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NCT Number	NCT03371485
EudraCT Number	2016-002577-35
Sponsor Protocol Number	CRUKD/17/003
Official Title	A Cancer Research UK Phase I trial of AST-VAC2 (allogeneic dendritic cell vaccine) administered weekly via intradermal injection in patients with advanced non-small cell lung cancer.
Document, Version & Date	Reporting Analysis Plan Version 2.0, dated 09Mar2023

CANCER RESEARCH UK

Reporting Analysis Plan

Protocol Number: CRUKD/17/003

Protocol Name: AST-VAC2

EudraCT Number: 2016-002577-35

[redacted]

RAP Final Version: 2.0

Date: 09Mar2023

Replaces Version: N/A

Date: N/A

Name: [redacted] Date:

Title: Clinical Study Manager (Sponsor)

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Name: [redacted] Date:

Title: Medical Advisor (Sponsor)

Signature:

Name: [redacted] Date:

Title: Chief Investigator

Signature:

SUMMARY OF CHANGES TO PREVIOUS REPORTING ANALYSIS PLAN VERSION

This summary of changes is intended to highlight the important revisions that were made during the most recent update to the reporting analysis plan (RAP) to generate the current version.

This document has been written based on information contained in the study protocol and data management plan detailed in the table below.

Protocol version	DMP version	RAP version	Revised section of RAP	Summary of changes	Date updated
5.0	2.0	1.0	5.9, 6.1 & 6.2	Section 5.9 – note added about patients with data censored for survival, reference to CEA listing added, Table 14 updated to refer to 'Date of Death or Last Contact'. Section 6.1 – CEA listing added Section 6.2 – RAP tables 4, 5 & 6 numbering for CSR revised	12Dec2022
Final review prior to database lock					
Protocol version	DMP version	RAP version	Revised section of RAP	Summary of changes	Date updated

Protocol amendments may be applicable during the study. The RAP will be reviewed against the amendments and updated where necessary.

The summary of changes table above should record all changes to the RAP in light of protocol amendments however if no changes were required, this should be recorded also.

CONTRIBUTORS

Medical Writer: [redacted]

Clinical Data Manager: [redacted]

Clinical Database Programmer: [redacted]

Translational Scientist: [redacted]

Biomarker Development Scientist: [redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	AE(s)	adverse event(s)
B	BP	blood pressure
C	CDD	Centre for Drug Development
	CRUK	Cancer Research UK
	CSR	Clinical Study Report
	CT	computerised tomography
	CTCAE	Common Terminology Criteria for Adverse Events
D	DNA	deoxyribonucleic acid
	DMP	Data Management Plan
E	eCRF	eCRF
	EDC	electronic data capture
	[redacted]	[redacted]
	ELISPOT	enzyme-linked immunospot
F	FAP	Full Analysis Population
	[redacted]	[redacted]
G	GCP	Good Clinical Practice
H	HLA	human leucocyte antigen
	hTERT	human telomerase reverse transcriptase
I	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	IMP	investigational medicinal product
	irCR	immune-related complete response
	irPD	immune-related progressive disease
	irPR	immune-related partial response
	irRC	Immune-Related Response Criteria
	irSD	immune-related stable disease
	ISR(s)	injection site reaction(s)
M	MedDRA	Medical Dictionary for Regulatory Activities
	MRI	magnetic resonance imaging
N	NCI	National Cancer Institute
	NSCLC	non-small cell lung cancer
O	OS	overall survival
P	PBMC(s)	peripheral blood mononuclear cell(s)
	PD	pharmacodynamic
	PK	pharmacokinetic
R	RAP	Reporting Analysis Plan
	[redacted]	[redacted]
S	SAE(s)	serious adverse event(s)
	SFU	spot forming units
	SOP	Standard Operating Procedure
T	TEAE	treatment emergent adverse event
	[redacted]	[redacted]
	[redacted]	[redacted]
W	WHO	World Health Organisation

Table of Contents

1. INTRODUCTION

This document explains in detail the reporting analyses that will be carried out for Phase I trial of AST-VAC2 vaccine in patients with non-small cell lung cancer.

The analyses described in this RAP are based upon and supplement those described in the current study protocol.

To support reproducibility of the research, a clear and comprehensive account of pre-planned reporting (or statistical) analyses must be available. This RAP will establish the essential items to be considered for interim and/or final reporting requirements.

2. TRIAL OBJECTIVES

Primary objectives and endpoints

Primary objective	Endpoint
To assess the safety and tolerability of the target dose of AST-VAC2 given as six intradermal injections at Weeks 1, 2, 3, 4, 5 and 6 in patients with advanced non-small cell lung cancer (NSCLC).	Determining the frequency and causality of each adverse event to AST-VAC2 and grading severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02 or protocol specific grading system for injection site reactions (ISRs).

Secondary objectives and endpoints

Secondary objectives	Endpoint
To determine the immunogenicity (peripheral response) of AST-VAC2 in patients with advanced NSCLC.	Observation of the total number of patients showing durable peripheral immune response, defined as a change in one validated assay at two time points after at least two vaccinations. Immunological response will be measured in patient blood by human telomerase reverse transcriptase (hTERT) specific T cells as measured by enzyme-linked immunospot (ELISPOT) analysis at the following time points: • baseline, • vaccination weeks 3, 4 and 6, • 2 weeks post last vaccination and • 3, 6 and 12 months post first vaccination. Immunological change after vaccination is defined as 2.5 fold change over baseline (ratio baseline to post-treatment samples). Individual patient timepoints will be reported as spot forming units (SFU)/10^6 peripheral blood mononuclear cells (PBMCs). Sample will be considered reportable when spot count of peptide pool is greater than peptide pool specific cut-off (as defined in validation).
To document any tumour response(s) in patients receiving the AST-VAC2 vaccine.	Re-assessment of tumour size at end of vaccination visit with Magnetic Resonance Imaging (MRI) or Computerised Tomography (CT) using Immune-Related Response Criteria (irRC).
To determine the 2-year overall survival (OS) in patients receiving the AST-VAC2 vaccine.	Measurement of OS at 2 years post first vaccination.

Tertiary objectives and endpoints

Tertiary objective	Endpoint
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted] - [redacted] - [redacted] - [redacted]

3. TRIAL DESIGN

Table 1: Trial Design

A	Study design	This is a first in man, open label, multi-centre, Phase I trial to investigate the safety, immunogenicity and patient survival following administration of the AST-VAC2 vaccine. Only one target dose (1×10^7 cells) will be explored. A reduced dose/administration schedule may be considered if required, based on emerging safety data.
B	Patient group	Patients with advanced NSCLC.
C	Sample size	Approximately eight patients will be entered into this trial. The final number will depend on emerging safety data, the number of patient replacements required and vaccine availability.
D	Study intervention	Patients will receive six AST-VAC2 vaccinations, administered weekly over six weeks. They will attend an end of vaccination visit 30 days after their last AST-VAC2 vaccination, and attend follow-up visits up to 12 months after their first AST-VAC2 vaccination. After which, patients will be followed up for safety quarterly by telephone for five years (post first vaccination). Information on OS will be collected for up to 2 years after the first vaccination for all patients or until all patients have died, whichever event occurs first.
E	Study analysis	Safety evaluations will be conducted after the first patient has received AST-VAC2 and then again after the second and third patients have been treated. Once open recruitment has been initiated, safety review will be performed at regular intervals (as required). A safety review committee, consisting of all Investigators, representatives of the Sponsor and representatives of the drug company (observers only), will review emerging study data, with particular reference to ensuring that patients are able to complete the vaccination schedule without AST-VAC2 toxicity-related delays. See protocol Section 3.3.2. An interim analysis will be conducted once all patients administered AST-VAC2 have withdrawn, died or completed their 2-year follow-up visit for survival. Once this condition is met, a data cut-off will be established. All patient visits occurring on or before this date will be analysed and summarised in the clinical study report, including safety data to date and assessment of OS at 2 years. Any data collected after this date will be summarised in a supplemental report for the final analysis to satisfy the safety reporting requirements for AST-VAC2 as an advanced therapy investigational medicinal product (ATIMP). The final analysis will be conducted after one of the following conditions is met: • The trial is terminated early, e.g. due to toxicity; • The End of Trial has been reached (when all patients have either withdrawn from the trial or died, or the last patient

		has completed their final follow-up visit [whichever is the latter]). Once one of these conditions is met, a data cut-off will be established. All patient visits occurring on or before this date will be analysed and summarised in a supplemental report. Due to the small sample size, there are no formal statistical analyses planned for this trial.
F	Dose escalation schedule	There is no dose escalation schedule for this study, only one dose will be explored. Stopping rule criteria can be found in protocol Section 3.3.3.

For full details of the trial design, background and rationale for the study, please refer to the current study protocol.

4. PATIENT POPULATION AND ENDPOINTS

Patients must fulfil all the inclusion/exclusion criteria to be eligible for entry to the trial. Refer to the study protocol for the complete list of inclusion and exclusion criteria.

4.1 Patient Populations

The analysis sets are defined as follows:

Full Analysis Population (FAP):	All patients who enrolled onto the main trial. Patients who are enrolled in error onto the main trial (due to ineligibility/administrative error), prior to receiving any AST-VAC2 vaccinations, will be excluded from the FAP.
Safety Population:	All enrolled patients who received at least one AST-VAC2 vaccination. This population will also be used for overall survival at 2 years post first AST-VAC2 vaccination. Patients are evaluable for survival regardless of whether they go on to receive another anti-cancer therapy.
HLA Population:	All patients who had a sample taken for HLA analysis.
[redacted]	[redacted]
Secondary Immunogenicity Endpoint Population:	All eligible patients who received at least three AST-VAC2 vaccinations and have had a baseline blood sample and at least two post-vaccination blood samples taken.
[redacted]	[redacted]
Response Population:	All eligible patients who have received at least one AST-VAC2 vaccination and have had a baseline assessment of disease and at least one repeat disease assessment measured according to irRC. For details of irRC, refer to Appendix 3 of the study protocol. If rapid tumour progression occurs before completion of the scheduled six AST-VAC2 vaccinations, the patient will be classified as having early progression. Patients with early progression will be included in the response population.

5. DATA CONVENTIONS AND GENERAL ANALYSIS

5.1 Patient disposition

Patients excluded from any population (defined in Section 4.1) will be detailed.

The accrual and trial discontinuation details will be presented descriptively. This should include details of:

- Screening failure patients
    - Pre-screening – patients were pre-screened for human leucocyte antigen (HLA) status as part of the study. The number of patients who underwent HLA screening and the number of patients HLA A*02:01 positive and negative will be summarised.
    - Overall screening failure information is available via the e-screening logs and will be described descriptively.
- Information on ineligible patients who were enrolled and/or received AST-VAC2.
- Reasons for vaccination discontinuation by number of vaccinations received will be described by counts and percentages. Reasons for vaccination discontinuation other than disease progression will be detailed and summarised separately (Section 5.3).

5.2 Baseline characteristics

Demographics and baseline characteristics will be summarised for all enrolled patients.

Table 2: Summary of Patient Demography *(Full Analysis Population)*

	All Patients N=X
Patients	
Sex	
Male	N (%)
Female	
Age (Years)	
Mean	
Median	
Min	
Max	
WHO performance status	
0	N (%)
1	
2	
3	
4	

*Footnote: [redacted] withdrew from the study prior to first vaccination

In case of pre-treatment characteristics with multiple measurements per patient before the start of treatment (laboratory assessments, vital signs), the baseline measurement will be considered the last value prior to or on the first day of vaccination.

Baseline performance status assessments will be summarised with frequency counts.

For the cancer history, histologic diagnosis, number of baseline lesions, and involvement in the different sites will be summarised. If incomplete dates are recorded, the rules described in Section 5.10 will be used for imputation.

The primary tumour sites and baseline lesions will be recorded in order to categorise them accurately in the analysis.

A frequency tabulation of the different types of previous oncologic surgery (excluding only diagnostic or palliative procedures), radiotherapy, or anti-cancer systemic therapy will be given.

Table 3: Primary Diagnosis at Baseline *(Full Analysis Population)*

	No. of Patients (N=XX)
Primary tumour type	
	N (%)
Stage at study entry	
Stage I	
Stage II	
Stage III	
Stage IV	
Not applicable	
Not known	

Table 3 will be manually generated for the Clinical Study Report (CSR) based on the programmed table from the clinical trial database to allow for better grouping by primary tumour type.

Table 4: Summary of Prior Treatment for Malignant Disease *(Full Analysis Population)*

	No. of Patients (N=XX)
Prior treatment	
Surgery	N (%)
Radiotherapy	
Chemotherapy/other	

Table 5: Summary of Prior Lines of Chemotherapy/Other Therapy *(Full Analysis Population)*

	No. of Patients (N=XX)
Lines of chemotherapy/other	
1	N (%)
2	
3	
4	
5, etc	
Median (range)	X (X-X)

Table 5 will be manually generated for the Clinical Study Report based on the 'Previous Treatment for Malignant Disease – Chemotherapy/Other Therapy' listing.

Table 6: Summary of Baseline Disease Sites *(Full Analysis Population)*

Baseline disease type	**No. of Patients (N=XX)**	**Patient Numbers**
Primary tumour	N (%)	XX/XXX, XX/XXX
Local recurrence		
Regional nodes		
Metastatic nodes		
Lung metastases		
Liver metastases		
Etc		

5.3 Patient withdrawal

Reasons for patient withdrawal from vaccination will be provided as the data are available and will be presented descriptively.

5.4 Protocol deviations

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee and Competent Authorities. Therefore, it applies to deviations related to patient inclusion and clinical procedures (e.g. assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g. issues related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the Investigator, etc.).

Protocol deviations are captured throughout the trial open phase on the Sponsor's central tracker and can be filtered by study and by deviation category or on the study specific pharmacokinetic/pharmacodynamic (PK/PD) deviations tracker (and the PK/PD tab [version 1] of the standard study tracker for deviations prior to set up of PK/PD deviations tracker). Standard deviation categories have been defined by the Sponsor and are further defined by those which are deemed reportable (important deviations) in the CSR. Those deviations which have been coded as CSR reportable

will be summarised for all patients, according to the categories allocated at identification. Deviations are reviewed manually as per Sponsor standard operating procedures (SOPs).

A summary table with the number of patients with deviations will be presented per criterion. Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio.

The following are pre-defined protocol deviations with a direct bearing on the primary outcome and therefore will be reported in the CSR. A summary including but not necessarily restricted to the following categories will be presented:

- Ineligible patients as per protocol.
- Patient not withdrawn as per protocol.
- Excluded concomitant medication.
- Incorrect investigational medicinal product (IMP) dose or schedule.

Table 7: Protocol Deviations per Criterion

Deviation criteria	Number of Patients	Patient Numbers
Contraindicated medication		
Dosing error		
Eligibility criteria		
IMP (administration of expired/quarantined IMP)		
Missed visit or investigation		
PK/PD samples and endpoints [redacted]		
Visit or investigation conducted outside of window		
Imaging		
Other (serious breach/urgent safety measure not reported in required timelines)		

[redacted] Deviations relating to all the other PD samples/endpoints will be documented in the individual PD reports and not in this summary table.

5.5 Treatment compliance

Patients are expected to receive six AST-VAC2 vaccinations over a period of six weeks with an interval of 7 days (+/-1 day) between each of the vaccination days.

Dose reductions (i.e., reduced dose or modified number of vaccinations) are not expected but would be considered by the Sponsor and Chief Investigator based on vaccine availability or if plateaued immune responses were observed with fewer vaccinations in those patients already treated.

Vaccination could be delayed if one or more adverse events (excluding injection site reactions) related to AST-VAC2 (highly probably, probably or possibly related) are still present, have not resolved to Grade ≤1 and are considered by the Investigator to be clinically significant and a clear contraindication to vaccination. In those instances, vaccination should be delayed for up to 2 weeks until the adverse events (AEs) have recovered to Grade ≤1. Patients who require a dose interruption of greater than 2 weeks will be reviewed on a case-by-case basis to determine if the patient should be withdrawn from the trial.

Any delays, reductions or omissions to the vaccination schedule will be summarised. The reasons for the dose modifications will be detailed.

A patient is considered to have completed vaccination if the response to 'Did the subject complete 6 vaccinations?' is 'Yes'. Treatment compliance and any treatment modifications will be reported descriptively.

5.6 Safety

Descriptive statistics will be used for evaluation of safety. The incidence and grade of AEs and laboratory abnormalities will be calculated considering the most severe grade per patient and will be displayed in frequency tables using counts and percentages.

Deaths and serious adverse events (SAEs) and events resulting in vaccination discontinuation will be described.

Additional safety analyses may be determined at any time, in order to most clearly enumerate rates of toxicities and to further define the safety profile of AST-VAC2.

Other safety parameters (vital signs, physical examination, electrocardiograms and World Health Organisation [WHO] performance status) will be presented in the data listings.

- The Safety Population is composed of all patients that receive at least one AST-VAC2 vaccination. The Safety Population will be used for the general safety presentations.
- Events will be coded and classified according to the Medical Dictionary for Regulatory Activities (MedDRA; the version used will be shown as a footnote on the AE listing). Toxicity evaluation (grading) will be made according to NCI CTCAE version 4.02 except for ISRs, which have a study specific grading system (please refer to Protocol Section 9.8).
- As far as all the toxicities are concerned (except for ISRs), the NCI CTCAE grade will be used wherever an NCI CTCAE grading exists. For summary tables, the protocol-specific grading for ISRs will be mapped to the CTCAE grades, in order to summarise all the AEs (see below).
- As a convention, the term "Grade" will always be used. Toxicities will be described according to the maximum NCI CTCAE grade or, for ISRs which do not form the subject of NCI CTCAE classification, according to protocol-specific grade.
- Maximum CTCAE grade for all AEs will be captured.

Protocol-specific grading for ISRs	CTCAE grade	Label used in summary tables
Grade 1	Grade 1	Grade 1
Grade 2	Grade 2	Grade 2
Grade 3	Grade 3	Grade 3
Grade 4	Grade 4	Grade 4

5.7 Adverse Events

Pre-treatment AEs will be defined as those where “Did this AE start prior to first vaccination?” is ticked. Treatment Emergent AEs (TEAEs) will be defined as those where “Did this AE start prior to first vaccination?” is not ticked.

Related AEs are those where causality to IMP is considered to be Possible, Probable or Highly Probable.

The frequency of adverse events will be summarised overall. A patient can be counted multiple times per row for the No. of Episodes but will only be counted once per row for the No. of Patients.

Table 8: Frequency of All Adverse Events *(Safety Population)*

SYSTEM ORGAN CLASS Preferred Term	No. of Episodes Reported	No. of Patients N=XX
All AEs	N	N (%)
BLOOD AND LYMPHATIC…		
Anemia		
CARDIAC DISORDERS		
Sinus tachycardia		
Etc		

There will be additional versions (as required) of the above table based on pre-treatment AEs, TEAEs, treatment emergent SAEs (any AE that is considered Serious) and related TEAEs.

Overview of TEAEs will be presented for all patients. An AE is considered to have led to withdrawal if an adverse event with “Did the AE cause the subject to be discontinued from the study?” is recorded as yes.

Table 9: Overview of Treatment Emergent Adverse Events *(Safety Population)*

Patients with TEAEs	Overall No. of Patients N=XX
Patients with >=1 TEAE	N (%)
Patients with >= 1 TE SAE	
Patients with >= 1 related TEAE	
Patients with >= 1 CTCAE Grade 3, 4 or 5 TEAE	
Patients with >= 1 AE leading to withdrawal*	
Patients who died due to TEAE	

*Footnote: AEs that lead to withdrawal of vaccination; patients remained on study for assessment of response, safety and overall survival.

TEAEs leading to withdrawal of vaccination will be summarised descriptively. Patients will be included if an AE has “Action taken” recorded as “Drug Withdrawn” or “Did the AE cause the subject to be discontinued from the study?” is recorded as yes.

All TEAEs and related TEAEs by worst CTCAE grade within an episode will be presented by number of TEAEs and by number of patients (see Table 10 and Table 11, respectively).

Table 10: Frequency of Treatment Emergent Adverse Events and Related Treatment Emergent Adverse Events by Worst CTCAE Grade within an Episode *(Safety Population)*

SYSTEM ORGAN CLASS Preferred Term	All TEAEs							AST-VAC2 Related TEAEs						
			_____Grade_____							_____Grade_____				
	Total		1	2	3	4	5	Total		1	2	3	4	5
Overall total	N		N	N	N	N	N	N		N	N	N	N	N
BLOOD AND LYMPHATIC…														
Anaemia														
CARDIAC DISORDERS														
Sinus tachycardia														
Etc														

Table 11: Frequency of Patients with Treatment Emergent Adverse Events and Related Treatment Emergent Adverse Events by Worst CTCAE Grade within an Episode *(Safety Population)*

SYSTEM ORGAN CLASS Preferred Term	All TEAEs						AST-VAC2 Related TEAEs					
	No. of patients with >=1 AE (N=XX)						No. of patients with >=1 AE (N=XX)					
	_____Grade_____						_____Grade_____					
	Total	1	2	3	4	5	Total	1	2	3	4	5
Overall total	N (%)	N	N	N	N	N	N (%)	N	N	N	N	N
BLOOD AND LYMPHATIC…												
Anaemia												
CARDIAC DISORDERS												
Sinus tachycardia												
Etc												

5.8 Laboratory results

Laboratory results (haematology, biochemistry and urinalysis) will be presented in data listings as an appendix to the CSR. Any significant out of range values are captured as AEs and will be presented in the summary AE tables (see Section 5.7).

5.8.1 Additional safety tables

A table of ISR grade by vaccination number will be produced.

Table 12: Summary of Injection Site Reactions by Grade and Vaccination Number *(Safety Population)*

	Vaccination number at onset						
ISR Grade	Total	1	2	3	4	5	6
1	N	N	N	N	N	N	N
2							
3							
4							
5							

5.8.2 Stopping rule criteria

Any AEs that meet the stopping rule criteria will be presented descriptively.

5.9 Efficacy

Documentation of tumour response is a secondary objective of this trial. Anti-tumour activity will be measured according to the modified irRC; (see Protocol Appendix 3) at 30 days (+/- 5 days) after the last AST-VAC2 vaccination in all patients. The overall response will be presented for the 'Response Population' (see Table 13).

The response rate is defined as the ratio of patients with any response (immune-related complete response [irCR] or immune-related partial response [irPR]) to the total number of patients included in the efficacy population.

Overall survival will be assessed in the 'Safety Population' and is defined as the time from the first AST-VAC2 vaccination to the date of death (regardless of whether the patient went on to receive other anti-cancer treatments) or date of last contact (if patient is still alive or lost to follow-up). Survival will be summarised for each patient as shown in Table 14. Patients with data censored for survival will be indicated with a '+' after the number of days.

CEA data will be listed per patient.

Table 13: Overall Response *(Response Population)*

Overall Tumour Response	No. of Patients N=XX
irCR	X (XX.X%)
irPR	
irSD	
irPD	
NE	
Response rate (irCR + irPR)	

Table 14: Summary of Survival *(Safety Population)*

Patient	Time to Death (or Last Contact) (days)
XX/XXX	N
XX/XXX	
XX/XXX	
XX/XXX	
Median (range)	X (X-X)

Table 15: Two Year Survival *(Safety Population)*

Patients alive	Patients deceased
N (%) [XX/XXX, XX/XXX…]	N (%) [XX/XXX, XX/XXX…]

5.10 General data conventions

There is only one dose level for this study, as specified in the study protocol. Patients who deviate from the assigned dose and/or schedule will be clearly described in the CSR with regards to their treatment modification and if applicable in the list of protocol deviations (Section 5.4).

Continuous variables will be summarised and presented with summary statistics.

The median OS will be presented.

Categorical variables will be summarised in frequency tables. Percentages in the summary tables will be rounded and may therefore not always add up to exactly 100%.

The convention in Rave is that an unknown day resolves to 1st of the month and an unknown month resolves to January. Dates may be ordered by this; however, CRUK do not perform calculations on unknown dates except as stated below.

Durations of AEs: the start date of an AE is considered as Day 1 of the event and should be included in all duration calculations (i.e. if an AE starts and stops on same day, the duration should be reported as one day).

- For unrelated AEs, those with missing or partially completed end dates will not be excluded from analysis and the duration of the AE will be calculated from the first day of the month (if unknown) or first day of the year (based on RAVE conventions).
- For related AEs, prior to final data lock, an end date will be either i) confirmed AE end date or ii) stabilisation of AE. Cases where this is not possible are if the patient was lost to follow up. If lost to follow-up then the AE would stay as not recovered/not resolved. In this case duration would not be calculated.

Time to onset of AEs from IMP administration: the time to onset should be calculated from the date of the first AST-VAC2 vaccination and AEs occurring within a specific vaccination window (e.g. start date from date of 2nd vaccination to before date of 3rd vaccination) should also have times to onset calculated from the date of the last vaccination administered in that window (e.g. Vaccination 2). Onset time will be

calculated as 0 if the AE occurs on the same day as the dose; however, if the start time is missing, onset time will not be calculated (only applicable when the drug admin has a start time entered).

AE assignment: AE is assigned to the vaccination number it begins in. This is regardless of whether the AE start time shows the AE started before the dose that day. The only exception is for the first vaccination; if 'Did AE occur prior to first dose' is checked then no vaccination number will be assigned.

Duration of treatment: this is from the day of the first vaccination until the day of the final vaccination. Duration of treatment will be described using summary statistics.

Completed vaccination: AST-VAC2 vaccinations are to be given once a week for 6 weeks. A patient is considered to have completed vaccination when vaccination data entered is for each of those expected weekly visits (despite dose modifications).

Treated patients: If the drug administration form in the eCRF has the 'date of vaccination' completed, this constitutes a treated patient.

5.11 Decimal places

When data are used in calculations it important that rounding is only conducted when the final test result is obtained (to avoid accumulation of errors).

All percentages should be presented to 1 decimal place. If a percentage value is less than 0.1% on rounding, then use '<0.1%'.

Days to be presented to 0 decimal places.

5.12 Statistical software

Medidata Rave will be used as the Electronic Data Capture (EDC) system for the trial.

SAS 9.4 will be used to generate data listings and summary tables/graphs.

5.13 Supplementary analysis – Pharmacodynamics (data collected outside of the clinical database)

Pharmacodynamic analyses will be described in supplementary lab reports [redacted]. There are no primary endpoint pharmacodynamic assays for this study.

5.13.1 HLA Pre-screening

DNA extracted from whole blood taken at pre-screening will be analysed by Luminex (or similar method) for HLA-A*02:01 allelic string *(HLA population)*. The whole A* allele will be reported for each patient.

Results are reported per patient within 14 days of receipt of the sample. The HLA-A*02:01 status (positive or negative) is also captured in the clinical database on the enrolment eCRF.

[redacted]

The final report is expected no more than two months after completion [redacted].

No formal statistical analysis is planned. The data will be summarised in the CSR and the final report included as an appendix.

5.13.2 Secondary endpoints

5.13.2.1 Identification of peptide specific T cells *(Secondary Immunogenicity Endpoint Population)*

Immunological response will be measured in whole blood (PBMCs) by hTERT specific T cells as measured by ELISPOT analysis at the following time points:

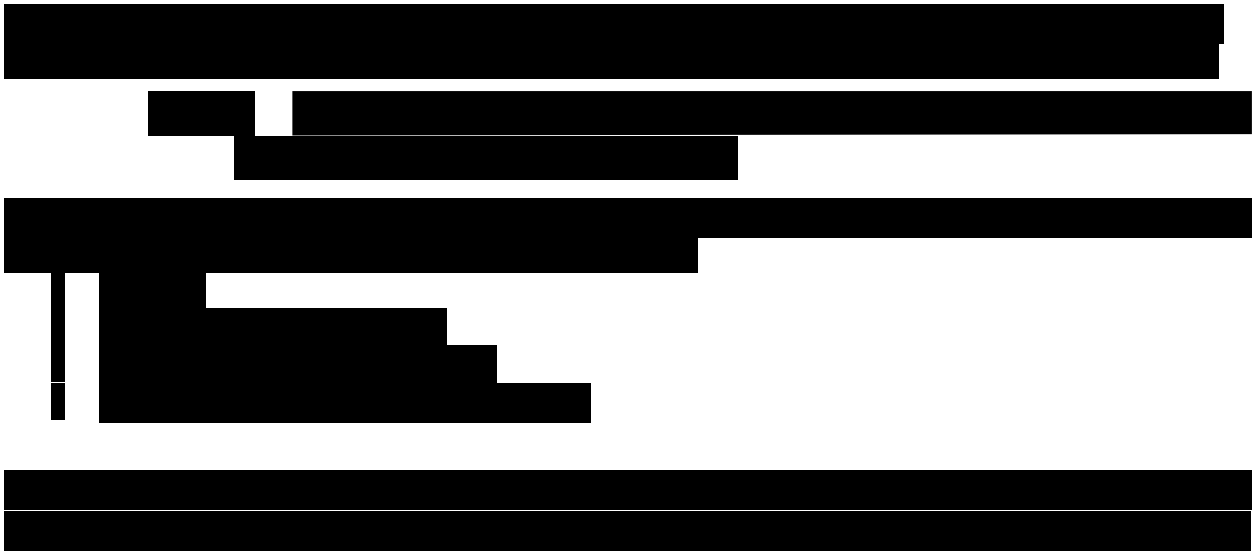
- baseline,
- vaccination weeks 3, 4 and 6,
- 2 weeks post last vaccination and
- 3, 6 and 12 months post first vaccination.

Vaccine induced ELISPOT response in blood will be reported longitudinally for each patient. The total number of patients showing durable peripheral immune response, defined as a change in one validated assay at two time points after at least two vaccinations (where a change is defined as 2.5 fold change over baseline [after removal of background], assay control and >35 spots/10^6 cells) will be reported.

Interim reports are expected at timepoints to be agreed between the Sponsor and the laboratory. Interim reports will be provided within one month of completing the agreed patient analyses. A final report is expected no more than 10 weeks after the last sample is analysed.

The data will be reported in tables and graphs/figures. No formal statistical analysis is planned. The results will be summarised in the CSR and the final report included as an appendix.

5.13.3 Tertiary endpoints



[redacted]

[redacted]

5.14 Other statistical analysis

5.14.1 Stratification and covariate analysis

No stratification or covariate analysis is planned.

5.14.2 Multivariate analysis

No multivariate analysis is planned.

5.14.3 Subgroup analysis

Given the small number of patients to be vaccinated, no subgroup analyses are planned.

5.14.4 Interim analysis

An interim analysis will be conducted once all patients administered AST-VAC2 have withdrawn, died or completed their 2-year follow-up visit for survival. Once this condition is met, a data cut-off will be established. All patient visits occurring on or before this date will be analysed and summarised in the clinical study report including safety data to date and assessment of OS at 2 years.

Any data collected after this date will be summarised in a supplemental report produced for the final analysis to satisfy the safety reporting requirements for AST-VAC2 as an advanced therapy investigational medicinal product (ATIMP).

The relevant data will be uploaded to ClinicalTrials.gov after the CSR is approved.

5.14.5 Final analysis

The final analysis will be conducted after one of the following conditions is met:

- The trial is terminated early (e.g. due to toxicity)
- The End of Trial has been reached (defined as the date when all patients have either withdrawn from the trial or died, or the last patient has completed their final follow-up visit [whichever is the latter]. The final follow-up visit is scheduled to take place 5 years after the patient's first vaccination).

Once one of the conditions is met, a data cut-off date will be established. All patient follow-up visits occurring on or before this date will be analysed and summarised in a supplemental report.

6. TABLES LISTINGS AND FIGURES

6.1 LISTINGS

CSR Appendix Subsection	CSR Listing Number	Listing	New Listing Name for CSR
16.2.1 Discontinued Patients	**16.2.1.1**	Vaccine Received	Vaccine Received
	16.2.1.2	End of Vaccination	Vaccination Completion
16.2.2 Protocol Deviations	**16.2.2.1**	*To be provided from the central deviation tracker*	*N/A*
16.2.3 Patients excluded from Efficacy Analysis	**16.2.3.1**	Enrolment	Enrolled Patients
16.2.4 Demographic and Baseline Data	**16.2.4.1**	Demographics	Patient Demography
	16.2.4.2	Diagnosis	Diagnosis of Primary Disease
	16.2.4.3	Medical History	Medical History
	16.2.4.4	Medical Procedures	Medical Procedures
	16.2.4.5	Prior and Concomitant Medications	Prior and Concomitant Medications
	16.2.4.6.1	Surgery	Previous Treatment for Malignant Disease - Surgery
	16.2.4.6.2	Chemotherapy/other therapy	Previous Treatment for Malignant Disease – Chemotherapy/Other Therapy
	16.2.4.6.3	Radiotherapy	Previous Treatment for Malignant Disease - Radiotherapy
	16.2.4.7	Physical Examination	Physical Examination
	16.2.4.8	Chest X-ray Results	Chest X-ray
16.2.5 Compliance and Drug Administration	**16.2.5.1**	Drug Administration - Vaccination	Drug Administration - Vaccination
16.2.6 Efficacy Response	**16.2.6.1**	Immune Response Index Lesions	Immune Response Index Lesions
	16.2.6.2	Immune Response Non-Index Lesions	Immune Response Non-Index Lesions
	16.2.6.3	Immune Related Response Criteria	Immune Related Response
	16.2.6.4	New Anti-Cancer Therapy	New Anti-Cancer Therapy
	16.2.6.5	Survival	Survival
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	16.2.6.9	CEA Sample	CEA Sample
16.2.7 Safety	**16.2.7.1**	Adverse Events	Adverse Events

	16.2.7.2	Adverse Events by SOC	Adverse Events by SOC
	16.2.7.3	Follow-Up	Follow Up
	16.2.7.4	WHO	WHO Performance Status
	16.2.7.5	Haematology	Haematology: Haemoglobin, WBC, Neutrophils, Lymphocytes, Eosinophils, Platelets
	16.2.7.6	Biochemistry	Biochemistry: Sodium, Potassium, Adjusted calcium, Phosphate, Urea, Creatinine, Total Protein, Albumin, Bilirubin, ALP, ALT, AST, CRP
	16.2.7.7	Urinalysis	Urinalysis: Glucose, Protein, Blood, pH
	16.2.7.8	Vital Signs	Vital Signs
	16.2.7.9	Pregnancy	Pregnancy
	16.2.7.10	ECG	ECG

6.2 SUMMARY TABLES

Table Number in RAP	**CSR Table Number**	**Table Name**
Table 1	N/A	Trial Design
N/A: to be produced as part of lab reporting	In-text table	Human Leucocyte Antigen Status at Screening
Table 2	14.1.1	Summary of Patient Demography (Full Analysis Population)
Table 3	14.1.2	Primary Diagnosis at Baseline (Full Analysis Population)
Table 6	14.1.3	Summary of Baseline Disease Sites (Full Analysis Population)
Table 4	14.1.4	Summary of Prior Treatment for Malignant Disease (Full Analysis Population)
Table 5	In-text table (will refer to listing)	Summary of Prior Lines of Chemotherapy/Other Therapy (Full Analysis Population)
Table 7	In-text table (will refer to listing)	Protocol Deviations per Criterion
Table 9	14.3.1	Overview of Treatment Emergent Adverse Events (Safety Population)
Table 8	14.3.2	Frequency of All Adverse Events (Safety Population)
N/A: based on Table 8	14.3.3	Frequency of Pre-Treatment Adverse Events (Safety Population)
N/A: based on Table 8	14.3.4	Frequency of Treatment Emergent Adverse Events (Safety Population)
N/A: based on Table 8	14.3.5	Frequency of Treatment Emergent Serious Adverse Events (Safety Population)

N/A: based on Table 8	14.3.6	Frequency of Related Treatment Emergent Adverse Events (Safety Population)
Table 10	14.3.7	Frequency of Treatment Emergent Adverse Events and Related Treatment Emergent Adverse Events by Worst CTCAE Grade within an Episode (Safety Population)
Table 11	14.3.8	Frequency of Patients with Treatment Emergent Adverse Events and Related Treatment Emergent Adverse Events by Worst CTCAE Grade within an Episode (Safety Population)
Table 12	14.3.9	Summary of Injection Site Reactions by Grade and Vaccination Number (Safety Population)
Table 13	14.2.1	Overall Response (Response Population)
Table 14	14.2.2	Summary of Survival (Safety Population)
Table 15	14.2.3	Two Year Survival (Safety Population)

7. PRESENTATION OF RESULTS IN CLINICALTRIALS.GOV INCLUDING ADDITIONAL TABLES

The following information will be used for presentation and upload of trial data on ClinicalTrials.gov. The data presented will be consistent with the final CSR but will be tabulated in a format that fits with the ClinicalTrials.gov requirements[1].

The tables programmed for ClinicalTrials.gov will **not** form part of the Clinical Study Report (CSR).

7.1 Arms and Interventions

The trial will be presented as a single group design.

Data will be presented for one arm.

Treatment arm:	Participants with advanced NSCLC, to receive AST-VAC2
Treatment Arm type:	Experimental
Arm Description:	Participants will receive up to a maximum of six vaccinations over six weeks. Each weekly AST-VAC2 vaccination will be administered as a split dose via two intradermal injections at a target dose defined as 1 x 10^7 viable cells. There is no dose escalation planned during the study; only one dose level will be explored.
Intervention type:	Biological/Vaccine
Intervention Name(s):	AST-VAC2
Other Intervention Name(s):	N/A
Intervention Description:	Allogeneic dendritic cell vaccine.

[1] ClinicalTrials.gov Results Data Element Definitions for Interventional and Observational Studies found here

7.2 Participant Flow

The participant flow section of the results upload will include the following details. The programmed table output for reason not completed may be re-categorised to ClinicalTrials.gov categories and reviewed by Clinical Study Manager for approval.

Period Title	Overall Study
Arm/Group Title	Experimental: AST-VAC2
Arm/Group Description	Participants will receive up to a maximum of six vaccinations over six weeks. Each weekly AST-VAC2 vaccination will be administered as a split dose via two intradermal injections at a target dose defined as 1 x 10^7 viable cells. There is no dose escalation planned during the study; only one dose level will be explored.
	Number of Participants
Started (participants enrolled into main trial)	*
Completed (6 vaccinations)	
Not completed	
Reason not completed	
Adverse Event	
Death	
Lack of Efficacy	
Lost to Follow-up	
Physician Decision	
Pregnancy	
Protocol Violation	
Withdrawal by Subject	
Disease Progression	

Sponsor's decision to terminate the trial	
Started (participants entered follow-up period)	
Completed (2-year OS follow up)	
Not completed	
Reason not completed	
Lost to follow-up	
Withdrawal of consent	
Death	
Declined to attend follow-up visit	

7.3 Baseline Characteristics

The baseline characteristics section of the results upload will include the following details. The programmed table output for reason not completed may be re-categorised to ClinicalTrials.gov categories and reviewed by Clinical Study Manager for approval.

Note: CDD trials don't routinely collect data on race. Ethnicity information is collected for some trials, where ethnicity information is collected, the standard category of Race will be entered as "not collected" (or equivalent) on ClinicalTrials.gov and Ethnicity information provided as an additional baseline measure.

Arm/Group Title	Experimental: AST-VAC2
Arm/Group Description	Participants will receive up to a maximum of six vaccinations over six weeks. Each weekly AST-VAC2 vaccination will be administered as a split dose via two intradermal injections at a target dose defined as 1 x 10^7 viable cells. There is no dose escalation planned during the study; only one dose level will be explored.
Overall Baseline Participants	Number of Participants
Baseline Analysis Population Description	*
Age, Number Analysed	
Age, Median (Full range)	
Sex, Number Analysed	
Male, number of participants	
Female, number of participants	
Ethnicity	Not collected

7.4 Reported Adverse Events (clinicaltrials.gov template sections)

AE Reporting Timeframe: Safety data will be collected from the time of informed consent until 2 years from the first dose of AST-VAC2 for this interim report. Patients are followed-up for 5 years; if there are any changes to information reported at end of trial, this will be updated. The average (median and range) time from consent to the end of follow up will be calculated from the database presented in the AE tables.

All-Cause Mortality will be presented as per the ClinicalTrials.gov template as follows (based on a programmed table):
Note: CT.gov Definition of Total all cause mortality: Total of *all* anticipated and unanticipated deaths due to **any cause**.

	Experimental: AST-VAC2	
	Affect/At Risk (%)	# Events
Total All Cause Mortality*		

Serious Adverse events will be presented as per the ClinicalTrials.gov template as follows (based on a programmed table):

	Experimental: AST-VAC2	
	Affect/At Risk (%)	# Events
Total		
<AE term>		
<AE term>		
<AE term>		

Other (non-Serious) Adverse events will be presented as per the clinicaltrials.gov template as follows (based on a programmed table):

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	Experimental: AST-VAC2	
	Affect/At Risk (%)	# Events
Total		

<AE term>		
<AE term>		
<AE term>		

7.5 Outcome Measures

Primary and secondary endpoints will be reported on the ClinicalTrials.gov website as outcome measures as follows. Results will be reported for all Primary and Secondary Endpoints.

Primary Objectives	Endpoints	Outcome Measures
To assess the safety and tolerability of AST-VAC2	Determining the frequency and causality of each adverse event to AST-VAC2 and grading severity according to the NCI CTCAE Version 4.2 or protocol specific grading system for injection site reactions (ISRs).	**Measure Title:** Frequency and Causality of Serious Adverse Events (SAEs), Non-Serious Adverse Events (NSAEs) and Grade ≥3 Adverse Events (AEs) to AST-VAC2 **Measure Description:** Number of SAEs, NSAEs and Grade ≥3 AEs overall and number of SAEs, NSAEs and Grade ≥3 AEs related to AST-VAC2. AEs categorised according to Medical Dictionary for Regulatory Activities version (v) X and graded for severity according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.02 or protocol specific grading system for injection site reactions (ISRs; Section 9.8 of protocol). AEs assessed by the reporting study doctors for a causal relationship to AST-VAC2. Related are those AEs with a causality of possible, probable or highly probable. **Time Frame:** From the time of informed consent up to 2 years from the first dose of AST-VAC2, a median (range) of XX days (XX-XX). **Measure Type:** Number **Measure of dispersion/precision:** Not applicable
		Measure Title: Number of Participants Experiencing ISRs by Grade **Measure Description:** Number of participants experiencing ISRs Grade 1 to 4 according to protocol-specific grading of ISRs (Section 9.8 of protocol). **Time Frame:** From the time of informed consent up to 2 years from the first dose of AST-VAC2, a median (range) of XX days (XX-XX). **Measure Type:** Count of participants **Measure of dispersion/precision:** Not applicable

Secondary Objectives	Endpoints	Outcome Measures
To determine the immunogenicity (peripheral response) of AST-VAC2	Observation of the total number of patients showing durable peripheral immune response, defined as a change in one validated assay at two time points after at least two vaccinations.	**Measure Title:** Number of Participants Showing a Durable Peripheral Immune Response **Measure Description:** Immunological response in whole blood (peripheral blood mononuclear cells) by human telomerase reverse transcriptase (hTERT) specific T cells measured by enzyme-linked immunospot (ELISPOT), with a durable peripheral immune response defined as a change in one validated assay at two time points after at least two vaccinations (where a change is defined as 2.5 fold change over baseline [after removal of background], assay control and >35 spots/10^6 cells). **Time Frame:** Screening, vaccination weeks 3, 4 and 6; 2 weeks post last vaccination and 3, 6 and 12 months post first vaccination. **Measure Type:** Count of participants **Measure of dispersion/precision:** Not applicable
		Measure Title: Mean Fold Change in hTERT Specific T Cells Over Baseline by Timepoint **Measure Description:** Immunological response in whole blood (peripheral blood mononuclear cells) by hTERT specific T cells measured by ELISPOT and presented as mean fold change in spots/10^6 cells (after removal of background) from baseline to each timepoint assessed. **Time Frame:** Screening, vaccination weeks 3, 4 and 6; 2 weeks post last vaccination and 3, 6 and 12 months post first vaccination. **Measure Type:** Mean **Measure of dispersion/precision:** Full range
To document any tumour response(s) in patients receiving the AST-VAC2 vaccine.	Re-assessment of tumour size at end of vaccination visit with MRI or CT using Immune-Related Response Criteria (irRC).	**Measure Title:** Tumour Response According to Immune-Related Response Criteria (irRC) Post Vaccination **Measure Description** Number of participants with complete response, partial response, stable disease, progressive disease or who

		were not evaluable at radiological disease assessment (computerised tomography and/or magnetic resonance imaging) at the End of Vaccination visit according to irRC (Appendix 3 of protocol). **Time Frame:** Baseline to End of Vaccination visit (30 days post last vaccination). **Measure Type:** Count of participants **Measure of dispersion/precision:** Not applicable
To determine the 2-year overall survival (OS) in patients receiving the AST-VAC2 vaccine.	Measurement of overall survival at two years post first vaccination.	**Measure Title:** Overall survival at 2 Years Post First Vaccination **Measure Description** Number of participants alive at 2 years post their first vaccination. **Time Frame:** From first AST-VAC2 vaccination to 2 years post first vaccination. **Measure Type:** Count of participants **Measure of dispersion/precision:** Not applicable

7.5.1 Outcome Measure 1 – Frequency and causality of AEs and SAEs to AST-VAC2 *(Safety Population)*

The following table will be programmed to provide results for frequency and causality of AEs and SAEs to AST-VAC2.

Arm/Group Title		Experimental: AST-VAC2
Frequency and causality of AEs, SAEs and Grade ≥3 AEs to AST-VAC2 Measure type: Number Unit of measure: not applicable	Number of participants analysed	<N>
	SAEs	<data>
	Non-serious AEs	<data>
	Grade ≥3 AEs	<data>
	Related SAEs	<data>
	Related non-serious SAEs	<data>
	Related Grade ≥3 AEs	<data>

7.5.2 Outcome Measure 2 - Number of participants experiencing ISRs by grade *(Safety Population)*

The following table will be programmed to provide results for number of participants experiencing ISRs Grade 1 to 4.

Arm/Group Title		Experimental: AST-VAC2
Participants experiencing ISRs Grade 1 to 4 Measure type: Count of participants Unit of measure: participants	Number of participants analysed	<N>
	Grade 1	<data>
	Grade 2	<data>
	Grade 3	<data>
	Grade 4	<data>

7.5.3 Outcome Measure 3 – Number of participants showing a durable peripheral immune response *(Secondary Immunogenicity Endpoint Population)*

The following table will be programmed to provide results for the number of participants with a durable periperal immune response.

Arm/Group Title		Experimental: AST-VAC2
Participants showing a durable peripheral immune response Measure type: Count of participants Unit of measure: participants	Number of participants analysed	<N>
	Durable response	<data>
	Non-durable response	<data>
	Undetermined (baseline sample did not pass acceptance criteria or insufficient timepoints)	<data>

7.5.4 Outcome Measure 4 – Mean fold change over baseline by timepoint *(Secondary Immunogenicity Endpoint Population)*

The following table will be programmed to provide results for the mean fold change from baseline.

Arm/Group Title		Experimental: AST-VAC2
Overall Number of Participants Analysed		<N>
Mean fold change over baseline Measure type: Mean Unit of measure: full range	Number of participants analysed	<N>
	Week 3	<data>
	Number of participants analysed	<N>
	Week 4	<data>
	Number of participants analysed	<N>
	Week 6	<data>
	Number of participants analysed	<N>
	2 weeks post last vaccination	<data>
	Number of participants analysed	<N>
	3 months post first vaccination	<data>
	Number of participants analysed	<N>
	6 months post first vaccination	<data>
	Number of participants analysed	<N>
	12 months post first vaccination	<data>

7.5.5 Outcome Measure 5 - Tumour response according to Immune-Related Response Criteria (irRC) post vaccination *(Response population)*

The following table will be programmed to provide results for tumour response.

Arm/Group Title		Experimental: AST-VAC2
Tumour response according to irRC post vaccination Measure type: Count of participants Unit of measure: participants	Number of participants analysed	<N>
	Complete response (irCR)	<data>
	Partial response (irPR)	<data>
	Stable disease (irSD)	<data>
	Progressive disease (irPD)	<data>
	Not evaluable (NE)	<data>

7.5.6 Outcome Measure 6 – Overall survival at 2 years post first vaccination *(Safety Population)*

The following table will be programmed to provide results for overall survival.

Arm/Group Title		Experimental: AST-VAC2
Overall survival at 2 years post first vaccination Measure type: Count of participants Unit of measure: participants	Number of participants analysed	<N>
	Alive	<data>
	Deceased	<data>

7.6 Statistical Analyses

No statistical analyses are to be performed on the primary or secondary endpoints.

8. REPORTING OF CLINICAL TRIAL RESULTS TO PATIENTS AND PUBLIC

When considering preparation of information that is for patients and their carers/families. It is important to take into account the language used and to allow opportunity to tailor information depending on the patients' experience/current situation:

- Refer to Guidance on use of Plain Language and Readability checks in the PICD toolkit here

At the End of the Trial

At the end of the trial summary results in lay language will be provided on the CRUK website at the following link: A trial of a vaccine called AST-VAC2 in non small cell lung cancer.

Additionally, a link to the CRUK lay summary of the results will be added to the HRA website.

CRUK CDD will provide Investigator Sites with a .pdf copy of the results from the CRUK trials database for distribution to patients and their families (as appropriate and at the discretion of the investigator).

9. REFERENCES

- Guidelines for the Content of Statistical Analysis Alans in Clinical Trials, JAMA December 2017, Volume 318, Number 23. Gamble et al.