STATISTICAL ANALYSIS PLAN (SAP)

Protocol Title:	**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
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Statistical Analysis Plan (SAP)

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Protocol Version No./Date:	6.0/09-DEC-2021
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1.0 Approvals

Sponsor	
Sponsor Name:	[redacted]
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Signature /Date:	[redacted] 10 JAN 2023

2.0 Change History

Version/Date	Change Log
1.0 16-Sep-2020	Created as new
1.1 19-Aug-2022	Added partial AE imputation for determining if unsolicited AEs fall within 28 days of each vaccination Changed the HBV DNA summary table from fold change from baseline to number and percentage of participants in each category Removal of HBpgRNA and HBcrAg exploratory analyses Addition of ICS and ELISpot definitions and analyses Actual dose of nivolumab in mg/kg will be derived using baseline weight as weight is only collected at screening not at each visit Added source of vital signs toxicity grading Added visit windows for local/systemic reactogenicity Updated list of laboratory parameters based on data received Added list of DMC outputs to the appendix Added laboratory toxicity grade appendix
1.2 09-Dec-2022	Updated for Dry run 2 comments Added HBsAg repeated measures analysis Removed Kaplan-Meier analysis of HBeAg and HBsAg loss Updated the seroconversion definitions Added ICS and ELISpot analyses using non-parametric tests Removed analyses for Month 3 boost (as no participants had the Month 3 boost) Changed solicited AE analyses to combine the investigator (CRF) and eDiary data into a single analysis and removed the visit windowing for local/systemic reactogenicity Added ALT and AST summary by time point
2.0 05-Jan-2023	Up-versioned for signature Updated ELISpot responder definition

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under [redacted] Protocol HBV002. This SAP only addresses primary, secondary, and select exploratory endpoints. All other exploratory endpoints to be analysed will be described in separate documentation.

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Endpoints to be Analysed and the Analysis Sets (Estimands)
- Study Definitions
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). Any further changes to the protocol or eCRF may necessitate updates to the SAP.

6.1 Changes from Protocol

The following changes in the planned analysis to the protocol have been done:

- The per-protocol analysis set will be a subset of the intent-to-treat analysis set instead of the safety analysis set as indicated in the protocol (due to data being summarised according to randomised treatment). In addition, instead of excluding all participants with major protocol deviations, only participants with major protocol deviations that could potentially bias trial analyses will be excluded
- With the exception of Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST), which will include tables summarising results and changes from baseline for each time point, other laboratory measurements and all vitals sign variables will be listed only instead of being summarised using descriptive statistics as indicated in the protocol
- Shift tables of laboratory results, vital signs, and physical examinations will be summarised using the worst post-baseline result overall, rather than by time point as indicated in the protocol
- Line plots of laboratory results and vital signs over time will be presented by participants, rather than scatter plots of worst change from baseline as indicated in the protocol

7.0 Study Objectives

Note (*): While the protocol's primary and secondary objectives as written do not explicitly differentiate between ChAdOx1-HBV plus MVA-HBV vaccines with and without nivolumab (i.e., Group 3 and Group 4), the intent was to evaluate the safety, reactogenicity, and immunogenicity for each treatment group. Therefore, this SAP has been developed to evaluate each group's effect on these objectives.

Note (**): While the protocol's secondary objective as written does not explicitly reference the MVA-HBV-only group (i.e., Group 1), the intent was to evaluate each treatment group's effect on Hepatitis B markers. Therefore, this SAP has been developed to evaluate each group's effect on these markers.

7.1 Primary Objectives

- Determine the safety and reactogenicity of the following in participants with Chronic Hepatitis B Virus (CHB) infection and virally suppressed with oral antiviral medication:
  - MVA-HBV vaccine

- ChAdOx1-HBV plus MVA-HBV vaccines
- ChAdOx1-HBV plus MVA-HBV vaccines and nivolumab*

7.2 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**:
  - ChAdOx1-HBV plus MVA-HBV vaccines without nivolumab
  - ChAdOx1-HBV plus MVA-HBV vaccines with nivolumab

7.3 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

8.0 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 14 centres in 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-HBV vaccines with or without the anti-PD-1 antibody, nivolumab.

The overall duration of the study is estimated to be approximately 17 months from study initiation (first participants in) to study completion. The individual participants' participation is approximately 10.5 months from enrolment to study completion unless prematurely discontinued. The study consists of a 42-day screening period, a study period of 9 months, and an end of study visit.

All treatment groups will receive study vaccine regimen on Day 0 and Day 28. In addition, participants will be asked to return to the study site at Day 7, Day 35, Month 3, Month 6, and Month 9. Participants will also be contacted by phone on Day 1 and Day 29. Some participants may receive an additional MVA-HBV boost at Month 3 and will be contacted by phone the day after this booster dose at Month 3 + 1 day and attend a further clinic visit on Month 3 + 7 days, if it occurs.

Solicited adverse events will be captured from 0 to 7 days post-vaccinations. Immunogenicity and safety assessments including unsolicited adverse events, laboratory tests, vital signs, and physical examinations will be assessed until the end of study (Month 9).

Participants will be randomised to all open groups in a 1:1:1:1 allocation as each group is initiated. In Group 1, MVA-HBV participant safety data 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 safety data 7 days after the first 6 participants in Group 2 have received ChAdOx1-HBV.

The overall study design is displayed in **Figure 1** below.

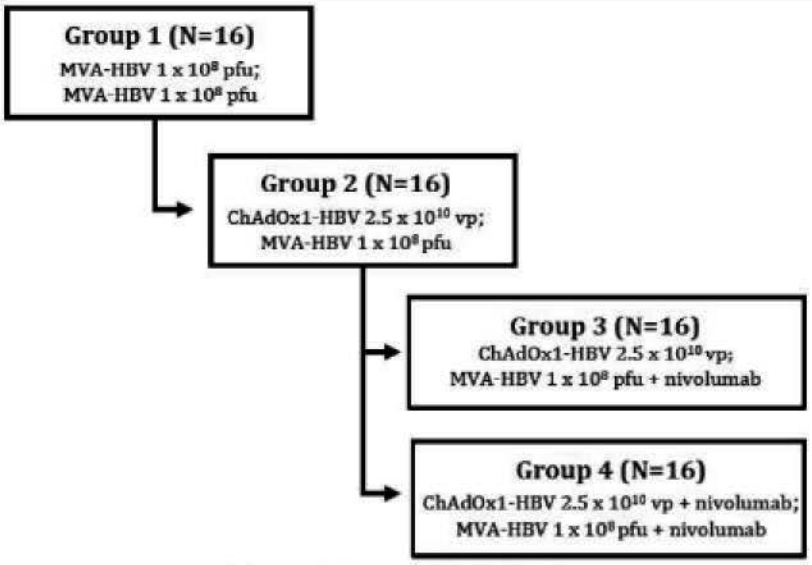

Figure 1 Overall Study Design

An interim safety and immunogenicity look will be performed to evaluate immunogenicity and safety data from all participants up to the cut-off date.

8.1 Sample Size Considerations

The sample size of 16 participants per treatment group was originally 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.

Following the interim analysis, enrolment into Groups 1 and 4 ceased (with n=10 and 9, respectively), and enrolment continued for Groups 2 and 3 in a 1:1 randomisation allocation.

8.2 Randomisation

Participants will be randomised to all open treatment groups in a 1:1:1:1 allocation as each group is initiated.

Randomisation will be performed via the IXRS (Interactive Voice/Web Response System). At Day 0, eligible participants will be assigned to Group 1, Group 2, Group 3, or Group 4. Initially only Group 1 will be open and at least 6 participants will be randomised directly into this group. After the Safety Monitoring Committee (SMC) confirms that Group 2 can be initiated, at least 6 participants will be randomised directly into Group 2. Finally, once the SMC confirms that Groups 3 and 4 can be opened, participants will be randomised to all open treatment groups backfilling the randomisation scheme until 16 participants have been randomised to each treatment group.

Each participant will receive a unique randomisation number when he/she is assigned to the treatment group. Participants will be allocated to treatment groups according to the randomisation code.

9.0 Study Endpoints

9.1 Endpoints/Estimands

The below table links the endpoints to the study objectives.

Objectives	Endpoints/Estimands	Population
Primary		

Objectives	Endpoints/Estimands	Population
• 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	• Safety and reactogenicity of the vaccine(s): incidence of adverse events (AEs), serious adverse events (SAEs), ≥ Grade 3 study vaccine-related AEs within 4 weeks of vaccination • Safety of the vaccines with nivolumab: incidence of AEs, SAEs, ≥ Grade 3 AEs within 4 weeks of dosing • Incidence of adverse events of special interest • Number and proportion of participants reporting treatment-emergent AEs 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	Safety
Secondary		
• 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	• 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)	• Immunogenicity (for ICS, ELISpot, and HBsAg analyses) • ITT (for HBsAg, HBeAg, HBV DNA, and seroconversion analyses)

Objectives	Endpoints/Estimands	Population
• Determine the effect of the following on the level of hepatitis B markers: – ChAdOx1-HBV plus MVA-HBV vaccines without nivolumab – ChAdOx1-HBV plus MVA-HBV vaccines with nivolumab		
Exploratory		
• 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	• 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	Immunogenicity

Note: This SAP only addresses primary, secondary, and select exploratory endpoints. All other exploratory endpoints to be analysed will be described in separate documentation.

9.2 Population Sets

9.2.1 Enrolled Participants

Enrolled participants are defined as participants who met all the eligibility criteria.

9.2.2 Intent-to-treat Analysis Set

The intent-to-treat analysis set is defined as all randomised participants. Participants will be presented according to the treatment group that they were randomised to. This will be the primary analysis set for all demography and HBsAg, HBeAg, seroconversion, and HBV DNA immunogenicity analyses.

9.2.3 Safety Analysis Set

The safety analysis set is defined as all participants who received at least one vaccination. Participants will be presented according to the vaccination regimen actually received as defined in **Table 2**. This will be the analysis set for all safety analyses.

9.2.4 Per-protocol Analysis Set

The per-protocol analysis set is defined as all participants in the intent-to-treat analysis set who received the correct study vaccine at both vaccinations and who had no major protocol deviations that could potentially bias trial analyses. Participants will be presented according to the treatment group they were randomised to.

9.2.5 Immunogenicity Analysis Set

The immunogenicity analysis set is defined as all participants in the per-protocol set who have available immunogenicity data to evaluate the immunogenicity endpoints and do not have any major protocol deviations that could impact on the results of the immunological analysis.

Immunology data from at least baseline and one post-baseline time point (for ICS and ELISpot) is required. Participants will be presented according to the treatment group that they were randomised to. This will be the analysis set for Intracellular Cytokine Staining (ICS) and Enzyme-linked Immunosorbent Spot (ELISpot) immunogenicity analyses.

10.0 Conventions and Derivations

10.1 Treatment Groups

In the outputs, the treatment groups will be labelled as Group 1, Group 2, Group 3 and Group 4, rather than the full description of the first and second vaccinations, in order to conserve space. The definitions of these 4 groups are described in **Table 1**.

Table 1 Treatment Groups

Treatment Group	1st Vaccination	2nd Vaccination
Group 1	MVA-HBV 1 x 10^8 pfu	MVA-HBV 1 x 10^8 pfu
Group 2	ChAdOx1-HBV 2.5 x 10^{10} vp	MVA-HBV 1 x 10^8 pfu
Group 3	ChAdOx1-HBV 2.5 x 10^{10} vp	MVA-HBV 1 x 10^8 pfu + Nivolumab 0.3 mg/kg
Group 4	ChAdOx1-HBV 2.5 x 10^{10} vp + Nivolumab 0.3 mg/kg	MVA-HBV 1 x 10^8 pfu + Nivolumab 0.3 mg/kg

For the safety analysis, the actual treatment groupings are assigned as follows:

- Group 1 = MVA-HBV in 1st vaccination
- Group 2 = ChAdOx1-HBV in 1st vaccination, No Nivolumab in 2nd vaccination
- Group 3 = ChAdOx1-HBV in 1st vaccination, Nivolumab in 2nd vaccination
- Group 4 = ChAdOx1-HBV + Nivolumab in 1st vaccination

The possible combinations of treatments at the first and second vaccinations and the resulting actual treatment group are described in **Table 2**.

Table 2 Actual Treatment Groups

Randomisation	Actual 1st Vaccination Given	Actual 2nd Vaccination Given	Treatment Group Assigned for the Safety Analysis
Group 1	MVA-HBV	MVA-HBV	Group 1
Group 2	ChAdOx1-HBV	MVA-HBV	Group 2

Randomisation	Actual 1st Vaccination Given	Actual 2nd Vaccination Given	Treatment Group Assigned for the Safety Analysis
Group 3	ChAdOx1-HBV	MVA-HBV + Nivolumab	Group 3
Group 4	ChAdOx1-HBV + Nivolumab	MVA-HBV + Nivolumab	Group 4
Group 1	MVA-HBV	No vaccination given	Group 1
Group 2	ChAdOx1-HBV	No vaccination given	Group 2
Group 3	ChAdOx1-HBV	No vaccination given	Group 2
Group 4	ChAdOx1-HBV + Nivolumab	MVA-HBV (Nivolumab not given)	Group 4
Group 4	ChAdOx1-HBV + Nivolumab	No vaccination given	Group 4
Group 3	ChAdOx1-HBV	MVA-HBV (Nivolumab not given)	Group 2
Group 4	ChAdOx1-HBV (Nivolumab not given)	MVA-HBV + Nivolumab	Group 3
Group 4	ChAdOx1-HBV (Nivolumab not given)	MVA-HBV (Nivolumab not given)	Group 2
Group 4	ChAdOx1-HBV (Nivolumab not given)	No vaccination given	Group 2

10.2 Baseline and Change from Baseline

Baseline is defined as the last non-missing assessment taken prior to the first dose of study vaccine.

Change from baseline is defined as:

Observed result at nominal time point – observed result at baseline

Change from baseline on the log scale is defined as $\log_{10} T1 - \log_{10} T0$.

10.3 Study Days and Visit Windows

Study Day 0 is defined as the date of the first vaccination, as recorded on the study vaccination administration eCRF. Other study days are defined relative to Study Day 0.

One month is defined as 30.4 days.

The scheduled study visits along with the predefined allowable visit windows are included in Table 3 below. No visit windowing will be performed for analysis purposes. Study results will be presented using the eCRF visits.

Table 3 Study Visits

Visit Name	Scheduled Vaccination	Study Day (Visit Window)
Screening		Day -42 to -1
Day 0/Baseline	Vaccination 1	Day 0
Day 1		Day 1 (+ 1d)
Day 7		Day 7 (+/- 1d)
Day 28	Vaccination 2	Day 28 (+ 2d)
Day 29		Day 29 (+ 1d)

Day 35		Day 35 (+/- 1d)
Month 3	MVA-HBV Boost[a]	Day 91 (+/- 7d)
Month 3 + Day 1[a]		Day 92 (+ 1d)
Month 3 + Day 7[a]		Day 98 (+/- 1d)
Month 6		Day 182 (+/- 7d)
Month 9		Day 273 (+/- 7d)

[a] Only for participants who received the booster dose of MVA-HBV at Month 3 per the investigator's discretion.

10.4 Immunogenicity Endpoints

Immunogenicity samples (peripheral blood mononuclear cells; PBMCs) will be collected at planned time points.

The lower limit of quantification (LLoQ) for HBsAg is a value of 0.05 IU/mL, and any HBsAg value less than 0.05 IU/mL with be imputed by one-half of LLoQ, i.e., will be given a value of 0.025 IU/mL.

Any participants with a HBsAg < LLoQ will be classified as HBsAg-negative; participants with a HBsAg ≥ LLoQ will be classified as HBsAg-positive.

10.4.1 Geometric Mean (GM)

The geometric mean (GM) will be calculated as the anti-logarithm of the mean of the log-transformed result. The geometric standard deviation (GSD) will be calculated as the anti-logarithm transformation of the standard deviation of the log-transformed result. The 95% confidence interval will be calculated as the anti-logarithm transformation of the upper and lower limits for a two-sided confidence internal for the mean of the log-transformed results.

10.4.2 Seroconversion Rate

Seroconversion rates for HBeAg, HBeAb, HBsAg, and HBsAb will be defined as the following:

- **HBeAg seroconversion rate** is defined as the proportion of participants infected with Hepatitis B virus who are HBeAg positive at baseline and who are HBeAg negative at Month 9.
- **HBeAb seroconversion rate** is defined as the proportion of participants infected with Hepatitis B virus who are HBeAb negative at baseline and who are HBeAb positive at Month 9.
- **HBsAg seroconversion rate** is defined as the proportion of participants infected with Hepatitis B virus who are HBsAg positive at baseline and who have HBsAg < LLoQ (i.e. negative) at Month 9.
- **HBsAb seroconversion rate** is defined as the proportion of participants infected with Hepatitis B virus who are HBsAb negative at baseline and who are HBsAb positive at Month 9.

In addition, **sustained HBeAb positivity** is defined as the proportion of participants infected with Hepatitis B virus who are HBeAb positive at both baseline and Month 9.

10.4.3 ICS Response

Using the count data for each cytokine, cytokine responses (in percentages) are calculated based on the total number of respective T cell counts (CD4+ or CD8+) for each stimulation antigen separately (Core, Pol 1+2, Pol 3+4, Pre-S1/S2+S, DMSO).

For example:

> CD4+ count = 83237 and CD4/CD107a+CD154+IFNg+IL2+TNFa+ count = 236, gives CD4/CD107a+CD154+IFNg+IL2+TNFa+ percent = 0.2835.

Overall cytokine response (%) for each T cell (CD4+, CD8+) by stimulation antigen is then calculated as:

- For CD4+: the sum of every CD4+ cytokine combination (%) where at least one of the following cytokines/functions is positive [+] (regardless of CD107a positivity). I.e., every CD4+ parameter except:
  - CD107a+CD154-IFNg-TNFa-IL-2-
  - CD107a-CD154-IFNg-TNFa-IL-2-
- For CD8+: the sum of every CD8+ cytokine combination (%) where at least one of the following cytokines/functions is positive (regardless of CD154 positivity). I.e., every CD8+ parameter except:
  - CD107a-CD154+IFNg-TNFa-IL-2-
  - CD107a-CD154-IFNg-TNFa-IL-2-

Missing values will not be imputed for this analysis.

Following the percent overall cytokine response calculation, for background (DMSO)-subtracted analyses only, the percent overall DMSO response is then subtracted from each percent overall cytokine response. To calculate the DMSO-stimulated response, no further calculations are required.

Background-subtracted responses that result in a negative value (<0) are set to zero.

Each cytokine pair per T cell (see **Table 4**) is also summed to form 15 cytokine combinations per stimulation antigen (required for the figures and listings). Note the all-negative response has not been included. For example:

CD4/CD107a+CD154+IFNg+IL2+TNFa+ (%) = 0.2835 and
CD4/CD107a-CD154+IFNg+IL2+TNFa+ (%) = 0.1
gives *IFNg+ / IL2+ / TNFa+ / CD154+* (%) = 0.3835.

Table 4 ICS Cytokine Response Combinations

T Cell	Cytokines (%)	Cytokine combination naming
CD4+	CD4/CD107a+CD154+IFNg+IL2+TNFa+ CD4/CD107a-CD154+IFNg+IL2+TNFa+	IFNg+ / IL2+ / TNFa+ / CD154+
	CD4/CD107a+CD154-IFNg+IL2+TNFa+ CD4/CD107a-CD154-IFNg+IL2+TNFa+	IFNg+ / IL2+ / TNFa+ / CD154-
	CD4/CD107a+CD154+IFNg+IL2+TNFa- CD4/CD107a-CD154+IFNg+IL2+TNFa-	IFNg+ / IL2+ / TNFa- / CD154+
	CD4/CD107a+CD154-IFNg+IL2+TNFa- CD4/CD107a-CD154-IFNg+IL2+TNFa-	IFNg+ / IL2+ / TNFa- / CD154-
	CD4/CD107a+CD154+IFNg+IL2-TNFa+ CD4/CD107a-CD154+IFNg+IL2-TNFa+	IFNg+ / IL2- / TNFa+ / CD154+
	CD4/CD107a+CD154-IFNg+IL2-TNFa+ CD4/CD107a-CD154-IFNg+IL2-TNFa+	IFNg+ / IL2- / TNFa+ / CD154-
	CD4/CD107a+CD154+IFNg+IL2-TNFa- CD4/CD107a-CD154+IFNg+IL2-TNFa-	IFNg+ / IL2- / TNFa- / CD154+

T Cell	Cytokines (%)	Cytokine combination naming
	CD4/CD107a+CD154-IFNg+IL2-TNFa- CD4/CD107a-CD154-IFNg+IL2-TNFa-	IFNg+ / IL2- / TNFa- / CD154-
	CD4/CD107a+CD154+IFNg-IL2+TNFa+ CD4/CD107a-CD154+IFNg-IL2+TNFa+	IFNg- / IL2+ / TNFa+ / CD154+
	CD4/CD107a+CD154-IFNg-IL2+TNFa+ CD4/CD107a-CD154-IFNg-IL2+TNFa+	IFNg- / IL2+ / TNFa+ / CD154-
	CD4/CD107a+CD154+IFNg-IL2+TNFa- CD4/CD107a-CD154+IFNg-IL2+TNFa-	IFNg- / IL2+ / TNFa- / CD154+
	CD4/CD107a+CD154-IFNg-IL2+TNFa- CD4/CD107a-CD154-IFNg-IL2+TNFa-	IFNg- / IL2+ / TNFa- / CD154-
	CD4/CD107a+CD154+IFNg-IL2-TNFa+ CD4/CD107a-CD154+IFNg-IL2-TNFa+	IFNg- / IL2- / TNFa+ / CD154+
	CD4/CD107a+CD154-IFNg-IL2-TNFa+ CD4/CD107a-CD154-IFNg-IL2-TNFa+	IFNg- / IL2- / TNFa+ / CD154-
	CD4/CD107a+CD154+IFNg-IL2-TNFa- CD4/CD107a-CD154+IFNg-IL2-TNFa-	IFNg- / IL2- / TNFa- / CD154+
CD8+	CD8/CD107a+CD154+IFNg+IL2+TNFa+ CD8/CD107a+CD154-IFNg+IL2+TNFa+	IFNg+ / IL2+ / TNFa+ / CD107+
	CD8/CD107a-CD154+IFNg+IL2+TNFa+ CD8/CD107a-CD154-IFNg+IL2+TNFa+	IFNg+ / IL2+ / TNFa+ / CD107-
	CD8/CD107a+CD154+IFNg+IL2+TNFa- CD8/CD107a+CD154-IFNg+IL2+TNFa-	IFNg+ / IL2+ / TNFa- / CD107+
	CD8/CD107a-CD154+IFNg+IL2+TNFa- CD8/CD107a-CD154-IFNg+IL2+TNFa-	IFNg+ / IL2+ / TNFa- / CD107-
	CD8/CD107a+CD154+IFNg+IL2-TNFa+ CD8/CD107a+CD154-IFNg+IL2-TNFa+	IFNg+ / IL2- / TNFa+ / CD107+
	CD8/CD107a-CD154+IFNg+IL2-TNFa+ CD8/CD107a-CD154-IFNg+IL2-TNFa+	IFNg+ / IL2- / TNFa+ / CD107-
	CD8/CD107a+CD154+IFNg+IL2-TNFa- CD8/CD107a+CD154-IFNg+IL2-TNFa-	IFNg+ / IL2- / TNFa- / CD107+
	CD8/CD107a-CD154+IFNg+IL2-TNFa- CD8/CD107a-CD154-IFNg+IL2-TNFa-	IFNg+ / IL2- / TNFa- / CD107-
	CD8/CD107a+CD154+IFNg-IL2+TNFa+ CD8/CD107a+CD154-IFNg-IL2+TNFa+	IFNg- / IL2+ / TNFa+ / CD107+

T Cell	Cytokines (%)	Cytokine combination naming
	CD8/CD107a-CD154+IFNg-IL2+TNFa+ CD8/CD107a-CD154-IFNg-IL2+TNFa+	IFNg- / IL2+ / TNFa+ / CD107-
	CD8/CD107a+CD154+IFNg-IL2+TNFa- CD8/CD107a+CD154-IFNg-IL2+TNFa-	IFNg- / IL2+ / TNFa- / CD107+
	CD8/CD107a-CD154+IFNg-IL2+TNFa- CD8/CD107a-CD154-IFNg-IL2+TNFa-	IFNg- / IL2+ / TNFa- / CD107-
	CD8/CD107a+CD154+IFNg-IL2-TNFa+ CD8/CD107a+CD154-IFNg-IL2-TNFa+	IFNg- / IL2- / TNFa+ / CD107+
	CD8/CD107a-CD154+IFNg-IL2-TNFa+ CD8/CD107a-CD154-IFNg-IL2-TNFa+	IFNg- / IL2- / TNFa+ / CD107-
	CD8/CD107a+CD154+IFNg-IL2-TNFa- CD8/CD107a+CD154-IFNg-IL2-TNFa-	IFNg- / IL2- / TNFa- / CD107+

10.4.4 ELISpot Pooled Peptide Responders

The total (pooled over antigens) response for a participant at a given time point is calculated using the average (of the sample performed in triplicate) background-subtracted results (SFU/10^5 PBMC) for each stimulation antigen:

- Total = Core + Pol1 + Pol2 + Pol3 + Pol4 + Pre-S + S
- Total (adjusted) = Core + Pol1 + Pol2 + Pol3 + Pre-S + S

For example using the average background-subtracted results (SFU/10^6 PBMC) for each participant: Core=20, Pol1=26.67, Pol2=35, Pol3=56.67, Pol4=55, Pre-S=1.67, S=210, gives Total=405.

A participant is considered to have a response if the total (pooled over antigens) response is defined as greater than 51.6 SFU/10^6 PBMCs or two times the background (DMSO) for that time point, whichever is higher.

Missing values will not be imputed for this analysis.

10.5 Adverse Events (AEs)

An adverse event is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and does not necessarily have a causal relationship with this treatment.

All AEs entered on the eCRF will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or later.

10.5.1 AE Severity

The severity of AEs will be graded by the investigator as Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-threatening), or Grade 5 (Fatal).

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.

Missing severity will not be imputed.

10.5.2 AE Causality

For unsolicited AEs, the Investigator will determine a causal relationship to the study vaccines and nivolumab.

Missing information regarding relationship to study vaccines or nivolumab, related/not related, will be handled using the worst-case approach. That is, unsolicited AEs with missing relationship to either study vaccines or nivolumab will be considered as "related".

10.5.3 Serious Adverse Events (SAEs)

A serious adverse event (SAE) is defined as any adverse event 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 participants 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)

All criteria leading to an AE being classified as a SAE will be recorded on the eCRF.

10.5.4 Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is an event of scientific and medical concern specific to the Sponsor's product.

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.

All AESI will be identified by investigator assessment, using the AEs listed above as a guideline, and will recorded on the eCRF.

10.5.5 Solicited AEs

For the Solicited AE analysis, data collected on both the eDiary (*Solicited Adverse Event*) and the CRF (*Local/Systemic Reactogenicity*) will be summarised together using the maximum reported intensity grade from either source.

Post-vaccine assessments on the day of the first vaccination and up to and including 7 days post-vaccination will be summarised under the First vaccination, and post-vaccine assessments on the day of

the second vaccination and up to and including 7 days post-vaccination will be summarised under the Second vaccination. This is the 7-day reactogenicity period. Pre-vaccine assessments for the first and second vaccination will not be included in the summaries and will be listed only.

The severity values will be mapped from the two sources as shown in Table 5. For erythema, induration, and fever, the eDiary values will be mapped to the intensity grades as described in Section 10.5.5.1.

Table 5 Solicited AE Severity

Severity	Solicited AE (eDiary) categories	Local/systemic reactogenicity (CRF) categories
Grade 0	0 – None	None
Grade 1	1 – No interference with activity	Mild
Grade 2	2 – Some interference with activity	Moderate
Grade 3	3 – Significant; prevents daily activity	Severe
Grade 4	4 – ER visit or hospitalisation	Life Threatening

10.5.5.1 Handling of Solicited AE (eDiary) data

Solicited adverse events are recorded in the eDiary for 7 days post-vaccination (Day 0 to Day 7, Day 28 to Day 35, and Month 3 to Month 3 + 7 days [only applicable for booster participants]). All solicited AEs are considered causally related to the study treatment.

Solicited local symptoms including pain, induration (swelling), warmth, and erythema (redness), and solicited systemic symptoms including feverishness, chills, myalgia (muscle ache), fatigue (tiredness), headache, nausea, arthralgia (joint ache), and malaise (a general feeling of unwell) will be reported in a standardised manner over a period of 7 consecutive days after vaccination.

These solicited AEs and their intensity grades are based on the Food and Drug Administration (FDA) Guidance on Toxicity Grading Scale as described in Appendix 1 of the Protocol. If induration (swelling) or erythema (redness) are recorded as < 25mm in diameter in the eDiary, then this will be categorised as no event (grade 0) for the purpose of analysis. Derived intensity grades for induration and erythema are done based only on the numeric value of the parameter assessed, and clinical signs and symptoms will not be considered.

In addition, oral temperature will also be recorded for 7 days post-vaccination. Fever is defined as oral temperature ≥38°C and the intensity grades are derived as specified in Appendix 1 of the Protocol.

Solicited AEs with missing intensity will not be included in the 'Any' count of the respective solicited AE.

10.6 Treatment-Emergent Events

Treatment-emergent events are defined as those occurring during or after the first study vaccine administration.

10.7 Prior and Concomitant Medications

All medications will be coded using World Health Organisation (WHO) Drug Dictionary version B3 March 2020 or later.

Medications will be classified as prior or concomitant.

Prior medications are defined as any medication with an end date prior to first study vaccination (Day 0).

Concomitant medications are defined as any medication with a start or end date on or after date of first study vaccination.

10.8 Missing Data Values

All statistical analysis will be based on observed values. Apart from handling missing AE relatedness, missing values will neither be replaced, nor estimated.

10.9 Handling of Missing or Partial Dates

Missing or partial dates will only be imputed for the purpose of determining the timing of AEs or concomitant medications in relation to study vaccine dosing and for calculating the time since first diagnosis and duration of current anti-viral therapy.

Listings will present the original, reported dates.

10.9.1 Unsolicited AE Missing or Partial Dates

Unsolicited AEs will be considered treatment-emergent unless the partial start date indicates that the event began prior to first vaccination, i.e. if the month and/or year are before the month of first study vaccination.

For the purpose of determining if the unsolicited AEs falls within 28 days of each vaccination (vaccination date + 27 days), the following imputation of missing and partial start dates will be performed:

Missing day, month, and year

The day, month, and year of date of first vaccination will be assigned to the missing fields.

Missing day and month

If the year of the incomplete start date is the same as the year of the date of first vaccination, then the day and month of the date of first vaccination will be assigned to the missing fields.

If the year of the incomplete start date is before the year of the date of first vaccination, then December 31 will be assigned to the missing fields.

If the year of the incomplete start date is after the year of the date of first vaccination, then 01 January will be assigned to the missing fields.

Missing month only

The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

If the month and year of the incomplete start date are the same as the month and year of the date of first vaccination, then the day of the date of first vaccination will be assigned to the missing day.

If either the year is before the year of the date of first vaccination or if both years are the same but the month is before the month of the date of first vaccination, then the last day of the month will be assigned to the missing day.

If either the year is after the year of the date of first vaccination or if both years are the same but the month is after the month of the date of first vaccination, then the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

10.9.2 Concomitant Medication Missing or Partial End Dates

Medications with partial end dates will only be considered prior if the partial end date indicates that the medication was stopped prior to first study vaccination. All other medications with missing or partial end dates will be considered concomitant.

10.9.3 HBV History Missing or Partial Dates

If the date of first diagnosis or start date of current anti-viral therapy is partial, the following rules will take effect:

- Missing day, but month and year are present: the day will be imputed as the 15th day of the month, or date of informed consent, whichever is earlier
- Missing day and month, but year is present: the day and month will be imputed as the 1st July of the year, or date of informed consent, which is earlier
- Missing day, month, and year: no imputations will occur and the participant will be excluded from all summaries related to time since HBV diagnosis and duration of current anti-viral therapy

10.10 Multiple Assessments at a Time Point

If a participant has more than one assessment taken at the same time point (e.g. laboratory results, vital signs), for baseline the latest date and time prior to first study vaccination is used. For post-baseline visits, the worst clinical value in the direction of the toxicity presented will be used in the analysis for that time point. All values will be listed.

In cases where solicited AE or daily temperature records are recorded on both the eDiary and CRF with the same date/time, for the primary analysis we will select the CRF record to use. If the solicited AE or daily temperature record was only collected on either the eDiary or the CRF, then all records will be considered for the primary analysis.

For a sensitivity analysis, all records including records identified as duplicates will be used. All records will be listed.

11.0 Interim Analyses

11.1 Interim Analyses

An interim analysis will be performed for all data collected when at least 20 participants have been enrolled (with four participants randomised to Group 3 and Group 4) and followed for 3 months.

As the study is open-label, no unblinding needs to occur, and as such the interim analyses will be performed by the PRA team. The results of the interim analysis will be used to determine the development plans for the Phase 3 study.

The interim analysis will contain a subset of the CSR outputs as listed in Section 16.0. The details of how the analyses will be performed are specified within each section of the statistical methods part of this SAP.

11.2 Safety Monitoring Committee

A safety monitoring committee (SMC) will be appointed to review the study data throughout the study and at specific time points.

11.3 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be utilised for this study. Ad hoc meetings of the DMC may be called at the discretion of the SMC or if any of the study stopping or holding rules are met.

A DMC charter including a detailed description will be prepared. A subset of CSR outputs as listed in Section 16.0 will be produced for review at these meetings.

12.0 Statistical Methods

All statistical analyses will use SAS version 9.4 or higher.

Unless otherwise noted, categorical variables will be summarised using counts and percentages. Percentages will be rounded to one decimal place, except 100% which will be displayed without any decimal places, and percentages will not be displayed for zero counts. Denominators used for percentages will be the population N unless otherwise specified.
For tables with a percent cut-off, the cut-off is applied to the percentage before rounding.

Continuous variables will be summarised using the number of observations (n), mean, Standard Deviation (SD), median, Q1, Q3, minimum, and maximum. Summaries of HBsAg will present the number of observations (n), geometric mean (GM), geometric standard deviation (GSD), median, minimum, and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data, the mean, GM, median, Q1, and Q3 to a further decimal place and the SD and GSD to two additional decimal places. All values will be presented to a maximum 4 decimal places.

Where relevant, estimates will be presented with 95% two-sided confidence intervals using the same number of decimal places as the parameter estimate. P-values ≥0.001 will be reported to three decimal places; p-values less than 0.001 will be reported as <0.001.

Participants will be summarised by treatment group (Group 1, 2, 3, or 4) and in addition by Total for demography and safety tables. In general, all categories specified in the eCRF will be presented in summary tables.

Unless otherwise specified, all data collected during the study will be presented in the participant data listings by treatment group, study site, and participant ID.

12.1 Participant Disposition

The number and percentage of participants screened, enrolled, and randomised in the study will be presented, together with the number and percentage of participants included in each analysis set. The number of screen failures and participants enrolled but not randomised will also be presented. Reasons for exclusion from each analysis set will not be tabulated but will be listed.

Reason for screen failure, including inclusion and exclusion criteria not met, will be listed.

The participant disposition for the study including the number and percentage of participants who completed the study, withdrew from the study prematurely, and a breakdown of the corresponding reasons for withdrawal will be summarised using the Intent-to treat analysis set. In addition, the number and percentage of participants completing the vaccine regimen and discontinuing the vaccine regimen along with a breakdown of the corresponding reasons for discontinuation will be summarised. Listings of end of study and end of treatment status will be presented for all randomised participants.

A tabulation of the number and percentage of participants screened, enrolled, and randomised to each treatment group in each country and centre will be presented using all screened participants.

12.2 Protocol Deviations

The study specific Protocol Deviation Guidance Document defines all important protocol deviations.

Per PRA processes, important protocol deviations data will be entered into our system of record (PSO). The study team and the Sponsor will conduct on-going reviews of the deviation data from PSO and the resulting set of evaluable participants throughout the study, adjusting the deviation criteria as seems appropriate.

Protocol deviations will be classified into major (important) or minor (non-important) deviations. Protocol deviations leading to a participant's exclusion from the Per-protocol analysis set and Immunogenicity analysis set will be reviewed based on their possible impact on the study results in a data review meeting prior to database lock. The Per-protocol analysis set and Immunogenicity analysis set must be finalised at the post-freeze data review meeting (or earlier) prior to database lock.

A summary of the number and percentage of protocol deviations by deviation type (major, minor) and category will be provided using the Intent-to-treat analysis set. In addition, a by-participant listing of all protocol deviations will be presented.

12.3 Demographic and Baseline Characteristics

All demographic and baseline characteristics analyses will use the Intent-to-treat analysis set unless otherwise stated.

Frequency distributions and summary statistics for demographics and baseline characteristics including sex, race, ethnicity, age at informed consent (years), age group (18-64 years, ≥ 65 years), height (cm), weight (kg), and BMI (kg/m^2) will be summarised using the Intent-to-treat analysis set and additionally the Per-protocol analysis set and Immunogenicity analysis set. Date of informed consent and randomisation will be listed along with demographic and baseline data. A listing of randomisation information by date and time of randomisation, randomisation number, participant ID, and treatment group assigned will be presented.

A listing of childbearing potential will be presented for female participants only.

Medical and surgical history will be summarised by system organ class (SOC) and preferred term (PT) according to MedDRA version 23.0 or later. HBV history including time since first HBV diagnosis (years), current anti-viral therapy, and duration of current anti-viral therapy (years) will be presented.

Time since first HBV diagnosis (years) and duration of current anti-viral therapy (years) will be calculated as: [date of informed consent – date of first diagnosis/start date of anti-viral therapy]/365.25.

Medical and surgical history and HBV history will be listed separately.

Usage of alcohol, recreational drugs, and tobacco categorised by current, past, and never used will be tabulated. Type of tobacco used will also be presented for the number and percentage of participants. The number of alcohol or type of tobacco units consumed and date of last drink, last drug use, and last use of each type of tobacco will be listed.

12.4 Prior and Concomitant Medications

Prior and concomitant medications, categorised by WHO drug dictionary preferred term (PT), will be summarised separately using the Intent-to-treat analysis set. The number and percentage of participants using each medication will be displayed together with the number and percentage of participants using at least one medication.

All prior and concomitant medications will be presented in a combined listing by participant.

12.5 Extent of Study Treatment Exposure

Exposure analyses will be summarised using the Safety analysis set.

The investigator records all injections of study vaccines or nivolumab given to the participant in the eCRF.

The number and percentage of participants who received both doses and the number and percentage of participants who received the first dose of the vaccine regimen only will be summarised.

Actual dose of nivolumab in mg/kg and mg will be derived using the planned dose, baseline weight (kg), and percentage of nivolumab infused. The reason study vaccine or nivolumab was not administered will be tabulated along with the reason not fully administered and percentage administered (if not fully administered) for nivolumab. This will be split by vaccination day.

The type of vaccine, administration date and time, vial lot #, location administered, percentage of vaccine administered, reason not administered, and if the participant was observed per protocol will be listed for study vaccination administration. For nivolumab administration, infusion date, start and stop time, planned dose (mg), actual dose given (mg/kg and mg), reason not administered, reason not fully administered, percentage administered, and if the participant was observed per protocol will be listed.

12.6 Immunogenicity Analyses

12.6.1 Secondary Endpoints

The secondary endpoints are:

- Magnitude and avidity of HBV specific CD4+ and CD8+ (ICS response, ELISpot)
- Effect on the frequency and magnitude of HBV infection markers (HBsAg, HBsAb seroconversion, Hepatitis DNA, HBeAg)

All HBV disease marker and immunogenicity results will be listed.

12.6.1.1 Reduction in HBsAg levels

Descriptive statistics including n, GM, GSD, median, minimum, maximum and 95% Exact confidence intervals (as defined in Section 10.4.1) for HBsAg will be summarised at Baseline, Day 7, Day 28, Day 35, Month 3, Month 6, and Month 9 and fold change from baseline to each visit as applicable. The number and percentage of participants with HBsAg loss of > 0.5 $\log_{10}$ and > 1.0 $\log_{10}$ from baseline at each visit will be presented. The denominator for the percentage will be the number of participants with non-missing values at the visit. This analysis will be presented using the Intent-to-treat analysis set, Per-protocol analysis set and Immunogenicity analysis set.

A repeated mixed measures model be used to assess HBsAg change from baseline at the scheduled time points (Day 7, Day 28, Day 35, Month 3, Month 6, and Month 9) using the Intent-to-treat analysis set. Least squares means, standard errors, 95% confidence intervals, and p-values will come from a repeated measures model on Change from baseline on the log scale (as defined in Section 10.2) with fixed factors for treatment group, time point, and treatment group * time point interaction, a covariate for $\log_{10}$ baseline HBsAg, and a random effect for participant. An unstructured covariance matrix will be used to account for within-participant variability. This will be calculated using the SAS procedure proc mixed.

12.6.1.2 HBeAg Status

A summary of the number and percentage of participants with positive and negative baseline HBeAg status and HBeAg status at Month 9 will be presented using the Intent-to-treat analysis set.

12.6.1.3 Seroconversion Rate for HBeAg, HBeAb, HBsAg, and HBsAb

The number and percentage of participants meeting the criteria for HBeAg, HBeAb, HBsAg, and HBsAb seroconversion and sustained HBeAb positivity as defined in Section 10.4.2 will be presented at Month 9. The denominator for the percentage will be the number of participants fulfilling the baseline part of the seroconversion criteria (i.e. positive antigen or negative antibody at baseline, as applicable) with non-missing values at Month 9. This analysis will be presented using the Intent-to-treat analysis set.

12.6.1.4 Reduction in Hepatitis B DNA

The number and percentage of participants with No HBV DNA detected, < 20 IU/mL HBV DNA detected, and ≥ 20 IU/mL HBV DNA detected will be summarised at all planned time points (Baseline, Day 35, Month 3, Month 9). This analysis will be presented using the Intent-to-treat analysis set.

12.6.1.5 ICS response

These analyses will be presented using the Immunogenicity analysis set.

Background-subtracted overall cytokine response (%) as defined in Section 10.4.3 will be presented for each T cell (CD4+ and CD8+) and stimulation antigen (Core, Pol 1+2, Pol 3+4, Pre-S1/S2+S). Descriptive statistics including n, mean, standard deviation, median, minimum, maximum, and 95% CI for the median based on order statistics will be presented for absolute values, change from baseline, and fold change from baseline at all planned time points (Baseline, Day 7, Day 28, Day 35, Month 3, Month 6, Month 9).

DMSO overall cytokine response (%) will be presented similarly to background-subtracted overall cytokine response.

Graphical summaries using dot plots for the background-subtracted overall cytokine response (%) analysis above will be presented by planned time point separately for each T cell and stimulation antigen. The median overall cytokine response (%) per treatment group will be represented by a horizontal line. A dot plot will also be provided for DMSO overall cytokine response (%) results.

In addition, the median background-subtracted overall cytokine response for the stimulation antigens (Core, Pol 1+2, Pol 3+4, Pre-S1/S2+S) will be displayed altogether in a stacked bar plot for each treatment group by planned time point.

The 15 background-subtracted cytokine combinations (%) (see **Table 4**) and background-subtracted overall cytokine response (%) at Day 35 will be presented using polyfunctional profile plots separately for each T cell and stimulation antigen. Each of the cytokine combinations will be presented under the plot using Boolean values (+, -).

Also, for the background-subtracted overall cytokine response, to identify statistically significant differences between baseline and Day 35, a Wilcoxon signed-rank test using change from baseline will be performed within each of the four treatment groups for each T cell and stimulation antigen.

The median background-subtracted overall cytokine response for each T cell and stimulation antigen will be presented by all planned time points (Baseline, Day 7, Day 28, Day 35, Month 3, Month 6, Month 9) and p-values based on 2-sided Wilcoxon-Mann-Whitney (Wilcoxon rank sum) tests for pairwise comparisons between all treatment groups will also be presented. No adjustments will be made for the multiple comparisons.

All cytokine combinations (see **Table 4**) and overall response will be listed by T cell (CD4+ and CD8+), stimulation antigen, and time point. Only derived cytokine combinations will be included in this listing.

12.6.1.6 ELISpot response

These analyses will be presented using the Immunogenicity analysis set.

Average background-subtracted antigen specific IFNg ELISpot response (SFU/10^6 PBMC) will be presented for each stimulation antigen (Core, Pol1, Pol2, Pol3, Pol4, Pre-S, S, Total, and Total (adjusted) [as defined in Section 10.4.4]). Descriptive statistics including n, mean, standard deviation, median, minimum, maximum, and 95% CI for the median based on order statistics will be presented for absolute values, change from baseline, and fold change from baseline at all planned time points (Baseline, Day 7, Day 28, Day 35, Month 3, Month 6, Month 9).

Also, for the average background-subtracted antigen specific IFNg ELISpot response, to identify statistically significant differences between baseline and Day 35, a Wilcoxon signed-rank test using change from baseline will be performed within each of the four treatment groups for each stimulation antigen.

Similar to the graphical summaries described for the ICS analysis, for average background-subtracted antigen specific IFNg ELISpot response (SFU/10^6 PBMC) a dot plot will be presented by planned time point separately for each stimulation antigen (Core, Pol1, Pol2, Pol3, Pol4, Pre-S, S, Total, Total adjusted).

A stacked bar chart will also be displayed for the median total (pooled over antigens) response (SFU/10^6 PBMC) by treatment group and planned time point.

In addition, a line plot of mean ± SD of the total (pooled over antigens) response (SFU/10^6 PBMC) for each treatment will be displayed by planned time point.

A summary of the number and percentage of participants who meet the total (pooled over antigens) responder criteria as defined in Section 10.4.4 will be presented at all planned time points.

The average (from samples run in triplicate), background-subtracted antigen-specific IFNg ELISpot response (SFU/10^6 PBMC) will be listed by stimulation antigen (Core, Pol1, Pol2, Pol3, Pol4, Pre-S, S, Total) for each participant at each time point.

12.7 Safety Analyses

All safety analyses will be presented using the Safety analysis set.

12.7.1 Primary Endpoints

The primary endpoints are:

- Safety and reactogenicity of the vaccine(s): incidence of AEs, SAEs, ≥ Grade 3 study vaccine-related AEs within 4 weeks of vaccination
- Safety of the vaccines with nivolumab: incidence of AEs, SAEs, ≥ Grade 3 AEs within 4 weeks of dosing
- Incidence of AESI
- Number and proportion of participants reporting TEAEs 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

12.7.1.1 Adverse Events

The number and percentage of participants reporting each adverse event, including the number of events, will be summarised by SOC and PT coded according to the MedDRA dictionary. Participants are only counted once within each SOC and PT. AEs will be sorted by decreasing frequency within each SOC and PT according to the overall treatment group.

In addition, summaries will be provided for the subset of AEs, SAEs, and Grade 3 or greater AEs that occurred within 28 days of first vaccination and second vaccination (vaccination day + 27 days) separately.

AESI will also be tabulated by PT for all events occurring during the study.

12.7.1.2 Laboratory Data

The number and percentage of participants with investigator assessed potentially clinically significant post-baseline values will be tabulated by laboratory category (haematology, biochemistry). Potentially clinically significant laboratory values as assessed by the investigator will be documented as AEs.

ALT and AST at at each scheduled time point (Baseline, Day 7, Day 28, Day 35, Month 3, Month 6, and Month 9) and changes from baseline at each time point will be summarised by treatment group using descriptive statistics.

Haematology and biochemistry (including liver function tests) laboratory parameters listed in **Table 6** will be presented using line plots of laboratory results by parameter and time point (including unscheduled visits) by participant.

Laboratory data values of the form of "< x" (i.e., below the lower limit of quantification) or > x (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of toxicity grading but displayed as "< x" or "> x" in the listings. Standard International (SI) units will be used for all laboratory parameters displayed in the figures and listings.

Table 6 Laboratory Tests

Category	Parameters
Haematology	leukocytes, basophils, basophils/leukocytes, eosinophils, eosinophils/leukocytes, lymphocytes, lymphocytes/leukocytes, monocytes, monocytes/leukocytes, neutrophils, neutrophils/leukocytes, haematocrit, haemoglobin, erythrocyte mean corpuscular haemoglobin, erythrocyte

Category	Parameters
	mean corpuscular haemoglobin concentration, erythrocyte mean corpuscular volume, erythrocytes, erythrocyte cell morphology, erythrocytes distribution width, platelets, fibrotest score, fibrotest stage, prothrombin intl. normalised ratio, prothrombin time, AST to platelet ratio index
Biochemistry (including liver function tests)	alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, bilirubin, direct bilirubin, urea nitrogen, creatinine, potassium, sodium, albumin, haptoglobin, alpha-2 macroglobulin, apolipoprotein A1
Urinalysis (dipstick)	specific gravity, pH, erythrocytes, protein, glucose, ketones, bilirubin, urobilinogen, leukocytes, nitrite
Urinalysis (drug screen)	amphetamine, barbiturates, benzodiazepine, cannabinoids, cocaine, methadone, opiate, phencyclidine, propoxyphene, tricyclic antidepressants
HBV disease markers	HBsAg, HBsAb, HBeAg, HBeAb, HBV DNA, HBcAb
Viral measurements	HIV antibodies, HCV antibodies, HDV antibodies

12.7.1.3 Vital Signs

Vital sign values will be considered potentially clinically significant if they meet either the low or high potentially clinically significant criteria listed in **Table 7**. The number and percentage of participants with any potentially clinically significant post-baseline value overall and by each criteria will be tabulated.

Table 7 Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter (unit)	Lower Limit	Upper Limit
Pulse rate (beats per minute)	< 45	> 130
Systolic blood pressure (mmHg)	< 80	> 155
Diastolic blood pressure (mmHg)		> 100
Temperature (°C)		≥ 39.0

A graphical display of each parameter by time point will be presented similarly to laboratory data.

12.7.2 Other Safety Endpoints

12.7.2.1 Other Adverse Events

An overall summary of treatment-emergent adverse events, including the number of events reported, will be provided for:

- Any AEs
- Any AEs within 28 days of first vaccination
- Any AEs within 28 days of second vaccination
- Any grade 3 or greater AEs within 28 days of first vaccination
- Any grade 3 or greater AEs within 28 days of second vaccination
- Any AEs related to study vaccines
- Any AEs related to nivolumab

- Any AEs related to study vaccines or nivolumab
- Any grade 3 or greater AEs related to study vaccines
- Any grade 3 or greater AEs related to nivolumab
- Any grade 3 or greater AEs related to study vaccines or nivolumab
- Any AEs with outcome of death
- Any serious AEs
- Any serious AEs related to study vaccines
- Any serious AEs related to nivolumab
- Any serious AEs related to study vaccines or nivolumab
- Any AEs leading to discontinuation of study vaccines
- Any AEs leading to discontinuation of nivolumab
- Any AEs leading to discontinuation of study vaccines or nivolumab
- Any AEs of special interest

Deaths will be identified using the AE eCRF.

In addition, individual summary tables by SOC and PT will be provided for each category (with the exception of any AEs with outcome of death) in the overall TEAE table and presented similarly to the primary endpoint in Section 12.7.1.1. A by-participant summary of all TEAEs leading to death, serious TEAEs, and TEAEs leading to discontinuation of study vaccines or nivolumab will be produced.

AEs leading to discontinuation of study vaccines or nivolumab are defined as any AE with Action Taken with Study Vaccines = 'Drug Withdrawn' or Action Taken with Nivolumab = 'Permanently Discontinue' recorded on the Unsolicited AEs eCRF.

TEAEs will be further summarised by maximum severity (grade 1, grade 2, grade 3, grade 4, grade 5) within each SOC and PT. Participants with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.

Non-treatment-emergent AEs will be presented by SOC and PT.

All adverse events (including non-treatment-emergent events) recorded on the eCRF will be listed separately.

12.7.2.2 Solicited Adverse Events

For each solicited symptom (grouped by local symptoms and systemic symptoms), the number and percentage of participants reporting an event will be summarised by vaccination (first vaccination, second vaccination) and overall.

For participants experiencing a solicited symptom (i.e. reporting a severity Grade 1 or higher), an additional summary of solicited symptoms by maximum severity after each vaccination (first vaccination, second vaccination) and overall will be presented.

Percentages for both analyses are based on the number of participants reporting the severity of any solicited symptom on any day within the 7-day reactogenicity period following each vaccination (as defined in Section 10.5.5).

Both analyses will be presented for the primary analysis and repeated for the sensitivity analysis (as defined in Section 10.10).

Solicited AEs, local and system reactogenicity, and diary body temperature will be listed separately. A combined listing including solicited symptoms from both the eDiary and CRF for the 7-day reactogenicity period will also be presented.

12.7.2.3 Laboratory Data

Laboratory values will be evaluated according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA) presented in **Appendix 1**. Derived toxicity grades are done based only on the numeric value of the parameter assessed.

The number and percentage of participants with each toxicity grade will be tabulated by baseline and maximum post-baseline worst result for each parameter and direction of change. Shift tables of laboratory results by worst change from baseline grade will be presented for the following parameters and direction of change:

- Haematology: leukocytes (low) [WBC decrease], leukocytes (high) [WBC increase], eosinophils (high) [eosinophils], lymphocytes (low) [lymphocytes decrease], neutrophils (low) [neutrophils decrease], haemoglobin (low) [haemoglobin], platelets (low) [platelets decrease], prothrombin time (high) [prothrombin time]
- Biochemistry: alanine aminotransferase (high) [alanine aminotransferase], aspartate aminotransferase (high) [aspartate aminotransferase], alkaline phosphatase (high) [alkaline phosphatase], direct bilirubin (high) [bilirubin increase], urea nitrogen (high) [blood urea nitrogen], creatinine (high) [creatinine], potassium (low) [hypokalaemia], potassium (high) [hyperkalaemia], sodium (low) [hyponatremia], sodium (high) [hypernatremia], albumin (low) [hypoalbuminemia]

Participants with any out of range values as determined using the central lab reference ranges will be listed.

All haematology, biochemistry, urinalysis, urine dipstick, and viral measurement results will be listed separately. In addition, investigator assessed clinically significant laboratory results (haematology, biochemistry, urinalysis) will be listed.

Pregnancy test results for female participants of childbearing potential will be listed.

12.7.2.4 Vital Signs

Shift tables of worst change from baseline in each participant will be presented by parameter. Worst change is defined as the lowest and highest post-baseline toxicity grades for pulse rate (bradycardia, tachycardia) and systolic blood pressure (hypotension, hypertension), and as the highest post-baseline toxicity grades for diastolic blood pressure (hypertension) and temperature (fever). Toxicity grades are based on the Food and Drug Administration (FDA) Guidance on Toxicity Grading Scale as described in Appendix 1 of the Protocol.

All vital sign data will be included in a by-participant listing. Participants with any treatment-emergent out of range vital sign values, defined as outside of the normal range criteria specified in **Table 8**, will be listed separately.

Table 8 Vital Signs Normal Ranges

Vital Sign Parameter (unit)	Normal range
Pulse Rate (beats/min)	45-130 (inclusive)
Systolic Blood Pressure (mmHg)	90-140 (inclusive)
Diastolic Blood Pressure (mmHg)	< 91
Temperature (°C)	< 38.0

12.7.2.5 Physical Examinations

All physical examination data with corresponding clinically significance will be listed only.

13.0 References

Food and Drug Administration, C. f. B. E. a. R. "Guidance for Industry: Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

14.0 Important Protocol Deviation Identification Listings

Not applicable.

15.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
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 Immunosorbent Spot
FDA	Food and Drug Administration
GM	Geometric Mean
GSD	Geometric Standard Deviation
HBcAb	Hepatitis B Core-related Antibody
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
ICS	Intracellular Cytokine Staining
IXRS	Interactive Voice/Web Response System
LFTs	Liver Function Tests
LLoQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MVA	Modified Vaccinia Virus Ankara
PBMC	Peripheral Blood Mononuclear Cell
Pfu	Plaque Forming Units
PT	Preferred Term
RNA	Ribonucleic Acid
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SFU	Spot-forming Unit
SI	Standard International
SMC	Safety Monitoring Committee
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
Vp	Viral Particles

16.0 List of DMC and Interim Analysis Outputs

TFL	DMC	Interim
Table 14.1.1.3 Participant Disposition	✓	✓
Table 14.1.2.1 Demographic Characteristics	✓	✓
Table 14.2.1 Summary of HBsAg Geometric Mean by Time Point	✓	✓
Table 14.3.1.1 Summary of Exposure	✓	✓
Table 14.3.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	✓	✓
Table 14.3.2.13 Grade 3 or Greater Treatment-Emergent Adverse Events Related to Study Vaccines by System Organ Class and Preferred Term	✓	✓
Table 14.3.2.14 Grade 3 or Greater Treatment-Emergent Adverse Events Related to Nivolumab by System Organ Class and Preferred Term	✓	✓
Table 14.3.2.16 Participants with Treatment-Emergent Adverse Events with Outcome of Death	✓	✓
Table 14.3.2.17 Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	✓	✓
Table 14.3.2.18 Participants Who Experienced Serious Treatment-Emergent Adverse Events	✓	✓
Table 14.3.2.25 Participants Who Experienced Treatment-Emergent Adverse Events Leading to Discontinuation of Study Vaccines or Nivolumab	✓	✓
Table 14.3.2.27.a Solicited Adverse Events by Intensity Grade after each Vaccination	✓	✓
Table 14.3.2.27.b Solicited Adverse Events by Intensity Grade after each Vaccination – Sensitivity Analysis including all data	✓	✓
Table 14.3.2.28 Local and Systemic Reactogenicity by Vaccination and Time Point	✓	✓
Table 14.3.3.1.1 Potentially clinically significant Post-baseline Laboratory Results	✓	✓
Table 14.3.3.2.3 Participants With an Out of Range Haematology Result	✓	✓
Table 14.3.3.3.3 Participants With an Out of Range Biochemistry Result	✓	✓
Table 14.3.4.1 Potentially Clinically Significant Vital Sign Results	✓	
Listing 16.2.1.2 End of Study	✓	✓
Listing 16.2.1.3 End of Treatment	✓	✓
Listing 16.2.7.1 Treatment-Emergent Adverse Events	✓	✓
Listing 16.2.7.2 Solicited Adverse Events (eDiary)	✓	✓
Listing 16.2.7.3 Local and Systemic Reactogenicity	✓	✓

Appendix 1. Tables for Laboratory Abnormalities

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hyponatremia (mEq/L)	132 - 134	130 - 131	125 - 129	
Hypernatremia (mEq/L)	144 - 145	146 - 147	148 - 150	---
Hypokalemia (mEq/L)	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	---
Hyperkalemia (mEq/L)	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	---
Blood Urea Nitrogen (mg/dL)	23 - 26	27 - 31	>31	---
Creatinine (mg/dL)	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5
Hypoalbuminemia (g/dL)	2.8 – 3.1	2.5 – 2.7	<2.5	---
Alanine Aminotransferase (U/L)	1.1 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
Aspartate Aminotransferase (U/L)	1.1 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
Alkaline Phosphatase (U/L)	1.1 – 2.0 x ULN	>2.0 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
Bilirubin Increase (mg/dL) – when accompanied by any increase in LFT; increase by factor	1.1 – 1.25 x ULN	>1.25 – 1.5 x ULN	>1.5 – 1.75 x ULN	>1.75 x ULN
Bilirubin Increase (mg/dL) - when LFT is normal; increase by factor	1.1 – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 3.0 x ULN	>3.0 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.
ULN is the upper limit of the normal range.

Haematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Haemoglobin [Female] (g/dL)	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Haemoglobin [Female] Decrease from Baseline Value (g/dL)	>0 – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Haemoglobin [Male] (g/dL)	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Haemoglobin [Male] Decrease from Baseline Value (g/dL)	>0 – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC Decrease (10^3/uL)	2.500 – 3.500	1.500 – 2.499	1.000 – 1.499	<1.000
WBC Increase (10^3/uL)	10.800 – 15.000	15.001 – 20.000	20.001 – 25.000	>25.000
Lymphocytes Decrease (10^3/uL)	0.750 – 1.000	0.500 – 0.749	0.250 – 0.499	<0.250
Neutrophils Decrease (10^3/uL)	1.500 – 2.000	1.000 – 1.499	0.500 – 0.999	<0.500
Eosinophils (10^3/uL)	0.650 – 1.500	1.501 – 5.000	>5.000	—
Platelets Decrease (10^3/uL)	125.000 – 140.000	100.000 – 124.000	25.000 – 99.000	<25.000
Prothrombin Time (sec)	1.0 – 1.10 x ULN	>1.10 – 1.20 x ULN	>1.20 – 1.25 x ULN	>1.25 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.
ULN is the upper limit of the normal range.

Urine*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Urine Erythrocytes (rbc/hbf)	1 – 10	11 – 50	>50	---
Urine Glucose	Trace	+	++	---
Urine Protein	Trace	+	++	---

* 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.