Statistical Analysis Plan

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PRA Project Id:	ALMFCS01-FPCS01
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Title:	A phase I, randomised, double-blind, placebo-controlled, multi-centre, ascending-dose trial to evaluate the safety, tolerability and immunogenicity of Vaccine FP-02.2 in HBeAg-negative hepatitis B patients as an add-on treatment to entecavir or tenofovir.
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1.0 Approvals

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Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomic Therapeutic Classification
BMI	Body Mass Index
CI	Confidence Interval
CSR	Clinical Study Report
CTMS	Clinical Trials Management System
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISPOT	Enzyme-linked Immuno Spot
ET	Early Termination
HBeAg	Hepatitis B e-Antigen
HBsAb	Antibody to Hepatitis B Surface Antigen
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HIV	Human Immunogenicity Virus
HLA	Human Leukocyte Antigen
IFN-γ	Interferon-gamma
IP	Investigational Product
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
PBMC	Peripheral Blood Mononuclear Cells
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-emergent Adverse Event
TFL	Tables, Figures and Listings
WHO	World Health Organisation

2.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Altimmune Protocol FP02.2_CS_01.

3.0 Scope

This SAP provides a detailed outline of the safety and immunogenicity analyses to be performed in accordance with Study Protocol FP02.2_CS_01 Version 1.0, version 6 dated 11AUG2016, and will address the analysis presentation of the interim review of data as well as the final review of all data for the completed study.

The primary analysis will be performed with safety and immunogenicity through Day 85. After completion of all Day 85 assessments, along with data entry, resolution of any data queries, and all immunogenicity testing, the database will be locked, and the analyses will be performed. No statistical stopping rules will be established for the review of these data and no statistical hypotheses will be reviewed or tested.

This SAP also addresses results and analyses through Study Day 225 for the analysis of the study follow up period. The database will be locked for this analysis when all available immunogenicity, virology and safety data through Day 225 (inclusive of earlier visits) have been entered, reviewed, and all queries related to the data have been addressed.

This plan is a living document that will be created during the trial start-up. Statistical Analysis Plan 1 will be drafted upon finalisation of the electronic case report form (eCRF) and maintained throughout the lifecycle of the trial. Statistical Analysis Plan 2 will be finalised prior to database lock. Both SAP 1 and SAP 2 will require sign off from the PRA Project Manager/Director and Altimmune.

The SAP outlines the following:

- Study objectives
- Study design
- Variables analysed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, investigational product exposure, concomitant medications and assessments of safety

4.0 Introduction

This SAP should be read in conjunction with the study protocol and eCRF. This version of the plan has been developed using the protocol version 6 dated 11AUG2016 and corresponding eCRF. Any further changes to the protocol or eCRF may necessitate updates to the SAP.

The SAP is to be developed in two stages. The purpose is to “finalise” a SAP so that programming may start earlier in the process. Versions of the SAP up to initial Altimmune approval will be known as SAP 1. Changes following approval of SAP 1 will be tracked in a SAP Change Log and a final version of the SAP, known as SAP 2, will be issued for Altimmune approval after the blinded data review meeting but prior to database lock.

4.1 Changes from Protocol

Section 10.9.7 of the protocol calls for physical examination results to be summarised descriptively. As described later in the SAP, the completion of each physical exam will be listed only to avoid duplication of data.

The definition of the immunogenicity Analysis Set has been amended to include a criterion that subjects must have received all 3 planned doses of investigational product (IP) and with no important protocol deviations adjudicated as relevant by the medical team.

5.0 Study Objectives

Primary

To assess the safety and tolerability of Vaccine FP-02.2 at Day 85 following vaccinations on Days 1, 29 and 57.

Secondary

To measure immunological response of Vaccine FP-02.2 at Day 85 following vaccinations on Days 1, 29 and 57.

6.0 Study Design

This is a double-blind, randomised, placebo-controlled, dose-ascending study to evaluate the safety, tolerability and immunogenicity of Vaccine FP-02.2 in HBeAg-negative hepatitis B subjects as an add-on treatment to entecavir or tenofovir.

Actively treated subjects will receive either a Low or High dose of Vaccine FP-02.2 with or without IC31®.

A placebo arm is included in the study. Safety and immunogenicity data generated from the placebo arm will allow comparison to data generated from the Vaccine FP-02.2 High and Low dose study arms. The placebo group is also necessary to understand the rate of natural HBsAg seroconversion in an untreated study arm. An IC31® alone arm is included in the study which will additionally allow comparison of safety and immunogenicity data with data generated from the Vaccine FP-02.2 High and Low dose/IC31® study arms.

Approximately 60 subjects (excluding replacements for subjects deemed ineligible after dosing) will complete this trial and will be assigned equally to 6 study arms.

Screening will occur up to 28 days prior to the first injection.

Up to 3 days before the first injection, eligible subjects will be randomised to treatment arm as shown in Table 2. Subjects will receive 3 injections at intervals of 28 days (Day 1, Day 29, and Day 57). On the days of the injections the subjects will stay in the clinic for at least 4 hours after the first injection and 2 hours after the second and third injections and be monitored closely including an assessment of local reactions at the injection site. Approximately 24 hours after the first injection, the subjects will be asked to attend the clinic for safety assessments. For subsequent injections, subjects will receive a telephone call approximately 24 hours after each injection for safety follow-up. The subjects will be asked to return to the clinic 7 days after each injection for further assessments as well as 28 days after the last injection (Day 85). A follow-up visit will be performed 6 months after the end of the treatment period (i.e. 6 months after the last dose).

The first cohort starts with a low dose of Vaccine FP-02.2, 150µg/peptide (1350µg total peptide or placebo). The next cohort receives a higher dose of Vaccine FP-02.2, 500µg/peptide (4500µg total peptide) or a low dose of Vaccine FP-02.2, 150µg/peptide, in conjunction with 500nmol/20nmol KLK/ODN1a IC31® (IC31®) or placebo or IC31® alone. The final cohort will test the high dose of Vaccine FP-02.2, in conjunction with IC31® or IC31® alone. See Table 2.

For each cohort, dosing will start with a sentinel group consisting of one subject from each treatment arm, included in the cohort. After the assessments on Day 8, the Safety Review Committee (SRC) will meet and review the safety data from the sentinel group and recommend whether or not the remaining subjects of a cohort should be dosed.

In order to progress to the next cohort, the SRC with input from the Investigators contributing subjects will meet to review safety data up to Day 36 from Cohort 1. Following this review subjects may be dosed in Cohort 2 assuming the SRC has identified no safety concerns. Similarly, subjects may be dosed in Cohort 3 after review of safety data up to and including Day 36 from subjects in Cohort 2.

Trial Flow Chart

Table 1 Flow chart

	Screening	1st			2nd			3rd				Follow- up
Visit Number	**-[6] (SV)**	**1[6] (SV)**	**2[6] (SV)**	**3[6] (SV)**	**4[6] (SV)**	**- (TC)**	**5[6] (SV)**	**6 (SV)**	**- (TC)**	**7[6] (SV)**	**8[6] (SV)**	**9[6, 9] (SV)**
Study Day	**-28 to -1**	**1**	**2**	**8**	**29**	**30**	**36**	**57**	**58**	**64**	**85**	**225**
Visit Windows	**±2 days**			**±1 day of Day 8**	**28 (±7 days) days after Visit 1**		**7 (±1 day) days after Visit 4**	**28 (±7 days) days after Visit 4**		**7 (±1 day) after Visit 6**	**28 (±1 day) after Visit 6**	**24 (±4 weeks) weeks after Visit 6**
Procedure												
Informed consent	X											
Review eligibility	X	X			X			X				
Randomisation	X											
Vaccination		X			X			X				
Phone call						X			X			X[5]
HBsAg, HBsAb	X	X			X			X			X	X
HBV DNA	X											X
Vital signs	X	X	X	X	X		X	X		X	X	X
Medical history	X											
Dispense Diary		X[2]			X[2]			X[2]				
Injection Site Tolerability		X[1]	X	X	X[1]	X	X	X[1]	X	X		
Pregnancy test[4]	X	X[3]			X[3]			X[3]			X	
Safety lab tests	X			X	X[3]		X	X[3]		X	X	X
Physical examination[5]	X	X	X	X	X		X	X		X	X	X
Fibroscan	X											
Alcohol, drugs of abuse, HIV, HDV and HCV serology	X											
Concomitant medication	X	X	X		X			X			X	
Blood for PBMC[7]	X	X[3]		X	X[3]		X	X[3]		X	X	X
12-lead ECG	X											X
Documentation of AEs	X	X	X	X	X	X	X	X	X	X	X	X[8]

AE: adverse event; CMI: cell-mediated immunity; DNA: deoxyribonucleic acid; ECG: electrocardiogram HBsAg/Ab: Hepatitis B surface Antigen/Antibody; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Hepatitis D virus; HIV: Human Immunodeficiency Virus; SV: Site Visit; TC: Telephone Call

[1] On the days of the vaccination, injection site tolerability will be assessed by the Investigator up to a minimum of 4 hours after the first injection and approximately 24 hours and 7 days after the first injection. For subsequent injections, injection site tolerability will be assessed by the Investigator up to 2 hours on the day of injection by the study site. Further assessment of injection site tolerability will be recorded using diary cards from 2 hours to 7 days after injection. Data from the diary cards will be transcribed into the appropriate eCRF.
[2.] The injection site diary is given to subjects after the 1st, 4th and 6th visit, but can only be reviewed post drug, i.e. at the next sequential visit.

[3] Prior to injection of IMP.
[4] Women of childbearing potential only. Serum pregnancy test will be performed at screening; a urine pregnancy test will be performed at other scheduled time points.
[5] A full physical examination will be conducted at screening and a brief physical examination will be performed at other time points indicated and will include examination of general appearance, injection site, respiratory and cardiovascular systems and the abdomen, particularly the upper right quadrant.
[6] Visit intervals are as follows:

- screening and randomisation: subjects must be screened -1 to 28 days (±2 days) and can be randomised to treatment up to 3 days prior to the first injection.
- first dose: Visits 1 and 2 must be done on Days 1 and 2, respectively; Visit 3 may be done within ± 1 day of Day 8.
- second dose: Visit 4 may be done 28 days (± 7 days) after Visit 1; subjects must be contacted the day after Visit 4; Visits 5 should be done 7 (± 1 day) days after Visit 4.
- third dose: Visit 6 may be done 28 days (± 7 days) after Visit 4; subjects must be contacted the day after Visit 6; Visits 7 and 8 may be done 7 (± 1 day) and 28 (±1 day) days after Visit 6.
- follow-up: Visit 9 must be done at 24 (± 28 days) weeks after the last dose (Visit 6).

[7] PBMC samples for CMI; in consenting subjects HLA typing and other genomic analyses may also be performed.
[8] Only SAEs and AESIs need to be documented during Follow-up (Visit 9).
[9] Subjects will be contacted at approximately 4 week intervals during the follow-up phase.

6.1 Sample Size Considerations

The study is designed to provide descriptive statistics of preliminary safety and immunogenicity assessments only, and thus no formal sample size calculation has been performed. It is planned to randomise 10 subjects into each of the six treatment arms, which is considered an appropriate study size at this phase of development of Vaccine FP-02.2.

6.2 Randomisation

Subjects will be randomly assigned to blinded treatment groups by the Interactive Response Technology (IRT) cohorts as described in Table 2. The first 15 subjects, forming cohort 1, will be randomised in a 2:1 ratio to either FP-0.2 low dose or placebo. The 30 subjects in cohort 2 will be randomised in a 2:2:1:1 ratio to FP-0.2 low dose + IC31® adjuvant, FP-0.2 high dose, Placebo or IC31® adjuvant only. Finally, the final 15 subjects in cohort 3 will be randomised in a 2:1 ratio to either FP-0.2 high dose + IC31® adjuvant or IC31® adjuvant only respectively.

Following completion of the Screening activities, subjects who meet the all the inclusion and none of the exclusion criteria will be registered by the IRT.

The first subjects in each treatment arm of a cohort (i.e. active alone, active +IC31®, placebo and IC31® alone, as applicable) will form the sentinel group. Where possible, all sentinel subjects per treatment will be dosed at the same clinical site. Subsequently subjects in each cohort will be randomised to the applicable active or control treatment, to meet the required number of subjects to be dosed in each arm.

Table 2: Study Cohorts and Treatment Arms

Cohort	Treatment arm	Planned number of subjects
1	Placebo	5
	FP-0.2 Low dose	10
2	Placebo	5
	IC31® adjuvant only	5
	FP-0.2 Low dose + IC31® adjuvant	10
	FP-0.2 High dose	10
3	IC31® adjuvant only	5
	FP-0.2 High dose + IC31® adjuvant	10

Subjects in Cohort 1 were randomised according to a randomisation list prepared by Hammersmith Medical Research, and subjects in Cohort 2 and 3 will be randomised according to a randomisation list prepared by Parexel, following the transition of the study to PRA.

7.0 Study Variables and Covariates

7.1 Primary Variables

- Solicited adverse events (AEs) related to injection site tolerability during the week following each vaccine administration.
- Unsolicited AEs through day 85
- Serious adverse events (SAEs) and AEs of special interest (AESIs) through 6 months after last vaccine dose
- Vital signs
- ECGs
- Safety laboratory assessments including laboratory assessment of liver inflammation and function

7.2 Secondary Variables

FP-02.2-specific T cell immunity (measured by the number of cells producing interferon gamma (IFN-γ) in response to exposure to 9 individual peptides. Further details are given in section 12.7.1.

8.0 Study Time point Definitions

8.1 Baseline

Unless specified otherwise, baseline will be defined as the latest assessment taken prior to the first dose of investigational product.

8.2 Relative Day

Relative day will be calculated as the date of assessment or event minus the date of IP plus 1 (eg, the day of first dose will be Day 1). For days prior to the first dose of IP (the day prior to first dose will be Day -1), relative day will be calculated as the current date minus the date of first dose of IP.

8.3 Study Visit Intervals

As per Table 1, Visit intervals are as follows:

- Screening and randomisation: subjects must be screened -1 to 28 days (±2 days) and can be randomised to treatment up to 3 days prior to the first injection.
- First dose: Visits 1 and 2 must be done on Days 1 and 2, respectively; Visit 3 may be done within ± 1 day of Day 8.
- Second dose: Visit 4 may be done 28 days (± 7 days) after Visit 1; subjects must be contacted the day after Visit 4; Visits 5 should be done 7 (± 1 day) days after Visit 4.
- Third dose: Visit 6 may be done 28 days (± 7 days) after Visit 4; subjects must be contacted the day after Visit 6; Visits 7 and 8 may be done 7 (± 1 day) and 28 (±1 day) days after Visit 6.
- Follow-up: Visit 9 must be done at 24 (± 28 days) weeks after the last dose (Visit 6).

The scheduled assessments may shift in instances where a visit window is used; subsequent visit dates should be recalculated from the date of the new visit. If a second dose visit is missed, the dose can be given 6 weeks after the first dose and noted as out of window. If the dose is later than 6 weeks, the second dose visit can be skipped and given at Visit 3 at 8 weeks as per schedule to avoid a delay in the schedule. Subjects receiving fewer than 3 doses during the study will be excluded from the Immunogenicity Analysis Set defined below in Section 9.4

Data will be summarised according to the scheduled visit that the data was recorded under in the eCRF. Data from unscheduled or repeated visits will not be included in the summary tables except in derivation of baseline values, but will be listed. If an assessment is repeated due to a damaged sample leading to unusable data in the original instance, the correct sample as identified by medical review will be mapped to the scheduled visit.

Where this SAP refers to summaries ‘by visit’ or ‘by assessment time point’ etc., this is taken to be visits and assessments as per protocol version 6. Under previous versions of the protocol, additional visits were in place, giving a different structure.

For subjects that consented to earlier protocol versions and attended additional visits to version 6 as per the protocol they consented to, the results from these assessments will not contribute to summaries by visit. These data will be included in individual subject listings only.

8.4 Study Visit Labelling

Visits will be labelled in table summaries (according to the schedule outlined in Table 1) as follows:

- "Screening"
- "Baseline"
- "Visit X, Day X (Pre/Post-Dose X)" for all scheduled visits, apart from screening and baseline.
- "Day X (TC)" For post-treatment calls relating to injection site tolerability.
- "Last visit" Defined as a subject's last visit in the study prior to termination or completion.

Listings will use the same visit labels and will also include "Unscheduled" as applicable.

Note that in the summary tables 'Baseline' will be the value derived as described in Section 8.1, which will usually be the Visit 1, Day 1 assessment, but may also be a screening or unscheduled assessment.

9.0 Analysis Sets

Membership of analysis sets will be determined at a blinded data review meeting convened by Altimmune conducted between database freeze and database lock.

9.1 Randomised Set

The Randomised Set consists of all subjects for whom a randomisation number has been assigned.

9.2 Safety Analysis Set

The Safety Analysis Set will contain all subjects who were randomised and received at least 1 injection of Vaccine FP-02.2, Vaccine FP-02.2/IC31®, placebo or IC31®. The Safety Analysis Set will be used for all safety analyses and will be analysed according to the treatment received.

9.3 Full Analysis Set

The Full Analysis Set comprises all members of the Safety Analysis Set with at least one complete post-vaccination immunogenicity result.

9.4 Immunogenicity Analysis Set

The Immunogenicity Analysis Set comprises all members of the Full Analysis Set with immunogenicity assessments at screening followed by days 1, 8, 29, 36, 57, 64 and 85, a full set of 3 doses of investigational product and with no important protocol deviations adjudicated as relevant by the medical team. Subjects with missing day 1 peripheral blood mononuclear cells (PBMC) may be included if screening PBMC data are available to calculate a baseline. Section 12.2 gives more information about the classification of important protocol deviations.

10.0 Interim Analyses

10.1 Safety Review Committee meetings

10.1.1 Continued Recruitment to a Cohort

After the assessments on Day 8, the SRC will meet and review the safety data from the sentinel group and recommend whether or not the remaining subjects of a cohort should be dosed. Any principal investigator with subjects in the sentinel group will provide input to the SRC meeting. The SRC will use listings from the clinical database at the appropriate time point for cohort recruitment decisions rather than outputs programmed using SAS.

10.1.2 Dose Escalation

In order to progress to the next cohort, the SRC with input from the Investigators contributing subjects will meet to review safety data up to Day 36 from Cohort 1. Following this review subjects may be dosed in Cohort 2 assuming the SRC has identified no safety concerns. Similarly, subjects may be dosed in Cohort 3 after review of safety data up to and including Day 36 from subjects in Cohort 2.

If safety and tolerability data are not acceptable the SRC may recommend lowering the dose of FP-02.2 or omitting the use of IC31®.

All data used to support dose escalation will be quality checked as per the data management plan. Dose decisions between cohorts will be documented. The SRC will use listings from the clinical database at the appropriate time point for dose escalation decisions rather than outputs programmed using SAS.

10.2 Primary and Follow-up Analyses

After all participants in cohort 3 have completed Day 85, the primary analysis of the safety data collected up to Day 85, immunogenicity (except HLA genotyping) and virology data will be performed. A secondary follow-up analysis of all immunology and safety data, including those collected between Day 86 and Day 225 for all cohorts will be conducted. The Investigators, all site staff, the subjects and trial monitors will remain blinded between the two analyses. Staff at PRA and Altimmune will unblind at the primary analysis at Day 85 of the final participant in cohort 3.

For the primary analysis, the data will be cut at day 85 for each individual subject regardless of their current progress in the study. Adverse events and concomitant medications occurring after day 85 will not be included in the outputs for the primary analysis.

The information from the primary analysis is required to inform the design of the next clinical study and confirm the formulation and dose to use.

This SAP describes the analyses that will be done at both of these time points. The same tables, figures and listings listed in Appendix 1 will be produced at both time points.

11.0 Data Review

11.1 Data Handling and Transfer

Data handling and transfer will be discussed in greater detail in the PRA Data Management Plan.

11.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Data issues identified during programming in preparation for dry runs will be raised to Data Management. The post-freeze TFL run on the frozen database will be discussed with Altimmune in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA statistician and Altimmune must approve database lock.

11.3 Blinded Data Review Meeting

A Blinded Data Review meeting will be convened by Altimmune after the database has been frozen but prior to database lock and before the study is unblinded.

The terms of reference of the Blinded Data Review Meeting shall include but not be limited to:

- the determination of whether important protocol deviations are relevant to the interpretation of the immunogenicity and virology data
- the allocation of subjects to analysis sets

- a review of missing data and of outliers
- a review of the distribution of the efficacy variables, considering any implications for the proposed method of statistical analysis
- the finalisation of the SAP

The Blinded Data Review Report will include the final categorisations of important and non-important protocol deviations, lists of the members of the various analysis sets and the rationale for any changes to the SAP.

The Blinded Data Review Report will be finalised before the blind will be broken. Formal records shall be kept of when the SAP was finalised as well as when the blind was subsequently broken.

12.0 Statistical Methods

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

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. Percentages will not be displayed for zero counts.

Continuous variables will be summarised using the number of observations (n), mean, standard deviation (SD), median, quartiles, minimum and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data, the median, quartiles and mean to a further decimal place and the SD to two additional decimal places. The maximum presentation of decimal places will be to 4 decimal places.

No formal hypothesis testing will be performed for this study. All endpoints are considered as exploratory and will be summarised descriptively. However, standard errors and 95% confidence intervals (CIs) will be displayed for change from baseline for specified immunogenicity and virology endpoints.

No pooling of centres, stratification or analysis by subgroups will be performed during this study.

12.1 Subject Disposition

The number of subjects included in each subject set (i.e., Randomised Set, Safety Analysis Set, Full Analysis Set and Immunogenicity Analysis Set) will be summarised by treatment group.

The number and percentage of subjects who prematurely discontinued during the study will be presented by treatment group for Days 1-85 for the primary analysis, and for Days 86-225 in addition for the follow-up analysis. Reasons for premature discontinuation as recorded on the termination page of the eCRF will be summarised (number and percentage) for each treatment group. All subjects who prematurely discontinued will be listed by discontinuation reason for the Randomised Set. In addition, each individual subject's membership of each analysis set will be listed.

12.2 Protocol Deviations

Per PRA processes, important protocol deviations data will be entered into our Clinical Trials Management System (CTMS). The study team and Altimmune will conduct on-going reviews of the deviation data from CTMS and the resulting set of evaluable subjects throughout the study, adjusting the 'important' deviation criteria as seems appropriate. The evaluable subjects set (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 subjects with important protocol deviations by treatment group will be produced for the Randomised Set.

All protocol deviation data will be listed for the Randomised Set.

12.3 Treatments

12.3.1 Extent of Investigational Product Exposure

The total number of injections administered will be presented descriptively, both as continuous data and using the following categories on the Safety Analysis Set:

- Number of injections administered [1,2,3]

In addition, the number of subjects with 1, 2 or 3 injections not fully administered will be summarised. The reasons for any dosing interruptions/incomplete administrations will be included in the data listing.

As investigational product is administered via injection by the site, treatment compliance will not be calculated.

12.3.2 Concomitant Medications

Version WHO DDE B2 Mar_2017 of the WHO Drug Dictionary will be used to classify prior and concomitant medications by preferred term.

Prior medication is defined as any medication with the start date and time prior to the date and time of the first dose of investigational product. All prior medication will be recorded on the appropriate eCRF page.

Concomitant medication refers to all treatments taken at any time from the date and time of the first dose of investigational product through 30 days after the last dose of investigational product. It is possible for a medication to be considered both prior and concomitant. For instance, a medication that begins prior to the first does of investigational product and continues during the study.

Concomitant medications will be coded to Anatomical Therapeutic Chemical (ATC) group (level 2) and preferred term. For summaries, multiple medication usage by a subject in the same ATC level or preferred term category will be counted only once.

For the Day 85 analysis the following summary will be presented for the Safety Analysis Set by treatment group:

- All concomitant medications by preferred term.

For the Day 225 analysis the following summaries will be presented for the Safety Analysis Set by treatment group:

- Concomitant medications that were started prior to first dose of investigational product and continued after the first dose of investigational product (i.e., medications that are considered both prior and concomitant) by ATC level 2 and preferred term
- Concomitant medications that were started on or after the first dose of investigational product by ATC level 2 and preferred term.

All prior and concomitant medication for individual subjects will be listed.

12.4 Demographic and Baseline Characteristics

12.4.1 Assessments at Screening only

12.4.1.1 Screening Information

Screening information for each subject screened will be listed, including the dates of screening and enrolment and whether study entry criteria were met.

As per protocol, if a subject is screened and not dosed within the required time-window, that subject may be re-screened. In the event of a subject being re-screened, they will be assigned a new subject number.

Whether or not a subject is a re-screen, and their previously used subject number under their initial screen will be included in screening listings.

12.4.1.2 Fibroscan

A Fibroscan will be performed at screening only to assess for evidence of Liver cirrhosis (Liver cirrhosis is defined as a Fibroscan measurement of >11.5 KPa). Individual subject results will be listed for all subjects screened.

12.4.1.3 Alcohol and Drug Screen

A urine dipstick test for drug abuse and alcohol screen will be performed at screening only. Individual subject results will be listed for all subjects screened.

12.4.1.4 Test for HIV, HDV and HCV

A test for the presence of Human Immunodeficiency Virus (HIV), Hepatitis D Virus (HDV) and Hepatitis C Virus (HCV) will be performed at screening only. Individual subject results will be listed for all subjects screened.

12.4.2 Demographics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group for the Safety Analysis Set. Demographic tables will be repeated for the Full Analysis Set and Immunogenicity Analysis Set.

Subject demographics including age, sex, race, country (at the time of the study), ethnicity, weight, height, and body mass index (BMI) will be summarised for the Safety Analysis Set. Continuous variables will be summarised by descriptive statistics including number of subjects, mean, standard deviation, median, quartiles, minimum, and maximum. Categorical variables will be summarised by the number of subjects in each category and the percentage of subjects out of the total in the respective analysis set.

Height and weight at screening will be used to calculate BMI using the formula below:

$$BMI = Weight\ [kg]/\ Height\ [m]^2.$$

A listing will be created to show all the demographics and baseline characteristics for each subject in the Randomised Set.

Medical history will be presented by system organ class (SOC) and preferred term for the Safety Analysis Set and listed for individual subjects in the Randomised Set. Medical history will be coded using MedDRA version 20.0 preferred terms.

12.5 Efficacy Analyses

No efficacy analyses will be performed for this study.

12.6 Safety Analyses

All safety analyses will be performed using the Safety Analysis Set unless specified otherwise.

The summary tables by visit will show assessments up to and including Day 85 for the main analysis up to and including the Day 225 follow-up assessments for the follow-up analysis. In the summaries by visit, data will be summarised by scheduled visit as collected in the eCRF. In addition, a “Final visit” will be used for summaries by time point. This visit will consist of the final on-treatment assessment, either the last visit in the study, or the last visit before termination. Unscheduled visits will be displayed in the individual subject data listings only.

12.6.1 Adverse Events

Adverse events will be coded using Version 20.0 or newer of MedDRA.

Treatment-emergent adverse events (TEAEs) are those which first occur or increase in severity or relationship probability to investigational product after the first dose of investigational product through 30 days after last dose of investigational product. Note that SAEs and AESIs are collected through 6 months after last dose of investigational product; therefore, all SAEs and AESIs will be summarized, not just treatment-emergent events.

All AEs which change in severity or relationship to investigational product are assigned a new start date and captured as a new record.

If more than 1 AE with the same preferred term is reported before the date of the dose of investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the study under the preferred term.

An overall summary of TEAEs, including the number and percentage of subjects who experience, and absolute count of treatment-emergent events for:

- Any TEAE
- Any TEAE by maximum severity
- Any TEAE considered possibly related to investigational product (defined as CRF response of “Reasonable Possibility”)
- Any TEAE considered possibly related to investigational product by maximum severity
- Any SAEs
- Any SAEs considered possibly related to investigational product
- Any AEs with outcome of death
- Any AESIs (Hepatic flares and autoimmune conditions)
- Any TEAE leading to discontinuation of investigational product

The number and percentage of subjects reporting TEAEs, SAEs, or AESIs will be tabulated in the following ways by treatment group.

- By SOC and preferred term (including absolute count of events).
- By SOC, preferred term and maximum severity.
- By SOC and preferred term for TEAEs possibly related to investigational product in the opinion of the investigator (including absolute count of events).
- By SOC and preferred term for SAEs (including absolute count of events).
- By SOC and preferred term for possibly related SAEs (including absolute count of events).
- By SOC and preferred term for TEAEs leading to discontinuation of investigational product (including absolute count of events).
- By SOC and preferred term for AEs with fatal outcome (including absolute count of events).
- By SOC and preferred term for AESIs (including absolute count of events).

Adverse events of special interest will be identified from the existing study AEs by medical review prior to database lock.

All AEs will be listed by subject. Separate listings will be provided for SAEs, AEs related to investigational product, AEs leading to discontinuation of investigational product, AEs with fatal outcome and suspected unexpected SAEs.

12.6.2 Injection Site Reactions

12.6.2.1 Investigator Assessment

On the days of the vaccination, injection site tolerability will be assessed by the Investigator up to a minimum of 4 hours after the first injection and approximately 24 hours and 7 days after the first injection. For subsequent injections, injection site tolerability will be assessed by the Investigator up to 2 hours on the day of injection by the study site.

Investigator assessed injection site reactions will be graded according to Table 3 below:

Table 3: Grading for investigator assessed injection site tolerability

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Erythema/redness	0-2.4 cm	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative
Swelling	0-2.4 cm	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
Induration/hardening	0-2.4 cm	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
Pain/tenderness (Pain on pressure)	Absent	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalisation
Pain (spontaneous; pain without pressure)	Absent	Does not interfere with activity	Repeated use of non-opioid pain reliever >24 hours or interferes with activity	Any use of opioid pain reliever or prevents daily activity	Emergency room visit or hospitalisation
Pruritis/itching	Absent	Mild	Moderate	Severe	Not applicable
Wheal(s)	0-2.4 cm	2.5-5 cm	5.1-10 cm	> 10cm	Not applicable
Burning sensation	Absent	Mild	Moderate	Severe	Not applicable

For the Day 85 analysis the following investigator assessed summaries will be presented for the Safety Analysis Set by treatment group:

- The number and percentage of subjects with any injection site reactions by type, and any severe reactions by type
- The number and percentage of subjects with injection site reactions will be summarised by maximum severity at any time point and for each study time point.

For the Day 225 analysis the following investigator assessed summary will be presented for the Safety Analysis Set by treatment group:

- The number and percentage of subjects with injection site reactions by severity and time point.

Severe injection site reactions are those assigned a grade 3 or 4 from the above table.

Individual injection site reaction examination results will be listed. In addition, any injection site reactions that are considered by the investigator to be adverse will be recorded as an AE in the eCRF. Any injection site reaction that meets the criteria of serious will be reported as an SAE.

12.6.2.2 Patient-reported Diary Cards

Additionally, a diary card will be provided to the subjects to record injection site reactions from 4 hours (first injection) or 2 hours (subsequent injections) post injection to 7 days post injection. Data from the diary card will be transcribed into the appropriate eCRF page as below:

Table 4: Grading for subject diary-assessed injection site tolerability

Size of the reaction (please measure the longest dimension or longest side):

Small: 2.4 cm or smaller patch of skin

Medium: 2.5 - 5 cm patch of skin

Large: 5.1 - 10 cm patch of skin

Very large: larger than 10 cm patch of skin

Discomfort of the reaction:

Mild it didn't stop me doing my normal daily activities

Moderate it interfered with my normal daily activities, but it didn't stop me doing them

Very bad: it stopped me doing my normal daily activities

Reaction	Present?	If yes, how bad was the reaction?			
		Grade 0	Grade 1	Grade 2	Grade 3
Redness	Yes/No	Small	Medium	Large	Very large
Swelling	Yes/No	Small	Medium and mild	Large or moderate	Very large or very bad
Hardening	Yes/No	Small	Medium and mild	Large or moderate	Very large or very bad
Pain on touch	Yes/No	Absent	Mild	Moderate	Very bad
Pain without touch	Yes/No	Absent	Mild	Moderate	Very bad
Itching	Yes/No	Absent	Mild	Moderate	Very bad
Burning	Yes/No	Absent	Mild	Moderate	Very bad
Lump	Yes/No	Small	Medium	Large	Very large

Severe injection site reactions from the diary card data are those reported as either 'Very large' in the case of size-based reactions (redness, swelling etc.) or 'Very bad' in terms of pain-based reactions (pain on touch, itching etc.).

For the Day 85 analysis the following diary assessed summary will be presented for the Safety Analysis Set by treatment group:

- The number and percentage of subjects with any injection site reactions recorded on the diary card by type, and any severe reactions by type, and most recent injection number.

For the Day 225 analysis the following diary assessed summary will be presented for the Safety Analysis Set by treatment group:

- The number and percentage of subjects with injection site reactions by severity and time point.

The categories on the table are chosen to follow closely the choices in the investigator assessment and will be displayed as follows:

Table 5: Diary card to CSR table mapping of injection site reaction terms

Diary Card	Table
Redness	Erythema/redness
Swelling	Swelling
Hardening	Induration/hardening
Pain on touch	Pain/ tenderness (Pain on pressure)
Pain without touch	Pain (spontaneous / pain without pressure
Itching	Pruritis/ itching
Burning	Burning sensation
Lump	Lump

Subject assessed individual injection site reaction examination results will be listed.

12.6.3 Laboratory Data

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point will be presented by treatment group for the following clinical laboratory variables in Table 6.

Table 6: Clinical laboratory safety test analytes to be presented in summary tables

Panel	Parameters	
Haematology	White blood cells (leukocytes) Red blood cells (erythrocytes) Haemoglobin Haematocrit Mean corpuscular volume Mean corpuscular haemoglobin Mean corpuscular haemoglobin concentration	Neutrophils [a] Lymphocytes [a] Monocytes [a] Eosinophils [a] Basophils [a] Platelets
Serum biochemistry	Sodium Potassium Urea Creatinine Albumin Calcium Phosphate Glucose Total protein C-reactive protein	Aspartate transaminase (AST) Alkaline phosphatase (ALP)[b] Alanine aminotransferase (ALT) Creatine kinase [c] Gamma-glutamyl transferase (gamma glutamyl transpeptidase) (GGT) Lactate dehydrogenase Total and direct bilirubin
Coagulation	International normalised ratio of prothrombin time (INR)	
Urinalysis	Protein Bilirubin Urobilinogen Ketones Glucose	Leukocyte esterase Red blood cells pH Nitrites Specific gravity

[a] Given as both absolute count and as a percentage of total leukocyte count. In cases where only absolute counts or percentages of these leukocyte subtypes are recorded, the missing percentage or absolute count will be derived.

[b] Alkaline phosphatase iso-enzymes (liver-specific and bile duct specific) will be measured if original alkaline phosphatase test result is above the upper limit of normal.

[c] Creatine kinase MB or Troponin T will be measured where clinically indicated.

In addition, if protein and/or blood is/are detected during urinalysis then a microscopic examination will be conducted consisting of leukocytes, erythrocytes, casts and bacteria.

Laboratory results will be categorised as low, normal or high in relation to the local laboratory reference range, and shift tables from baseline to each time point will be presented.

Clinical laboratory test values are assessed for clinical significance by the investigator. The number and percentage of subjects with post-baseline clinically significant values will be tabulated by treatment group. The percentages will be calculated relative to the number of subjects with at least 1 post-baseline assessment.

All laboratory results will be listed, including microscopic urinalysis results if collected.

12.6.4 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressure, pulse rate and temperature) and their changes from baseline at each post-baseline visit and at the end of study will be presented by treatment group.

Individual vital signs results will be listed.

12.6.5 Electrocardiogram (ECG)

Shifts from baseline to follow-up in the reader's interpretation of each ECG result ('Normal', 'Abnormal Clinically Significant' or 'Abnormal not clinically significant') will be presented by treatment group. In addition, the reader's interpretation will be listed for each individual subject.

12.6.6 Physical Examination

A complete (or abbreviated) physical examination will be performed at the time points described in Table 1. Abnormalities identified at the screening visit will be documented in the subject's source documents and on the medical history eCRF. Changes after the screening visit that are considered clinically significant by the investigator will be captured as AEs on the AE eCRF page. As such, any abnormalities will be included in the medical history or adverse events tables and listings. A listing indicating the date and time of physical examination will be produced.

12.6.7 Pregnancy Testing

A serum pregnancy test will be performed in all women of childbearing potential at the Screening Visit. Urine pregnancy tests will be performed during the remainder of the study at the times indicated in the flow chart.

Individual pregnancy test results will be listed only.

12.7 Immunogenicity Analysis

The immunogenicity analyses will be performed first in the Immunogenicity Analysis Set and repeated in the Full Analysis Set if any subjects were excluded from the Immunogenicity Analysis Set.

12.7.1 Immunogenicity Variables

The primary immunological outcome variable is the number of PBMC producing IFN-γ (ELISpot score) in response to exposure to the following 9 individual peptides (P877, P151, P113, P856(K), P753(K), P376, P797(K), P277(K) and P1266(K)) or a mix of the 9 peptides (LPMIX9), measured using 2 different assays: (1) an ex-vivo IFNγ ELISpot and (2) a cultured IFNγ ELISpot.

ELISpot scores will be constructed from the raw IFN-g ELISpot counts. Description of the algorithm used to calculate ELISpot score are presented for information only in Appendix 2.

12.7.1.1 Immune Response

Descriptive statistics (mean, SD, median, quartiles, minimum and maximum) will be generated by treatment group and time point for the following ELISpot score variables:

- ELISpot scores and change from Baseline for individual peptides and LPMIX9
- Sum ELISpot scores and change from baseline across the 9 individual long peptides

Sum ELISpot score is defined as the sum of the 9 ELISPOT scores from the 9 individual peptides.

In addition, standard errors and 95% CIs derived from a one-sample t-test will be presented for change from baseline.

Baseline is defined as the mean of the ELISpot scores prior to the first injection.

In addition, line plots of the mean (± SE) ELISPOT scores over time will be presented by treatment group for each individual peptide, LPMIX9 and the sum score of the 9 individual peptides for the cultured assay over the Immunogenicity Analysis Set. If the Full Analysis differs from the Immunogenicity Analysis Set, then the figures will be repeated for the Full Analysis Set.

Similarly, line plots of each individual patient's ELISPOT score over time will be presented, grouped by treatment group for each individual peptide, LPMIX9 and the sum score of the 9 individual peptides for the cultured assay over the Immunogenicity Analysis Set. If the Full Analysis differs from the Immunogenicity Analysis Set then the figures will be repeated for the Full Analysis Set.

12.7.2 Exploratory Immunogenicity Analyses

PRA Health Sciences and/or Altimmune may conduct exploratory analyses of the immunogenicity data.

Any exploratory analyses presented in the Clinical Study Report must be clearly described as 'exploratory'.

Descriptive statistics for observed values at a nominal visit as well as change from baseline values may be presented by cohort, country, and/or gender.

12.8 Virology Analysis

Blood samples will be collected for the assessment of virological parameters at the times indicated in Table 1.

Descriptive statistics for Virology parameters values:

- Quantitative Hepatitis B surface antigen (HBsAg) [presented in log10]
- Hepatitis B virus (HBV) DNA

and changes from baseline (in SI units) at each assessment time point will be presented by treatment group and visit for all subjects in the Immunogenicity Analysis Set and repeated for the Full Analysis Set if different.

Standard errors and 95% CIs derived from a one-sample t-test will be presented for change from baseline for HBsAg.

In addition, a line plot of the change from baseline in log10 HBsAg at each timepoint will be presented by treatment group.

The antibody to hepatitis B surface antigen (HBsAb) will be summarised by 'seroconverted' or 'not seroconverted' by visit for the Immunogenicity Analysis Set and repeated over the Full Analysis set if different. Seroconversion corresponds to HBsAb > 10 mIU/mL.

Individual subject results for all virology parameters will be listed for the Full Analysis Set.

13.0 Allowances for the 'Rescue Study' Transition

13.1 Legacy Data

This study is a "rescue study," actively in conduct and recruiting subjects. The database that was originally used to collect patient data was Medrio, and was managed by Hammersmith Medicines Research Ltd (HMR), under a separate contract with Altimmune. The Medrio database collected patient data up to and including Version 5 (Amendment 4) of the protocol prior to the date of transition, November 30th 2016. The Medrio database contained information on 17 subjects (15 enrolled and 2 screen failures) in Cohort 1, at various stages of completion up until the date of transition given above. For more information please consult the data management plan.

PRA have designed the eCRF in compliance and accordance with Version 6 (Amendment 5) of the protocol dated 11-AUG-2016, upon which this SAP is based, and any future updates to Version 6 (Amendment 5).

Any previously collected data in Medrio that was not specifically required to be collected under previous protocol versions will not be collected by PRA, and will not be transcribed into the PRA database, but will

remain in the original database. These types of data include, free text fields, and ECG specific parameters. PRA will request from HMR SAS datasets of the historic legacy data to enable the creation of consolidated SDTM datasets for programming and analysis.

The data that were collected on previous eCRFs not maintained by PRA and not required by protocol, will be placed in a separate listing for each individual subject and will not contribute to any summary tables.

14.0 Allowances for Missing Data

Other than the parameters described in this section, no further imputation for missing data will be performed.

14.1 Immunogenicity

Any laboratory, immunogenicity or virology data that are below the limits of quantification will be imputed to one-half of the lower limit of quantification (LLOQ) for quantitative summaries and analyses.

14.2 Missing Date and Time Information for Prior or Concomitant Medications

14.2.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. 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.

14.2.1.1 Missing day, month and year

- The day, month and year of the date of the first dose of investigational product will be assigned to the missing fields.

14.2.1.2 Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, 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 the first dose of investigational product, then 01 January will be assigned to the missing fields.

14.2.1.3 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 the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, 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 the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

14.2.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is

before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

14.2.2.1 Missing day, month and year

- The day, month and year of the date of the last dose of investigational product will be assigned to the missing fields.

14.2.2.2 Missing day and month

- If the year of the incomplete stop date is the same as the year as of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the first dose of investigational product, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

14.2.2.3 Missing month only

- If the day and year of the incomplete stop date are the same as the day and year of the date of the last dose of investigational product, then the month of the date of the last dose of investigational product will be assigned to the missing month.
- If the day and year of the incomplete stop date are not the same as the day and year of the date of the last dose of investigational product, then December will be assigned to the missing month.

14.2.2.4 Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day.
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

14.2.3 Incomplete Start Time

If the start time is missing then if the start date (or imputed start date) is the same as the date of dose, then set to the time of dose. Otherwise, set missing start times to 00:00.

14.2.4 Incomplete Stop Time

If the stop time is missing then set it to 23:59.

14.3 Missing Date and Time Information for Adverse Events

For AEs, only incomplete (i.e., partially missing) start dates and times will be imputed.

14.3.1 Incomplete Start Date and time

Follow same rules as in section 14.2.1 and section 14.2.3.

14.4 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the dose of investigational product, then a severity of “Mild” will be assigned. If the severity is missing for an AE starting on or after the date of first dose of investigational product, then a severity of “Severe” will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

14.5 Missing Relationship Assessment for Adverse Events

If relationship to product is missing for an AE, then a relationship of “Possibly related” will be assigned. The imputed values for relationship assessment will be used for incidence summaries, while the actual values will be used in data listings.

15.0 Validation

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

Appendix 1 Tables, Figures, Listings, and Supportive SAS Output Appendices

List of Post-Text Tables, Figures, Listings, and Supportive SAS Output Appendices:			
Output	**Title 1**	**Title 2**	**Top Line**
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Table 14.1.1.2	Important Protocol Deviations	Randomised Set	
Table 14.1.2.1	Demographic Characteristics	Safety Analysis Set	X
Table 14.1.2.2	Demographic Characteristics	Full Analysis Set	
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Table 14.1.3	Medical History by System Organ Class and Preferred Term	Safety Analysis Set	
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Table 14.2.1.7	Sum ELISPOT Score results by Time point – Ex-vivo Assay	Full Analysis Set	
Table 14.2.1.8	Sum ELISPOT Score results by Time point – Cultured Assay	Full Analysis Set	X
Figure 14.2.1.9	Line Plot of Mean (±SE) ELISPOT Score against Time by Treatment Group and Peptide – Cultured Assay	Immunogenicity Analysis Set	
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Figure 14.2.1.11	Line Plot of Individual Subjects' ELISPOT Score against Time by Treatment Group and Peptide – Cultured Assay	Immunogenicity Analysis Set	
Figure 14.2.1.12	Line Plot of Individual Subjects' ELISPOT Score against Time by Treatment Group and Peptide – Cultured Assay	Full Analysis Set	
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Table 14.3.2.4	Serious Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set	
Table 14.3.2.5	Possibly Treatment-Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set	
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Table 14.3.3.2.3	Shift Summary of Biochemistry Results by Reference Range and Time Point	Safety Analysis Set	X
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Listing 16.2.7.3	Adverse Events Considered Possibly Related to Investigational Product	Safety Analysis Set	
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16.2.14			

Appendix 2 ELISpot Score Calculation

A single data point for each PBMC sample is obtained **within** the analytical laboratory following the process outlined in the table below.

Steps 1 – 4 are performed by the analytical laboratory conducting the ELISpot assays. Steps 5 – 8 are performed in a validated SAS program to generate the final data set for statistical analysis by PRA.

	Step #	Process
Generation of raw data and QC checks performed by Altimmune Analytical Laboratory	1	ELISpot (*ex vivo* or cultured) set up to test responses to 9 peptides and LPMIX9. Negative assay controls: no peptide background control. Positive assay controls: stimulation with PHA, a T cell mitogen. N = 3 replicates for each individual peptide, LPMIX9, PHA. N = 6 replicates for no peptide background control. Number of PBMC applied per well: 0.5 - 2 x 10^5 for ex vivo ELISpot, 0.5 – 1% harvested PBMC for cultured ELISpot.
	2	ELISpot raw data output: number of Spot Forming Cells per well (SFC per well)
	3	Quality control #1: visual inspection of wells, values from failed wells excluded and flagged in raw data.
	4	Quality control #2: positive control PHA threshold: entire sample excluded if PHA fails. PHA threshold for *ex vivo* ELISpot: mean PHA values > 1500 SFC/10^6 PBMC PHA threshold for cultured ELISpot: mean PHA values for single sample > [mean PHA values for subject's samples across all timepoints] – [2SD PHA values for subject's samples across all timepoints.
Data manipulation performed by Altimmune in SAS validated program	5	For ex vivo ELISpot, all ELISpot Spot Forming Cells (SFC) will be converted to Spot Forming Cells per million PBMC. (SFC per million PBMC = SFC per well / PBMC per well * 1000000). For cultured ELISpot, all ELISpot SFC will be converted to Spot Forming Cells per million input PBMC. (SFC per million input PBMC = SFC per well / % harvested PBMC applied to well * 100).
	6	For all peptides the mean SFC per million PBMC/input PBMC over the three replicate measurements (wells) will be calculated.
	7	For the negative controls the mean and standard deviation SFC per million PBMC over the six replicate measurements will be calculated.
	8	Ex vivo ELISPOT: for each peptide the ELISPOT score is obtained by:

		a. first calculating the excess over background
		
		excess over background = mean SFC per million PBMC (peptide) – mean SFC per million PBMC (negative control)
		
		b. then checking to see if the threshold has been reached:
		IF (excess over background) < maximum {25 and [2 x SD IFN-γ producing cells per million (negative control)]} THEN ELISPOT score = 0;
		ELSE
		ELISPOT score = excess over background.
		
		Cultured ELISPOT: for each peptide the ELISPOT score is obtained by:
		a. Applying assay positivity threshold: test antigen SFC/10^6 input PBMC reported if > 3SD background SFC/10^6 input PBMC.
		b. For test antigen responses reported as positive in a., calculate excess over background.
		= mean SFC per million input PBMC (peptide) – mean SFC per million input PBMC (negative control)