patients in centres with access to the PBMC processing facilities. For information about CMI response assays to be performed, please refer to Table 13 and Table 19.
[e] For information about humoral response assays to be performed, please refer to Table 12 and Table 18
[f] For information about urinalysis tests to be performed, please refer to Table 10 and Table 15. ***Routine urinalysis is done by dipstick. A microscopic examination* and albumin to creatinine ratio (ACR) *should be done (locally) if there is blood or protein reported from urine dipstick. If urine albumin and/or creatinine values are <LLOQ due to which the ACR cannot be calculated, it should be documented in the eCRF.***
[g] Additional blood sampling for biochemical/hematological testing may need to be performed in case of abnormal lab parameters. For more information, please refer to Section 8.5.3.
[h] For more information please refer to Section 6.7.
[i] For more information, please refer to Section 6.8.
[j] If liver ultrasound is not possible, alternative liver imaging examination (*e.g.* magnetic resonance or computerized tomography) may be performed at the discretion on the investigator. If it is not possible to perform a liver ultrasound at screening, a routine ultrasound performed within 180 days prior to the vaccination visit 1, can be used for eligibility assessment. For Germany, please see the country-specific requirements in Section 12.
[k] Blood samples for creatinine**,** FibroTest and Liver kidney microsomal type 1 (LKM-1) autoantibody tests should be collected after a minimum 8 hour fast.
[l] CCI [redacted]
[m] At Screening, a physical examination should be performed based on the clinical history of the patient. Physical examination at each subsequent study visit will be performed only if the patient indicates during questioning and test result review that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate. At Screening and at each vaccination, vital signs (including systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest) should be collected. Collected information needs to be recorded in the eCRF.
[n] Procedure not applicable if vaccination could not be administered at that vaccination visit.
[o] Procedure not applicable if vaccination was not administered at preceding vaccination visit.
CCI [redacted]
[q] The minimum requirements at Visits 2, 5, 9, 13 and 17 are safety assessment including, but not limited to, recording of solicited symptoms, unsolicited AEs within 30 days post-vaccination, SAEs, MAEs, AESIs, SAEs related to study participation, or to a concurrent GSK medication/vaccine, AEs/SAEs leading to study withdrawal, pregnancy and pregnancy outcome, intercurrent medical conditions leading to elimination from per-protocol

analyses and concomitant medications/vaccinations. The collection of data for safety assessment can be performed remotely (e.g. via phone contact). Other study procedures including biological samples collection and physical examination are optional at the discretion of the Investigator. However, efforts should be made for the patients needed for the first iSRC review in Step C to perform Visit 2 at the site to allow collection of biological samples for safety evaluation by iSRC. For patients participating to TH HBV VV-031 HBS:001 study, biological samples collection specific to that study remains mandatory for Visits 2 and 5.

[r] The randomization is performed after screening and prior Visit 1. All eligibility criteria should be confirmed before vaccination at Day 1 visit (i.e. Visit 1).

[s] In the sites/countries where a home nursing is possible according to local regulations, the patients may be offered the option to have a home visit. Only selected visits will have the option to be performed as a home visit, these may include biological samples collection, patients' assessments and data collection. The full specifications of the home nursing services will be outlined in the SPM.

[t] The screening window is extended from 90 days to 180 days except for CBC, INR, liver chemistry and HBV-DNA for which testing should be repeated if the interval between blood sampling at screening visit and the first dose vaccination at Visit 1 exceeds 90 days.

CCI [redacted]

[v] In case of a TTS event, an additional blood sample 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. For more information, please refer to Section 5.7.2**.**

CCI [redacted]

In Table 5:

AE: Adverse events; AESI: Adverse event of special interest; AFP: alpha-fetoprotein; CBC: complete blood count; CMI: cell-mediated immunity; DNA: Deoxyribonucleic acid; eCRF: electronic Case Report Form; GSK: GlaxoSmithKline; HBV: hepatitis B virus; INR: international normalized ratio; MAE: medically attended event; ml: milliliter; pIMDs: potential immune-mediated diseases; qHBsAg: quantitative hepatitis B surface antigen; SAE: serious adverse event; Vacc: vaccination.

Note: The double-line border following Visit 22 indicates the analyses which will be performed on all data (*i.e*. data that are as clean as possible) obtained up to Visit 22.

● 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.

Refer to Section 5.6.18 for study procedures to be adapted during special circumstances.

[a] For information about biochemical and biomarkers tests to be performed, please refer to Table 10 and Table 15. For information about virological tests to be performed, please refer to Table 11.

[b] For information about hematological tests to be performed, please refer to Table 10 and Table 15.

[c] For information about CMI response assays to be performed, please refer to Table 13 and Table 19.

[d] For information about humoral response assays to be performed, please refer to Table 12 and Table 18.

[e] For information about urinalysis tests to be performed, please refer to Table 10 and Table 15. ***Routine urinalysis is done by dipstick. A microscopic examination* and albumin to creatinine ratio (ACR) *should be done (locally) if there is blood or protein reported from urine dipstick. If urine albumin and/or creatinine values are <LLOQ due to which the ACR cannot be calculated, it should be documented in the eCRF.***

[f] For detailed information, please refer to Section 6.7.

[g] For detailed information, please refer to Section 6.8.

[h] Additional blood sampling for biochemical/hematological testing may need to be performed in case of abnormal lab parameters. For more information, please refer to Section 8.5.3.

[i] Blood samples for creatinine and FibroTest tests should be collected after a minimum 8 hour fast**.**

[j] If liver ultrasound is not possible, alternative liver imaging examination (*e.g*. magnetic resonance or computerized tomography) may be performed at the discretion on the investigator. If it is not possible to perform a liver ultrasound at screening, a routine ultrasound performed within 180 days prior to the vaccination visit 1, can be used for eligibility assessment. For Germany, please see the country-specific requirements in Section 12.

[k] If procedure has not been performed at the respective timepoints, it should be done at earliest convenience.
[l] For patients in Step A: the minimum requirements of Visits 19 and 21 are safety assessment including recording of solicited symptoms, unsolicited AEs within 30 days post-vaccination, SAEs, MAEs, AESIs, SAEs related to study participation, or to a concurrent GSK medication/vaccine, AEs/SAEs leading to study withdrawal, pregnancy and pregnancy outcome, intercurrent medical conditions leading to elimination from per-protocol analyses and concomitant medications/vaccinations. The safety assessment can be performed via telephone contact. Other study procedures including biological samples collection and physical examination are optional at the discretion of the Investigator. For patients in Step B and Step C, Visits 19 and 21 are cancelled.
[m] In the sites/countries where a home nursing is possible according to local regulations, the patients may be offered the option to have a home visit. Only selected visits will have the option to be performed as a home visit, these may include biological samples collection, patients' assessments and data collection. The full specifications of the home nursing services will be outlined in the SPM.
[n] Procedure to be performed in addition to the other procedures only if Unscheduled visit is planned in order to check for contraindication to the subsequent vaccination in case no biological samples have been collected since the previous vaccination visit due to special circumstances. Please refer to Section 5.6.18.
[o] In case of a TTS event, collection of an additional blood sample within 2 weeks of the diagnosis of the TTS for exploratory testing is optional. 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. For more information, please refer to Section 5.7.2.

In Section 8.1.5.2.1, the following changes are made:

Recently, following COVID-19 vaccines, thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed very rarely following vaccination with adenovector-based COVID-19 vaccines. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases had a fatal outcome. ***The majority of these cases occurred within the first two weeks following adenovector-based COVID-19 vaccination and mostly in women under 60 years of age (applicable for all patients except for the patients in Belgium). OR*** The majority of these cases occurred within the first three weeks following adenovector-based COVID-19 vaccination and mostly in individuals under 60 years of age ***(applicable for the patients in Belgium only).***

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