CLINICAL STUDY PROTOCOL

A Phase 1b/2a, Open-Label Study to Evaluate the Safety, Tolerability and Immunogenicity of VTP-300 With or Without Nivolumab in Participants with Chronic Hepatitis B Infection

Study Code: HBV002

EUDRACT Number: 2020-000190-25

NCT Number: NCT04778904

Version: 6.0
09 December 2021

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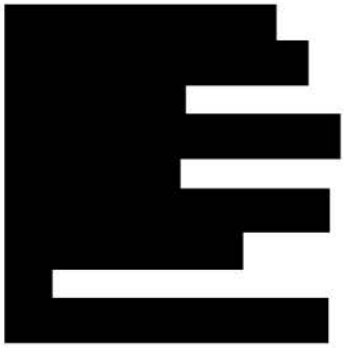
Sponsor's Authorised Representative: [redacted]

Signature Date

Printed Name

ADMINISTRATIVE AND CONTACT INFORMATION

Sponsor Medical Oversight Contact:



Contract Research Organisation:

Chief Investigator:

SAE/Pregnancy Reporting

INVESTIGATOR AGREEMENT

I, the undersigned, agree to conduct this study in accordance with this protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), the ethical principles set forth in the Declaration of Helsinki, and with local regulatory requirements.

Signature & Date (DD-MM-YYYY)

Printed Name

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PROTOCOL AMENDMENT CHANGE HISTORY

This is Version 6.0 of the protocol. The purpose of this amendment is to update the randomisation scheme following a review of interim data, which showed surface antigen responses in Groups 2 and 3. Groups 1 and 4 will be closed and patients will be randomised to Groups 2 and 3 only.

The original protocol (Version 1.0) was issued on 07 February 2020 and amended to Version 2.0 on 24 March 2020, to Version 3.0 on 18 April 2020 to Version 4.0 on 21 July 2020 and Version 5.0 on 04 May 2021.

For detailed protocol amendment changes refer to Appendix 6.

SUMMARY OF MAIN CHANGES

Version 6.0, 09 Dec 2021	
Summary and Justification of Change	**Section Changed**
Closing enrolment of Groups 1 and 4 due to interim data accrued on the first 27 patients to the 3-month time point	3.1.1 Study Overview 4.1 Number of Participants 5.2 Investigational Products Administered 5.7 Method of Assigning Participants to Treatment Groups
Change to overall recruitment number due to closing of Groups 1 and 4	3.1.1 Study Overview 4.1 Number of Participants
Justification for protocol changes and supporting information added	3.2 Discussion of Study Design, Including the Choice of Control Groups
Clarification on timings for Day 35 visit following second vaccination (Day 28)	6.3.2 Clinic Visits: Day 7, Day 35 and Month 3+ 7 days

Minor editorial changes have also been made to ensure consistency within the protocol. The synopsis has been updated to reflect all changes as appropriate.

Version 5.0, 04 May 2021	
Summary and Justification of Change	**Section Changed**
Added clarification for exclusion criterion #5 on exclusion levels for cirrhosis and advanced fibrosis.	4.3 Exclusion Criteria
Added clarification that exclusion criterion #13 that controlled thyroid disease is not exclusionary	4.3 Exclusion Criteria
Updated wording on the use of non-oral adenoviral vaccines since the development and approval of the AstraZeneca/Oxford University COVID-19 Vaccine	4.3 Exclusion Criteria 5.10 Prior and Concomitant Vaccines and Medications
Added wording on re-screening of participants to describe when and how re-screens should occur	6.1 Screening and Baseline Assessments
Updated wording to allow sites to take temperature according to their standard practice.	7.4.3 Vital Signs
Updated wording for consistency with ICH SAE reporting guidelines.	8.2.5 Reporting Requirements and Procedures for SAEs
Due to slower than anticipated enrolment, wording has been updated to allow for enough participants to receive study vaccine(s) to provide sufficient data for a meaningful review.	10.2.3 Interim Analyses
Correction of typographical errors – footers corrected to V5.0 and SmPC reference to current version 30 November 2020	Appendix 2

Specified that Month 3 booster dose is only applicable to UK participants	1.5 Study Rationale 3.1.1 Study Overview 3.2 Discussion of Study Design, Including the Choice of Control Groups 5.2 Investigational Products Administered 5.2.1 Study Vaccines 5.8.2.1 Dosing Schedule 6 Study Procedures at Each Visit/Schedule of Assessments 6.2 Treatment Day Assessments (Day 0, and Day 28 and Month 3 [Booster]) 6.3.1 Telephone Calls: Day 1, and Day 29 and Month 3 + 1 Day (MVA-HBV Boost) 6.3.2 Clinic Visits: Day 7, and Day 35 and Month 3 + 7 Days (MVA-HBV Boost) 6.3.3 Clinic Visit: Months 3 and 6

Version 4.0, 21 July 2020	
Summary of Changes	**Section Changed**
The dose of ChAdOx1-HBV to be used in this study has been confirmed as 2.5 x 10^{10} vp. A summary of the current available data from Study HBV001 has been provided and clarification of which data from that study has been reviewed to confirm the current dose has been added	1.4 Summary of Clinical Experience 3.2 Discussion of Study Design, Including the Choice of Control Groups 5.2.1 Study Vaccines 5.8.1 Selection of Doses in the Study
The potential of a booster dose of MVA-HBV to be given at Month 3 (as part of planned clinic visit) if there is a 0.5 log or greater drop in the hepatitis B surface antigen, at the Investigator's discretion and after discussion with the Sponsor	1.5 Study Rationale 3.1.1 Study Overview 3.2 Discussion of Study Design, Including the Choice of Control Groups 5.2 Investigational Products Administered 5.2.1 Study Vaccines 5.8.2.1 Dosing Schedule 6 Study Procedures at Each Visit/Schedule of Assessments 6.2 Treatment Day Assessments (Day 0, and Day 28 and Month 3 [Booster]) 6.3.1 Telephone Calls: Day 1, and Day 29 and Month 3 + 1 Day (MVA-HBV Boost) 6.3.2 Clinic Visits: Day 7, and Day 35 and Month 3 + 7 Days (MVA-HBV Boost) 6.3.3 Clinic Visit: Months 3 and 6 7.4.4 Physical Examination
Clarifications have been added that: • the study will be stopped for a death related to study vaccine • an appropriate substantial amendment will be filed if the DMC recommends resumption of the study, following a halt in enrolment	3.1.3 Stopping Criteria/Holding Criteria
The HBV DNA threshold for participant inclusion in the study was made consistent with published definitions of viral suppression and Study HBV001 (40 IU/mL)	4.2 Inclusion Criteria
The definition of post-menopausal status has been clarified in the relevant inclusion criterion to specify that the amenorrhoea	4.2 Inclusion Criteria

Version 4.0, 21 July 2020	
Summary of Changes	**Section Changed**
must be at least 12 months and without an alternative medical cause	
The duration of contraception requirements has been clarified to address the requirements for nivolumab (5 months post dose)	4.2 Inclusion Criteria
Exclusion criteria were added and revised to address appropriate risk mitigation for nivolumab	4.3 Exclusion Criteria
Clarification that the participants in Groups 3 and 4 will be initiated after evaluation of safety data 7 days after the first 6 participants in Group 2 have received ChAdOx1-HBV and not both study vaccines	5.7 Method of Assigning Participants to Treatment Groups 8.1.4 Safety Monitoring Committee
Additional guidance on the timing of nivolumab following vaccination and criteria to confirm that infusion may proceed have been provided	5.8.2.3 Nivolumab Preparation and Administration 6 Study Procedures at Each Visit/Schedule of Assessments 6.2 Treatment Day Assessments (Day 0 and Day 28)
Clarification regarding the use of on-going medications for Hepatitis B infection in that patients should remain on the same dose as when they entered the study and that antiviral medication should not be withdrawn Oral antiviral medications include: entecavir, tenofovir (tenofovir alafenamide fumarate or tenofovir disoproxil fumarate), or besifovir	5.10 Prior and Concomitant Vaccines and Medications
Due to the COVID-19 pandemic and to ensure the safety of participants and centre staff, clarification that study centres will follow any local procedures in line with testing has been added	6 Study Procedures at Each Visit/Schedule of Assessments
Clarification that the screening tests for HBV at screening are quantitative HBV DNA and quantitative HBsAg has been added	6 Study Procedures at Each Visit/Schedule of Assessments 6.1 Screening and Baseline Assessments
Due to the potential teratogenic effects of nivolumab and contraception requirements for 5 months post dose, additional pregnancy	6 Study Procedures at Each Visit/Schedule of Assessments 6.3.3 Clinic Visit: Months 3 and 6

Version 4.0, 21 July 2020	
Summary of Changes	**Section Changed**
testing at the 3- and 6-month visits for patients in Groups 3 and 4 has been included	
Clarification that international normalized ratio will be measured at screening only, prothrombin time will be measured at screening and Month 9 and activated partial thromboplastin time will not be measured was added	6.1 Screening and Baseline Assessments 6.3.3 Clinic Visit: Months 3 and 6 6.3.4 Clinic Visit: Month 9 (End of Study Visit)
Clarification that urea nitrogen and direct bilirubin (not total bilirubin) will be measured as part of the biochemistry panel and that bilirubin will be measured as part of the urinalysis was added	7.1.4.2 Biochemistry 7.1.4.4 Urinalysis
The protocol has been updated to include a reference to Section 4.8 of the Summary of Product Characteristics (SmPC) for nivolumab to determine expectedness of any serious adverse reactions	8.2.5.3 Medical Review and Reporting by the Sponsor
To be consistent with the Statistical Analysis Plan, separate definitions for the intent-to-treat and safety analysis sets have been included	10.2.1 Analysis Sets
To help with the planning of future studies, an interim analysis of all available data to be performed in June 2021 has been added	10.2.3 Interim Analyses
Toxicity management guidelines for nivolumab have been added	Appendix 2 Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Nivolumab

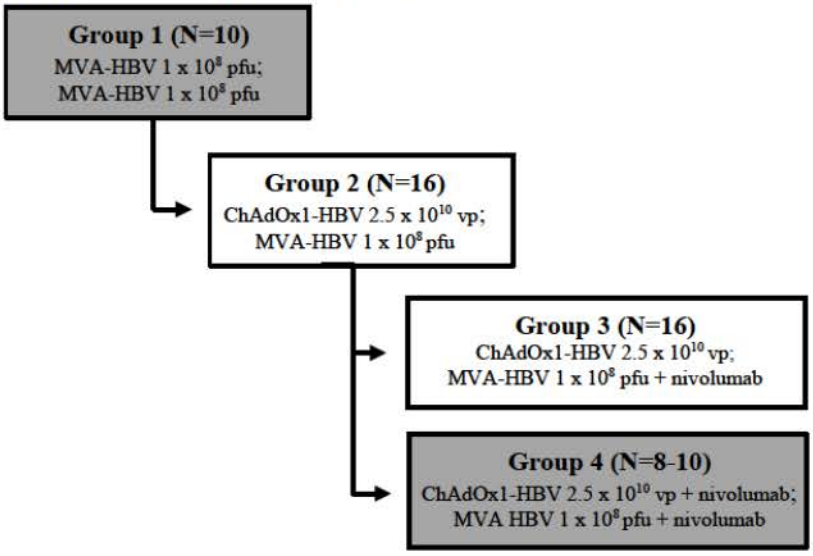
Version 3.0, 18 April 2020	
Summary and Justification of Change	**Section Changed**
The storage temperature has been corrected to ≤-70ºC to allow for the safe storage of both vaccines.	5.4 Storage

Minor editorial changes have also been made. The synopsis has been updated to reflect all changes as appropriate.

PROTOCOL SYNOPSIS

Title of Study:	A Phase 1b/2a, Open-Label Study to Evaluate the Safety, Tolerability and Immunogenicity of VTP-300 With or Without Nivolumab in Participants with Chronic Hepatitis B Infection
Short Title:	First in human study of VTP-300
Sponsor:	Vaccitech Ltd.
Protocol Number:	HBV002
Chief Investigator:	Professor Eleanor Barnes Professor of Hepatology and Experimental Medicine Nuffield Department of Medicine University of Oxford Oxford, OX3 7BN UK
Study Centres:	Up to 15 centres in Asia (South Korea and Taiwan) and Europe (UK)

Objectives:	**Endpoints:**
Primary Objectives • Determine the safety and reactogenicity of the following in participants with chronic HBV (CHB) infection and virally suppressed with oral antiviral medication: – MVA-HBV vaccine – ChAdOx1-HBV plus MVA vaccines – ChAdOx1-HBV plus MVA vaccines and nivolumab	***Primary Endpoints*** • Safety and reactogenicity of the vaccine(s): incidence of adverse events, serious adverse events (SAEs), ≥Grade 3 study vaccine-related adverse events within 4 weeks of vaccination • Safety of the vaccines with nivolumab: incidence of adverse events, SAEs, ≥Grade 3 adverse events within 4 weeks of dosing • Incidence of adverse events of special interest • Number and proportion of participants reporting treatment-emergent adverse events within each treatment group • Number and proportion of participants within each treatment group with potentially clinically significant laboratory values and vital signs within each treatment group • Change from baseline in laboratory tests and vital sign measurements to each time point of collection
Secondary Objectives • Determine the immunogenicity of the following in participants with CHB infection and virally suppressed with oral antiviral medication: – MVA-HBV vaccine – ChAdOx1-HBV plus MVA-HBV vaccines – ChAdOx1-HBV plus MVA-HBV vaccines administered with nivolumab • Determine the impact of PD-1 blockade timing relative to vaccination on immunogenicity in participants with CHB infection and virally suppressed with oral antiviral medication • Determine the effect of the following on the level of hepatitis B markers in participants with CHB infection and virally suppressed with oral antiviral medication:	***Secondary Endpoints*** • Magnitude and avidity of HBV specific CD4+ and CD8+ T cells induced by each regimen • Effect on the frequency and magnitude of HBV infection markers (HBsAg, hepatitis B surface antibody seroconversion, hepatitis B DNA, HBeAg)

– ChAdOx1-HBV plus MVA-HBV vaccines without nivolumab – ChAdOx1-HBV plus MVA-HBV vaccines with nivolumab	
Exploratory Objectives • Assess the HBV specific cellular immune response generated by ChAdOx1-HBV plus MVA-HBV vaccines • Determine the effect of ChAdOx1 HBV plus MVA-HBV with or without nivolumab on hepatitis B biomarkers	***Exploratory Endpoints*** Exploratory endpoints may include, but may not be limited to: • Effect on hepatitis B core-related Ag (HBcrAg) • Effect on hepatitis B pregenomic RNA (HBpgRNA) • Induction of individual phenotypic subsets of CD4+ and CD8+ T cells induced by vaccination • The T cell breadth of response to the HBV proteins encoded by the ChAdOx1-HBV plus MVA-HBV vaccines • Frequency of regulatory T cells responses
Study Design:	This is a Phase 1b/2a, multicentre study of ChAdOx1-HBV and MVA-HBV vaccines (VTP-300). The study is planned to be conducted at up to 15 centres in up to approximately 52 participants chronically infected with Hepatitis B Infection and virally suppressed with approved oral anti-HBV therapies. This is an open-label study comparing the safety, tolerability and immunogenicity of MVA-HBV alone, ChAdOx1-HBV followed by MVA-HBV, ChAdOx1-HBV plus MVA vaccines with or without nivolumab. The study design is shown in Figure S1. Version 6.0 of the study protocol has closed randomisation to Groups 1 and 4, recruitment will now be in a 1:1 ratio between Groups 2 and 3 only. **Figure S1 Overall Study Design**  Abbreviations: ChAdOx1=chimpanzee adenovirus vector; HBV=hepatitis B virus; MVA=modified vaccinia virus Ankara; pfu=plaque forming units; vp=viral particles; Greyed Groups = closed All treatment groups will receive study vaccine on Day 0 and Day 28. In Group 1, MVA HBV will be evaluated 7 days after the first dose of study vaccine in the first 6 participants prior to initiation of the prime-boost regimen of ChAdOx1-HBV followed by MVA-HBV (Group 2). Participants in Groups 3 and 4 will be dosed in parallel to receive ChAdOx1-HBV (with and without nivolumab) on Day 0 followed by MVA-HBV with nivolumab on Day 28. Groups 3 and 4 will be initiated after evaluation of data 7 days after the first 6 participants in Group 2 have received ChAdOx1-HBV. The evaluations will be

	carried out by a Safety Monitoring Committee consisting of the Sponsor Medical Monitor, the Country Lead Investigators for South Korea, Taiwan, and the UK and the Medical Monitor. If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor (UK participants only). A Data Monitoring Committee will be appointed to perform unscheduled reviews of the available safety and tolerability study data and make recommendations concerning the continuation, modification or termination of the study if one of the study stopping or holding rules is met.
Duration of Study:	***Duration for each Participant***: Up to 10.5 months (up to 1.5 months for screening and 9 months on the study with study vaccine given on Day 0). ***Duration of whole Study*:** It is planned that the study will take 17 months to implement, enrol and read out.
Participant Numbers:	It is planned that approximatley 52 participants with CHB infection and virally suppressed with oral antiviral medication will be enrolled in the study.
Inclusion and Exclusion Criteria:	***Inclusion Criteria*** 1. Adult males or females aged ≥18 to ≤65 years at screening (according to country/local regulations) 2. BMI ≤32kg/m^2 3. Able to provide informed consent indicating they understand the purpose of, and procedures required, for the study and are willing to participate 4. If female, willing not to become pregnant up to 8 weeks after last dose of study vaccine and up to 5 months after the last dose of nivolumab 5. If female: Not pregnant or breast feeding and one of the following: • Of non-childbearing potential (i.e. women who have had a hysterectomy or tubal ligation or are post-menopausal, as defined by no menses in ≥1 year and without an alternative medical cause) • Of childbearing potential but agrees to practice highly effective contraception for 4 weeks prior to study vaccine and 8 weeks after study vaccine and 5 months after the last dose of nivolumab. Highly effective methods of contraception include one or more of the following: – Male partner who is sterile (medically effective vasectomy) prior to the female participant's entry into the study and is the sole sexual partner for the female participant – Combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation: – oral – intravaginal – transdermal – Progestogen-only hormonal contraception associated with inhibition of ovulation: – oral – injectable – implantable – An intrauterine device – Bilateral tubal occlusion 6. Documented evidence of chronic HBV infection (e.g. HBsAg positive ≥6 months with detectable HBsAg levels at screening) 7. Receipt of only either entecavir, tenofovir (tenofovir alafenamide fumarate or tenofovir disoproxil fumarate), or besifovir for at least 12 months before screening

	8. Virally suppressed (HBV-DNA viral load < 40 IU/mL for ≥ 1 year) 9. HBsAg levels <4000 IU/mL ***Exclusion Criteria*** 1. Presence of any significant acute or chronic, uncontrolled medical/psychiatric illness 2. Hepatitis C virus (HCV) antibody positive. 3. HIV antibody positive 4. Co-infection with hepatitis D virus 5. Documented cirrhosis or advanced fibrosis indicated by a liver biopsy within 6 months prior to screening (Metavir activity grade A3 and stages F3 and F4; Ishak stages 4 – 6). In the absence of a documented liver biopsy, either 1 of the following (not both): • Screening Fibroscan with a result > 9 kilopascals (kPa) (or the equivalent) within ≤ 6 months of screening, OR • Screening FibroTest >0.48 and aspartate aminotransferase (AST) to platelet ratio index (APRI) of >1. 6. ALT >3 x upper limit of normal (ULN), international normalized ratio (INR) >1.5 unless the participant was stable on an anticoagulant regimen affecting INR, albumin <3.5 g/dL, direct bilirubin >1.5 x ULN, platelet count < 100,000/µL. 7. A history of liver decompensation (e.g. ascites, encephalopathy or variceal haemorrhage) 8. Prior hepatocellular carcinoma 9. Chronic liver disease of a non-HBV aetiology 10. History or evidence of autoimmune disease or known immunodeficiency of any cause 11. Presence of active infection 12. Evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis 13. Past history of thyroid disorder or abnormal thyroid function at screening that is still active and uncontrolled 14. Prolonged therapy with immunomodulators (e.g. corticosteroids such as prednisone > 10 mg/day) or biologics (e.g. monoclonal antibodies, IFN) within 3 months of screening 15. Receipt of immunoglobulin or other blood products within 3 months prior to enrolment 16. Receipt of any investigational drug or vaccine within 3 months prior to screening 17. Receipt of any adenoviral-based vaccine within 3 months prior to administration of ChAdOx1-HBV on Day 0, or plan to receive an adenoviral-based vaccine within 3 months after Day 0. 18. Receipt of any live vaccines within 30 days prior to screening 19. Receipt of any inactivated vaccines within 14 days prior to screening, 20. History of severe hypersensitivity or anaphylactic reactions likely to be exacerbated by any component of the vaccine or nivolumab 21. Malignancy within 5 years prior to screening with the exception of specific cancers that are cured by surgical resection (e.g. except basal cell skin carcinoma of the skin and cervical carcinoma). Participants under evaluation for possible malignancy are not eligible 22. Current alcohol or substance abuse judged by the Investigator to potentially interfere with participant safety and compliance 23. Significant cardiac disease or unstable uncontrolled cardiac disease

	24. Any laboratory test which is abnormal, and which is deemed by the Investigator to be clinically significant 25. Cytotoxic agents, other anti HBV or traditional herbal medicines which, in the opinion of the Investigator, may have activity against HBV within the previous 6 months prior to randomization 26. Any other finding that, in the opinion of the Investigator, deems the participant unsuitable for the study
Study Vaccines:	ChAdOx1-HBV and MVA-HBV are non-replicating viral vectors encoding HBV consensus sequences from a group C genotype. They will be given, with and without nivolumab, by intramuscular injection into the deltoid muscle in the non-dominant arm. All participants will receive two doses of study vaccine separated by 28 days. If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor (UK participants only). The study vaccines to be given in each treatment group are shown in Table S1. **Table S1 Study Vaccine Treatment Groups in HBV002**

Treatment Group	Study Vaccine Day 0	Study Vaccine Day 28
Group 1 (N=10)	MVA 1 x 10^8 pfu	MVA 1 x 10^8 pfu
Group 2 (N=16)	ChAdOx1-HBV 2.5 x 10^{10} vp	MVA 1 x 10^8 pfu
Group 3 (N=16)	ChAdOx1-HBV 2.5 x 10^{10} vp	MVA 1 x 10^8 pfu + nivolumab 0.3 mg/kg
Group 4 (N=8-10)	ChAdOx1-HBV 2.5 x 10^{10} vp + nivolumab 0.3 mg/kg	MVA 1 x 10^8 pfu + nivolumab 0.3 mg/kg

Abbreviations: ChAdOx1=chimpanzee adenovirus vector; HBV=hepatitis B virus; MVA=modified vaccinia virus Ankara; N=number of participants; pfu=plaque forming units; vp=viral particles
Greyed groups = closed

Study Procedures and Frequency:	The safety, tolerability and immunologic assessments to be performed are: • Haematology (full blood count, haemoglobin, haematocrit, erythrocytes, mean cell volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, fibrinogen, prothrombin time and INR, and platelets) will be analysed at screening, pre-vaccination on Days 0 and 28, on Days 7 and 35, and on Months 3, 6 and 9 • Biochemistry (sodium, potassium, urea nitrogen, creatinine and albumin) will be analysed at screening, pre-vaccination on Days 0 and 28, on Days 7 and 35, and on Months 3, 6 and 9 • Liver function tests (alkaline phosphatase, gamma-glutamyl transpeptidase, ALT, AST and direct bilirubin) will be analysed at screening, pre-vaccination on Days 0 and 28, on Days 7 and 35, and on Months 3, 6 and 9 • HBV disease markers in serum will be analysed at screening, pre-vaccination on Days 0 and 28, on Days 7 and 35, and on Months 3 (pre-vaccination for UK participants having the MVA-HBV boost only), 6 and 9 • A full physical examination will be performed at screening, pre-vaccination on Days 0 and 28 and Month 3 (for UK participants having the MVA-HBV boost only) and on Month 9. A symptom-directed physical examination will be performed on Days 7 and 35, and on Months 3 and 6 • Vital signs will be performed at screening, pre-vaccination and post-vaccination Days 0 and 28, on Days 7 and 35, and on Months 3 (pre-vaccination for UK participants having the MVA-HBV boost only), 6 and 9 • Local and systemic reactogenicity (pain, induration, warmth, erythema at the vaccination site plus feverishness, chills, myalgia, fatigue, headache, nausea, arthralgia, malaise) will be captured pre-vaccination and post-vaccination on Days 0 and 28 and

	Month 3 for those having the MVA-HBV boost (UK participants only), and by eDiary for 7 days post-vaccination • Unsolicited adverse events will be recorded in the eCRF from the date the informed consent is signed, at all clinic visits to cover the period since the previous visit and during the visit • Serious adverse events and adverse events of special interest will be recorded from the date the informed consent is signed until the end of the study or resolved or until participant contact discontinues • Cellular immune responses will be measured in peripheral blood mononuclear cells samples taken on pre-vaccination on Days 0 and 28, on Days 7 and 35, and on Months 3 (pre-vaccination for UK participants having the MVA-HBV boost only), 6 and 9. Samples will be analysed by ELISPOT and intracellular cytokine staining
Statistical Methods and Analysis:	All data will be summarised using descriptive statistics. Immunogenicity and efficacy data may be subjected to additional statistical analysis.

ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

ABBREVIATION	DEFINITION
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
cccDNA	Covalently Closed Circular DNA
ChAdOx1	Chimpanzee Adenovirus Oxford 1
CHB	Chronic Hepatitis B Virus
CRF	Case Report Form
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
ELISPOT	Enzyme-linked Immunospot
eTMF	Electronic Trial Master File
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GM	Genetically Modified
GMO	Genetically Modified Organism
HBcrAg	Hepatitis B Core-related Antigen
HBeAg	Hepatitis B e-Antigen
HBpgRNA	Hepatitis B Pregenomic RNA
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HIV	Human Immunodeficiency Virus
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
INR	International Normalised Ratio
IRB	Institutional Review Board
LFTs	Liver Function Tests
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MVA	Modified Vaccinia Virus Ankara
NA	Nucleotide Analogue
PBMC	Peripheral Blood Mononuclear Cell
PD-1	Programmed Cell Death Protein 1
PDL-1	Programmed Death-ligand 1
pfu	Plaque Forming Units
PT	Prothrombin Time

ABBREVIATION	DEFINITION
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SI	Standard International
SMC	Safety Monitoring Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
vp	Viral Particles

1 BACKGROUND

1.1 Disease Review

Hepatitis B virus (HBV) is a complex, small deoxyribonucleic acid (DNA) virus that goes through a ribonucleic acid (RNA) intermediate life cycle requiring reverse transcription. After transmission through infected blood, contaminated body fluids or through perinatal transfer, the virus infects the liver and can then either integrate into the hepatocyte genome or can exist as a stable chromosomal closed circular DNA. Once infection takes place, HBV infection results in chronic liver disease in 5-10% of infected adults, whereas the rate for perinatal transmission is the opposite, with greater than 90% of infected neonates progressing to chronic disease [1]. After a chronic HBV (CHB) infection is established, the rate of natural clearance is minimal. Such CHB infection frequently progresses to necrotic inflammation and ongoing liver damage, which may lead to cirrhosis and hepatocellular carcinoma (HCC) [1].

1.2 Treatment Review

Highly effective prophylactic vaccines were implemented in the early 1980's; however, these vaccines are ineffective once infection is established [2]. Despite the wide use of prophylactic vaccines, there are an estimated 240 million CHB carriers and over 686,000 related deaths per year worldwide [3].

Two classes of antiviral therapies have been approved and recommended for treatment of hepatitis B: interferons (IFNs) and nucleotide analogues (NAs). The use of IFN results in higher rates of hepatitis B e-antigen (HBeAg) and hepatitis B surface antigen (HBsAg) loss compared to NAs.

Pegylated IFN administered for up to 52 weeks results in HBsAg loss in 3-7% of patients compared to 0-3% HBsAg loss after the same duration of NA therapy. Response to IFN is also more durable, and HBsAg loss may occur after cessation of treatment, while virological relapse is frequent after cessation of NA. However, IFN is less effective at suppressing viral replication compared to NAs, requires parenteral administration, is associated with significant side effects, and is contraindicated in patients with decompensated cirrhosis or severe exacerbations of hepatitis and those with autoimmune or psychiatric illnesses.

Nucleotide analogues are administered orally and have negligible adverse effects. The recommended first-line NAs, entecavir and tenofovir (tenofovir alafenamide fumarate or tenofovir disoproxil fumarate; hereafter referred to as tenofovir), have low risk of drug resistance; but the requirement for indefinite therapy increases the cost and the risk of non-adherence. [4]

Various combinations of IFN and NA have been evaluated, but most studies have not shown an added benefit compared to monotherapy [5,6,7]. A recent study showed that combination of pegylated IFN and tenofovir increased the rate of HBsAg loss to 9.1% at Week 72, but the benefit was mainly observed with those infected with HBV genotype A [8].

Many research programs are ongoing to develop new treatment concepts that focus on the clearance of HBsAg in a significant proportion of patients, with the principal aims of: 1) stopping treatment with no risk of virological relapse and no risk of liver disease progression and, 2) to further decrease the risk of HCC. Several potential target mechanisms for immune modulation to restore HBV specific immune responses in conjunction with profound inhibition of HBV replication and HBsAg production to attain immunological control are being evaluated [3].

The immune clearance of CHB is likely to depend on the use of modalities that induce effective CD8+ T cells [9,10]. For over two decades vaccination strategies to induce these CD8+ T cells to counter such infections as tuberculosis (TB), human immunodeficiency virus (HIV) and malaria have been investigated [11,12,13]. One platform approach that has induced remarkably high levels of T cells in man has been to use a non-replicating adenovirus "prime" followed by a heterologous viral vector "boost" utilising a non-replicating pox virus (modified vaccinia virus Ankara [MVA]) [14,15,16]. Non-replicating chimpanzee adenoviruses are often used rather than human adenoviruses, as there is minimal prior immunity to the vector itself [17,18]. The combination of chimpanzee adenoviruses (used in thousands of participants) plus MVA (administered to over 130,000 people) has been shown to induce large immune responses in man in malaria, TB, HIV, influenza, hepatitis C virus (HCV) and respiratory syncytial virus [13,16,19-22]. The chimpanzee adenovirus vector proposed in this study (chimpanzee adenovirus Oxford 1; ChAdOx1), a serogroup E adenovirus, has been administered to over 300 participants in trials of Middle East Respiratory Syndrome (MERS), influenza, TB, chikungunya, and prostate cancer, and has been safe and immunogenic. It has also been modified to enhance immunogenicity through the addition of a short shark invariant chain sequence and use of the tissue plasminogen promoter.

Hepatitis B virus circulates in the world as a number of genotypes (A-I), of which the most prevalent (especially in Asia) is genotype C [23]. The proteins expressed by ChAdOx1 in this study include most of the HBV genome from a genotype C consensus, including HBsAg, polymerase and core. In vitro experiments have demonstrated that the HBV polymerase was successfully inactivated through the insertion of point mutations at critical sites. In order to stop aggregation of surface antigen, this protein was split into two separate coding regions in the viral vectors.

The genetic HBV insert was then cloned into both the ChAdOx1 (chimpanzee adenovirus vectored hepatitis B virus vaccine; ChAdOx1-HBV) and the modified vaccinia virus Ankara (MVA; MVA-HBV) vectors.

This study is designed to assess the safety and immunogenicity of ChAdOx1-HBV and MVA-HBV, given either alone or with low doses of an anti-programmed cell death protein 1 (anti-PD-1) compound (nivolumab), and to assess the breadth of responses to the proteins encoded by these combinations. The T cell cross-reactivity to other genotypes will also be assessed. Doses of ChAdOx1 vaccines in previous studies have varied from 10^8 to over 5 x 10^{10} viral particles (vp) per dose and a dose of 2.5 x 10^{10} vp will be evaluated in this study to prepare for a further ChAdOx1/MVA heterologous prime-boost regimen. The dose of MVA of 1 x 10^8 pfu has been assessed safely in thousands of participants.

1.3 Summary of Non-clinical Studies

Immunogen design: 1,447 HBV genotype C nucleotide sequences (HBV database) were aligned, and an HBV genotype C consensus sequence was generated. Then, a patient's HBV genotype C sequence (accession number: KP017269.1 HBV isolate JP-02) that had maximum similarity to the consensus was chosen for use in the HBV immunogen design. The HBV immunogen encompasses three full length HBV-antigens (pre-core/core, polymerase and preS1/preS2/surface) along with truncated shark invariant chain and tissue plasminogen activator genetic adjuvants and is encoded in the chimpanzee adenoviral vector. Point mutations were introduced within the polymerase protein encoded in the immunogen in order to abolish its function and to ensure no replication-competent HBV genome could arise from the immunogen sequences. An HBV-polymerase assay performed by the laboratory of Prof. Michael Nassal at University Hospital Freiburg, Germany, confirmed the absence of

polymerase activity of the polymerase contained in the HBV immunogen. A schematic of the HBV immunogen in both ChAdOx1 and in MVA is shown in Figure 1.

Figure 1 Schematic of Hepatitis B Virus Immunogens

A. ChAdOx1 insert

B. MVA insert

The HBV immunogen was cloned and recovered into the ChAdOx1 vector genome to generate ChAdOx1-HBV and into MVA to generate MVA-HBV. Research stocks of the ChAdOx1-HBV vector were generated at the viral vector core facility of the Jenner Institute, University of Oxford.

Preclinical immunogenicity testing: ChAdOx1-HBV followed by MVA-HBV was found to be highly immunogenic when tested in mouse immunogenicity experiments in both inbred (C57BL/6) and outbred (CD-1) mice, measured using interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISPOT) and intracellular cytokine staining assays. Excellent T cell responses were also observed to core, polymerase and surface HBV antigens in HLA-A2 transgenic mice receiving the prime-boost regimen.

A Good Laboratory Practice toxicology study of ChAdOx1-HBV and a separate Good Laboratory Practice toxicology study of MVA-HBV were conducted at Covance (UK), and showed minimal toxicity other than expected local site effects (see Investigator's Brochures for further study details and results).

1.4 Summary of Clinical Experience

One clinical study (HBV001) to investigate reactogenicity and explore the safety of ChAdOx1-HBV in healthy and CHB participants is ongoing at doses of 2.5×10^9 and 2.5×10^{10} vp. At the higher dose, only localised swelling at the vaccination site and minor adverse events, which all resolved quickly, have been reported. There have been no reports of severe or serious adverse events (SAEs) or other safety concerns. There have been a large number of clinical studies using recombinant replication-incompetent adenoviruses followed by MVA to address a variety of diseases, such as HIV, HCV, TB, malaria, influenza and prostate cancer [24]. ChAdOx1 has been administered to over 300 participants (chikungunya, MERS, malaria, influenza and prostate cancer) and as the prime for an MVA boost in the malaria, influenza, tuberculosis and prostate cancer studies (NCT03203421, NCT01818362, NCT01623518, NCT01829490, NCT03815942 and NCT02390063). In all of those studies, extremely high levels of transgene-specific CD4+ and CD8+ T cells have been induced and there have been no vaccine-associated SAEs or evidence of autoimmunity. This is the first clinical study for the combination of the ChAdOx1-HBV and MVA-HBV vaccines.

Further information on ChAdOx1-HBV and MVA-HBV are contained in the respective Investigator's Brochures; these should be reviewed prior to study initiation.

1.5 Study Rationale

Chronic hepatitis B virus infection is a global public health challenge on the same scale as HIV and malaria. The current prophylactic vaccine has no effect on established chronic infection. Available treatments suppress viral replication, but they are not curative, largely due to the persistence of the viral covalently closed circular DNA (cccDNA), a transcriptional template in infected hepatocytes. Chronically infected patients fail to mount a cellular immune response that is sufficiently robust, functional, and sustained to clear the infection. Thus, in most cases, treatment must continue for life. However, even successfully virally suppressed patients may still develop liver cancer.

Many research programs are ongoing to develop new treatment concepts that focus on the clearance of HBsAg in a significant proportion of patients, with the principle aims of: 1) stopping treatment with no risk of relapse and no risk of liver disease progression and 2) to further decrease the risk of HCC.

Pre-clinical models still have considerable limitations in this indication, and important gaps in our understanding of the HBV replication cycle and the host immune response must be addressed to expand the exploitable vulnerabilities in the replication cycle that can be targeted therapeutically to cure the infection. A major effort has been made to compare the efficient integrated response resulting in HBV clearance of acute infection to the dysregulated response observed in patients with chronic hepatitis B. A complex interplay of innate and adaptive immune responses is essential for viral clearance and a failure of these responses can result in liver pathogenesis. CD8+ T cells are the main effector cells that eliminate the virus by cytolytic and non-cytolytic effector functions [25,26]. Sufficient CD4 T cell activity and the production of neutralising anti-HBV envelope antibodies may also be required for protective immunity [27].

Vaccitech is developing a prime boost vaccination strategy using two non-replicating viral vectors to deliver immunogens in various indications: ChAdOx1 followed by boosting with a heterologous vector, MVA, containing the same immunogen. These vectors are used to generate high magnitude CD4+ and CD8+ T-cell responses and also generate lasting cell-mediated immunity.

Adenoviral vectors represent exceptional priming vaccines but are difficult to reuse in the first few months after administration due to initial anti-vector immunity. For this reason, vaccine developers often use a different vector (known as a heterologous prime-boost) to augment the levels of the induced T cells [28,15].

MVA boosts and prolongs the CD4+ and CD8+ T cells induced by ChAdOx1. This two-dose heterologous vaccine regimen has been safe and immunogenic. ChAdOx1 and MVA including doses up to 5×10^{10} vp with ChAdOx1 and doses up to 2.5×10^{8} plaque forming units (pfu) with MVA were evaluated in various indications.

Chronic hepatitis B infection is also associated with upregulation of the PD-1/ programmed death-ligand 1 (PDL-1) inhibitor axis [29-32], and the use of checkpoint inhibitors has shown a therapeutic effect in some animal models [33]. Nivolumab and pembrolizumab have been administered to hundreds of hepatocellular carcinoma patients, many of whom were infected with hepatitis B, with no increase in liver toxicity and some effect on HBsAg reduction. In addition, a study of nivolumab, used at one tenth the licensed dose for oncology, combined with a partially immunogenic HBV vaccine was shown to be safe and to induce some HBsAg reduction [34]. The dose used was selected based on receptor occupancy studies which showed near maximal peripheral T cell receptor occupancy at 0.3 mg/kg. Further studies of anti-PD-1 and anti-PDL1 in chronic hepatitis B are underway.

Studies examining the effect of checkpoint inhibitors and many other interventions have focused on patients with low levels of serum hepatitis B DNA and levels of HBsAg measured at $< 10^4$ IU/mL, and in patients who have well controlled CHB while on antiviral agents, which at present is dominated by the use of tenofovir (or its prodrug, tenofovir alafenamide fumarate) or entecavir. Most functional cures either on therapy or at therapy discontinuation have been observed in such patients.

Thus, a prime-boost strategy using ChAdOx1 vector (ChAdOx1-HBV) and an MVA vector (MVA-HBV), with and without nivolumab will be evaluated in this study. In order to decrease potential safety issues, only participants with stable antiviral therapy in the previous one year with resultant low HBV DNA and HBsAg will be enrolled. As the T cell responses may wane with time, and a boost to the highest levels may be needed to sustain an ongoing response (as evidenced by some lowering of the HBsAg levels), a boost using the MVA vaccine is permitted at Month 3, at the discretion of the Investigator and concurrence of the Sponsor (UK participants only).

Comprehensive reviews of ChAdOx1-HBV and MVA-HBV are contained in the respective Investigator's Brochures; these and the Package Insert for nivolumab should be reviewed prior to study initiation.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objectives • Determine the safety and reactogenicity of the following in participants with CHB infection and virally suppressed with oral antiviral medication: – MVA-HBV vaccine – ChAdOx1-HBV plus MVA vaccines – ChAdOx1-HBV plus MVA vaccines and nivolumab	Primary Endpoints • Safety and reactogenicity of the vaccine(s): incidence of adverse events, SAEs, ≥Grade 3 study vaccine-related adverse events within 4 weeks of vaccination • Safety of the vaccines with nivolumab: incidence of adverse events, SAEs, ≥Grade 3 adverse events within 4 weeks of dosing • Incidence of adverse events of special interest (AESIs) • Number and proportion of participants reporting treatment-emergent adverse events within each treatment group • Number and proportion of participants within each treatment group with potentially clinically significant laboratory values and vital signs within each treatment group • Change from baseline in laboratory tests and vital sign measurements to each time point of collection
Secondary Objectives • Determine the immunogenicity of the following in participants with CHB infection and virally suppressed with oral antiviral medication: – MVA-HBV vaccine – ChAdOx1-HBV plus MVA-HBV vaccines – ChAdOx1-HBV plus MVA-HBV vaccine administered with nivolumab • Determine the impact of PD-1 blockade timing relative to vaccination on immunogenicity in participants with CHB infection and virally suppressed with oral antiviral medication • Determine the effect of C the following on the level of hepatitis B markers: – ChAdOx1-HBV plus MVA-HBV vaccines without nivolumab	Secondary Endpoints • Magnitude and avidity of HBV specific CD4 + and CD8+ T cells induced by each regimen • Effect on the frequency and magnitude of HBV infection markers (HBsAg, Hepatitis B surface antibody [HBsAb] seroconversion, hepatitis B DNA, HBeAg)

– ChAdOx1-HBV plus MVA-HBV vaccines with nivolumab

Exploratory Objectives

- Assess the HBV specific cellular immune response generated by ChAdOx1-HBV plus MVA-HBV vaccines
- Determine the effect of ChAdOx1-HBV plus MVA-HBV on hepatitis B biomarkers

Exploratory Endpoints

Exploratory endpoints may include, but may not be limited to:

- Effect on hepatitis B core-related Ag (HBcrAg)
- Effect on hepatitis B pregenomic RNA (HBpgRNA)
- Induction of individual phenotypic subsets of CD4+ and CD8+ T cells induced by vaccination
- The T cell breadth of response to the HBV proteins encoded by the ChAdOx1-HBV plus MVA-HBV vaccines
- Frequency of regulatory T cells responses

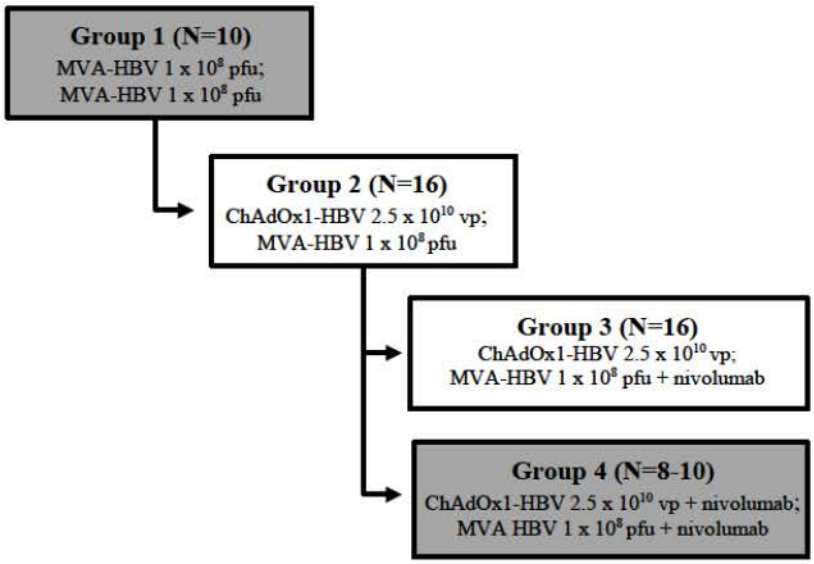
3 STUDY OVERVIEW

3.1 Overall Study Design and Methodology

3.1.1 Study Overview

This is a Phase 1b/2a, multicentre study of ChAdOx1-HBV and MVA-HBV vaccines (VTP-300). The study is planned to be conducted at up to 15 centres in up to approximately 52 participants chronically infected with Hepatitis B Infection and virally suppressed with approved oral anti-HBV therapies. This is an open-label study comparing the safety, tolerability and immunogenicity of MVA-HBV alone, ChAdOx1-HBV followed by MVA-HBV, and ChAdOx1-HBV plus MVA vaccine with the anti-PD-1 antibody, nivolumab. The study design is shown in Figure 2. Version 6.0 of the study protocol has closed Groups 1 and 4 to further randomisation; recruitment will now be in a 1:1 ratio between Groups 2 and 3 only. This is due to the fact that significant decreases in surface antigen were seen in Group 3 at month 3, and that 2/6 Group 2 patients also had a greater than 0.5 log decrease at that time point.

Figure 2 Overall Study Design



Abbreviations: ChAdOx1=chimpanzee adenovirus vector; HBV=hepatitis B virus; MVA=modified vaccinia virus Ankara; pfu=plaque forming units; vp=viral particles

Greyed Groups = closed

All treatment groups will receive study vaccine on Day 0 and Day 28. In Group 1, MVA-HBV will be evaluated 7 days after the first dose of study vaccine in the first 6 participants prior to initiation of the prime-boost regimen of ChAdOx1-HBV followed by MVA-HBV (Group 2). Participants in Groups 3 and 4 will be dosed in parallel to receive ChAdOx1-HBV (with and without nivolumab) on Day 0 followed by MVA-HBV with nivolumab on Day 28. Groups 3 and 4 will be initiated after evaluation of data 7 days after the first 6 participants in Group 2 have received ChAdOx1-HBV. The evaluations will be carried out by a Safety Monitoring Committee (SMC) consisting of the Sponsor Medical Monitor, the Country Lead Investigators for South Korea, Taiwan and the UK, and the trial Medical Monitor. If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor (UK participants only).

A Data Monitoring Committee (DMC) composed of three independent experts (two clinicians and one statistician) will be appointed to perform unscheduled reviews of the available safety and tolerability study data and make recommendations concerning the continuation, modification or termination of the study if one of the study stopping or holding rules defined in Section 3.1.3 is met.

3.1.2 Duration of Study

3.1.2.1 Duration for each Participant

Up to 10.5 months (up to 1.5 months for screening and 9 months on the study with study vaccine given on Day 0).

3.1.2.2 Duration of Whole Study

It is planned that the study will take 17 months to implement, enrol and read out.

The end of the study is defined as the date of database lock.

3.1.3 Stopping Criteria/Holding Criteria

There will be a review of the study data by the DMC when there is a reasonable possibility that the investigational vaccine caused any of the SAEs or severe adverse events listed below, based on the assessment of the Investigator, in one or more participants at any dose. Vaccinations will be put on hold pending this review:

- Death related to study vaccine
- Life-threatening adverse event or life-threatening suspected reaction
- Serious suspected adverse reaction
- Suspected unexpected serious adverse reaction (SUSAR)
- Acute allergic reaction or anaphylactic shock following the administration of vaccine investigational product
- Anaphylaxis or bronchospasm, indicative of an immediate hypersensitivity reaction to study vaccine
- If any participant has any of the following during the study:

– Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit of normal (ULN) and total bilirubin >2 x ULN or International Normalised Ratio (INR) >1.5

– ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

– Grade 4 diarrhoea, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, diabetes, other immune-related adverse reaction, or creatinine elevation

– Grade 3 myocarditis or pneumonitis

– Solicited local adverse events: If three out of the first 20 participants dosed with a study vaccine, or >10% of participants, thereafter, are followed by the same Grade 3 solicited local adverse event

- Solicited systemic adverse events: If three out of the first 20 participants dosed with a study vaccine, or >10% of participants, thereafter, are followed by the same Grade 3 solicited systemic adverse event
- Unsolicited adverse events: If three participants of the first 20 participants dosed, or >10% of participants, thereafter, develop a Grade 3 unsolicited adverse event of the same type that is considered related to study vaccine

Other potential reasons for discontinuation of the second planned dose of nivolumab for Group 4 are found in Appendix 2 – Toxicity Management Guidelines for Nivolumab.

If, following review of data, a recommendation is made by the DMC to resume study enrolment and vaccine administration, the DMC will record their judgment in a memorandum to the study file and notify the Sponsor. The DMC memorandum will be forwarded to the local Medical Monitor and Investigators and an appropriate substantial amendment filed.

If the study is terminated early, the Regulatory Authorities, IEC/IRBs and study centres will be notified within 15 days according to local requirements.

3.1.4 Individual Stopping Rules (All Vaccinated Study Participants)

In addition to the above stated group holding rules, stopping rules for individual participants will apply (i.e. in addition to withdrawal of individuals from a second vaccination). Study participants who present with at least one of the following stopping rules will be withdrawn from further vaccination in the study:

- **Local reactions:** injection site ulceration, abscess or necrosis
- **Laboratory AEs**:
  - The participant develops a Grade 3 laboratory adverse event considered possibly, probably or definitely related within 7 days after vaccination and persisting continuously at Grade 3 for >72 hours
- **Systemic solicited adverse events:**
  - The participant develops a Grade 3 systemic solicited adverse event considered possibly, probably or definitely related within 2 days after vaccination (day of vaccination and one subsequent day) and persisting continuously at Grade 3 for >72 hours
- **Unsolicited adverse events:**
  - The participant has any Grade 3 adverse event considered possibly, probably or definitely related to vaccination, persisting continuously at Grade 3 for >72 hours
  - The participant has an SAE considered possibly, probably or definitely related to vaccination
  - The participant has an acute allergic reaction or anaphylactic shock following the administration of vaccine investigational product

If the participant has an acute illness (moderate or severe illness with or without fever) or a fever (oral temperature > 37.5°C) at the scheduled time of administration of investigational product, the participant will not receive the vaccine at that time. The vaccine may be administered to that participant at a later date within the time window specified in the protocol or the participant may be withdrawn from the study at the discretion of the Investigator.

All vaccinated participants will be followed for safety until resolution or stabilisation (if determined to be chronic sequelae) of their SAEs.

3.2 Discussion of Study Design, Including the Choice of Control Groups

This is a first in human study of the combination of ChAdOx1-HBV followed by MVA-HBV vaccines (VTP-300) and is designed to assess the safety and reactogenicity of these vaccines given with and without nivolumab in the target CHB population.

Standard clinical study safety assessments are used including adverse events, laboratory tests, vital signs and physical examinations. Foreseeable adverse events following vaccination are solicited from participants daily for the first 7 days post-vaccination using an electronic diary (eDiary; plus an assessment at the study centre on each vaccination day). Specific grading scales are defined for severity of solicited and unsolicited adverse events and abnormal laboratory results for participants in the lead-in phase (Section 8.2.4.1). Study stopping/holding criteria have been defined, with a DMC review mandated if one of these is met (Section 3.1.3).

The ChAdOx1-HBV dose is 2.5×10^{10} vp, based on the review of the two doses studied in HBV001 (2.5×10^{9} vp and 2.5×10^{10} vp). Safety data from all healthy volunteers was reviewed from HBV001 by the SMC, and the higher dose was chosen to use in this study. To further minimise the risk that immune responses generated by vaccination do not result in liver toxicity, only those participants whose DNA levels are well controlled on antivirals will be included in the study, and those with advanced liver fibrosis or cirrhosis will be excluded. The safety of MVA-HBV will be evaluated by the SMC after the first 6 participants have received the first dose, to include at least 7 days safety data, prior to initiation of the prime-boost regimen of ChAdOx1 followed by MVA with and without nivolumab.

Doses of ChAdOx1 vaccines in previous studies have varied from 1×10^{8} to over 5×10^{10} vp per dose with 2.5×10^{10} vp appearing to be nearly optimal. A phase 1 study is examining the safety and immunogenicity of two ChAdOx1-HBV doses, 2.5×10^{9} vp and 2.5×10^{10} vp, with the expectation that the latter dose will be safe and chosen for further development. MVA has been used in many trials at doses that range from 1×10^{7} to 2.5×10^{8} pfu, and in most studies the dose of 1-2 $\times 10^{8}$ pfu is studied. This dose has been shown to be safe and immunogenic in thousands of participants to date. Thus, pending new information, the doses chosen for this study are 2.5×10^{10} vp of ChAdOx1-HBV and 1×10^{8} pfu of MVA-HBV. As the T cell responses may wane with time, and a boost to the highest levels may be needed to sustain an ongoing response (as evidenced by some lowering of the HBsAg levels), a boost using the MVA vaccine is permitted at Month 3, at the discretion of the Investigator and concurrence of the Sponsor (UK participants only).

As an open-label study, data on the first 27 patients from this current study through 3 months follow-up has been reviewed (Group 1, N=9, for each of Groups 2, 3, and 4, N=6).

There is a difference between Group 3 and the other groups at the 3-month time point ($p<0.01$), with the mean $\log_{10}$ surface antigen reductions from the average of the screening and baseline values for Groups 1, 2, 3, and 4 of -0.09, -0.35, -1.04 and -0.13, respectively. In Group 3 the Month 3, $\log_{10}$-transformed change from baseline values range from -0.32 to -1.64 (undetectable), and only Group 2 has individuals with more than a 0.5 log drop (2/6, both with a baseline < 100 IU/mL).

Although these numbers are small, the highly significant trend leads to the conclusion that administration of low dose nivolumab at the time of the MVA-HBV boost is likely beneficial, and administration at the time of ChAdOX1-HBV prime ablates these improvements. Thus, to increase the likelihood of patient benefit, the sponsor will close Groups 1 and 4, and continue with the planned N=16 for Groups 2 and 3.

The present standard measure to assess the likelihood of functional cure is the level of circulating HBsAg, although the exact contributions of episomal cccDNA or integrated DNA are not entirely clear. Other measures under investigation to assess virologic effects include measurement of hepatitis B DNA and effect on hepatitis eAg seroconversion. Other measure of virologic activity under study and without full licensure include measurement of hepatitis B core-related antigen, and measurement of circulating hepatitis B full length pre-genomic RNA.

3.3 Benefit Risk Assessment

There are potential known and unknown risks associated with vaccination. With any vaccine, including those that are licensed, there is a rare risk of anaphylaxis which can be fatal. Participants will therefore be observed in the clinic for at least 30 minutes post-vaccination and post-nivolumab infusion.

Intramuscular injection of vaccines frequently causes the local and systemic signs and symptoms that are being collected as adverse events. These will be solicited from the participant for the first 7 days after each vaccination to ensure they are not occurring more frequently or are more severe than expected based on previous experience with the same or similar viral vectors. After this time, unsolicited adverse events will be collected at each clinic visit throughout the study.

With any new treatment there is always a possibility of unexpected adverse events. Holding and stopping rules have been defined for the study (see Section 3.1.3) and the DMC will perform a review of safety data if one of these is met. There are also routinely scheduled reviews of safety during the lead-in phase by the SMC. Further detail is provided in the Investigator's Brochure.

The ChAdOx1 and MVA vectors have been widely administered for many pathologies without significant safety concerns (see Section 1.4). Further detail is provided in the Investigator's Brochure.

As this is an early development study with little clinical data, there may be no benefit to study participants. The participants will however receive additional monitoring of their HBV status compared to the standard of care.

Nivolumab, at full dose, is associated with a variety of adverse effect, including potential death. Common adverse effects include thyroiditis, colitis, pneumonitis, hepatitis, myocarditis, and other adverse immune related effects. In the published data using nivolumab at 0.3 mg/kg the most common adverse events were fatigue, headache and cough, with no immune-related adverse events observed [35].

4 STUDY POPULATION

4.1 Number of Participants

It is planned that up to approximately 52 participants with CHB infection and virally suppressed with oral antiviral medication will be enrolled in the study. Chronic HBV participants will be recruited/deemed eligible by hepatologists, infectious disease specialists or physicians experienced in treating CHB participants. Centres not meeting the enrolment expectations will be considered for replacement with the addition of a new centre. If participants leave the study before all follow-up visits are completed (for any reason), they may be replaced at the discretion of the study team. A log of all participants enrolled into the study (i.e. having given informed consent) will be maintained in the Investigator's Site File (ISF) at the study centre irrespective of whether they have been treated with vaccine or not.

Version 6.0 of the protocol has closed Groups 1 and 4 to further randomisation following analysis of on-going data; Groups 2 and 3 will continue to recruit approximately 16 participants in a 1:1 ratio.

The number of participants is based on feasibility considerations rather than formal sample size calculations. A total of up to approximately 52 participants with CHB infection is considered sufficient to confirm the safety, tolerability and immunogenicity of ChAdOx1-HBV followed by MVA-HBV, ChAdOx1-HBV plus MVA vaccines with or without nivolumab, and to answer the objectives of the study.

The statistical considerations used to determine the number of participants planned and evaluable are presented in Section 10.1.

4.2 Inclusion Criteria

Participants must meet *all* the following criteria to be eligible for the study:

1. Adult males or females aged ≥18 to ≤65 years at screening (according to country/local regulations)
2. BMI ≤32kg/m^2
3. Able to provide informed consent indicating they understand the purpose of, and procedures required, for the study and are willing to participate
4. If female, willing not to become pregnant up to 8 weeks after last dose of study vaccine and up to 5 months after the last dose of nivolumab
5. If female: Not pregnant or breast feeding and one of the following:
   - Of non-childbearing potential (i.e. women who have had a hysterectomy or tubal ligation or are post-menopausal, as defined by no menses in ≥1 year and without an alternative medical cause)
   - Of childbearing potential but agrees to practice highly effective contraception for 4 weeks prior to study vaccine and 8 weeks after study vaccine and 5 months after the last dose of nivolumab. Highly effective methods of contraception include one or more of the following:
     - Male partner who is sterile (medically effective vasectomy) prior to the female participant's entry into the study and is the sole sexual partner for the female participant
     - Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- An intrauterine device
- Bilateral tubal occlusion

6. Documented evidence of chronic HBV infection (e.g. HBsAg positive ≥6 months with detectable HBsAg levels at screening)
7. Receipt of only either entecavir, tenofovir (tenofovir alafenamide fumarate or tenofovir disoproxil fumarate), or besifovir for at least 12 months before screening
8. Virally suppressed (HBV-DNA viral load below 40 IU/mL for ≥ 1 year)
9. HBsAg levels <4000 IU/mL

4.3 Exclusion Criteria

Participants who meet *any* of the following criteria are not eligible for the study:

1. Presence of any significant acute or chronic, uncontrolled medical/psychiatric illness
2. Hepatitis C virus antibody positive.
3. HIV antibody positive
4. Co-infection with hepatitis D virus (HDV)
5. Documented cirrhosis or advanced fibrosis indicated by a liver biopsy within 6 months prior to screening (Metavir activity grade A3 and stages F3 and F4; Ishak stages 4 – 6).

   In the absence of a documented liver biopsy, either 1 of the following (not both):
   - Screening Fibroscan with a result > 9 kilopascals (kPa) (or the equivalent) within ≤ 6 months of screening, OR
   - Screening FibroTest >0.48 and AST to platelet ratio index (APRI) of >1.
6. ALT >3 x ULN, international normalized ratio (INR) >1.5 unless the participant was stable on an anticoagulant regimen affecting INR, albumin <3.5 g/dL, direct bilirubin >1.5 ULN, platelet count <100,000/µL.
7. A history of liver decompensation (e.g. ascites, encephalopathy or variceal haemorrhage)
8. Prior hepatocellular carcinoma
9. Chronic liver disease of a non-HBV aetiology
10. History or evidence of autoimmune disease or known immunodeficiency of any cause
11. Presence of active infection
12. Evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis
13. Past history of thyroid disorder or abnormal thyroid function at screening that is still active and uncontrolled

14. Prolonged therapy with immunomodulators (e.g. corticosteroids such as prednisone > 10 mg/day) or biologics (e.g. monoclonal antibodies, IFN) within 3 months of screening
15. Receipt of immunoglobulin or other blood products within 3 months prior to enrolment
16. Receipt of any investigational drug or vaccine within 3 months prior to screening
17. Receipt of any adenoviral-based vaccine within 3 months prior to administration of ChAdOx1-HBV on Day 0, or plan to receive an adenoviral-based vaccine within 3 months after Day 0
18. Receipt of any live vaccines within 30 days prior to screening
19. Receipt of any inactivated vaccines within 14 days prior to screening
20. History of severe hypersensitivity or anaphylactic reactions likely to be exacerbated by any component of the vaccine or nivolumab
21. Malignancy within 5 years prior to screening with the exception of specific cancers that are cured by surgical resection (e.g. except basal cell skin carcinoma of the skin and cervical carcinoma). Participants under evaluation for possible malignancy are not eligible
22. Current alcohol or substance abuse judged by the Investigator to potentially interfere with participant safety and compliance
23. Significant cardiac disease or unstable uncontrolled cardiac disease
24. Any laboratory test which is abnormal, and which is deemed by the Investigator to be clinically significant.
25. Cytotoxic agents, other anti HBV or traditional herbal medicines which, in the opinion of the Investigator, may have activity against HBV within the previous 6 months prior to randomization
26. Any other finding that, in the opinion of the Investigator, deems the participant unsuitable for the study

4.3.1 Removal of Participants from Therapy or Assessment

4.3.1.1 Contraindications to Vaccination

The following events constitute contraindications to administration of study vaccine at that point in time; if any one of these events occurs at the time scheduled for vaccination, the participant may be vaccinated within 28 days of the scheduled time, or withdrawn from the study at the discretion of the Investigator.

- Acute disease at the time of vaccination. Acute disease is defined as the presence of a moderate or severe illness with or without fever. All study vaccines can be administered to participants with a minor illness such as diarrhoea, mild upper respiratory infection with or without low-grade febrile illness
- Temperature of >37.5°C (100.4°F) at the time of vaccination

4.3.1.2 Study Discontinuation

Participants may choose to discontinue both treatment and study assessments. In this case, the Investigator or research worker should attempt to ascertain the reason for a participant's discontinuation of safety follow-up assessments, without compromising their right to withdraw at any time without giving a reason, and record this in the electronic Case Report Form (eCRF). Note that, unless the participant specifically revokes their earlier consent for information about

their progress, clinical information will continue to be collected and participant information will be retained in the trial database and used for intention-to-treat analyses of study outcome.

Participants **may** be withdrawn from the study in the event of:

- A severe adverse event or SAE
- Difficulties in obtaining blood or other samples
- Failure of the participant to comply with the protocol requirements or to cooperate with the Investigator

Participants **must** be withdrawn from the study in the event of:

- Withdrawal of consent

Participants will be withdrawn from study vaccination (if it has not yet been administered) in the event of:

- For safety reasons, it being in the best interest of the participant that he/she be withdrawn, in the Investigator's opinion
- A positive pregnancy test or if the participant is non-compliant with the contraception requirements (see Section 4.2)
- Development of a medical condition that requires concomitant treatment with a potentially toxic therapy

4.3.2 Study Termination

The study may be terminated, either at one centre or all centres for the following reasons:

- The discovery of an unexpected, serious or unacceptable risk to participants enrolled in the study
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation or development of ChAdOx1-HBV and MVA-HBV vaccines. In the event of the Sponsor's decision to no longer supply study vaccine, ample notification will be provided so that appropriate adjustments to treatment can be made.
- Serious failure of the Investigator to comply with ICH GCP [36] or local regulations
- Submission of knowingly false information from the study centre to the Sponsor, the independent ethics committee (IEC)/institutional review board (IRB) or regulatory authorities
- Major, repeated, non-adherence to the protocol

The Sponsor must be informed immediately in the event of any major protocol violation or serious breach of ICH GCP.

5 INVESTIGATIONAL MEDICINAL PRODUCTS

The Investigator must ensure that study vaccines and nivolumab are handled only by study team members who have been appropriately trained for the conduct of this clinical study and that dosing is only performed by study team members who fully understand the procedures outlined in this section, the Investigator's Brochure and the Pharmacy Manual. A Delegation of Authority Log will be maintained by the study centre and will identify the individual(s) authorised to prepare and administer the study vaccine.

5.1 Identity of Investigational Medicinal Products

5.1.1 Study Vaccines

ChAdOx1-HBV is a genetically-modified (GM) non-replicating chimpanzee adenovirus vector encoding HBV consensus sequences from a group C genotype. The ChAdOx1 virus has been engineered to be replication deficient.

ChAdOx1-HBV is formulated in isotonic buffered saline comprising of 10 mM L-histidine, 35 mM NaCl, 7.5% sucrose (w/v), 1 mM $MgCl_2.6H_2O$, 0.1% (w/v) Polysorbate 80, 0.1 mM ethylenediaminetetraacetic acid, 0.5% ethanol (v/v), water for injections to 1 mL, pH 6.6 to a target concentration of 1 x 10^{11} vp/mL.

MVA-HBV is a GM poxvirus that is non-replicating in mammalian cells encoding the same HBV consensus sequences as ChAdOx1-HBV. The MVA virus is no longer able to replicate in humans and has safely been administered to over 130,000 people. It both boosts and prolongs the CD4+ and CD8+ T cells induced by ChAdOx1.

MVA-HBV is formulated in saccharose 50 g/L, 50 mM NaCl, 10 mM TRIS, 10 mM sodium glutamate, pH 8.0 to a target final concentration of 2.0 x 10^8 pfu/mL.

The ChAdOx1-HBV and MVA-HBV vaccines will be supplied in glass vials. The vials are stoppered with sterilised European Pharmacopoeial/United States Pharmacopoeial Type 1 chlorobutyl and bromobutyl rubber stoppers respectively and sealed with aluminium/copolymer caps.

The study vaccines are manufactured to Good Manufacturing Practice and released by a qualified person.

5.1.2 Nivolumab

Nivolumab is approved in all of the participating countries (South Korea, Taiwan and the UK) for oncologic indications. It is provided as a 10 mg/mL solution in a glass vial with a coated butyl rubber stopper and sealed with an aluminium cap.

5.2 Investigational Products Administered

The IMPs to be given in each treatment group are shown in Table 1. Groups 1 and 4 are closed to further randomization. Groups 2 and 3 will continue to recruit approximately 16 participants in a 1:1 ratio.

Table 1 Study Vaccine Treatment Groups in HBV002

Treatment Group	Study Vaccine Day 0	Study Vaccine Day 28
Group 1 (N=10)	MVA 1 x 10^8 pfu	MVA 1 x 10^8 pfu
Group 2 (N=16)	ChAdOx1-HBV 2.5 x 10^{10} vp	MVA 1 x 10^8 pfu
Group 3 (N=16)	ChAdOx1-HBV 2.5 x 10^{10} vp	MVA 1 x 10^8 pfu + nivolumab 0.3 mg/kg
Group 4 (N=8-10)	ChAdOx1-HBV 2.5 x 10^{10} vp + nivolumab 0.3 mg/kg	MVA 1 x 10^8 pfu + nivolumab 0.3 mg/kg

If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor (UK participants only).

5.2.1 Study Vaccines

All participants will receive two doses of study vaccine, with or without nivolumab, on Day 0 and Day 28. Both vaccinations will be given by intramuscular injection into the deltoid muscle, to the same, non-dominant arm in a participant, where possible. If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV at Month 3, at the Investigator's discretion and after discussion with the Sponsor (UK participants only).

The ChAdOx1-HBV dose is 2.5 x 10^{10} vp, based on the review of the two doses studied in study HBV001. This dose, or higher, of ChAdOx1-based vaccines has been safely used in hundreds of participants (see Investigator's Brochure), and thousands of people have been immunised with a ChAdOx1 COVID-19 vaccine at a dose of 5 x 10^{10} vp.

The dose of MVA-HBV will be fixed at 1 x 10^8 pfu, as taken from historical data of previous studies. A 1.5 x 10^8 pfu MVA dose was used in nearly 2,000 healthy participants in influenza studies conducted by Oxford University and Vaccitech.

5.2.2 Nivolumab

Nivolumab will be administered via intravenous infusion over 30 minutes, following vaccination. The dose to be used in this study (0.3 mg/kg) is one tenth that commonly indicated for cancer immunotherapy. Full prescribing and safety information for nivolumab can be found in the SmPC or package Insert.

5.3 Labelling, Packaging and Shipping

The vials of study vaccine will be labelled according to local regulations.

Study vaccine will be shipped by the Contract Manufacturing Organisation (CMO) to the study centres on dry ice with a continuous temperature monitoring device. Nivolumab will also be provided and labelled for investigational use by the CMO.

Upon receipt, the pharmacist or designee must immediately inspect all vials for damage. Any damage or discrepancies from the packing list must be documented and promptly discussed with the Sponsor and the Study Monitor to determine the appropriate action. The temperature

monitors should be downloaded according to the accompanying instructions in the shipment. Temperature records must be sent to the Sponsor and the centre will receive written confirmation that the vials are clinically released before they are used. If the temperature monitor has been out of range, then the shipment should be placed into quarantine and the Sponsor and Study Monitor contacted immediately to determine whether the study vaccine may be used.

At the start of the study, a sufficient number of study vaccine vials will be shipped to each study centre based on projected recruitment at each centre with appropriate overage in case of spillage or breakage. Further study vaccine supplies may be requested following the re-supply process in the Pharmacy Manual.

5.4 Storage

Vials of ChAdOx1-HBV and MVA-HBV must be stored in a continuously monitored ≤-70ºC freezer and nivolumab must be stored in the outer carton (to protect from light) between 2 and 8ºC in a continuously monitored refrigerator.

All study vaccine and study-labelled nivolumab must be kept in a secured location with no access for unauthorised personnel.

5.5 Accountability

The pharmacist or designee is required to maintain accurate accountability records for the study vaccine. Instructions and forms to be completed and kept for accountability will be provided to the pharmacist or designee. If the pharmacist or designee wishes to use study centre-specific accountability forms, these must be reviewed and approved in advance by the Sponsor. Upon completion of the study, all accountability records will be copied and the copies filed in the electronic Trial Master File (eTMF). The originals must be maintained at the study centre with the rest of the study records.

The number of vials of study vaccines and nivolumab received and dispensed must be recorded on a participant by participant basis, including the applicable batch number.

5.6 Destruction or Disposal

The Sponsor will provide instructions for the return of unused ChAdOx1-HBV and MVA-HBV vaccines and study-labelled nivolumab. Genetically modified organism (GMO) waste, including empty vials after full study vaccine accountability has been conducted, will be destroyed by appropriately licensed vendors. This destruction will be recorded with an original copy kept at the centre and a copy sent to the eTMF.

5.7 Method of Assigning Participants to Treatment Groups

Participants have so far been randomised to all open groups in a 1:1:1:1 allocation as each group is initiated. Protocol Version 6.0 closes Groups 1 and 4 to further randomisation and all remaining participants will be randomised to Groups 2 and 3 only in a 1:1 ratio.

A sentinel participant will be dosed in cohort 1, and the rest of the cohort will only be enrolled at least 48 hours later. Following the 7-day safety assessment of the first 6 participants in Group 1 by the SMC, Group 2 will be initiated. Groups 3 and 4 will be initiated after evaluation of safety data 7 days after the first 6 participants in Group 2 have received ChAdOx1-HBV. At the screening visit, participants will be sequentially allocated a screening number once written, informed consent has been obtained. They will be identified by this number until entry into study.

Participants fulfilling entry criteria will be allocated an enrolment number and allocated to treatment based on the treatment schedule prepared by statistician.

Once screening and enrolment numbers have been assigned, no attempt will be made to use those numbers again. If an enrolment number is allocated incorrectly, no attempt will be made to remedy the error once the study vaccine has been dispensed. Any participants that are withdrawn prior to either vaccination will be replaced on a case by case basis following discussion with the Sponsor. Discontinued participants following vaccination who do not complete all follow-up visits will be replaced following discussion with the Sponsor.

Any replacement participants will be given the next sequential participant number.

The treatment schedule list will be held by the statistician during the study.

5.8 Selection of Doses, Dosing Schedule and Administration

5.8.1 Selection of Doses in the Study

The ChAdOx1-HBV dose is 2.5 x 10^{10} vp, based on the review of the two doses studied in study HBV001 (2.5 x 10^{9} vp and 2.5 x 10^{10} vp). Safety data from all healthy volunteers was reviewed from HBV001 by the SMC, and the higher dose was chosen to use in this study. This dose, or higher, of ChAdOx1-based vaccines has been safely used in hundreds of participants (see Investigator's Brochure), and thousands of people have been immunised with a ChAdOx1 COVID-19 vaccine at a dose of 5 x 10^{10} vp. The dose of MVA-HBV will be fixed at 1 x 10^{8} pfu as taken from historical data of previous studies. A 1.5 x 10^{8} pfu MVA dose was used in nearly 2,000 healthy participants in influenza studies conducted by Oxford University and Vaccitech.

The dose of nivolumab will be fixed at 0.3 mg/kg to be given intravenously over 30 minutes.

5.8.2 Selection and Timing of Dose for each Participant

5.8.2.1 Dosing Schedule

The participants will be allocated to dosing group depending on the treatment schedule and groups open at the time of randomisation. Vaccination will be performed on Day 0, after eligibility has been reconfirmed, and on Day 28.

If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV at Month 3, at the Investigator's discretion and after discussion with the Sponsor (UK participants only).

There are no restrictions in the time of day that the vaccination should be administered or in timing of vaccination in relation to meals.

5.8.2.2 Study Vaccine Preparation and Administration

ChAdOx1-HBV and MVA-HBV vials should be allowed to reach room temperature before use.

The study vaccines will be provided at 1 x 10^{11} vp/ml ChAdOx1-HBV and 2 x 10^{8} pfu/ml for MVA-HBV. The appropriate doses will be prepared by dilution of individual vials on a per participant basis by study staff according to the procedure in the Pharmacy Manual. Dose Preparation kits including equipment will be provided by the Sponsor.

Both vaccinations will be given by intramuscular injection into the deltoid muscle, to the same, non-dominant arm in a participant, where possible. All vaccinations will be made by a suitably

qualified health professional. A second study team member will perform a check of the vaccine dilution to ensure the right dilution is performed.

The suitably qualified healthcare professional will wear gloves, eye protection and an apron or laboratory coat/gown during the procedure. The vaccination site will be covered with a sterile dressing to minimise dissemination of the recombinant virus into the environment. This should absorb any virus that may leak out through the needle track. The sterile dressing will be removed approximately 10 minutes after vaccination. The dressing will be discarded as GMO waste. No further dressing coverage is needed.

Allergic reactions to vaccination are possible, therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available and a medically qualified study team member trained to recognise and treat anaphylaxis must be present in the clinic during the entire vaccination procedure and post-vaccination observation period.

5.8.2.3 Nivolumab Preparation and Administration

Nivolumab will be prepared according to the Pharmacy Manual.

In Groups 3 and 4, the patients will be observed for 30 minutes after vaccination. If there are no safety concerns (vital signs and reactogenicity), nivolumab will be infused over 30 minutes and the patients will be observed in the study centre for a further 30 minutes post-infusion.

5.8.2.4 Dose and Schedule Modifications

Every effort will be made to administer the planned doses of study vaccines and nivolumab.

5.9 Blinding

This is an open label study; therefore, no procedures for blinding are necessary. The study team members and participant will know the treatment the participant is receiving.

5.10 Prior and Concomitant Vaccines and Medications

Patients will have been taking antivirals for at least 12 months before screening. Once randomised to the study, oral antiviral medication should not be withdrawn. Patients should remain on the same dose of antivirals that they were on when they entered the study for the duration of the study.

Allowed antiviral medications include: entecavir, tenofovir (tenofovir alafenamide fumarate or tenofovir disoproxil fumarate), or besifovir.

Prior and concomitant medications include prescription and non-prescription drugs or other treatments, and any vaccines other than the study vaccine.

Recently used and ongoing medications will be reviewed and recorded during screening.

Concomitant medications used by participants post-vaccination will coincide with the collection period of adverse events. All medications taken to treat solicited AEs will be recorded in the eDiary and will be discussed with the participant at the scheduled clinic visits during the study. All medications taken to treat unsolicited AEs and SAEs will be recorded in the eCRF by questioning the participant at each visit whether they took any concomitant medications since the previous visit.

The name of the medication, treatment start and stop dates (or 'ongoing'), and indication must be recorded on the concomitant medication eCRF. The indication recorded on the concomitant medication eCRF must correspond to a medical term/diagnosis recorded on the adverse event

eCRF, or to a pre-existing condition noted in the participant's medical history, or be noted as prophylaxis, e.g. dietary supplement.

Also, participants should not receive any adenoviral-based vaccine within 3 months prior to or 3 months after administration of ChAdOx1-HBV on Day 0.

5.11 Treatment Compliance

Vaccine administration will take place at the study centre and will be performed by a suitably qualified healthcare professional. The precise date and time of vaccination shall be documented in the source documents and eCRF. The study will be monitored by a Study Monitor approved by the Sponsor. During monitoring visits, all procedures will be monitored for compliance with the protocol. Source documents will be reviewed and compared with the data entries in the eCRFs to ensure consistency.

5.12 Post-study Treatment

The Sponsor does not intend to provide ChAdOx1-HBV nor MVA-HBV after the end of the study or after any early participant withdrawal, as there is currently no clinical data supporting their efficacy. These participants will remain under the care of their healthcare professionals and treated according to standard care. If new information becomes available that would inform the benefit of repeat dosing, this will be considered as a protocol amendment at a later time.

6 STUDY PROCEDURES AT EACH VISIT/SCHEDULE OF ASSESSMENTS

The study consists of the following:

- A 42-day screening period before the start of study treatment
- A study period of 9 months
- An end of study visit

The schedule of assessments at each visit is shown in Table 2 and listed in Section 6.1 to Section 6.3.1. The study assessments are described in Section 7.

Note: any additional visits or assessments performed during the study e.g. to assess adverse events must also be recorded on the unscheduled procedures or unscheduled visits in the eCRF.

Unsolicited adverse events will be recorded from the date the informed consent is signed and at all clinic visits, by questioning the participant at each visit whether they had any adverse events since the previous visit and by observing the participant during clinic visits.

Serious adverse events and AESIs will be recorded from the date the informed consent is signed until the end of the study and/or resolved or until participant contact discontinues.

Solicited AEs and medication taken to treat solicited AEs will be collected daily in the eDiary for 7 days post-vaccination.

All medications taken to treat unsolicited AEs and SAEs will be recorded in the eCRF by questioning the participant at each visit whether they took any concomitant medications since the previous visit.

Due to the COVID-19 pandemic, study centres will follow any local procedures in line with testing to ensure the safety of participants and staff.

6.1 Screening and Baseline Assessments

Written informed consent for participation in the study must be obtained before performing any study specific screening tests or evaluations according to the process in Section 13.4.

The following will be performed at screening:

- Demographic data will be collected
- Height and weight will be measured
- A medical and disease history will be recorded, including any medications being taken
- A blood sample will be taken for HIV, HCV, HBV (quantitative HBV DNA and quantitative HBsAg), HDV diagnostic testing
- A urinalysis dipstick test will be performed
- A urine drug screen will be performed
- A urine pregnancy test will be performed, childbearing status recorded and if of childbearing potential, assessment of contraceptive measures performed
- Blood samples will be taken for haematology (including prothrombin time [PT] and INR), biochemistry and liver function tests (LFTs)
- A full physical examination will be performed
- Vital signs (pulse rate, blood pressure and temperature) will be measured

Table 2 Overall Schedule of Assessments at Each Study Visit

Visit/Call	Screen	Vaccination Clinic	Telephone Call	Clinic	Vaccination Clinic	Telephone Call	Clinic			End of Study / Early Discontinuation Clinic
Timepoint (window)	Day							Month		
	-42 to -1	0	1 (+1d)	7 (±1d)	28 (+2d)	29 (+1d)	35 (±1d)	3 (±7d)	6 (±7d)	9 (±7d)
Informed consent	X									
Baseline/eligibility variables										
Demographics	X									
Inclusion and exclusion criteria	X									
Height and weight	X									
Medical and disease history	X									
HIV, HCV, HBV (quantitative HBV DNA and quantitative HBsAg), HDV serology	X									
Urinalysis	X									
Urine drug screen	X									
Urine pregnancy test (β-hCG)	X	X [a]			X [a]			X [f]	X [f]	X
Laboratory eligibility and safety tests										
Haematology	X	X [a]		X	X [a]		X	X	X	X
Biochemistry	X	X [a]		X	X [a]		X	X	X	X
Liver function tests	X	X [a]		X	X [a]		X	X	X	X
Study vaccination										
Vaccination dose		X			X			X [g]		
Post-dose observation		X			X			X [g]		
Nivolumab dose (Group 3 only) [b]					X					
Other safety assessments										
Full physical examination	X	X [a]			X [a]			X [a]		X
Symptom-directed physical examination				X			X	X	X	
Vital signs	X	X		X	X		X	X	X	X
Local/systemic reactogenicity		X [c]	X	X	X [c]	X	X	X [c]		
Unsolicited adverse events [d]	X	X	X	X	X	X	X	X	X	X
Serious adverse events and adverse events of special interest	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X
Blood for HBV disease markers [e]		X [a]		X	X [a]		X	X	X	X
Immunogenicity assessments										
Blood for cellular immunogenicity assessments		X [a]		X	X [a]		X	X [a]	X	X

[a] Pre-vaccination on Day 0, Day 28, and Month 3 (for UK participants having an MVA-HBV boost)

[b] Participants in Group 3 will receive nivolumab on Day 28.Group 4 is now closed. The patients will be observed for 30 minutes after vaccination. If there are no safety concerns (vital signs and reactogenicity), nivolumab will be infused over 30 minutes and the patients will be observed in the study centre for a further 30 minutes post-infusion.

[c] Captured pre-vaccination and post-vaccination on Days 0 and 28, and Month 3 (for UK participants having an MVA-HBV boost) , via eDiaries for 7 days post-vaccination and then at the clinic assessment 7 days post-vaccination (Day 7 or 35)

[d] Recorded in the eCRF from the date the informed consent is signed, at all clinic visits to cover the period since the previous visit and during the visit

[e] Individual disease markers tested according to the Study Laboratory Manual

[f] Pregnancy testing at Month 3 in Groups 1 and 2 if an MVA-HBV boost is given, and at Months 3 and 6 in Groups 3 and 4
[g] If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV at Month 3, at the Investigator's discretion and after discussion with the Sponsor (UK participants only). These patients will also have a telephone call the day after the boost vaccination and a clinic visit 7 days post-boost, as per Day 1 and Day 7.

All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before the first dose of study vaccine. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants who do not meet eligibility criteria may be rescreened at the discretion of the Investigator. Only abnormal/ out of window tests are required to determine eligibility. Re-screening can occur at any point with the allowed overall screening window (up to 42 days).

6.2 Treatment Day Assessments (Day 0, Day 28 and Month 3 [MVA-HBV Boost (UK participants only)])

The following will be performed pre-vaccination:

- Re-check of eligibility criteria (Day 0 only)
- A urine pregnancy test will be performed
- Blood samples will be taken for haematology, biochemistry and LFTs
- A full physical examination will be performed
- Vital signs (pulse rate, blood pressure and temperature) will be measured
- A baseline assessment of local and systemic reactogenicity will be performed (see Appendix 1)
- Blood samples will be taken for immunogenicity assessments and HBV disease markers

Participants will then receive study vaccine by intramuscular injection in the non-dominant arm, and will be observed for 30 minutes post vaccination for safety concerns. Nivolumab will then be administered via an infusion, if applicable, according to Table 1. All participants will be assessed in the clinic for at least 30 minutes post-vaccination and post-nivolumab infusion in case of immediate adverse events. The first participant in each cohort will be observed for 1 hour. In the first cohort, the second participant will not be dosed until 48 hours after the first sentinel participant.

The following will be performed post-vaccination:

- The vaccination site will be covered with a sterile dressing during the observation period; it will then be removed and disposed of as GMO waste
- Vital signs (pulse rate, blood pressure and temperature) will be measured at the end of the observation period
- Local and systemic reactogenicity will be assessed at the end of the observation period
- On Day 0, an eDiary, tape measure and thermometer will be provided to perform self-assessment of local and systemic reactogenicity for 7 days after the vaccinations. Participants will be reminded to do the following daily for the 7 days after each vaccination:
  - Take and record their temperature
  - Measure and record the size of vaccination site redness
  - Assess the other solicited adverse events listed in the eDiary

6.3 Follow-up Period Assessments

6.3.1 Telephone Calls: Day 1, Day 29 and Month 3 + 1 Day (MVA-HBV Boost [UK participants only])

- Reminder to complete eDiary for collection of local and systemic reactions during 7 consecutive days post-vaccination

6.3.2 Clinic Visits: Day 7, Day 35 and Month 3 + 7 Days (MVA-HBV Boost [UK participants only])

- Blood samples will be taken for haematology, biochemistry and LFTs
- A symptom-directed physical examination will be performed if required
- Vital signs (pulse rate, blood pressure and temperature) will be measured
- Local and systemic reactogenicity
- Blood samples will be taken for immunogenicity assessments and HBV disease markers

These visits should be anchored to the date of Vaccination and scheduled to occur 7±1 day after vaccination. If vaccination is administered on any day other than Day 28, the follow up visit should be scheduled 6-8 days after the date of actual vaccination. All other study visits after Day 0 (except day 35) are anchored to Day 0.

6.3.3 Clinic Visit: Months 3 and 6

- For participants enrolled at UK sites, check hepatitis B surface antigen Day 35 result (Month 3 only)
  - If a participant has a 0.5 log or greater drop in hepatitis B surface antigen, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor. Please see Section 6.2 for the assessments to be performed.
- A urine pregnancy test will be performed (Months 3 and 6 in Groups 3 and 4 only)
- Blood samples will be taken for haematology, biochemistry and LFTs
- A symptom-directed physical examination will be performed if required
- Vital signs (pulse rate, blood pressure and temperature) will be measured
- Blood samples will be taken for immunogenicity assessments and HBV disease markers

6.3.4 Clinic Visit: Month 9 (End of Study Visit)

- A urine pregnancy test will be performed
- Blood samples will be taken for haematology (including PT), biochemistry and LFTs
- A full physical examination will be performed
- Vital signs (pulse rate, blood pressure and temperature) will be measured
- Blood samples will be taken for immunogenicity assessments and HBV disease markers

6.4 Assessments at Unscheduled Visits

Unscheduled visits may be required according to by the participant's condition, assessments performed will be recorded in the eCRF.

6.5 Participant Discontinuation

Participants have the right to withdraw consent from the study at any time for any reason, including their future care. The Investigator should however try to find out why a participant withdraws from the study and document the reason for withdrawal in the source documents and eCRF.

If there is a medical reason for withdrawal, the participant will remain under the supervision of the Investigator until satisfactory health has returned.

Participants who are withdrawn from the study prior to completion of the scheduled study procedures for any reason should complete the end of study visit assessments as far as possible.

7 DETAIL OF STUDY ASSESSMENTS

7.1 Demographic and Baseline Assessments

The following will be collected at screening to determine eligibility and baseline status of the participant. Baseline safety assessments will also be performed as detailed in Section 7.4.

7.1.1 Demographic Data and Baseline Variables

Demographic data will include age, gender and race/ethnicity, smoking history, use of alcohol and drugs of abuse.

7.1.2 Medical and Disease History

Disease history (including date of diagnosis) and any allergies or other clinically significant diseases and surgeries will be recorded.

7.1.3 Prior Medications and Therapies

All prior therapies and procedures will be recorded.

All other prior medications (e.g. prescription drugs, over the counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the participant in the 28 days before the screening visit will also be recorded (see Section 5.10).

7.1.4 Laboratory Eligibility/Safety Tests

Haematology, biochemistry, LFTs and viral serology blood tests and urinalysis will be performed at screening for all participants. Samples will be analysed at the central laboratory. Results from tests must be reviewed by the Investigator (or a designee who is a medically qualified study team member) and managed in accordance with the study centre procedures. The clinical significance of all results outside of the normal range will be determined by the Investigator to determine eligibility and may be reported as an adverse event at the discretion of the Investigator.

Additional laboratory safety tests may be performed if the Investigator deems them to be necessary to fully evaluate an adverse event. In the event that the Investigator elects to order non-protocol-specified laboratory tests, the Investigator must record the rationale for the tests and a determination of clinical significance of the result in the source documents. The Investigator must keep the local Medical Monitor informed of adverse events of clinical significance.

Abnormal results and findings will be discussed as applicable with the participant and the participant will be referred for follow-up with their healthcare provider if necessary.

7.1.4.1 Haematology

A sample of venous blood will be collected according to the central laboratory procedures.

The following will be measured: full blood count, haemoglobin, haematocrit, erythrocytes, mean cell volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, PT and platelets.

7.1.4.2 Biochemistry

A sample of venous blood will be collected according to the central laboratory procedures.

The following biochemistry parameters will be measured: sodium, potassium, urea nitrogen, creatinine and albumin and LFTs (alkaline phosphatase, gamma-glutamyl transpeptidase, ALT AST and direct bilirubin).

7.1.4.3 Human Immunodeficiency Virus, Hepatitis B Virus, Hepatitis C Virus and Hepatitis D Virus Diagnostic Testing

Blood samples will be tested for: HIV antibodies, HCV antibodies, HBsAg, HBeAg, HBcrAg, HBsAb, HBeAb, hepatitis B core antibody, HBV DNA, HBpgRNA, HDV serology

7.1.4.4 Urinalysis

A urine sample will be obtained to screen for drugs of abuse.

A urine sample will be collected in a sterile container for dipstick urinalysis. The following will be tested: blood, bilirubin, glucose, ketones, leucocytes, nitrite, pH, protein, specific gravity and urobilinogen. The Investigator may order additional urine tests to be performed.

7.1.5 Urine Pregnancy Test

A urine pregnancy test will be performed in female participants of childbearing potential at screening and confirmed to be negative pre-vaccination on Day 0 and 28 and at Month 3 if a booster dose of MVA-HBV is given (UK participants only), and at Month 3 and 6 for those in Group 3 and 4, as per local standard procedures and at each of the timepoints according to Table 2.

7.2 Immunogenicity Assessments

Immunogenicity samples (peripheral blood mononuclear cells; PBMCs) will be taken for planned and potential exploratory analyses at each of the timepoints according to Table 2.

Immunogenicity studies will include (but are not limited to) analysis of samples ex vivo by multiparameter flow cytometry (including Mean Fluorescence Intensity measurements) and ex vivo IFN-γ ELISPOT assays. The latter will be used for epitope mapping. Innate immune responses may be measured primarily by RNA sequencing of samples and may be assessed in other assays if cell numbers permit. Additional immunogenicity assessments may be performed.

7.2.1 Exploratory Analysis

HBV-specific CD4+, CD8+ and T cell subsets within PBMC will be further defined by phenotypic markers of activation, differentiation and memory. Peripheral blood mononuclear cells will also be used in IFN-γ ELISPOT assays to determine the breadth of HBV-specific T cell responses (defined by number of peptide pools or individual peptides recognised). These data may be used to build immunologic models of the immune system.

Blood or PBMC samples may be used for extraction of RNA and subsequent unbiased analysis of innate immune responses before and after vaccination by RNA sequencing.

Serum blood samples will be used for analysis of HBpgRNA and HBcrAg.

7.3 Efficacy Assessments

Formal efficacy will not be assessed in the study, although changes in HBsAg will be followed.

7.4 Safety Assessments

7.4.1 Adverse Events

Recording and reporting of adverse events is described in detail in Section 8.2.

7.4.1.1 Solicited Adverse Events

Solicited adverse events are events the participant is specifically asked about. These adverse events are commonly observed soon after receipt of vaccines and relate to local and systemic signs and symptoms. Solicited adverse events will be collected daily in the eDiary for 7 days post-vaccination.

For this study, solicited adverse events to be collected include:

- Vaccination site reactions: pain, induration, warmth, erythema (redness)
- Systemic adverse events: feverishness, chills, myalgia, fatigue, headache, nausea, arthralgia, malaise

Participants will be asked to record the presence of these symptoms and grade the severity as described in Section 8.2.4.1. Oral temperature will be measured using the thermometer provided and the diameter of induration will be measured with the tape measure provided.

7.4.1.2 Unsolicited Adverse Events

Unsolicited adverse events are other events meeting the criteria for adverse events (see Section 8.2.1) apart from those the participant is specifically asked about. Unsolicited adverse events, hospitalisations, other SAEs and AESIs will be collected for the duration of the study.

Participants will collect unsolicited adverse events in the eDiary and these will be reviewed during telephone calls with the participant and relevant information (event term, start and end date, severity, causality, outcome and seriousness) collected and entered into the eCRF as described in Section 8.2.4.

7.4.2 Laboratory Safety Tests

Laboratory safety tests will be performed at each of the timepoints according to Table 2, as per Sections 7.1.4.1 and 7.1.4.2. Extra laboratory safety tests may be performed if the Investigator deems them to be necessary to fully evaluate an adverse event. In the event that the Investigator elects to order non-protocol-specified laboratory tests, the Investigator must record the rationale for the tests and a determination of clinical significance of the result in the source documents. The Investigator must keep the local Medical Monitor informed of adverse events of clinical significance.

Abnormal results and findings will be discussed as applicable with the participant, and the participant will be referred for follow-up with their healthcare provider if necessary.

Results from the LFTs obtained on the study must be reviewed by the Investigator (or a designee who is a medically qualified study team member) and managed in accordance with the study centre procedures. The clinical significance of all results outside of the normal range will be determined by the Investigator and may be reported as an adverse event at the discretion of the Investigator.

7.4.3 Vital Signs

Vital signs will be performed at screening, pre-vaccination and post-vaccination (at the end of the observation period) at the vaccination visit, at all visits during the follow-up and the end of study visit. At each timepoint blood pressure, pulse rate and temperature, will be measured after the participant has been in a sitting position for 5 minutes.

7.4.4 Physical Examination

A skin, respiratory, cardiovascular, abdominal and lymphatic system examination will be performed at screening, pre-vaccination on Day 0, Day 28 and Month 3 (for UK participants having the MVA-HBV boost only) and on Month 9. A symptom-directed physical examination will be performed at all other clinic visits if required. Results will be recorded as normal, abnormal and not clinically significant or abnormal and clinically significant.

8 SAFETY MANAGEMENT

8.1 Responsibilities for Ensuring the Safety of Study Participants

The national Regulatory Authorities, the study Sponsor, the Institutions through which the research is performed and all members of the Investigator's study team share responsibility for ensuring that participants in this study are exposed to the least possible risk of adverse events that may result from participation in this protocol.

8.1.1 Investigator

The Investigator has a personal responsibility to closely monitor study participants and an inherent authority to take whatever measures necessary to ensure their safety. The Investigator may delay a participant's study vaccine administration or pause study vaccine administration in the whole study if they have some suspicion that the study vaccine might place a participant at significant risk. The Investigator determines severity and causality for each adverse event.

Responsibilities of the Investigator may be assigned to a designee who is a medically qualified study team member, however the accountability for the specific task remains with the Investigator.

8.1.2 Study Sponsor

The Sponsor also has an institutional responsibility to ensure participant safety. This responsibility is vested in the local Medical Monitor, SMC and DMC.

8.1.3 Local Medical Monitor

The local Medical Monitor is the Sponsor's representative and is a credentialed physician or surgeon in their country of residence with the necessary expertise to act in such capacity. The local Medical Monitor reviews the safety of the product for protocols in a specific region and can add another causality assessment to the Investigator's causality assessment. The causality assessment given by the Investigator must not be downgraded by the local Medical Monitor. If the Medical Monitor disagrees with the Investigator's causality assessment, the opinion of both the Investigator and Sponsor should be provided with the report.

8.1.4 Safety Monitoring Committee

A SMC, consisting of the Sponsor Medical Monitor, the Country Lead Investigators for South Korea, Taiwan and the UK, and the trial Medical Monitor, will be appointed to review the study data throughout the study and at specific time points, and make recommendations concerning the continuation, modification, or termination of the study. The SMC will perform the following:

- Scheduled evaluation of study conduct and progress, and review of the cumulative safety and efficacy data. Scheduled meetings will take place as follows:

- Kick off meeting before the first participant is enrolled
- 7 days after the first 6 participants in Group 1 have received the first dose of MVA-HBV
- 7 days after the first 6 participants in Group 2 have received ChAdOx-HBV and MVA-HBV
- 7 days after the first 6 participants in Groups 3 and 4 have received ChAdOx1-HBV, with or without nivolumab

- Ad hoc evaluation of ALT or AST results >10 x ULN, or ALT or AST >5 x ULN for more than 3 weeks, and if considered of concern, refer to the DMC.

8.1.5 Data Monitoring Committee

A DMC, composed of three independent experts (two clinicians and one statistician), will be appointed to review the study data and make recommendations concerning the continuation, modification, or termination of the study. The DMC will perform the following:

- Evaluation of study conduct and progress and review of the cumulative safety and efficacy data. Meetings will take place as follows:
  - Kick off meeting before the first participant is enrolled
  - Perform unscheduled review of data if one of the study stopping or holding rules is met, see Section 3.1.3.
  - Meet if requested by the SMC

The DMC will operate in accordance with the study-specific DMC Charter, which will be agreed prior to the start of enrolment.

The chair of the DMC may be contacted for advice and independent review by the Investigator or Sponsor in any other situation where the Investigator or Sponsor feels independent advice or review is important.

The DMC will also be notified within 24 hours of the Investigators' being aware of any study vaccine-related SAEs. The DMC has the power to place the study on hold if deemed necessary.

Following review of data by the DMC, a recommendation to resume, modify or halt study enrolment and vaccine administration will be made, and the DMC will record their judgment in a memorandum to the study file and notify the Sponsor. In the event of halting or modification of the protocol, the DMC memorandum will be forwarded to the local Medical Monitor and Investigators.

8.1.6 Institutional Review Boards and Ethics Committees

The IEC/IRB has institutional responsibility for the safety of participants in clinical studies. The IEC/IRB has the authority to terminate, suspend or require changes to a clinical study.

8.1.7 National Regulatory Authority

Since the national regulatory authority receives all expedited safety reports for the study it also has the authority to terminate, suspend or require changes to a clinical study.

8.2 Adverse Events

8.2.1 Definitions

8.2.1.1 Adverse Event

An adverse event is:

- Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment

- An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of study vaccine, whether or not considered related to the investigational product

An adverse event includes but is not limited to:

- Any clinically significant worsening of a pre-existing condition
- An adverse event occurring from overdose (i.e. a dosage higher than that prescribed by a healthcare professional for clinical reasons, or a dosage higher than that described in the Investigator's Brochure or on the marketed product label) of an investigational or marketed product, whether accidental or intentional
- An adverse event occurring from abuse (e.g. use for non-clinical reasons) of an investigational or marketed product
- An event related to a medical procedure or associated with the discontinuation of the previous use of an investigational or marketed product required by protocol (protocol related adverse event)
- Not all vital sign or laboratory abnormalities will be considered an adverse event. Usually these will be considered as an adverse event:
  - If Grade 3 (severe) or greater in severity
  - If judged to be clinically significant by the Investigator
  - If accompanied by clinical symptoms
  - If meeting the definition of a SAE
  - If resulting in dose modification, interruption or discontinuation of study vaccine
  - If requiring specific treatment

8.2.1.2 Adverse Reaction

An adverse reaction is defined as any untoward and unintended response to study vaccine related to any dose administered.

An unexpected adverse reaction is an adverse reaction in which the nature or severity of which is not consistent with the Investigator's Brochure or Prescribing Information.

8.2.1.3 Serious Adverse Event

SAEs are adverse events meeting at least one of the following criteria:

- It results in **death** (i.e. the adverse event caused or led to the fatality). Serious does not describe an event which hypothetically might have caused death if it were more severe
- It was immediately life-threatening (i.e. the adverse event placed the participant at immediate risk of dying. It does not refer to an event which hypothetically may have led to death if it were more severe)
- It required inpatient **hospitalisation** or prolonged hospitalisation beyond the expected length of stay. Hospitalisations for scheduled treatments and elective medical/surgical procedures related to a pre-existing condition that did not increase in severity or frequency following receipt of study vaccine, are not serious by this criterion. Hospitalisation is defined as a hospital admission or an emergency room visit for a period greater than 24 hours
- It resulted in a persistent or significant **disability/incapacity** (i.e. substantial reduction of the participant's ability to carry out activities of daily living)

- It resulted in a **congenital anomaly or birth defect** (i.e. an adverse finding in a child or foetus of a participant exposed to the study vaccine prior to conception or during pregnancy)
- Other **medically important conditions** that may not result in death, threaten life or require hospitalisation (i.e. the adverse event does not meet any of the above serious criteria) may be considered an SAE when, based on appropriate medical judgment, they may jeopardise the participant and require medical or surgical intervention to prevent one of the serious outcomes listed in these criteria (e.g. allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse)

An **SAE** is an adverse event meeting the outcome criteria for seriousness regardless of relationship to the study vaccine. The following are not (and should not be reported as) SAEs: hospitalisation for scheduled treatments and elective medical/surgical procedures related to a pre-existing condition that did not increase in severity or frequency following receipt of study vaccine, and admissions for social reasons.

8.2.1.4 Suspected Unexpected Serious Adverse Reaction

A SUSAR is any suspected adverse reaction related to the study vaccine that is both unexpected and serious.

8.2.2 Study Reporting Period for Adverse Events

The reporting period for all adverse events begins on the date the informed consent is signed. Solicited adverse events are recorded in the eDiary up to 7 days post-vaccination. All other events are recorded in the eCRF at all clinic visits throughout the study. All SAEs and/or AESIs are recorded until the final study visit and for all serious or study vaccine-related adverse events until these are resolved or until participant contact discontinues. Severe adverse events or SAEs that continue at the end of the study will be attempted to be followed until resolved or stabilised.

Adverse event information will be collected at study visits and participant will be instructed to call study team members to report any abnormalities during the intervals between study visits and to come to the study centre if medical evaluation is needed and the urgency of the situation permits.

8.2.3 Reporting Exemptions

No reporting exemptions have been identified for this study.

8.2.4 Recording and Assessment of Adverse Events by the Investigator

Solicited adverse events are recorded in the eDiary up to 7 days post-vaccination. All other adverse events are recorded in the eCRF at all clinic visits throughout the study. All adverse events, both those observed by study team members and those spontaneously reported by the participant, will be recorded in the eCRF. Solicited adverse events will be reported using pre-defined terms. Unsolicited adverse events will be reported using a recognised medical term or diagnosis that accurately reflects the event.

Adverse events will be assessed by the Investigator, or a medically qualified study team member, for severity, relationship to study vaccine, action taken, outcome and whether the event meets criteria as an SAE according to the following guidelines:

8.2.4.1 Assessment of Severity

Whenever possible, the severity of adverse events will be graded according to the toxicity table in Appendix 1. The scale shown in Table 3 will be used to assess severity of adverse events not listed in Appendix 1.

Table 3 Severity Grading of Adverse Events not listed in the Toxicity Table for Clinical and Laboratory Abnormalities

Grade	Severity	
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated; no disruption of normal daily activity.
2	Moderate	Minimal, local, or non-invasive intervention indicated; discomfort sufficient to reduce or affect daily activity.
3	Severe	Severe or medically significant, but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; inability to work or perform normal daily activity.
4	Life-threatening	Represents an immediate threat to life.
5	Fatal	Death as a result of this adverse event

A change in severity of an adverse event will not be recorded as a new adverse event. Only the highest severity level that occurs during the entire period of the adverse event will be recorded on the eCRF with the onset and resolution dates encompassing the entire duration of the event.

Note: It is important to distinguish between serious and severe adverse events. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.2.1.3.

8.2.4.2 Assessment of Relationship

Solicited adverse events of vaccination site reactions will be considered causally related to study treatment.

For all other adverse events, the Investigator will determine a **causal relationship** to the study vaccine. A number of factors will be considered in making this assessment, including: 1) the temporal relationship of the event to the administration of the study vaccine 2) whether an alternative aetiology has been identified and 3) biological plausibility.

Causality of all adverse events should be assessed by the Investigator using the following question:

"Is there a reasonable possibility that the adverse event may have been caused by the study vaccine?"

- **YES (related):** There is a reasonable possibility that the study vaccine contributed to the adverse event
- **NO (not related):** There is no reasonable possibility that the adverse event is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the adverse event

The Investigator is required to provide an assessment of relationship of AEs to the vaccine or study procedures and determines causality. The Sponsor and local medical monitor can add another causality assessment to the Investigator's causality. However, the causality given by the Investigator must not be downgraded by the Sponsor or the local medical monitor. If the

Sponsor or the local medical monitor disagrees with the Investigator's causality assessment, the opinion of both the Investigator, the Sponsor and the local medical monitor should be provided with the report.

Every effort should be made by the Investigator to determine the existence of any pre-existing conditions (e.g. headache in adults or rashes in infants on study Day 0 with onset prior to study vaccination) that must be taken into consideration when assessing causal relationship of an adverse event. Pre-existing conditions should be recorded in the eCRF as baseline history and substantiated by appropriate source documentation. Intermittent conditions such as headaches may not be present on study Day 0 but may represent an adverse event if the intensity or duration of the event is worse than usual following study vaccine.

8.2.4.3 Action Taken with Study Vaccine

The action taken with the study vaccine will be recorded as None, as only one dose is given.

8.2.4.4 Assessment of Outcome

The outcome of the adverse event will be assessed as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Not recovered/resolved
- Unknown
- Fatal

8.2.5 Reporting Requirements and Procedures for SAEs

All SAEs are reported to the Sponsor for the entire study period. Suspected unexpected serious adverse reactions are reported even after the study is over, if the Sponsor, local Medical Monitor or Principal Investigator becomes aware of them. The study centre will be provided with specific reporting procedures including the SAE paper form and any supplemental reporting forms to be used. SAEs will be reported on the SAE paper form and the adverse event eCRF using a recognised medical term or diagnosis that accurately reflects the event.

SAEs will be assessed for severity, causal relationship to the study vaccine or alternative aetiology by the Sponsor and Investigator. The onset and resolution dates of the event and medical care taken in response to the event will be documented. If the event has not resolved by the end of the study, it will be documented as "ongoing" on the eCRF, however, follow-up of the SAE must continue until resolved or the condition has stabilised. Information recorded on the eCRF must be substantiated in the source documents.

The SAE paper form should be completed with all information known at the time and scanned and emailed to the local Medical Monitor and to MHGSafety@prahs.com. If email service is not available due to technical reasons, the toll-free fax numbers will be used for SAE reporting.

Likewise, fatal or life-threatening SAEs will have to be reported via MHGSafety@prahs.com or the toll-free fax numbers. If the local Medical Monitor is required by the protocol or chooses to suspend enrolment s/he shall immediately create a written memorandum for record to the study file and telephonically notify the Sponsor of this act.

Contact information for all safety personnel are contained in the Team Contact List, which will be stored at the study centre in the ISF and maintained by the study Sponsor.

Investigators must not wait to collect additional information to fully document the event before notifying the local Medical Monitor of an SAE. The initial notification should include the following (at a minimum):

- Protocol number and name and contact number of the Investigator
- Participant identification
- Investigational product
- Event term

The Sponsor will notify the DMC of all SUSARs within 24 hours of becoming aware of an event and will provide all follow-up information in a timely manner.

8.2.5.1 Follow-up Information on an SAE

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained by the Investigator. For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor. In addition, an Investigator may be requested by the Sponsor to obtain specific information in an expedited manner. This information may be more detailed than that captured on the SAE form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes such as concomitant medication and illnesses must be provided.

After the initial SAE report, the Investigator is required to follow each participant proactively and to report new significant follow-up by submitting an updated SAE report form to the Sponsor (or designee). New significant information includes, but is not limited to, the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

8.2.5.2 Required Follow-up for SAEs

There should be attempted follow-up until the end of the study in all participants. If an SAE continues after this period, then the participant must be followed up until the event resolves or stabilises. The local Medical Monitor may specify a longer period of time, if required to assure the safety of the participant.

8.2.5.3 Medical Review and Reporting by the Sponsor

The Sponsor (or designee) will determine expedited reporting requirements for each reported SAE according to local requirements based upon:

- Investigator's assessment of causality and seriousness
- Expectedness

The expectedness of an SAE is assessed by the Sponsor in the overall classification of SAEs for expedited reportability. The current Investigator's Brochure section "Reference Safety

Information" will be used as the reference for determination of expectedness and risk assessment of vaccine-related adverse events and Section 4.8 of the Nivolumab SmPC will be used to assess the expectedness for nivolumab related events.

8.2.5.4 Sponsor Responsibility for Expedited Safety Reports

The Sponsor (or designee) will notify Investigators of all reportable SAEs. This notification will be in the form of an expedited safety report. Upon receiving such notices, the Investigator must review and retain the notice with other study related documentation.

The Investigator should also comply with the IEC/IRB procedures for reporting any other safety information.

The Sponsor will ensure that SAEs are reported to the IECs/IRBs and regulatory authority(ies) according to local requirements.

SUSARs and other significant safety issues reported from the development programme shall be reported to the relevant regulatory authorities in all concerned countries according to local regulations (either as expedited safety reports and/or in aggregate reports), by the Sponsor (or designee).

8.2.6 Follow-up of Participants after Adverse Events

8.2.6.1 Investigator Follow-up

Treatment of any adverse events will be determined by the Investigator using his/her best medical judgment and according to current clinical practice guidelines. For management of nivolumab toxicities, please see the Safety Management Plan which includes information on nivolumab and potential nivolumab interactions. All applied measures as well as follow-up will be recorded in the appropriate eCRF.

The Investigator will continue follow-up on adverse events, including laboratory abnormalities and solicited adverse events, until the event has resolved, is otherwise satisfactorily explained, or the participant completes the study. The resolution date will be recorded on the eCRF as the last date on which the participant experienced the adverse event. If an adverse event resolution date is uncertain the Investigator should estimate the completion date based on medical judgment and interview of the participant. Approximate dates of resolution from phone or other communications may be taken as adverse event resolution dates. Some examples of estimation of adverse event resolution are: 1) an asymptomatic laboratory abnormality on one visit that has not been followed up between visits but has resolved by the next visit may be assumed to have resolved by the midpoint of the inter-visit interval; 2) A resolved adverse event that was treated may be assumed to have been resolved by the end of treatment.

Adverse events that are still present at the end of the study should be recorded as ongoing.

Information recorded on the eCRF must be substantiated in the source documents. If an adverse event evolves into a condition that becomes "serious," it will be designated as serious on the adverse event eCRF and a supplemental SAE report form will be completed.

Follow-up for SAEs must continue until resolution or stabilisation and the outcome reported to the Sponsor, even if this extends beyond the SAE reporting period.

8.2.7 Post-Study Adverse Events

At the final study visit, the Investigator should instruct each participant to report to the Investigator any subsequent adverse events that the participant's personal physician believes could be related to study vaccine or study procedures.

The Investigator should notify the Sponsor (or designee) of any death, SAE or other adverse event of concern occurring at any time after a participant has discontinued study vaccine if the event is believed to be related to study vaccine or study procedures. The Sponsor (or designee) should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a participant that participated in this study.

The Investigator should record the event in the eCRF; if the eCRF is no longer available, the Investigator should report the event directly to the Sponsor (or designee).

8.3 Events of Special Interest

Adverse events of special interest in this study are those previously reported with nivolumab in oncology indications requiring dose modification or termination (see SmPC), and prior studies in CHB patients, including the onset of any autoimmune disorder and hepatitis flares. These include pneumonitis, grade 3 or 4 diarrhoea, diabetes, thyroid diseases, colitis, nephritis, immune-related endocrinopathies, myocarditis, immune-related skin conditions, or other unspecified immune-related adverse reactions.

These events will be reported to the Sponsor as for SAEs (see Section 8.2.5).

8.4 Other Events Requiring Immediate Reporting

The Investigator must report the following events to the Sponsor or to the trial Medical Monitor within 24 hours of becoming aware of the event:

- Withdrawal of consent during the study for safety reasons
- Protocol deviation affecting the safety of a participant or involving the vaccination process
- Grade 3, or above adverse event thought to be an allergic reaction to the study vaccine
- Any event that, in the opinion of the Investigator, precludes further administration of the study vaccine
- Pregnancy (see Section 8.6)

8.5 Overdose or Incorrect Administration

Study vaccine overdose is the accidental or intentional use of the study vaccine in an amount higher than the dose being studied. An overdose or incorrect administration of study vaccine is not an adverse event unless it results in untoward medical effects:

- Any study vaccine overdose or incorrect administration of study vaccine should be recorded in the eCRF as part of the study vaccine administration information
- Any untoward medical effects associated with an overdose or incorrect administration of study vaccine should be recorded in the eCRF as an adverse event. If the associated adverse event fulfils serious criteria, the event should be reported to the Sponsor (or designee) within 24 hours of knowledge of the event

8.6 Management of Pregnancy

8.6.1 Notification and Follow-up

8.6.1.1 Pregnancies in Female Participants

Any pregnancies occurring during the study or within 6 months after the last dose of study vaccine must be reported to the Sponsor (or designee) within 24 hours of knowledge of the event. The paper pregnancy form should be completed with all information known at the time and scanned and emailed to MHGSafety@prahs.com or faxed to the toll-free fax numbers.

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the reporting window and must be immediately discontinued from study vaccine. The Investigator should counsel the participant, discussing the risks of the pregnancy and the unknown effects on the foetus. Monitoring of the participant should continue until conclusion of the pregnancy.

Male participants will be instructed to immediately inform the Investigator if their partner becomes pregnant during the reporting window. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study vaccine. The pregnant partner will need to sign an authorisation for use and disclosure of pregnancy health information to allow for follow-up on her pregnancy. The Investigator may provide information on the risks of the pregnancy and the unknown effects on the foetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

8.6.2 Outcome

Additional information on the course and outcome of the pregnancy should be provided to the Sponsor (or designee) when available using the pregnancy report form.

The following pregnancy outcomes will be considered to be SAEs and should be reported according to the procedure in Section 8.2.5. Pregnancy is not considered an adverse event unless one of these criteria is met:

- Spontaneous abortion (as the Sponsor considers spontaneous abortions to be medically significant events)
- Any congenital anomaly/birth defect in a child born to a female participant or female partner of a male participant

9 DATA QUALITY ASSURANCE AND QUALITY CONTROL

9.1 Protocol Deviations

Major protocol deviations are defined as those that result in harm to the study participants or significantly affect the scientific value of the reported results of the study. Other deviations will be considered minor.

Protocol deviations will be recorded on the source documents and with an explanation for the deviation. All protocol deviations will also be recorded as specified in the monitoring plan and statistical analysis plan.

Major protocol deviations that meet the criteria for a serious breach of ICH GCP [36] should be reported to the Sponsor immediately. No deviation from the inclusion/exclusion criteria will be permitted.

9.2 Monitoring and Source Document Verification

The Sponsor will arrange for the study to be monitored in accordance with the principles of ICH GCP [36]. The frequency of monitoring visits will be determined by the rate of participant recruitment.

The following are examples of items that will be reviewed at these visits:

- Compliance with the protocol
- Consent procedure
- Source documents
- Adverse event procedures
- Storage and accountability of study vaccine

The monitoring visits also provide the Sponsor with the opportunity to ensure that timely participant accrual and the other Investigator's obligations and all applicable requirements are being fulfilled.

The Investigator must permit the Study Monitor, the IEC/IRB, the Sponsor's auditors and representatives from regulatory authorities direct access to all source documents (see Section 11.1) for confirmation of the accuracy and reliability of data contained within the eCRF (source document verification). Participant confidentiality will be protected at all times. The Study Monitor will carry out source document verification at regular intervals. This is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

9.3 Data Management and Coding

Data for each participant will be recorded on an eCRF. Data collection must be completed for each participant who signs an informed consent form and receives at least one dose of study vaccine.

Electronic CRFs will be designed and produced by the Sponsor (or designee) and should be completed in accordance with instructions. The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be transcribed directly into the eCRFs using a secure internet connection. The eCRFs should be filled out completely by the Investigator (or designee) as stated on the delegation of responsibilities form. The eCRF system will be Food and Drug Administration (FDA) Code of Federal Regulations 21 Part 11 compliant.

The eCRFs must be reviewed and approved by the Investigator.

Data entered into the eCRF will be validated as defined in the data validation specifications. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customised checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and external data (e.g. laboratory data). A majority of edit checks will be triggered during data entry and will therefore facilitate efficient 'point of entry' data cleaning.

Data management personnel will perform both manual eCRF review and review of electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.

Manual queries may be added to the system by clinical data management, local Medical Monitor or Study Monitor. Clinical Data Managers and Study Monitors are able to remotely and proactively monitor the eCRFs to improve data quality.

External data will be transferred electronically into the study database. Discrepancies will be queried to the study centre and/or the laboratory until the electronic data and the database are reconciled.

All updates to queried data will be made by authorised study team members only and all modifications to the database will be recorded in an audit trail. Once all the queries have been resolved, eCRFs will be locked. Any changes to locked eCRFs will be approved by the Investigator.

Once the full set of eCRFs has been completed and locked, and SAE reconciliation has been completed, the Sponsor will authorise database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then only be made only by written agreement of the Sponsor. The Investigator will be provided with a copy of the eCRFs in a non-editable format.

Adverse events and medical/cancer history terms will be coded from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 22.0 or later). Prior and concomitant medications and therapies will be coded according to the World Health Organisation drug dictionary (Version Drug B3 Global September 2019 or later). Coding review will be performed by the Sponsor (or designee) prior to database lock.

The clinical data (in SAS® dataset format) will be transferred to the Sponsor at the end of the study.

10 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

10.1 Sample Size Determination

The sample size of 16 participants per group is chosen to assess the variability in both immunologic responses, as well as the potential change in HBsAg. With 16 participants, the trial also has an 80% chance to detect any severe or serious adverse event that would occur at a 10% incidence.

10.2 Statistical and Analytical Plans

This section presents a summary of the planned statistical analyses. Full details of the analysis will be described in the statistical analysis plan that will be approved before database lock. Any analysis that deviates from the statistical analysis plan will be documented and justified in the clinical study report.

The computer program package SAS® Enterprise Guide® (Version 9.4 or later) will be used for statistical analysis.

10.2.1 Analysis Sets

- The intent-to-treat set will consist of all participants who are randomised
- The safety analysis set will consist of all participants who received at least one vaccination (data will be summarised according to the vaccination actually received)
- The per-protocol analysis set will consist of all participants in the safety analysis set who received the correct study vaccine and who had no major protocol deviations
- The immunogenicity analysis set will consist of all participants in the per-protocol set and have available immunogenicity data to evaluate the immunogenicity endpoints and did not have any major protocol deviations that would impact on the results of the immunological analysis

Allocation of participants to the analysis sets (and whether any participant or specific data from a participant will be excluded) will be determined at the pre-database lock Data Review meeting.

10.2.2 Study Analyses

10.2.2.1 General Principles

The majority of the analysis will be descriptive in nature. Unless stated otherwise, continuous variables will be summarised using descriptive statistics (number of participants, mean, standard deviation, median, minimum and maximum values) and the number and percentage of participants will be used for categorical variables.

Data will be summarised by study vaccine, participant group and where appropriate, overall.

Immunogenicity and efficacy data may be subject to additional statistical analysis, which will be detailed in the SAP.

10.2.2.2 Disposition

Participant disposition, including reasons for study withdrawal if applicable, will be summarised descriptively.

10.2.2.3 Protocol Deviations

Protocol deviations will be listed including: nature (missed procedure(s), early or late procedure(s), missed visits, visit performed out of protocol defined window, prohibited medication taken, study vaccine dosing deviation, inclusion/exclusion criteria violation, participants not withdrawn but meeting withdrawal criteria, biological sample handling error, other) overall and categorised by major and minor.

10.2.2.4 Demographics and Baseline Data

The safety analysis set will be used for the analysis of demographic and baseline data.

Demographics and baseline characteristics will be listed and summarised descriptively. Medications and therapies will be summarised by anatomic therapeutic chemical classification.

10.2.2.5 Immunogenicity Analyses

The following endpoints will be presented by study vaccine and participant group:

- A multi-parameter index made of CD4+ magnitude, CD4+ avidity, and CD8+ magnitude
- Reduction in HBsAg titre at Months 3 and 9 (end of study visit); specifically those with loss of > 0.5 $\log_{10}$ and > 1.0 $\log_{10}$ from baseline
- Proportion of participants with HBeAg and HBsAg loss
- Proportion of HBeAg and HBsAg seroconversion (antibody positivity)
- Reduction of hepatitis B DNA level
- Effect on HBcrAg
- Effect of HBpgRNA

10.2.2.6 Safety Data

Safety data will be summarised descriptively.

Treatment emergent events are defined as those occurring after study vaccine administration.

10.2.2.6.1 Adverse Events

All adverse events will be listed, including the verbatim description and MedDRA preferred terms and system organ class (SOC).

TEAEs will be summarised by SOC and by preferred term. The incidence of TEAEs will be based on the numbers and percentages of participants with events and number of events. TEAEs will be further summarised by severity and relationship to study vaccine.

An overall summary of adverse event incidence will also be presented by study vaccine dose and overall to include the number and percentage of participants with at least one: TEAE, vaccine-related TEAE, Grade 3 to Grade 5 TEAE, death, SAE, vaccine-related SAE, AESI, vaccine-related AESI, TEAE leading to study vaccine discontinuation and TEAE leading to study discontinuation.

Narratives will be written for any deaths, other SAEs, AESIs, TEAEs leading to study vaccine discontinuation and TEAEs leading to study discontinuation.

10.2.2.6.2 Laboratory Safety Tests

Severity grading using the toxicity table in Appendix 1 will be assigned to laboratory safety values where applicable. Laboratory results in reported units and standard international (SI) units will be listed, including high and low flags, severity grades where applicable, the corresponding normal range and clinical significance.

Laboratory safety tests summaries will be based on results in SI units. Absolute and change from baseline results, including the worst change for each variable for each participant will be summarised using descriptive statistics.

Treatment emergent out of range results with the corresponding severity grade, normal ranges, baseline results and clinical significance will be separately listed. Shift tables will be used to show changes from baseline at each timepoint and the worst change in each participant and scatterplots of the worst change will be produced. The number of participants showing shifts of at least two severity grades will be summarised.

The number of participants with treatment emergent clinically significant laboratory safety test results and laboratory safety test results of Grade 3 or 4 will be summarised.

10.2.2.6.3 Vital Signs

Absolute and change from baseline vital sign results, including the worst change for each variable for each participant will be summarised using descriptive statistics. Treatment emergent out of range results with the corresponding normal ranges, baseline results and clinical significance will be separately listed. Shift tables will be used to show changes from baseline at each timepoint and the worst change in each participant and scatterplots of the worst change will be produced. The number of participants with treatment emergent clinically significant results will be summarised.

10.2.2.6.4 Physical Examination

Treatment emergent abnormal physical examination with the corresponding clinical significance will be are listed. Shift tables will be used to show changes in physical examination status from baseline at each timepoint and the worst shift in each participant will be included.

10.2.3 Interim Analyses

To help with the planning of future studies, an interim analysis of all available data will be performed when at least 20 participants have been enrolled and after their second dose of study vaccine.

Unblinded listings and summaries will be submitted to the DMC, as needed. The timing of the DMC submissions will be specified in the DMC Charter.

10.2.4 Handling Missing, Unused or Spurious Data

The SAP will describe and account for the occurrence of and extent of missing data, and its possible impact on the study analysis.

11 STUDY DOCUMENTATION, INSPECTIONS AND RECORD KEEPING

11.1 Study Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should contain all essential documents required by ICH GCP [36] and include:

1. Investigator's Site File (e.g. protocol and amendments, IEC/IRB and regulatory authority approval with correspondence, sample informed consent, study vaccine accountability records, staff curriculum vitae and authorisation forms, correspondence)
2. Participant source documents

   Source documents are defined as the results of original observations and activities of a clinical investigation, including medical notes. All source documents produced in this study will be maintained by the Investigator and made available for inspection. Source data include, but is not limited to, the following and will be identified in a source data location log:

   - Screening/enrolment log
   - Medical notes - which should be updated after each visit to include visit dates, medical history and cancer history, concomitant medication, any clinically relevant findings of clinical examinations or clinically relevant adverse events/medication changes, SAEs and information on participant withdrawal
   - Informed consent form
   - Safety laboratory reports
   - Visit dates
   - Study vaccine accountability and inventory forms
3. Participant eCRF data (which includes an audit trail containing a complete record of all changes to data) will be sent to the Investigator at the end of the study

11.2 Audits and Study Centre Inspections

Authorised personnel from regulatory authorities and the Sponsor quality assurance function may carry out inspections and audits respectively. The purpose of an audit or inspection is to ensure that ethical, regulatory and quality requirements are fulfilled in Sponsor studies.

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 time and the time of his staff to the auditor or inspector to discuss findings and any relevant issues.

11.3 Retention of Records

Records and documents pertaining to the conduct of this study and the distribution of study vaccine, including eCRFs, informed consent forms, laboratory safety test results and study vaccine inventory and accountability records, must be retained by the Investigator for at least 15 years after completion or discontinuation of the study, or according to local requirements, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

12 FINANCE AND INSURANCE

Financial arrangements are detailed in the Investigator Agreement between the Sponsor and Investigator.

Details of the Sponsor's arrangement for clinical study insurance to provide for compensation to participant for any claim for bodily injury or death arising from participation in the clinical study are provided in the informed consent form.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Local Regulations/Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformance with the protocol and the principles of the "Declaration of Helsinki" [37] or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

The study must fully adhere to ICH GCP [36] or with local regulations if they afford greater protection to the participant.

13.2 Regulatory Authority Approval

The study will not commence before approval from the national regulatory authority been granted according to local requirements. The Sponsor (or designee) will be responsible for the preparation, submission and confirmation of receipt of any regulatory authority approvals required prior to release of study vaccine for shipment to the study centre.

During the study, the Sponsor (or designee) is also responsible for submitting subsequent amendments and notifications to the regulatory authority according to local requirements.

13.3 Ethics Committee/Institutional Review Board Approval

The Investigator will be responsible for submitting all documents required by the IEC/IRB e.g. this protocol, the informed consent form relevant supporting information and all types of study specific participant recruitment information (including advertisements) and any other written information to be provided to participants, to the IEC/IRB for review. The Investigator or Sponsor should also provide the IEC/IRB with a copy of the Investigator's Brochure or product labelling, information to be provided to participants and any updates. If the IEC/IRB requires modification of the submitted information, the documentation supporting this requirement must be provided to the Sponsor (or designee).

The study must have the initial and at least annual (when required) approval of an IEC/IRB. The signed approval letter must identify the exact protocol title and number, documents approved and the date of approval of the protocol and the informed consent document. The Sponsor will not ship clinical supplies until a signed approval letter has been received and a Clinical Trial Agreement has been signed by the Sponsor and the study centre.

A list of IEC/IRB members must be provided to the Sponsor (or designee).

The Investigator or Sponsor should provide the IEC/IRB with reports, updates and other information (e.g. expedited safety reports, amendments and administrative letters) according to regulatory requirements or study centre procedures.

The Sponsor (or designee) will ensure the IEC/IRB is notified of any adverse events meeting the criteria for expedited reporting, annual updates and when the study has been completed according to local requirements. The Sponsor (or designee) will provide information to the Investigator who will be responsible for forwarding this to the IEC/IRB.

13.4 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from participants prior to conducting any study related procedures. All consent documentation must be in accordance with applicable regulations and ICH GCP [36]. Each participant is requested to sign and date the informed consent form after (s)he has received and read the participant

information sheet and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the participant's rights and responsibilities. participants will be given adequate time to evaluate the information given to them before signing and dating the informed consent form. The informed consent form also be signed and dated by the person obtaining consent. The original signed informed consent form for each participant will be retained on file by the Investigator and the second signed original given to the participant.

Informed consent forms must be retained for enrolled participants and for participants who are not subsequently enrolled and must be available for verification by the Study Monitor at any time.

In the event of changes to the informed consent form during the study, the Investigator must always use the most current IEC/IRB approved form for documenting written informed consent.

13.5 Protocol Amendments

The protocol (and other supporting documents that have received approval before the start of the study e.g. informed consent form) may not be modified without written approval from the Sponsor. In the event that an amendment to the protocol (and/or supporting documents) is required, it will be classified into one of the following categories by the Sponsor:

- Substantial amendments are those considered 'substantial' to the conduct of the clinical study and are likely to have a significant impact on e.g. the safety or physical or mental integrity of the participants, the scientific value of the study, the conduct or management of the study or the quality or safety of the study vaccine used in the study
- Non-substantial amendments only involve administrative or logistical changes, typographical errors

The Sponsor will determine if regulatory authority and/or IEC/IRB review is required prior to the implementation of the amendment according to local regulations. In general, substantial amendments may not be initiated without approval except when necessary to eliminate immediate hazards to the participants or when the change(s) involves. Non-substantial amendments do not require approval.

The Sponsor (or designee) is responsible for obtaining approval for substantial amendments from the regulatory authority. The Investigator is responsible for promptly informing the IEC/IRB of any substantial amendments and providing documentation of favourable opinion to the Sponsor (or designee).

13.6 Confidentiality of Study Documents and Participant Records

The Investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. The Sponsor (or designee) will maintain confidentiality standards by assigning a unique coded identification number to each participant included in the study. Participant names will never be included in data sets that are transmitted to the Sponsor or their representatives or to third parties as permitted by the informed consent form.

Participants should be identified by an identification code rather than by their names on eCRFs or other documents submitted to the Sponsor. The Investigator should keep a participant enrolment log relating codes to the names of participants. The Investigator should maintain documents not for submission to the Sponsor e.g. informed consent forms, in strict confidence.

Records will not be destroyed without giving the Sponsor prior written notice and the opportunity to further store such records, at the Sponsor's cost and expense.

Participant medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the informed consent form signed by the participant, unless permitted or required by law.

14 STUDY COMPLETION

All materials or supplies provided by the Sponsor will be returned to the Sponsor upon study completion. The Investigator will notify the IEC/IRB when the study has been completed. The study will be considered complete when the last participant completes their final follow-up visit and all the data clarification forms have been resolved. This report should be made within 3 months of the completion or termination of the study. The final report sent to the IEC/IRB should also be sent to the Sponsor and, along with the completed eCRFs, constitutes the final summary to the Sponsor, thereby fulfilling the Investigator's regulatory responsibility.

15 PUBLICATION OF DATA

The final study report will be made available to the Investigator for purposes of publications. The Investigator and study team must send all manuscripts, abstracts, and presentations using data from this study to the Sponsor for review prior to their submission. The Sponsor reserves the right to delete any part or parts of such materials deemed to be confidential or proprietary.

16 REFERENCES

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APPENDICES

Appendix 1 Toxicity Table for Clinical and Laboratory Abnormalities

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review at 301-827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2007

Contains Nonbinding Recommendations

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Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C. 262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See, for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study). Less extreme observations (e.g., mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

III. TOXICITY GRADING SCALE TABLES

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categorize adverse events observed during a clinical trial may assist you in monitoring safety and making required reports. Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate

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to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

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Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

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Systemic Illnes	Mild (Grade 1)	(Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

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B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	–
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	–
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test 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
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	—
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***"ULN" is the upper limit of the normal range.

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Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

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IV. REFERENCES

1. National Cancer Institute Common Toxicity Criteria, April 30, 1999. (http://ctep.cancer.gov/reporting/CTC-3.html)

2. Division of AIDS Table for Grading Severity of Adult Adverse Experiences; August 1992. (http://rcc.tech-res-intl.com/tox_tables.htm)

3. The Brighton Collaboration. Finalized Case Definitions and Guidelines. (http://brightoncollaboration.org/internet/en/index/definition___guidelines.html)

4. HIV Vaccine Trials Network Table for Grading Severity of Adverse Experiences; September 18, 2002. (http://rcc.tech-res-intl.com/tox_tables.htm)

5. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004. (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf)

6. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory Reference Values. New England Journal of Medicine. 2004;351:1548-1563.

Appendix 2 Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Nivolumab

Dose modification and toxicity management of infusion-reactions related to nivolumab

Nivolumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on nivolumab associated infusion reaction are provided.

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of nivolumab with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

	Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Dose Modification Schema and Supportive Care Guidelines for Nivolumab

AEs associated with nivolumab exposure may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of nivolumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications.

Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of nivolumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm aetiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue nivolumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with nivolumab are provided.

Immune-related adverse reaction	Severity	Treatment Modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment

Immune-related adverse reaction	**Severity**	**Treatment Modification**
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment
Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0). [a] During administration of the second phase of treatment (nivolumab monotherapy) following combination treatment, permanently discontinue treatment if Grade 3 diarrhoea or colitis occurs. Adapted from Summary of Product Characteristics for OPDIVO 10 mg/mL concentrate for solution for infusion, 30 November 2020		

Other Allowed Dose Interruption for Nivolumab

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays). Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

Appendix 3 Details of Changes Made in Protocol Amendment 2 (Protocol Version 3.0, 18 April 2020)

5.4 Storage

Vials of ChAdOx1-HBV and MVA-HBV must be stored in a continuously monitored ≤-~~6~~70ºC freezer and nivolumab must be stored in the outer carton (to protect from light) between 2 and 8ºC in a continuously monitored refrigerator.

Appendix 4 Details of Changes Made in Protocol Amendment 3 (Protocol Version 4.0, 21 July 2020)

Editorial changes are not included below.

1.2 Treatment Review

This study is designed to assess the safety and immunogenicity of ChAdOx1-HBV and MVA HBV, given either alone or with low doses of an anti-programmed cell death protein 1 (anti-PD-1) compound (nivolumab), and to assess the breadth of responses to the proteins encoded by these combinations. The T cell cross reactivity to other genotypes will also be assessed. Doses of ChAdOx1 vaccines in previous studies have varied from 10^8 to over $5 \times 10^{~~11~~10}$ viral particles (vp) per dose and a dose of 2.5×10^{10} vp will be evaluated in this study to prepare for a further ChAdOx1/MVA heterologous prime-boost regimen. The dose of MVA of 1×10^8 pfu has been assessed safely in thousands of participants.

1.4 Summary of Clinical Experience

One clinical study (HBV001) to investigate reactogenicity and explore the safety of ChAdOx1-HBV in healthy and CHB participants is ongoing **at doses of 2.5×10^9 and 2.5×10^{10} vp**. ~~To date~~**At the higher dose, only localised swelling at the vaccination site and minor adverse events, which have all resolved, have been reported. There have been** no **reports of** serious adverse events (SAEs) or other safety concerns~~have been reported~~.

1.5 Study Rationale

Thus, a prime-boost strategy using ChAdOx1 vector (ChAdOx1-HBV) and an MVA vector (MVA-HBV), with and without nivolumab will be evaluated in this study. In order to decrease potential safety issues, only participants with stable antiviral therapy in the previous one year with resultant low HBV DNA and HBsAg will be enrolled. **As the T cell responses may wane with time, and a boost to the highest levels may be needed to sustain an ongoing response (as evidenced by some lowering of the HBsAg levels, a boost using the MVA vaccine is permitted at Month 3, at the discretion of the Investigator and concurrence of the Sponsor.**

Section 3.1.1 Study Overview

All treatment groups will receive study vaccine on Day 0 and Day 28. In Group 1, MVA-HBV will be evaluated 7 days after the first dose of study vaccine in the first 6 participants prior to initiation of the prime-boost regimen of ChAdOx1-HBV followed by MVA-HBV (Group 2). Participants in Groups 3 and 4 will be dosed in parallel to receive ChAdOx1-HBV (with and without nivolumab) on Day 0 followed by MVA-HBV with nivolumab on Day 28. Groups 3 and 4 will be initiated after evaluation of data 7 days after the first 6 participants in Group 2 have received ~~both study vaccines~~**ChAdOx1-HBV**. The evaluations will be carried out by a Safety Monitoring Committee (SMC) consisting of the Sponsor Medical Monitor, the Country Lead Investigators for South Korea, Taiwan and the UK, and the trial Medical Monitor. **If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor.**

Section 3.1.3 Stopping Criteria/Holding Criteria

There will be a review of the study data by the DMC when there is a reasonable possibility that the investigational vaccine caused any of the SAEs or severe adverse events listed below, based on the assessment of the Investigator, in one or more participants at any dose. Vaccinations will be put on hold pending this review:

- Death **related to study vaccine**
- Life-threatening adverse event or life-threatening suspected reaction

If, following review of data, a recommendation is made by the DMC to resume study enrolment and vaccine administration, the DMC will record their judgment in a memorandum to the study file and notify the Sponsor. The DMC memorandum will be forwarded to the local Medical Monitor and Investigators **and an appropriate substantial amendment filed**.

3.2 Discussion of Study Design, Including the Choice of Control Groups

The ChAdOx1-HBV dose ~~will be~~ **is 2.5 x 10^{10} vp,** based on the ~~results~~**review** of ~~study HBV-001; safety and~~ the ~~induction of T cell activity, as measured~~**two doses studied in HBV001 (2.5 x 10^9 vp and 2.5 x 10^{10} vp). Safety data from all healthy volunteers was reviewed from HBV001** by ~~both magnitude of response as well as functionality~~**the SMC, and the higher dose was chosen to use in this study.** To further minimise the risk that immune responses generated by vaccination do not result in liver toxicity, only those participants whose DNA levels are well controlled on antivirals will be included in the study, and those with advanced liver fibrosis or cirrhosis will be excluded. The safety of MVA-HBV will be evaluated by the SMC after the first 6 participants have received the first dose, to include at least 7 days safety data, prior to initiation of the prime-boost regimen of ChAdOx1 followed by MVA with and without nivolumab.

Doses of ChAdOx1 vaccines in previous studies have varied from 1 x 10^8 to over ~~15~~ x ~~10^{11}~~**10^{10}** vp per dose with 2.5 x 10^{10} vp appearing to be nearly optimal. A phase 1 study is examining the safety and immunogenicity of two ChAdOx1-HBV doses, 2.5 x 10^9 vp and 2.5 x 10^{10} vp, with the expectation that the latter dose will be safe and chosen for further development. MVA has been used in many trials at doses that range from 1 x 10^7 to 2.5 x 10^8 pfu, and in most studies the dose of 1-2 x 10^8 pfu are studied. This dose has been shown to be safe and immunogenic in thousands of participants to date. Thus, pending new information, the doses ~~chosen~~**proposed** for this study are 2.5 x 10^{10} vp of ChAdOx1-HBV and 1 x 10^8 pfu of MVA-HBV. **As the T cell responses may wane with time, and a boost to the highest levels may be needed to sustain an ongoing response (as evidenced by some lowering of the HBsAg levels, a boost using the MVA vaccine is permitted at Month 3, at the discretion of the Investigator and concurrence of the Sponsor.**

4.2 Inclusion Criteria

4. If female, willing not to become pregnant up to 8 weeks after last dose of study vaccine **and up to 5 months after the last dose of nivolumab**
5. If female: Not pregnant or breast feeding and one of the following:
   - Of non-childbearing potential (i.e. women who have had a hysterectomy or tubal ligation or are post-menopausal, as defined by no menses in ≥1 year **and without an alternative medical cause**)
   - Of childbearing potential but agrees to practice highly effective contraception for 4 weeks prior to study vaccine and 8 weeks after study vaccine **and 5 months after the last dose of nivolumab.** Highly effective methods of contraception include one or more of the following:
     - Male partner who is sterile (medically effective vasectomy) prior to the female participant's entry into the study and is the sole sexual partner for the female participant

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- An intrauterine device
- Bilateral tubal occlusion

8. Virally suppressed (HBV-DNA viral load below ~~40~~**040** IU/mL for ≥ 1 year)

4.3 Exclusion Criteria

5. Documented cirrhosis or advanced fibrosis indicated by a liver biopsy within 6 months prior to screening.

   In the absence of a documented liver biopsy, either 1 of the following **(not both)**:

   - Screening Fibroscan with a result > 9 kilopascals (kPa) (or the equivalent) within ≤ 6 months of screening**, ~~or~~OR**
   - Screening FibroTest >0.48 and AST to platelet ratio index (APRI) of >1.

   ~~In the event of discordant results between non-invasive methods, the Fibroscan result will take precedence.~~

11. Presence of active infection

12. Evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis

13. History of thyroid disorder or abnormal thyroid function at screening

20. History of ~~allergic disease or~~**severe hypersensitivity or anaphylactic** reactions likely to be exacerbated by any component of the vaccine **or nivolumab**

~~Previous 20 Any history of anaphylaxis in reaction to vaccination~~

5.2 Investigational Products Administered

If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor.

5.2.1 Study Vaccines

All participants will receive two doses of study vaccine, with or without nivolumab, on Day 0 and Day 28. Both vaccinations will be given by intramuscular injection into the deltoid muscle, to the same, non-dominant arm in a participant, where possible. **If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV at Month 3, at the Investigator's discretion and after discussion with the Sponsor.**

The ChAdOx1-HBV dose ~~will be 2.5 x 10^{10} vp, and confirmed based on the review of study HBV 001.~~ **is 2.5 x 10^{10} vp, based on the review of the two doses studied in HBV001. This dose, or higher, of ChAdOx1-based vaccines has been safely used in hundreds of participants (see Investigator's Brochure), and thousands of people have been immunised with a ChAdOx1 COVID-19 vaccine at a dose of 5 x 10^{10} vp.** The dose of MVA-HBV will be fixed at 1 x 10^8 pfu, as taken from historical data of previous studies. **A 1.5 x 10^8 pfu MVA dose was used in nearly 2,000 healthy participants in influenza studies conducted by Oxford University and Vaccitech.**

5.7 Method of Assigning Participants to Treatment Groups

Participants will be randomised to all open groups on a 1:1:1:1 allocation as each group is initiated. A sentinel participant will be dosed in cohort 1, and the rest of the cohort will only be enrolled at least 48 hours later. Following the 7-day safety assessment of the first 6 participants in Group 1 by the SMC, Group 2 will be initiated. Groups 3 and 4 will be initiated after evaluation of safety data 7 days after the first 6 participants in Group 2 have received ~~both study vaccines~~**ChAdOx1-HBV**. At the screening visit, participants will be sequentially allocated a screening number once written, informed consent has been obtained. They will be identified by this number until entry into study.

5.8.1 Selection of Doses in the Study

The ChAdOx1-HBV dose ~~will be 2.5 x 10^{10} vp, and confirmed based on the review of study HBV 001~~ **is 2.5 x 10^{10} vp and confirmed based on the review of the two doses studied in HBV001 (2.5 x 10^9 vp and 2.5 x 10^{10} vp). Safety data from all healthy volunteers was reviewed from HBV001 by the SMC, and the higher dose was chosen to use in this study. This dose or higher of ChAdOx1-based vaccines has been safely used in hundreds of participants (see Investigator's Brochure), and thousands of people have been immunised with a ChAdOx1 COVID-19 vaccine at a dose of 5 x 10^{10} vp.** The dose of MVA-HBV will be fixed at 1 x 10^8 pfu, as taken from historical data of previous studies. **A 1.5 x 10^8 MVA dose was used in nearly 2,000 healthy participants in influenza studies conducted by Oxford University and Vaccitech.**

5.8.2.1 Dosing Schedule

The participants will be allocated to dosing group depending on the treatment schedule. Vaccination will be performed on Day 0, after eligibility has been reconfirmed, and on Day 28.

If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV at Month 3, at the Investigator's discretion and after discussion with the Sponsor.

5.8.2.3 Nivolumab Preparation and Administration

In Groups 3 and 4, the patients will be observed for 30 minutes after vaccination. If there are no safety concerns (vital signs and reactogenicity), nivolumab will be infused over 30 minutes and the patients will be observed in the study centre for a further 30 minutes post-infusion. ~~Nivolumab will be administered via intravenous infusion over 30 minutes, following vaccination.~~

5.10 Prior and Concomitant Vaccines and Medications

Patients will have been taking antivirals for at least 12 months before screening. Once randomised to the study, oral antiviral medication should not be withdrawn. Patients

should remain on the same dose of antivirals that they were on when they entered the study for the duration of the study.

Allowed antiviral medications include: entecavir, tenofovir (tenofovir alafenamide fumarate or tenofovir disoproxil fumarate), or besifovir.

Prior and concomitant medications include prescription and non-prescription drugs or other treatments, and any vaccines other than the study vaccine.

6 STUDY PROCEDURES AT EACH VISIT/SCHEDULE OF ASSESSMENTS

All medications taken to treat unsolicited AEs and SAEs will be recorded in the eCRF by questioning the participant at each visit whether they took any concomitant medications since the previous visit.

Due to the COVID-19 pandemic, study centres will follow any local procedures in line with testing to ensure the safety of participants and staff.

Table 2 Overall Schedule of Assessments at Each Study Visit

Visit/Call	Screen	Vaccination Clinic	Telephone Call	Clinic	Vaccination Clinic	Telephone Call	Clinic			End of Study / Early Discontinuation Clinic
Timepoint (window)	Day						Month			
	-42 to -1	0	1 (+1d)	7 (±1d)	28 (+2d)	29 (+1d)	35 (±1d)	3 (±7d)	6 (±7d)	9 (±7d)
HIV, HCV, HBV **(quantitative HBV DNA and quantitative HBsAg)**, HDV serology	X									
Urine pregnancy test (β-hCG)	X	X [a]			X [a]			X [f]	X [f]	X
Vaccination dose		X			X			X [g]		
Post-dose observation		X			X			X [g]		
Full physical examination	X	X [a]			X [a]			X [a]		
Local/systemic reactogenicity ~~[c]~~		X [c]	X	X	X [c]	X	X	X [c]		
Blood for cellular immunogenicity assessments		X [a]		X	X [a]		X	X [a]		

[a] Pre-vaccination ~~only~~**on Day 0, Day 28 and at Month 3 for patients having an MVA-HBV boost only**

[b] Participants in Group 3 will receive nivolumab on Day 28 only **while Group 4 will receive nivolumab on Days 1 and 28. The patients will be observed for 30 minutes after vaccination. If there are no safety concerns (vital signs and reactogenicity), nivolumab will be infused over 30 minutes and the patients will be observed in the study centre for a further 30 minutes post-infusion.**

[c] Captured pre-vaccination and post-vaccination on Days 0 and 28**, and Month 3 if an MVA-HBV boost is given**, via eDiaries for 7 days post-vaccination and then at ~~the telephone or~~ clinic assessment 7 days post vaccination (Day 7 or 35)

[f] Pregnancy testing at Month 3 in Groups 1 and 2 if an MVA-HBV boost is given, and at Months 3 and 6 in Groups 3 and 4

[g] If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV at Month 3, at the Investigator's discretion and after discussion with the Sponsor. These patients will also have a telephone call the day after the boost vaccination and a clinic visit 7 days post-boost, as per Day 1 and Day 7.

6.1 Screening and Baseline Assessments

The following will be performed at screening:

- A blood sample will be taken for HIV, HCV, HBV **(quantitative HBV DNA and quantitative HBsAg)**, HDV diagnostic testing
- Blood samples will be taken for haematology **(including prothrombin time [PT] and INR)**, biochemistry and liver function tests (LFTs)

6.2 Treatment Day Assessments (Day 0, Day 28 and Month 3 [MVA-HBV Boost])

Participants will then receive study vaccine by intramuscular injection in the non-dominant arm, ~~followed by nivolumab~~**and will be observed for 30 minutes post vaccination for safety concerns. Nivolumab will then be administered via an infusion,** if applicable, according to Table 1.

- On Day 0, an eDiary, tape measure and thermometer will be provided to perform self-assessment of local and systemic reactogenicity for 7 days after the vaccinations. ~~On Day 0~~ ~~p~~**P**articipants will be reminded to do the following daily for the ~~next~~ 7 days **after each vaccination**:

6.3.1 Telephone Calls: Day 1, ~~and~~ Day 29 and Month 3 + 1 Day (MVA-HBV Boost)

- Reminder to complete eDiary for collection of local and systemic reactions during 7 consecutive days post-vaccination

6.3.2 Clinic Visits: Day 7, ~~and~~ Day 35 and Month 3 + 7 Days (MVA-HBV Boost)

- Blood samples will be taken for haematology, biochemistry and LFTs

6.3.3 Clinic Visit: Months 3 and 6

- **Check hepatitis B surface antigen Day 35 result (Month 3 only).**
  - **If a participant has a 0.5 log or greater drop in hepatitis B surface antigen, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor. Please see Section 6.2 for the assessments to be performed.**
- **A urine pregnancy test will be performed (Months 3 and 6 in Groups 3 and 4)**
- Blood samples will be taken for haematology ~~(including prothrombin time [PT]/INR and activated partial thromboplastin time [aPTT])~~, biochemistry and LFTs

6.3.3 Clinic Visit: Months 3 and 6

-
- Blood samples will be taken for haematology (including PT~~/INR and aPTT~~), biochemistry and LFTs

7.1.4.2 Biochemistry

The following biochemistry parameters will be measured: sodium, potassium, urea **nitrogen**, creatinine and albumin and LFTs (alkaline phosphatase, gamma-glutamyl transpeptidase, ALT AST and ~~total and~~ direct bilirubin).

7.1.4.4 Urinalysis

A urine sample will be collected in a sterile container for dipstick urinalysis. The following will be tested: blood, ~~total and direct~~ bilirubin, glucose, ketones, leucocytes, nitrite, pH, protein, specific gravity and urobilinogen. The Investigator may order additional urine tests to be performed.

7.4.4 Physical Examination

A skin, respiratory, cardiovascular, abdominal and lymphatic system examination will be performed at screening~~, and~~ pre-vaccination on Day 0, Day 28 **and Month 3 (for those having the MVA-HBV boost only) and on Month 9**. A symptom-directed physical examination will be performed at all other clinic visits if required. Results will be recorded as normal, abnormal and not clinically significant or abnormal and clinically significant.

8.1.4 Safety Monitoring Committee

- Scheduled evaluation of study conduct and progress, and review of the cumulative safety and efficacy data. Scheduled meetings will take place as follows:
- Kick off meeting before the first participant is enrolled
- 7 days after the first 6 participants in Group 1 have received the first dose of MVA-HBV
- 7 days after the first 6 participants in Group 2 have received ChAdOx-HBV and MVA-HBV
- 7 days after the first 6 participants in Groups 3 and 4 have received ~~both study vaccines~~**ChAdOx1-HBV**, with or without nivolumab

8.2.5.3 Medical Review and Reporting by the Sponsor

The expectedness of an SAE is assessed by the Sponsor in the overall classification of SAEs for expedited reportability. The current Investigator's Brochure section "Reference Safety Information" will be used as the reference for determination of expectedness and risk assessment of vaccine-related adverse events **and Section 4.8 of the Nivolumab SmPC will be used to assess the expectedness for nivolumab related events**.

10.2.1 Analysis Sets

- The intent-to-treat **set will consist of all participants who are randomised**
- **The** ~~/~~safety analysis set will consist of all participants who received at least one vaccination (data will be summarised according to the vaccination actually received)

10.2.3 Interim Analyses

~~No formal interim analyses are planned as the study is open label.~~**To help with the planning of future studies, an interim analysis of all available data will be performed in June 2021.**

Unblinded listings and summaries will be submitted to the DMC, as needed. The timing of the DMC submissions will be specified in the DMC Charter.

Appendix 2 Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Nivolumab

Dose Modification Schema and Supportive Care Guidelines for Nivolumab

Table replaced with the appropriate information from the Summary of Product Characteristics for OPDIVO 10 mg/mL concentrate for solution for infusion, 24 January 2020

Appendix 5 Details of Changes Made in Protocol Amendment 4 (Protocol Version 5.0, 04 May 2021)

1.5 Study Rationale

Thus, a prime-boost strategy using ChAdOx1 vector (ChAdOx1-HBV) and an MVA vector (MVA-HBV), with and without nivolumab will be evaluated in this study. In order to decrease potential safety issues, only participants with stable antiviral therapy in the previous one year with resultant low HBV DNA and HBsAg will be enrolled. As the T cell responses may wane with time, and a boost to the highest levels may be needed to sustain an ongoing response (as evidenced by some lowering of the HBsAg levels), a boost using the MVA vaccine is permitted at Month 3, at the discretion of the Investigator and concurrence of the Sponsor **UK participants only.**

3.1.1 Study Overview

This is a Phase 1b/2a, multicentre study of ChAdOx1-HBV and MVA-HBV vaccines (VTP-300). The study is planned to be conducted at up to ~~14~~ **15** centres in 64 participants chronically infected with Hepatitis B Infection and virally suppressed with approved oral anti-HBV therapies.

The evaluations will be carried out by a Safety Monitoring Committee (SMC) consisting of the Sponsor Medical Monitor, the Country Lead Investigators for South Korea, Taiwan and the UK, and the trial Medical Monitor. If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor **(UK participants only).**

3.1.4 Individual Stopping Rules (All Vaccinated Study Participants)

All vaccinated participants will be followed for safety until resolution or stabilisation (if determined to be chronic sequelae) of their **S**AEs.

3.2 Discussion of Study Design, Including the Choice of Control Groups

As the T cell responses may wane with time, and a boost to the highest levels may be needed to sustain an ongoing response (as evidenced by some lowering of the HBsAg levels), a boost using the MVA vaccine is permitted at Month 3, at the discretion of the Investigator and concurrence of the Sponsor **(UK participants only).**

4.3 Exclusion Criteria

5. Documented cirrhosis or advanced fibrosis indicated by a liver biopsy within 6 months prior to screening **(Metavir activity grade A3 and stages F3 and F4; Ishak stages 4 – 6).**
13. **Past** ~~H~~history of thyroid disorder or abnormal thyroid function at screening **that is still active and uncontrolled**
17. ~~Any history of receipt of nonoral adenoviral vaccine~~ **Receipt of any adenoviral-based vaccine within 3 months prior to administration of ChAdOx1-HBV on Day 0, or plan to receive an adenoviral-based vaccine within 3 months after Day 0**

5.2 Investigational Products Administered

If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor **(UK participants only).**

5.2.1 Study Vaccines

All participants will receive two doses of study vaccine, with or without nivolumab, on Day 0 and Day 28. Both vaccinations will be given by intramuscular injection into the deltoid muscle, to the same, non dominant arm in a participant, where possible. If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA HBV at Month 3, at the Investigator's discretion and after discussion with the Sponsor **(UK participants only).**

5.8.2.1 Dosing Schedule

The participants will be allocated to dosing group depending on the treatment schedule. Vaccination will be performed on Day 0, after eligibility has been reconfirmed, and on Day 28.

If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV at Month 3, at the Investigator's discretion and after discussion with the Sponsor **(UK participants only).**

5.10 Prior and Concomitant Vaccines and Medications

The name of the medication, treatment start and stop dates (or 'ongoing'), and indication must be recorded on the concomitant medication eCRF. The indication recorded on the concomitant medication eCRF must correspond to a medical term/diagnosis recorded on the adverse event eCRF, or to a pre-existing condition noted in the participant's medical history, or be noted as prophylaxis, e.g. dietary supplement.

Also, participants should not receive any adenoviral-based vaccine within 3 months prior to or 3 months after administration of ChAdOx1-HBV on Day 0.

6.1 Screening and Baseline Assessments

[a] Pre-vaccination on Day 0, Day 28, **and** ~~**at**~~ Month 3 **(**for **UK participants** having an MVA-HBV boost**)** ~~**only**~~

[b] Participants in Group 3 will receive nivolumab on Day 28 only while Group 4 will receive nivolumab on Days 1 and 28. The patients will be observed for 30 minutes after vaccination. If there are no safety concerns (vital signs and reactogenicity), nivolumab will be infused over 30 minutes and the patients will be observed in the study centre for a further 30 minutes post-infusion.

[c] Captured pre-vaccination and post-vaccination on Days 0 and 28, and Month 3 **(for UK participants having an** MVA-HBV boost**)** ~~**is given**~~, via eDiaries for 7 days post-vaccination and then at the clinic assessment 7 days post-vaccination (Day 7 or 35)

[d] Recorded in the eCRF from the date the informed consent is signed, at all clinic visits to cover the period since the previous visit and during the visit

[e] Individual disease markers tested according to the Study Laboratory Manual

[f] Pregnancy testing at Month 3 in Groups 1 and 2 if an MVA-HBV boost is given, and at Months 3 and 6 in Groups 3 and 4

[g] If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV at Month 3, at the Investigator's discretion and after discussion with the Sponsor **(UK participants only).** These patients will also have a telephone call the day after the boost vaccination and a clinic visit 7 days post-boost, as per Day 1 and Day 7.

All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before the first dose of study vaccine. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants who do not meet eligibility criteria may be rescreened at the discretion of the Investigator. Only abnormal/ out of window tests are required to determine eligibility. Re-screening can occur at any point with the allowed overall window (up to 42 days).

6.2 Treatment Day Assessments (Day 0, Day 28 and Month 3 (MVA-HBV Boost [**UK participants only**])

6.3.1 Telephone Calls: Day 1, Day 29 and Month 3 + 1 Day (MVA-HBV Boost **[UK participants only])**

6.3.2 Clinic Visits: Day 7, Day 35 and Month 3 + 7 Days (MVA-HBV Boost **[UK participants only])**

6.3.3 Clinic Visit: Months 3 and 6

- **For participants enrolled at UK sites,** check hepatitis B surface antigen Day 35 result (Month 3 only)
  - If a participant has a 0.5 log or greater drop in hepatitis B surface antigen, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor. Please see Section 6.2 for the assessments to be performed.

7.1.5 Urine Pregnancy Test

A urine pregnancy test will be performed in female participants of childbearing potential at screening and confirmed to be negative pre-vaccination on Day 0 and 28 **and at Month 3 if a booster dose of MVA-HBV is given (UK participants only),** as per local standard procedures and at each of the timepoints according to Table 2.

7.4.3 Vital Signs

Vital signs will be performed at screening, pre-vaccination and post-vaccination (at the end of the observation period) at the vaccination visit, at all visits during the follow-up and the end of study visit. At each timepoint blood pressure, pulse rate and ~~oral~~ temperature, will be measured after the participant has been in a sitting position for 5 minutes.

7.4.4 Physical Examination

A skin, respiratory, cardiovascular, abdominal and lymphatic system examination will be performed at screening, pre-vaccination on Day 0, Day 28 and Month 3 (for ~~those~~ **UK participants** having the MVA-HBV boost only) and on Month 9. A symptom directed physical examination will be performed at all other clinic visits if required. Results will be recorded as normal, abnormal and not clinically significant or abnormal and clinically significant.

8.2.2 Study Reporting Period for Adverse Events

The reporting period for all adverse events begins on the date the informed consent is signed. Solicited adverse events are recorded in the eDiary up to 7 days post-vaccination. All other events are recorded in the eCRF at all clinic visits throughout the study. All SAEs and/or AESIs are recorded until the final study visit and for all serious or study vaccine-related adverse events until these are resolved or until participant contact discontinues. Severe adverse events or SAEs that continue at the end of the study will be attempted to be followed **until resolved or stabilised**.

8.2.5 Reporting Requirements and Procedures for SAEs

Investigators must not wait to collect additional information to fully document the event before notifying the local Medical Monitor of an SAE. The initial notification should include the following (~~at minimum~~**if available**):

8.2.6.1 Investigator Follow-up

Follow up for SAEs must continue until resolution **or stabilisation** and the outcome reported to the Sponsor, even if this extends beyond the SAE reporting period.

10.2.3 Interim Analyses

To help with the planning of future studies, an interim analysis of all available data will be performed ~~in June~~ when at least 20 participants have been enrolled and after their second dose of study vaccine. ~~2021.~~

Appendix 2 Toxicity Management Guidelines for Immune Related Adverse Events Associated with Nivolumab

Dose modification and toxicity management of infusion-reactions related to nivolumab

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

For further information, please refer to the Common Terminology Criteria for Adverse Events ~~v4.03~~ **v5.0** (CTCAE) at http://ctep.cancer.gov

Dose Modification Schema and Supportive Care Guidelines for Nivolumab

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version **4**5.0 (NCI-CTCAE v5.0).
[a] During administration of the second phase of treatment (nivolumab monotherapy) following combination treatment, permanently discontinue treatment if Grade 3 diarrhoea or colitis occurs.

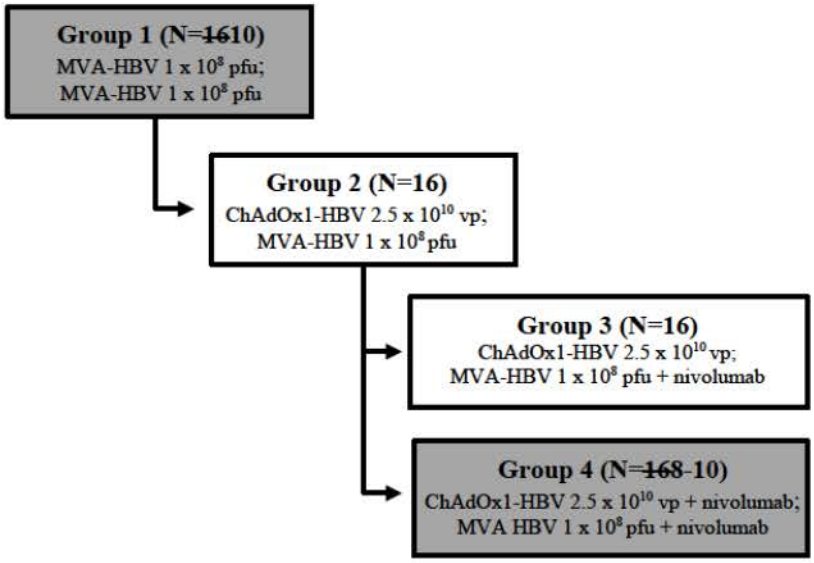
Adapted from Summary of Product Characteristics for OPDIVO 10 mg/mL concentrate for solution for infusion, ~~24 January 2020~~ **30 November 2020**

Appendix 6 Details of Changes Made in Protocol Amendment 5 (Protocol Version 6.0, 09 Dec 2021)

3.1.1 Study Overview

This is a Phase 1b/2a, multicentre study of ChAdOx1-HBV and MVA-HBV vaccines (VTP-300). The study is planned to be conducted at up to 15 centres in **up to approximately 52** ~~64~~ participants chronically infected with Hepatitis B Infection and virally suppressed with approved oral anti-HBV therapies. This is an open-label study comparing the safety, tolerability and immunogenicity of MVA-HBV alone, ChAdOx1-HBV followed by MVA-HBV, and ChAdOx1-HBV plus MVA vaccine with the anti-PD-1 antibody, nivolumab. The study design is shown in Figure 2. **Version 6.0 of the study protocol has closed Groups 1 and 4 to further randomisation, recruitment will now be in a 1:1 ratio between Groups 2 and 3 only. This is due to the fact that significant decreases in surface antigen were seen in Group 3 at month 3, and that 2/6 Group 2 patients also had a greater than 0.5 log decrease at that time point.**

Figure 3 Overall Study Design



Abbreviations: ChAdOx1=chimpanzee adenovirus vector; HBV=hepatitis B virus; MVA=modified vaccinia virus Ankara; pfu=plaque forming units; vp=viral particles

Greyed Groups = closed

4.2 Discussion of Study Design, Including the Choice of Control Groups

As the T cell responses may wane with time, and a boost to the highest levels may be needed to sustain an ongoing response (as evidenced by some lowering of the HBsAg levels), a boost using the MVA vaccine is permitted at Month 3, at the discretion of the Investigator and concurrence of the Sponsor (UK participants only).

As an open-label study, data on the first 27 patients from this current study through 3 months follow-up has been reviewed (Group 1, N=9, for each of Groups 2, 3, and 4, N=6).

There is a difference between Group 3 and the other groups at the 3-month time point ($p<0.01$), with the mean log10 surface antigen reductions from the average of the

screening and baseline values for Groups 1, 2, 3, and 4 of -0.09, -0.35, -1.04 and -0.13, respectively. In Group 3 the Month 3, log_{10}-transformed change from baseline values range from -0.32 to -1.64 (undetectable), and only Group 2 has individuals with more than a 0.5 log drop (2/6, both with a baseline < 100 IU/mL).

Although these numbers are small, the highly significant trend leads to the conclusion that administration of low dose nivolumab at the time of the MVA-HBV boost is likely beneficial, and administration at the time of ChAdOX1-HBV prime ablates these improvements. Thus, to increase the likelihood of patient benefit, the sponsor will close Groups 1 and 4, and continue with the planned N=16 for Groups 2 and 3.

The present standard measure to assess the likelihood of functional cure is the level of circulating HBsAg, although the exact contributions of episomal cccDNA or integrated DNA are not entirely clear.

4.1 Number of Participants

It is planned that **up to approximately 52** ~~64~~ participants with CHB infection and virally suppressed with oral antiviral medication ~~(16 participants per group)~~ will be enrolled in the study. Chronic HBV participants will be recruited/deemed eligible by hepatologists, infectious disease specialists or physicians experienced in treating CHB participants. Centres not meeting the enrolment expectations will be considered for replacement with the addition of a new centre. If participants leave the study before all follow-up visits are completed (for any reason), they may be replaced at the discretion of the study team. A log of all participants enrolled into the study (i.e. having given informed consent) will be maintained in the Investigator's Site File (ISF) at the study centre irrespective of whether they have been treated with vaccine or not.

Version 6.0 of the protocol has closed Groups 1 and 4 to further randomisation following analysis of on-going data; Groups 2 and 3 will continue to recruit approximately 16 participants in a 1:1 ratio.

The number of participants is based on feasibility considerations rather than formal sample size calculations. A total of **up to approximately 52** ~~64~~ participants with CHB infection is considered sufficient to confirm the safety, tolerability and immunogenicity of ChAdOx1-HBV followed by MVA-HBV, ChAdOx1-HBV plus MVA vaccines with or without nivolumab, and to answer the objectives of the study

5.2 Investigational Products Administered

The IMPs to be given in each treatment group are shown in Table 1. **Groups 1 and 4 are closed to further randomization. Groups 2 and 3 will continue to recruit approximately 16 participants in a 1:1 ratio**

Table 4 Study Vaccine Treatment Groups in HBV002

Treatment Group	Study Vaccine Day 0	Study Vaccine Day 28
Group 1 (N=~~16~~ 10)	MVA 1 x 10^8 pfu	MVA 1 x 10^8 pfu
Group 2 (N=16)	ChAdOx1-HBV 2.5 x 10^{10} vp	MVA 1 x 10^8 pfu
Group 3 (N=16)	ChAdOx1-HBV 2.5 x 10^{10} vp	MVA 1 x 10^8 pfu + nivolumab 0.3 mg/kg
Group 4 (N=~~16~~ 8-10)	ChAdOx1-HBV 2.5 x 10^{10} vp + nivolumab 0.3 mg/kg	MVA 1 x 10^8 pfu + nivolumab 0.3 mg/kg

If a participant has a 0.5 log or greater drop in hepatitis B surface antigen at Day 35, they may receive a booster dose of MVA-HBV, at the Investigator's discretion and after discussion with the Sponsor (UK participants only).

5.7 Method of Assigning Participants to Treatment Groups

Participants **have so far been randomised** ~~will be randomised~~ to all open groups on a 1:1:1:1 allocation as each group is initiated. **Protocol Version 6.0 closes Groups 1 and 4 to further randomisation and all remaining participants will be randomised to Groups 2 and 3 in a 1:1 ratio.**

A sentinel participant will be dosed in cohort 1, and the rest of the cohort will only be enrolled at least 48 hours later.

5.8.2.1 Dosing Schedule

The participants will be allocated to dosing group depending on the treatment schedule **and groups open at the time of randomisation**. Vaccination will be performed on Day 0, after eligibility has been reconfirmed, and on Day 28.

Table 5 Overall Schedule of Assessments at Each Study Visit

Visit/Call	Screen	Vaccination Clinic	Telephone Call	Clinic	Vaccination Clinic	Telephone Call	Clinic			End of Study / Early Discontinuation Clinic
Timepoint (window)	Day							Month		
	-42 to -1	0	1 (+1d)	7 (±1d)	28 (+2d)	29 (+1d)	35 (±1d)	3 (±7d)	6 (±7d)	9 (±7d)
Informed consent	X									
Baseline/eligibility variables										
Demographics	X									
Inclusion and exclusion criteria	X									
Height and weight	X									
Medical and disease history	X									
HIV, HCV, HBV (quantitative HBV DNA and quantitative HBsAg), HDV serology	X									
Urinalysis	X									
Urine drug screen	X									
Urine pregnancy test (β-hCG)	X	X [a]			X [a]			X [f]	X [f]	X
Laboratory eligibility and safety tests										
Haematology	X	X [a]		X	X [a]		X	X	X	X
Biochemistry	X	X [a]		X	X [a]		X	X	X	X
Liver function tests	X	X [a]		X	X [a]		X	X	X	X
Study vaccination										
Vaccination dose		X			X			X [g]		
Post-dose observation		X			X			X [g]		
Nivolumab dose (Group 3 ~~and 4~~ only) [b]			~~X~~		X					
Other safety assessments										

Visit/Call	Screen	Vaccination Clinic	Telephone Call	Clinic	Vaccination Clinic	Telephone Call	Clinic			End of Study / Early Discontinuation Clinic
Timepoint (window)	Day							Month		
	-42 to -1	0	1 (+1d)	7 (±1d)	28 (+2d)	29 (+1d)	35 (±1d)	3 (±7d)	6 (±7d)	9 (±7d)
Full physical examination	X	X [a]			X [a]			X [a]		X
Symptom-directed physical examination				X			X	X	X	
Vital signs	X	X		X	X		X	X	X	X
Local/systemic reactogenicity		X [c]	X	X	X [c]	X	X	X [c]		
Unsolicited adverse events [d]	X	X	X	X	X	X	X	X	X	X
Serious adverse events and adverse events of special interest	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X
Blood for HBV disease markers [e]		X [a]		X	X [a]		X	X	X	X
Immunogenicity assessments										
Blood for cellular immunogenicity assessments		X [a]		X	X [a]		X	X [a]	X	X

[a] Pre-vaccination on Day 0, Day 28, and Month 3 (for UK participants having an MVA-HBV boost)

[b] Participants in Group 3 will receive nivolumab on Day 28. **Group 4 is now closed** ~~only while Group 4 will receive nivolumab on Days 1 and 28.~~ The patients will be observed for 30 minutes after vaccination. If there are no safety concerns (vital signs and reactogenicity), nivolumab will be infused over 30 minutes and the patients will be observed in the study centre for a further 30 minutes post-infusion.

[c] Captured pre-vaccination and post-vaccination on Days 0 and 28, and Month 3 (for UK participants having an MVA-HBV boost) , via eDiaries for 7 days post-vaccination and then at the clinic assessment 7 days post-vaccination (Day 7 or 35)

6.3.2 Clinic Visits: Day 7, Day 35 and Month 3 + 7 Days (MVA-HBV Boost [UK participants only])

- Blood samples will be taken for immunogenicity assessments and HBV disease markers

These visits should be anchored to the date of Vaccination and scheduled to occur 7±1 day after vaccination. If vaccination is administered on any day other than Day 28, the follow up visit should be scheduled 6-8 days after the date of actual vaccination. All other study visits after Day 0 (except day 35) are anchored to Day 0.

7.1.5 Urine Pregnancy Test

A urine pregnancy test will be performed in female participants of childbearing potential at screening and confirmed to be negative pre-vaccination on Day 0 and 28 and at Month 3 if a booster dose of MVA-HBV is given (UK participants only), **and at Month 3 and 6 for those in Group 3 and 4,** as per local standard procedures and at each of the timepoints according to Table 2.