Statistical Analysis Plan

Study ID: ELI-002-001

Title of Study: First in Human Phase 1 Trial of ELI-002 Immunotherapy as Treatment for Subjects with Kirsten Rat Sarcoma (KRAS) Mutated Pancreatic Ductal Adenocarcinoma and Other Solid Tumors

NCT ID: NCT04853017

Date of Document: 16 September 2024

Protocol Title:	First in Human Phase 1 Trial of ELI-002 Immunotherapy as Treatment for Subjects with Kirsten Rat Sarcoma (KRAS) Mutated Pancreatic Ductal Adenocarcinoma and Other Solid Tumors
Protocol Number:	ELI-002-001
Protocol Version, Date	Version 8.0 Dated 07 Aug 2023 Version 7.0 Dated 25 Jan 2023 Version 6.0 Dated 02 Aug 2022 Version 5.0 Dated 08 Apr 2022 Version 4.0 DRAFT Dated 29 Jul 2021 Version 3.0 Dated 24 Feb 2021 Version 2.0 Dated 2 Sep 2020 Original Dated 13 Jul 2020
ICON ID:	5294/0001
Document Version, Date:	Version 3.0, 16Sep2024

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1.0 SIGNATURE PAGE

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2.0 REVISION HISTORY

Version/Date	Version name	Section	Changes implemented
Draft Version 0.2, 19Apr2021	Updated draft	N/A	N/A
Draft Version 0.3, 25Aug2021	Updated draft	All	Protocol Amendment 4.0
Draft Version 0.3, 14Dec2021	Updated draft	All	Updates per sponsor comments
Draft Version 0.3, 14Jan2022	Updated draft	All	Updates per sponsor comments
Draft Version 0.3, 31Mar2022	Updated draft	All	Updates per sponsor comments
Draft Version 0.4, 28Apr2022	Updated draft	All	Updates for consistency with mocks
Draft Version 0.5 30Aug2022	Updated draft	All	Updates as per Protocol Version 6.0
Draft Version 0.6 13Oct2022	Updated draft	All	Add clarification for section 8.4.2: the best response will be only be evaluated for neo-adjuvant participants Add cohorts 4 and 5 per Sponsor's request and approval.
Draft version 0.6 05Dec2022	Updated draft	All	Updates as per Client comments
Draft version 0.6 16Mar2023	Updated draft	7.4	Algorithms on Patient Reported Outcomes are added. Addressed comments from the client.
Version 1.0 14Apr2023	Final		As a part of the exploratory analysis added a summary of TEAE and RFS by tumor types.
Version 2.0 01Aug2023	Draft		SAP Addendum on the Immunogenicity and ctDNA is added as an APPENDIX.
Version 2.1 04 Dec2023	Updated draft		Updates per sponsor comments
Version 3.0 ddAug2024	Updated draft		Updates to add the following changes: • Tumor biomarker reduction and clearance definitions, and analyses • Duration of biomarker

			reduction and clearance definitions, and analyses • RFS windows and censoring rules • planned analyses following early termination of long-term follow up phase

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5.0 LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BOR	Best Overall Response
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events, Version 5
ctDNA	Circulating tumor Deoxyribonucleic Acid
DFR	Distribution-free resampling
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DRES	Disease Response Evaluable Set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
Fluorospot	Enzyme-linked immuno-spot
EORTC	European Organization for Research and Treatment of Cancer
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
IA	Interim Analysis

Abbreviation or special term	Explanation
ICANS	Immune effector Cell-Associated Neurotoxicity syndrome
ICH	International Conference on Harmonization
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Committee
IL	Interleukin
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IRT	Interactive Response Technology
ITT	Intent To Treat
IVS	In vitro stimulation
kg	Kilogram
KM	Kaplan-Meier
KRAS	Kirsten Rat Sarcoma
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mKRAS	Mutant Kirsten rat sarcoma
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NGS	Next-generation sequencing
NRAS	Neuroblastoma ras viral oncogene homolog
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PDAC	Pancreatic Ductal Adenocarcinoma
PDS	PD (Pharmacodynamic) /Biomarker Evaluable Set
PE	Physical examination
PFS	Progression Free Survival
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial Response

Abbreviation or special term	Explanation
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
QLQ	Quality of Life Questionnaire
QTc	Corrected Q Wave to T Wave Interval
RECIST	Response Evaluation Criteria In Solid Tumours
RFS	Relapse-Free Survival
RP2D	Recommended Phase 2 Dose
SAP	Statistical Analysis Plan
SC	Subcutaneous
SMC	Safety Monitoring Committee
STD	Standard Deviation
SOC	System Organ Class
SOC (observation)	Standard of Care (observation)
TE	Treatment Emergent
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
TNFα	Tumor Necrosis Factor alpha
TTF	Time to Treatment Failure
TTP	Time to Progression
ULN	Upper Limit of Normal
WHODDE	WHO Drug Dictionary Enhanced

6.0 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study Protocol ELI-002-001, Version 8.0 "First in Human Phase 1 Trial of ELI-002 Immunotherapy as Treatment for Subjects with Kirsten Rat Sarcoma (KRAS) Mutated Pancreatic Ductal Adenocarcinoma and Other Solid Tumors", dated 07 Aug 2023. The table of contents and templates for the Tables, Figures and Listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on the International Conference on Harmonization (ICH) E3 and E9 guidelines and iRECIST criteria.

All data analyses and generation of TFLs will be performed using SAS 9.4® or higher.

7.0 STUDY OBJECTIVES

7.1 Phase 1 Objectives (Phase 1: Dose Escalation)

7.1.1 Phase 1 Primary Objectives

- To assess the safety and tolerability of ELI-002 as adjuvant therapy for subjects with Kirsten Rat Sarcoma (KRAS) mutated Pancreatic Ductal Adenocarcinoma (PDAC) and other solid tumors who have minimal residual disease (MRD) identified using either circulating tumor DNA (ctDNA) or a serum tumor biomarker
- To define the maximum tolerated dose (MTD) (in the event there is an MTD) and the recommended Phase 2 dose (RP2D)

7.1.2 Phase 1 Secondary Objective

- To assess circulating tumor deoxyribonucleic acid (ctDNA) reduction and clearance, defined as the reduction or clearance of ctDNA compared to baseline, or if ctDNA was not detectable at baseline, serum tumor biomarker (such as carbohydrate antigen [CA]19-9, carcinoembryonic antigen [CEA], and CA-125) reduction and clearance compared to baseline.

7.1.3 Phase 1 Exploratory Objectives

- To report the median relapse-free survival (RFS) and median overall survival (OS)
- To assess the change relative to baseline in:
  - Serum cytokines interleukin (IL)-2, interferon gamma (IFNγ), IL-6, IL-10, and tumor necrosis factor alpha (TNFα)
  - Patient reported outcomes (PROs): European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire [QLQ]-C30 and QLQ-PAN26, QLQ-CR29, QLQ-OV28, QLQ-BIL21, or QLQ-LC13
  - To evaluate the immunogenicity of ELI-002. T cell responses to ELI-002 will be assessed using assays such as intracellular cytokine staining (ICS), (Fluorospot), and/or

dextramer+ T cells for subjects with human leukocyte antigen (HLA) alleles for which dextramer/s is/are available.

- Biomarker levels (ctDNA, CA19-9, CEA, and CA-125)
- To evaluate tumor-infiltrating T cells and the tumor microenvironment after dosing with ELI-002

- To correlate biomarker data to clinical safety and efficacy (RFS, OS)

8.0 STUDY DESIGN

ELI-002-001 is an open-label, Phase 1 trial of ELI-002 immunotherapy as adjuvant treatment for subjects with KRAS/neuroblastoma ras viral oncogene homolog (NRAS) mutated PDAC and other solid tumors who are at high risk for relapse (ie, presence of isolated tumor cells as detected by ctDNA or elevated serum tumor biomarkers in the subject's body, in which the primary tumor has been removed and is currently without clinical signs of disease).

8.1 General Study Design

The Phase 1 study is an open label, single arm, dose-escalation trial incorporating a 3+3 design. Approximately 18 subjects are planned to be enrolled in Phase 1 to evaluate the safety, tolerability and exploratory pharmacodynamic efficacy of subcutaneous ELI-002 using the adjuvant at 3 planned dose levels (Amph-CpG-7909 0.1 mg SC, 0.5 mg SC, 2.5 mg SC) in combination with a fixed dose of Amph-Peptides 2P (700 µg each, for a total of 1.4 mg). Additional cohorts may be added to explore intermediate or higher dose levels based on the cumulative safety review and preliminary review of pharmacodynamic responses. If additional cohorts are added, this will be documented in a study memo sent to all clinical sites and submitted to Institutional Review Boards, per Institutional Review Board guidance.

During the dose escalation study, ELI-002 2P will be comprised of 1.4 mg of two Amph-modified KRAS peptides G12D and G12R admixed with Amph-CpG-7909 to provide ELI-002 2P. Elicio plans to investigate the use of an Amph-Peptide 7P drug product containing all 7 Amph-Peptides (G12D, G12R, G12V, G12A, G12C, G12S, G13D) admixed with Amph-CpG-7909 (ELI-002 7P) in future clinical trials.

Subjects will receive the initial dose of ELI-002 and be monitored for ≥24 hours after initial dose in order to monitor for potential AEs such as cytokine release syndrome (CRS). In addition, there will be a 1-week stagger between enrollment of the first subject in a cohort and the subsequent subjects. In the absence of toxicity during the dose-limiting toxicity (DLT) assessment window, ELI-002 will be escalated. Planned cohort dose levels are listed below:

- Cohort 1 Dose Level 1: Amph-CpG-7909 0.1 mg with Amph-Peptides 2P
- Cohort 2 Dose Level 2: Amph-CpG-7909 0.5 mg with Amph-Peptides 2P
- Cohort 3 Dose Level 3: Amph-CpG-7909 2.5 mg with Amph-Peptides 2P

Additional cohorts are listed as follows:

- Cohort 4 Dose Level 4: Amph-CpG-7909 5.0 mg with Amph-Peptides 2P

- Cohort 5 Dose Level 5: Amph-CpG-7909 10.0 mg with Amph-Peptides 2P

Cohorts will consist of 3 to 6 subjects (the number will depend on whether DLTs are observed). In order to ensure an adequate number of evaluable subjects, up to 6 subjects may be enrolled per cohort even in the absence of a DLT. Once the RP2D is determined, the cohort evaluating the RP2D Phase 2 dose will be expanded as needed so that there is safety experience with at least 6 subjects at this dose level.

Dose escalation from one cohort to the next will be determined by the Safety Monitoring Committee (SMC) and will be based on treatment-emergent AEs, clinical laboratory data, physical examination (PE) findings including vital signs, after all subjects within a cohort have completed 28 days.

3+3 design:

In any cohort, if none of the first 3 subjects experience a DLT during the first 28 days following first administration of ELI-002 2P, the dose escalation will occur and 3 subjects will be enrolled in the cohort at the next dose level. However, if 1 of the 3 or 4 initial subjects in a cohort experiences a DLT, then 3 (or 2, if 4 were originally enrolled) additional subjects will be enrolled at the same dose level. If 2 or more of 3 subjects within a cohort experience a DLT, then this dose will be considered the toxic dose. If only 1 of 6 subjects within a cohort experiences a DLT during the first 28 days of treatment, then the next cohort may begin enrollment. If 2 or more of 6 subjects within a cohort experience a DLT during the first 28 days, then this dose will be considered the toxic dose. The trial may proceed at a lower dose, at a less frequent schedule, or omitting the Amph-CpG-7909 adjuvant while continuing to administer the Amph-Peptides 2P, based on emerging toxicity or pharmacodynamic data until the MTD is determined.

DLT definition:

A DLT will be defined as any event at least possibly related to ELI-002 as follows:

a. Any Grade ≥ 3 non-hematologic toxicity except asymptomatic laboratory abnormalities (see Protocol Section 12.2.1.1)
b. Any Grade ≥ 3 toxicity involving major organ systems for greater than 72 hours and occurring within 28 days of subcutaneous administration
c. Grade 3 CRS (Cytokine Release Syndrome) that does not resolve to ≤ Grade 2 within 7 days
d. Any Grade 4 CRS that does not improve to < Grade 2 within 72 hours
e. Any Grade ≥ 3 autoimmune disorder
f. Any Grade ≥ 3 rash that does not resolve to ≤ Grade 1 within 7 days with appropriate treatment

The DLT observation period will be 28 days following first dose.

MTD definition:

The MTD is defined as the highest dose level with a DLT incidence <33% of cohort subjects.

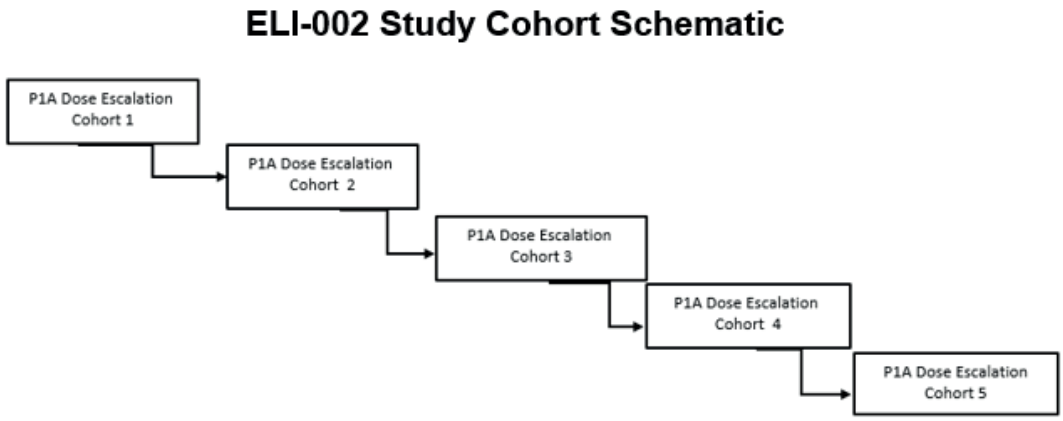
A trial memo will be sent to all sites following each SMC meeting summarizing the decision; if additional cohorts are to be enrolled, the dose level and schedule will be provided.

Safety monitoring is further detailed in the SMC Charter.

The RP2D will be defined in consideration of the MTD (if any), safety data, and pharmacodynamic data. The RP2D will be communicated to all sites in a trial memo following the last SMC cohort review. Once the RP2D is determined, the cohort evaluating the Phase 2 dose will be expanded as needed so that there is safety experience with at least 6 subjects at this dose level.

The Study Flow Chart is presented in Figure 1.

Figure 1: Study Flow Chart



8.2 Randomization and Blinding

ELI-002-001 is an open-label Phase 1 trial with a single arm. Treatment will not be blinded and there will not be randomization as part of this study.

8.3 Study Treatments and Assessments

The total duration of participation for each subject is approximately 3 years, and includes a Screening Period, an Immunization Period, a No Dosing 3-Month Period, a Booster Period, and a Follow-up Period.

- A Screening Period in which study specific procedures, including eligibility determination, will begin at Visit 1.
- An Immunization Period which will consist of 6 SC injections: 4 weekly injections (Visit 3 to Visit 6) followed by 2 injections every two weeks at Visit 7 and Visit 8.
- A No Dosing 3-Month Period in which subjects will continue to be observed and evaluated but no ELI-002 2P treatment will be given.

- A Booster Period, consisting of 4 weekly injections (Visit 12 to Visit 15), in which eligible subjects will receive further lymph node antigen exposure.
- A Follow-up Period which will provide continued safety and efficacy data collected during the follow-up from year 1 through year 3 (Visit 16 to visit 28).

Subjects who remain in the trial until the end of the Booster Period may be eligible to enroll in an Extension Protocol.

ELI-002 2P is an investigational product consisting of 2 drug products:

1. A mixture of lipid-conjugated peptide-based antigens (amphiphilic peptides, referred to as 'Amph-Peptides'). During the Phase 1 (dose escalation) study, the Amph-Peptide mixture (Amph-Peptides 2P) will be comprised of 1.4 mg of 2 Amph modified KRAS peptides, Amph-G12D, and Amph-G12R (0.7 mg/peptide). Elicio plans to investigate the use of an Amph-Peptide 7P drug product containing all 7 Amph-Peptides (G12D, G12R, G12V, G12A, G12C, G12S, G13D) in future clinical trials.

2. A lipid-conjugated immune-stimulatory oligonucleotide ('Amph-CpG-7909').

The ELI-002 2P admixture is prepared by combining the separately provided products with a diluent (10X PBS) prior to dosing. The KRAS Amph-Peptides are provided in 5.0 mM, pH 4.5 acetate buffer in a 2-mL glass vial. The Amph-CpG-7909 is provided in water for injection (WFI) in a 2-mL glass vial. These 2 drug products will then be provided to the clinical pharmacy for combination with 10X PBS (phosphate buffered saline) on a dose-by-dose basis at the proper ratio for administration to the subject as a drug product admixture.

Subjects will receive SC injections of ELI-002 2P during the Immunization Period at Visit 3 through Visit 8. Three months after the Immunization Period, subjects will receive SC injections of ELI-002 2P during the Booster Period at Visit 12 through Visit 15.

The doses evaluated in the Phase 1 cohorts are as shown in Table 1. All cohorts will enroll RAS mutated PDAC, CRC, non-small cell lung cancer (NSCLC) and other solid tumors (including ovarian, bile duct and gallbladder carcinoma).

Table 1: Phase 1 Cohort and Doses

Phase	Cohort	Tumor	Dose Level
Phase 1 (Dose escalation)	Cohort 1	KRAS/NRAS mutated solid tumors	Amph-CpG-7909 0.1 mg with 1.4 mg Amph-Peptides 2P
	Cohort 2		Amph-CpG-7909 0.5 mg with 1.4 mg Amph-Peptides 2P
	Cohort 3		Amph-CpG-7909 2.5 mg with 1.4 mg Amph-Peptides 2P
	Cohort 4		Amph-CpG-7909 5.0 mg with 1.4 mg Amph-Peptides 2P
	Cohort 5		Amph-CpG-7909 10.0 mg with 1.4 mg Amph-Peptides 2P

KRAS=Kirsten rat sarcoma; NRAS=neuroblastoma ras viral oncogene homolog.

A detailed description of procedures and assessments to be conducted during this study is summarized in the schedule of study assessments in Table 11 through Table 16.

Table 2: Schedule of Assessments- Screening and Observation

Assessment		Screening and Observation Period	
Visit	Surgery /Last Dose of Adjuvant Treatment	Visit 1	Visit 2
Day (± days)	0	Day 10 (Days 1-31)	Day 26 (±5 days)
Written informed consent		X[1]	
Tumor tissue and EDTA blood sample for whole exome sequencing (central laboratory)[2]		X[2]	
Pregnancy testing (urine)			X
Patient reported outcomes			X[3]
Demographics (including sex, age, race and ethnicity)			X
Height/weight			X
Record medical and medication history, including cancer history/prior treatments and current medications.			X
Review of eligibility criteria			X[4]
Physical examination			X[5]
Vital signs			X
Electrocardiogram			X
ECOG			X[6]
CT with contrast			X[7]
Clinical laboratory (local laboratory)			X[8]
Serum CA-125, CEA, CA19-9 (local laboratory)			X[9]
Covid-19 viral test (local laboratory)			X[10]
ctDNA (central laboratory)[10]			X[11]

Leukapheresis-PBMC collection for immunogenicity			X[12]
Adverse Events			X

CA=cancer antigen; CBC=complete blood count; CEA=carcinoembryonic antigen; CRC=colorectal cancer; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; DNA=deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; EDTA=ethylenediaminetetraacetic acid; IV=intravenous; mKRAS=mutant Kirsten rat sarcoma; mNRAS=mutant neuroblastoma; MRI=magnetic resonance imaging; PDAC=pancreatic ductal adenocarcinoma; PBMC=peripheral blood mononuclear cell resonance imaging; PDAC=pancreatic ductal adenocarcinoma; PBMC=peripheral blood mononuclear cell

1. The ICF has no expiration and can be signed at any time during or after the prior treatment (including surgery/resection). The screening window (56 days) begins when the first screening procedure is performed.
2. Depending on the clinical site location, a tumor and blood sample will be collected for KRAS mutation status. The tumor sample, if required, will be used for WES to determine KRAS mutation and to develop the tumor-informed personalized ctDNA test. Details are provided in the Central Laboratory Manual. Once a subject has consented, the trial coordinator will requisition a retrospective tumor tissue sample taken during surgical resection (if needed per clinical site location). Prior to shipment, a fresh 6-mL EDTA blood tube will also be collected. Tumor DNA will be sequenced for baseline tumor gene expression. The somatic DNA from the EDTA tube will serve as a control to ensure only tumor-specific DNA is included in the selection for ctDNA testing.
3. The patient reported outcomes (PROs) will include the general QLQ-C30, as well as a specific PRO for the subject's tumor type (see Protocol Section 11.3). PROs must be completed prior to other study visit procedures.
4. See Inclusion and Exclusion Criteria in Protocol Section 7.1 and Protocol Section 7.2, respectively. While mKRAS and ctDNA analyses will not be available at Visit 2, the expectation is that these will be reviewed, and full eligibility determined, prior to Visit 3.
5. Physical examinations are defined in Protocol Section 12.1.3.
6. To be eligible, ECOG performance status must be 0 to 1 (see Protocol Section 12.1.5)
7. To be eligible, post-operative CT must be negative for radiographic recurrent disease. CT imaging assessments will occur between 1 and 31 days post resection. For subjects with IV contrast allergy/intolerance, MRI may be performed.
8. See Inclusion Criterion #9 regarding laboratory values in Protocol Section 7.1. Safety laboratories should include CBC with differential: chemistry to include parameters listed in Protocol Section 12.1.6.3; hematology to include parameters listed in Protocol Section 12.1.6.1; coagulation to include parameters listed in Protocol Section 12.1.6.2; cytokine laboratories IL-2, IFNγ, IL-6, IL-10, and TNFα; viral testing to include parameters listed in Protocol Section 12.1.6.5. Details for central laboratory sample collections are provided in the Central Laboratory Manual.
9. See Inclusion #4 regarding serum biomarker values in Section 7.1. Biomarker values must be obtained ≥21 days post-surgery or last administration of adjuvant therapy whichever comes last in the specific subject's treatment plan.
10. Samples such as swabs, saliva, or others as appropriate may be used for Covid-19 viral testing according to the locally available assay.
11. Blood will be collected for ctDNA analysis at a central laboratory. Eligibility requires that subject's must be MRD positive must be positive, as measured by ctDNA blood test persisting ≥21 days post-surgery or after last administration of adjuvant treatment (whichever is last in the specific subject treatment plan) with 1 of the 2 ELI-002-specific mKRAS/mNRAS alleles. Details for blood collection are provided in the Central Laboratory Manual.
12. The leukapheresis sample must be collected once eligibility has been confirmed and prior to the first dose of ELI-002. The PBMCs may be used for immunogenicity and/or biomarker genetic sequencing. Details for central laboratory sample collections are provided in the Central Laboratory Manual.

Table 3: Schedule of Assessments- Immunization Period

Assessment	Immunization Period						
Visit	Visit 3		Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Day (± days)	Day 57 Baseline (prior to dosing)	Day 57 (dosing) (±3 days)	Day 64 (±3 days)	Day 71 (±3 days)	Day 78 (±3 days)	Day 92 (±3 days)	Day 106 (±3 days)
Dose #	-	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
Patient reported outcomes	X[1]		X[1]	X[1]	X[1]	X[1]	X[1]
Review medical history	X[2]						
Review cancer history/prior treatments	X						
Physical Exam	X[3]		X[3]	X[3]	X[3]	X[3]	X[3]
Vital signs	X	X	X	X	X	X	X
Weight	X		X	X	X	X	X
ECG	X						
ECOG	X		X	X	X	X	X
Concomitant medications	X		X	X	X	X	X
Clinical laboratory (local laboratory)	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]
ctDNA (central laboratory)[5]	X[5]				X[5]		
Whole blood-PBMC collection for immunogenicity testing (central laboratory)				X[4]		X[4]	
Serum collection of cytokine assay (local laboratory)	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]
High Resolution HLA typing (central laboratory)	X[6]						
Trial drug (ELI-002) administration		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]
Adverse events	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
Reactogenicity diary[9]		X	X	X	X	X	X

CA=carbohydrate antigen; CBC=complete blood count; CEA=carcinoembryonic antigen; CRC=colorectal cancer; CRS=cytokine release syndrome; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group: HLA=human leukocyte antigen; IFNγ=interferon gamma; IL=interleukin; mKRAS=mutant

Kirsten rat sarcoma; mNRAS=mutant neuroblastoma ras viral oncogene homolog; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cell; PDAC=pancreatic ductal adenocarcinoma; PE=physical examination; TNFα=tumor necrosis factor alpha

1. The patient reported outcomes (PROs) will include the general QLQ-C30, as well as a specific PRO for the subject's tumor type (see Section 11.3). PROs must be completed prior to other study visit procedures.
2. Subjects must have recovered from surgery without any ongoing medical/surgical issues. See Inclusion and Exclusion Criteria in Section 7.1 and Section 7.2, respectively.
3. Physical examinations are defined in Section 12.1.3. In addition, a neurological examination for baseline ICANS/ICE assessment will be performed at Visit 3, prior to dosing.
4. Safety laboratories should include CBC with differential: chemistry to include parameters listed in Section 12.1.6.3; hematology to include parameters listed in Section 12.1.6.1; coagulation to include parameters listed in Section 12.1.6.2. Cytokine laboratories IL-2, IFNγ, IL-6, IL-10, and TNFα; this testing should be performed and reviewed within 7 days prior to dosing. The PBMCs may be used for immunogenicity and/or biomarker genetic sequencing. Details for central laboratory sample collections are provided in the Central Laboratory Manual.
5. ctDNA blood testing will occur at a central laboratory. Details for blood collection are provided in the Central Laboratory Manual
6. High resolution HLA will be performed for all subjects, prior to first dose at Visit 3. Cohorts will be enrolled regardless of the HLA subtype (see Section 6.1.3 for details). Details for blood collection are provided in the Central Laboratory Manual.
7. ELI-002 administration: Subjects will receive the initial dose of ELI-002 and be monitored for ≥24 hours in order to monitor for potential adverse events such as CRS. For subsequent doses, subjects must be observed for safety for at least 1-hour postdose.
8. Check for signs of toxicity. See Section 6.7 for instructions regarding signs of toxicity and for criteria for stopping treatment administration.
9. Subjects will be provided with a paper reactogenicity diary at the end of the visit. They will be instructed to fill out the diary each day, for 7 days, at the same time per the instructions on the study template. Subjects will return the completed diary at the next scheduled visit. The site staff will review the diary with the subject and file in the subject study records. This completed diary will be used as source data for eCRF data entry

Table 4: Schedule of Assessments- No Dosing 3-Month Period

Assessment	No Dosing 3-Month Period		
Visit	**Visit 9**	**Visit 10**	**Visit 11**
Day (± days)	**Day 120 (±3 days)**	**Day 148 (±3 days)**	**Day 176 (±3 days)**
Patient reported outcomes	X[1]	X[1]	X[1]
Physical examination	X[2]	X[2]	X[2]
Vital signs	X	X	X
Weight	X	X	X
Changes in concomitant medications	X	X	X
CT with contrast		X[3]	
Clinical laboratory (local laboratories)	X[4]	X[4]	X[4]
ctDNA (central laboratory)[5]			X[5]
Leukapheresis-PBMC collection for immunogenicity testing (central laboratory)	X[6]		
Whole blood-PBMC collection for immunogenicity testing (central laboratory)			X[7]
Serum collection for cytokine (local laboratory)			X[4]
Serum CA-125/CEA/CA 19-9 (local laboratories)		X[4]	
Standard of care biopsy (local laboratory)		X[8]	
Adverse events	X	X	X

CA=carbohydrate antigen; CBC=complete blood count; CEA=carcinoembryonic antigen; CRC=colorectal cancer; CRP=C-reactive protein; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; IFNγ=interferon gamma; IL=interleukin; IV=intravenous; mKRAS=mutant Kirsten rat sarcoma; mNRAS=mutant neuroblastoma ras viral oncogene homolog; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cell TNFα =tumor necrosis factor alpha

1. The patient reported outcomes (PROs) will include the general QLQ-C30, as well as a specific PRO for the subject's tumor type (see Section 11.3). PROs must be completed prior to other study visit procedures.
2. Physical examinations are defined in Section 12.1.3.

3. A visit window of ±14 days is permitted for imaging assessments. For subjects with IV contrast allergy/intolerance, MRI may be performed. Unscheduled CT or MRI imaging may be performed at any time, if the investigator determines that there are clinical signs of disease progression.
4. Safety laboratories should include CBC with differential: chemistry to include parameters listed in Section 12.1.6.3; hematology to include parameters listed in Section 12.1.6.1; coagulation to include parameters listed in Section 12.1.6.2. Cytokine laboratories IL-2, IFNγ, IL-6, IL-10, and TNFα. Serum biomarkers CA-125 [ovarian], CA19-9 [PDAC] or CEA [CRC]. Details for central laboratory sample collections are provided in the Central Laboratory Manual
5. ctDNA blood testing will occur at a central laboratory. Details for blood collection are provided in the Central Laboratory Manual
6. The leukapheresis sample may be collected -7 days or +3 days from Visit 9. The PBMCs may be used for immunogenicity and/or biomarker genetic sequencing. Details for central laboratory sample collections are provided in the Central Laboratory Manual.
7. The PBMCs may be used for immunogenicity and/or biomarker genetic sequencing. Details for central laboratory sample collections are provided in the Central Laboratory Manual.
8. If new lesions are observed on radiographic imaging, a standard of care biopsy may be performed per iRECIST criteria to confirm disease progression and when the investigator judges that tissue can be safely obtained. If there is sufficient tissue obtained from the biopsy, the pathology lab should perform in situ gene expression and/or IHC for evaluation of tumor infiltrating T cells and the tumor microenvironment.

Table 5: Schedule of Assessments- Booster Period

Assessment	Booster Period			
Visit	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15/ End of Treatment**
Day (± days)	**Day 196 (±3 days)**	**Day 203 (±3 days)**	**Day 210 (±3 days)**	**Day 217 (±3 days)**
Dose #	**Dose 7**	**Dose 8**	**Dose 9**	**Dose 10**
Patient reported outcomes	X[1]	X[1]	X[1]	X[1]
Physical examination	X[2]	X[2]	X[2]	X[2]
Vital signs	X	X	X	X
Weight	X	X	X	X
ECOG	X	X	X	X
Concomitant medications	X	X	X	X
Clinical laboratory (local laboratory)	X[3]	X[3]	X[3]	X[3]
ctDNA (central laboratory)[4]	X[4]			
Whole blood-PBMC collection for immunogenicity testing (central laboratory)			X[5]	
Serum collection for cytokine assay (local laboratory)	X[3]	X[3]	X[3]	X[3]
Trial drug (ELI-002) administration	X[6]	X[6]	X[6]	X[6]
Adverse events	X[7]	X[7]	X[7]	X[7]
Reactogenicity diary[8]	X	X	X	X

CA=cancer antigen; CBC=complete blood count; CEA=carcinoembryonic antigen; CRC=colorectal cancer; ctDNA=circulating tumor deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; IFNγ=interferon gamma; IL=interleukin; IV=intravenous; mKRAS=mutant Kirsten rat sarcoma; mNRAS=mutant neuroblastoma ras viral oncogene homolog; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cell; PDAC=pancreatic ductal adenocarcinoma; TNFα =tumor necrosis factor alpha

1. The patient reported outcomes (PROs) will include the general QLQ-C30, as well as specific PROs for the subject's tumor type (see Protocol Section 11.6). PROs must be completed prior to other study visit procedures.
2. Physical examinations are defined in Protocol Section 12.1.3.

3. Safety laboratories should include CBC with differential: chemistry to include parameters listed in Protocol Section 12.1.6.3; hematology to include parameters listed in Protocol Section 12.1.6.1; coagulation to include parameters listed in Protocol Section 12.1.6.2. Cytokine laboratories TNFα =tumor necrosis factor alpha IL-2, IFNγ, IL-6, IL-10, and TNFα; this testing should be performed and reviewed within 7 days prior to dosing. Serum biomarkers CA-125 [ovarian], CA19-9 [PDAC] or CEA [CRC]. Details for central laboratory sample collections are provided in the Central Laboratory Manual.
4. ctDNA blood testing will occur at a central laboratory. Details for blood collection are provided in the Central Laboratory Manual
5. The PBMCs may be used for immunogenicity and/or biomarker genetic sequencing. Details for central laboratory sample collections are provided in the Central Laboratory Manual
6. ELI-002 administration for those subjects in Phase 1. Subjects must be observed for safety for at least 1-hour postdose.
7. Check for signs of toxicity. See Protocol Section 6.7 for instructions regarding signs of toxicity and for criteria for stopping treatment administration.
8. Subjects will be provided with a paper reactogenicity diary at the end of the visit. They will be instructed to fill out the diary each day, for 7 days, at the same time per the instructions on the study template. Subjects will return the completed diary at the next scheduled visit. The site staff will review the diary with the subject and file in the subject study records. This completed diary will be used as source data for eCRF data entry.

Table 6: Schedule of Assessments- Follow-up Period (Year 1 to Year 2)

Assessment	Follow-up Period								
Visit	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**	**Visit 20**	**Visit 21**	**Visit 22**	**Visit 23**	**Visit 24**
Day (± days)	**Day 231 (±3 days)**	**Day 259 (±3 days)**	**Day 315 (±3 days)**	**Day 399 (±3 days)**	**Day 483 (±3 days)**	**Day 567 (±3 days)**	**Day 651 (±3 days)**	**Day 735 (±3 days)**	**Day 819 (±3 days)**
Patient reported outcomes	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Physical Exam					X[2]				
Vital signs	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
ECOG	X	X	X	X	X	X	X	X	X
CT with contrast		X[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Clinical laboratory (local laboratory)	X[4]								
ctDNA (central laboratory)[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Whole blood-PBMC collection for immunogenicity testing (central laboratory)	X[6]								
Serum CA-125/CEA/CA 19-9 (local laboratory)		X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Serum collection for cytokine analysis (local laboratory)	X[4]								
Adverse events	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]
Standard of care biopsy (local laboratory)		X[8]		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]

CA=cancer antigen; CBC=complete blood count; CEA=carcinoembryonic antigen; CRC=colorectal cancer; ctDNA=circulating tumor deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; IFNγ=interferon gamma; IL=interleukin; IV=intravenous; mKRAS=mutant Kirsten rat sarcoma; mNRAS=mutant neuroblastoma ras viral oncogene homolog; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cell; PDAC=pancreatic ductal adenocarcinoma; TNFα =tumor necrosis factor alpha

1. The patient reported outcomes (PROs) will include the general QLQ-C30, as well as specific PROs for the subject's tumor type (see Protocol Section 11.6). PROs must be completed prior to other study visit procedures.
2. Physical examinations are defined in Protocol Section 12.1.3.
3. A visit window of ±14 days is permitted for imaging assessments during the Follow-up Period. For subjects with IV contrast allergy/intolerance, MRI may be performed.
4. Safety laboratories should include CBC with differential: chemistry to include parameters listed in Protocol Section 12.1.6.3; hematology to include parameters listed in Protocol Section 12.1.6.1; coagulation to include parameters listed in Protocol Section 12.1.6.2. Cytokine laboratories IL-2, IFNγ, IL-6, IL-10, and TNFα. Serum biomarkers CA- 125 [ovarian], CA19-9 [PDAC] or CEA [CRC]. Details for central laboratory sample collections are provided in the Central Laboratory Manual
5. ctDNA blood testing will occur at a central laboratory. Details for blood collection are provided in the Central Laboratory Manual
6. The PBMCs may be used for immunogenicity and/or biomarker genetic sequencing. Details for central laboratory sample collections are provided in the Central Laboratory Manual.
7. Long-term observation for post dose vaccination adverse events will be recorded if an adverse event began within 30 days of last dose of treatment and continues in the follow-up period.. See Protocol Section 6.7 for instructions regarding signs of toxicity.
8. If new lesions are observed on radiographic imaging, a standard of care biopsy may be performed per iRECIST criteria to confirm disease progression and when the investigator judges that tissue can be safely obtained. If there is sufficient tissue obtained from the biopsy, the pathology lab should perform in situ gene expression and/or IHC for evaluation of tumor infiltrating T cells and the tumor microenvironment.

Table 7: Schedule of Assessments- Follow-up Period (Year 2 to Year 3)

Assessment	Follow-up Period			
Visit	**Visit 25**	**Visit 26**	**Visit 27**	**Visit 28/ End of Study[6]**
Day (± days)	**Day 903 (±3 days)**	**Day 987 (±3 days)**	**Day 1071 (±3 days)**	**Day 1127 (±3 days)**
ECOG	X	X	X	X
CT with contrast	X[1]	X[1]	X[1]	X[1]
ctDNA (central laboratory)	X[3]	X[3]	X[3]	X[3]
Serum CA-125/CEA/CA 19-9 (local laboratory)	X[2]	X[2]	X[2]	X[2]
Adverse events	X[4]	X[4]	X[4]	X[4]
Standard of care biopsy (local laboratory)	X[5]	X[5]	X[5]	X[5]

CA=carbohydrate antigen; CBC=complete blood count; CEA=carcinoembryonic antigen; CRC=colorectal cancer; ctDNA=circulating tumor deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; IFNγ=interferon gamma; IL=interleukin; IV=intravenous; mKRAS=mutant Kirsten rat sarcoma; mNRAS=mutant neuroblastoma ras viral oncogene homolog; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cell; PDAC=pancreatic ductal adenocarcinoma; TNFα =tumor necrosis factor alpha

1. A visit window of ±14 days is permitted for imaging assessments during the Follow-up Period. For subjects with IV contrast allergy/intolerance, MRI may be performed. Unscheduled CT or MRI imaging may be performed at any time, if the investigator determines that there are clinical signs of disease progression.
2. Serum biomarkers CA-125 [ovarian], CA19-9 [PDAC] or CEA [CRC]. Details for central laboratory sample collections are provided in the Central Laboratory Manual
3. ctDNA blood testing will occur at a central laboratory. Details for blood collection are provided in the Central Laboratory Manual
4. Long-term observation for post dose vaccination adverse events will be recorded if an adverse event began within 30 days of last dose of treatment and continues in the follow-up period. See Section **Error! Reference source not found.** for instructions regarding signs of toxicity.
5. If new lesions are observed on radiographic imaging, a standard of care biopsy may be performed per iRECIST criteria to confirm disease progression and when the investigator judges that tissue can be safely obtained. If there is sufficient tissue obtained from the biopsy, the pathology lab should perform in situ gene expression and/or IHC for evaluation of tumor infiltrating T cells and the tumor microenvironment.
6. All enrolled subjects should be followed in the Follow-Up period for disease status and overall survival. As part of the study, sites may conduct searches of public records, such as those establishing overall survival status, to obtain survival data as needed (ie: a subject that is lost to follow up, withdraws from the study, etc.)

9.0 STUDY ENDPOINTS

9.1 Endpoints

9.1.1 Phase 1 Primary Endpoints

- To define the MTD of ELI-002 (in the event there is an MTD) and the recommended Phase 2 dose (RP2D)
- To evaluate safety as assessed by the incidence of adverse events (AEs) and clinically significant changes in laboratory tests and vital signs

9.1.2 Phase 1 Secondary Endpoint

- To report the proportion of subjects with ctDNA reduction and clearance, defined as reduction or clearance in ctDNA compared to baseline, or if ctDNA was not detectable at baseline, serum tumor biomarker (such as CA19-9, CEA, and CA-125) reduction and clearance compared to baseline

9.1.3 Phase 1 Exploratory Endpoints

- Median RFS, 1-Year RFS, and OS.
- Duration of biomarker (ctDNA or serum tumor biomarker) clearance and reduction, defined as time from the date of the first negative and/or decreased biomarker to the earliest date of any of the following events:
  - Subsequent increased/positive ctDNA
  - Subsequent disease relapse
  - Death due to any cause
- Change relative to baseline in:
  - Serum cytokines IL-2, IFNγ, IL-6, IL-10, and TNFα
  - PROs: EORTC QLQ-C30 and QLQ-PAN26, QLQ-CR29, QLQ-OV28, QLQ-BIL21 or QLQ-LC13
  - Immunogenicity of ELI-002 determined by magnitude of response and fold-change from baseline, using assays such as ICS, Fluorospot, and/or dextramer+ T cells for subjects with HLA alleles for which dextramer/s is/are available.1
  - Biomarker levels (ctDNA, CA19-9, CEA, and CA-125)
  - Immune cell infiltrate and tumor microenvironment if standard of care biopsies are obtained to confirm disease progression

Immunogenicity analyses are beyond the scope of this Statistical Analysis Plan and is provided as an appendix in this document.

10.0 SAMPLE SIZE AND POWER

Planned sample size:

Phase 1 Escalation: Approximately 18 subjects are planned to enroll: 3 to 6 subjects in Cohort 1; 3 to 6 subjects in Cohort 2; and 3 to 6 subjects in Cohort 3.

The sample size for Phase 1 is not based on power calculations, but rather on clinical judgement and the expectation that the objectives of this trial will be met with approximately 18 subjects enrolled in the 3+3 design.

11.0 ANALYSIS POPULATIONS

11.1 Full Analysis Set

The Full Analysis Set (FAS) will include all subjects who received any amount of ELI-002-2P vaccine. This population will be used for summaries of subject demographics, and baseline characteristics. Additional exploratory analyses may be performed for the subjects treated at the MTD and doses lower than the MTD at which biomarker (ctDNA, or if ctDNA was not detected at baseline, serum tumor biomarker) clearance/reduction is observed.

Planned treatment received will be used for FAS.

11.2 Safety Analysis Set

All subjects who received at least one dose of vaccine ELI-002-2P. This set will be used for the safety evaluation (AEs, clinical laboratory assessments, vital signs, ECGs, ECOG, PEs). No data will be imputed for the safety analysis set; only observed data will be summarized unless otherwise specified. Actual treatment received will be used for the Safety Analysis Set.

11.3 Per protocol Set

The Per Protocol Analysis Set will include all FAS subjects who have no major protocol violations. The exclusion list for this set will be identified prior to database lock. Analysis on the Per Protocol Analysis Set will be performed if warranted.

All violations and exclusions of subjects from analysis sets will be identified through programmatic checks, through medical reviews, and by clinical research associates during site monitoring. Protocol deviations will be classified as key (important) or non-key (not important) prior to the database lock.

11.4 PD (Pharmacodynamic)/Biomarker Evaluable Set (PDS)

The PD/Biomarker Evaluable Set will include subjects who receive any amount of trial treatment, with the additional requirement that relevant blood sampling data at the appropriate assessment time point(s) must be available for inclusion in the analysis for any PD parameter.

The PDS analysis set will be used for summary of Pharmacodynamic endpoints and biomarkers.

12.0 STATISTICAL CONSIDERATIONS AND ANALYSIS

12.1 Derived Variables

The Table provide the list of derived variables for Demographic and baseline characteristics, various duration derivations, drug compliance, baseline derivations and other important derivations applicable for this study.

Table 8: Derived variables

Variables	Formula
Demographic and Baseline characteristics	
Body mass index (BMI) (kg/m^2)	weight (kg)/[height (m)]^2
Derivation of Duration	
Study day at any visit	Date of interest – date of first dose of study treatment. One day is added if this difference is ≥ 0
Duration of study (Days)	(Date of study completion/discontinuation (for discontinued subjects) – date of first dose) + 1
Duration of Exposure to the study treatment (weeks)	Is [last date of booster dose – first date of immunization dose] + 1] / 7. IF treatment discontinuation, then last date of booster dose = last dose date prior to or at the date of treatment discontinuation.
Treatment Exposure and Compliance	
Cumulative Planned volume (mL)	Total planned volume for each dose* Planned number of doses for the duration of exposure
Cumulative actual volume administered (mL)	Total actual volume administered from exposure CRF page (Cumulative value of 'Actual volume administered' from Study Drug Administration)
Expected Dose	Calculated as the expected number of vaccinations multiplied by assigned dose in mg
Compliance (%)	(Cumulative actual volume administered /Cumulative planned volume)*100
Dose intensity (DI) for ELI-002 Amph-Peptides 2P	Amount of actual cumulative dose of ELI-002 Amph-Peptides 2P (mg) divided by expected dose given for a full 10 course of vaccinations.
Dose intensity (DI) for ELI-002 Amph-CpG-7909	Amount of actual cumulative dose of ELI-002 Amph-CpG-7909 (mg) divided by expected dose given for a full 10 course of vaccinations.
Relative dose intensity	Cumulative dose received divided by expected dose and multiplied by 100
Baseline Derivations	
Baseline value	Unless otherwise specified, the baseline value is defined as the last non-missing observation prior to administration of the first dose of study treatment. For most assessments, this would be the Visit 3 value. If Visit 3 is missing, the Visit 2 value will be used.
Change from baseline	Post baseline value – Baseline value
Fold change from baseline	(Post baseline value – Baseline value)/Baseline value
Biomarker Reduction/Clearance Note: All reporting will select the biomarker (ctDNA, CEA, or CA-19) which contains the best (i.e., largest decrease post-baseline) result per subject. If there is no decrease for a given subject, then "best" is the smallest increase.	

Clearance	Define as the percent change from baseline of the on-study ctDNA, or CA19-9, or CEA that achieved -100%. **Notes**: a. Clearance start will be the date of first clearance. b. Once clearance start date is identified for a biomarker, the same biomarker will be used to determine the clearance end date. c. Results will not be considered if a subject has already started taking subsequent anti-cancer therapy. d. If there is a tie for best response across biomarkers, select ctDNA first. ▪ For PDAC subjects, select CA19-9 second, CEA third. • For CRC subjects, select CEA second, CA19-9 third.
Reduction	Defined as the percent change from baseline of the on-study ctNDA, or CA19-9, or CEA that achieved any decrease (i.e., a negative percent change from baseline). **Notes**: a. Reduction start will be the date of first reduction. b. Once reduction start date is identified for a biomarker, the same biomarker will be used to determine the reduction end date. c. Results will not be considered if a subject has already started taking subsequent anti-cancer therapy. d. If there is a tie for best response across biomarkers, select ctDNA first. • For PDAC subjects, select CA19-9 second, CEA third. • For CRC subjects, select CEA second, CA19-9 third.
Duration of Biomarker Clearance/Reduction	
Clearance Duration	This is confirmed after clearance start by an increase above -100% change from baseline followed by a second increase above -100% at least 1 week afterwards. **Notes**: a. The end date will be the date of the first subsequent increase. b. If the increase cannot be confirmed by a second increase, then the potential end date of biomarker clearance will proceed to the next increase and so on. c. Subjects with confirmed clearance duration will not be censored.
Reduction Duration	This is confirmed after reduction start by an increase above the initial reduction followed by a second increase above the initial reduction at least 1 week afterwards.

	Notes: a. The end date will be the date of the first subsequent increase. b. The second increase may be above or below the first subsequent increase as long as it is above the first documented reduction. c. If the increase cannot be confirmed by a second increase, then the potential end date of biomarker reduction will proceed to the next increase and so on. d. Subjects with a confirmed reduction duration will not be censored.

12.2 Handling of Missing Data

In the case of progression free survival or overall survival analyses, missing data will be handled through the use of censoring at the "date of last tumor assessment", or "date last known to be alive," respectively (Details see Table). In the case of missing data for all other analyses, there will be no data imputation (i.e., missing data will be left as missing), unless otherwise specified.

12.3 Handling of Missing or Incomplete Dates

12.3.1 Imputation rules for missing or partial AE start /stop date

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1st of the month.

Compare the imputed AE start date with TE period to determine whether the AE is pre-treatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start Month as January and the Day as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pre-treatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.

If AE is NOT Ongoing, then AE stop date imputation is applicable.

If only Day of AE stop date is missing:

If the AE stop month and/or year are not same as that for the first dose date, then impute the AE stop day the last day of the month.

If Day and Month of AE stop date is missing:

If the AE stop year is the same as the year of discontinuation and discontinuation date is earlier than December 31st, then impute the AE stop day as the date of discontinuation.

If different from the above, then impute the AE stop day as the December 31st

If only Month of AE stop date is missing

If the AE stop year are the same as the year of discontinuation, then impute the AE stop month as the month of discontinuation

If different from the above, then impute the AE stop month as the December

If Day, Month and Year of AE stop date is missing:

No imputation, date is completely missing, assume Ongoing

12.3.2 Imputation rules for missing or partial concomitant medication start/stop dates

Missing or Partial Medication Start Date:

- If only DAY is missing, use the first day of the month.
- If DAY and Month are both missing, use the first day of the year.
- If DAY, Month and Year are all missing, no imputation.

Missing or partial medication stop date:

- If only DAY is missing, use the last day of the month.
- If DAY and Month are both missing, use the last day of the year.
- If DAY, Month and year are all missing, no imputation.

12.3.3 Imputation of missing exposure end dates

In general, completely missing exposure dates are not imputed.

12.4 Patient Reported Outcomes

12.4.1 EORTC QLQ-C30

The quality of life (QoL) questionnaire based on the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 is composed of both multi-item and single-item measures based on the QLQ-C30 CRF page. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. The scoring of scales is based on 30 item numbers (questions) is given in Table .

Table 9: Scoring the QLQ-C30 version 3.0

	Number of items	Item range*	Version 3.0 Item numbers

Global health status / QoL			
Global health status/QoL	2	6	29, 30
Functional scales			
Physical functioning	5	3	1 to 5
Role functioning	2	3	6, 7
Emotional functioning	4	3	21 to 24
Cognitive functioning	2	3	20, 25
Social functioning	2	3	26, 27
Symptom scales / items			
Fatigue	3	3	10, 12, 18
Nausea and vomiting	2	3	14, 15
Pain	2	3	9, 19
Dyspnoea	1	3	8
Insomnia	1	3	11
Appetite loss	1	3	13
Constipation	1	3	16
Diarrhea	1	3	17
Financial difficulties	1	3	28

* *Item range* is the difference between the possible maximum and the minimum response to individual items

The 3 Scale scores will be calculated by averaging items within scales and transforming average scores linearly. All of the scales range in score from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning whereas a high score for a symptom scale or item represents a high level of symptomatology or problems (Fayers et al., 2001).

Scoring algorithm

For all scales, the Raw Score (RS) is the mean of the component Items:

$$RS = (I1 + I2 + \cdots + In) / n$$

Functional score = {1- [(RS - 1) / range]} * 100

Symptoms scales / items and Global Health Status /QoL score = {(RS-1) / range} * 100

For missing items in a scale, if at least 50% of the items are answered using the standard formula for calculating the scale scores, ignore any items with missing values. If more than 50% of the items in a scale are missing, set the sale score if missing. For a single-item measure, set the score to missing.

12.4.2 EORTC PAN26

The Pancreatic Cancer Module is a Phase 3 completed supplementary questionnaire module to be employed in conjunction with the QLQ-C30. The QLQ-PAN26 consists of seven hypothesized scales to assess pancreatic pain, digestive symptoms, altered bowel habit, hepatic, body image, satisfaction with health care, and sexuality. In addition, ten single items measure other issues related to pancreatic cancer. The scoring approach and interpretation for this score are the same as QLQ-C30 (see Scoring algorithm

The scoring of scales based on 26 item numbers (questions 31 through 56) is given in Table.

Table 10: Scoring the QLQ-PAN26

	Number of items	Item range*	QLQ-PAN26 item numbers	Reverse scoring items
Symptom scales / items				
Pancreatic pain	4	3	31, 33 – 35	
Bloating	1	3	32	
Digestive symptoms	2	3	36, 37	
Taste	1	3	38	
Indigestion	1	3	39	
Flatulence	1	3	40	
Weight loss	1	3	41	
Weakness arms and legs	1	3	42	
Dry mouth	1	3	43	
Hepatic symptoms	2	3	44, 45	
Altered bowel habit	2	3	46, 47	
Body image	2	3	48, 49	
Troubled with side-effects	1	3	50	
Future Worries	1	3	51	
Planning of activities	1	3	52	
Functional Scale				
Satisfaction with healthcare	2	3	53, 54	53, 54
Sexuality	2	3	55, 56	

* *Item range* is the difference between the possible maximum and the minimum response to individual items;

12.4.3 EORTC BIL21

The BIL21 module for patients with Cholangiocarcinoma and Gall Bladder includes 21 items, conceptualized as consisting of scales and single items. The scoring of scales is based on 21 item numbers (questions 31 through 51) are given in Table . The scoring algorithm is similar to EORTC-QLQ-30 (see Scoring algorithm

Table 11: Scoring the QLQ-BIL21

	Number of items	Item range*	QLQ-BIL21 item numbers
Eating	4	3	31 – 34
Jaundice scale	3	3	35 - 37
Tiredness scale	3	3	38- 40
Pain scale	4	3	41 - 44
Anxiety scale	4	3	45 - 48
Treatment side effects	1	3	49

Drainage bags/tube	1	3	50
Weight loss	1	3	51

* *Item range* is the difference between the possible maximum and the minimum response to individual items;

12.4.4 EORTC CR29

The Colorectal Cancer Module is a supplementary questionnaire module to be employed in conjunction with the QLQ-C30. The QLQ-CR29 incorporates 4 multi-item scales and 19 single-item assessing a range of symptoms and problems common among patients with colorectal cancer. The scoring approach for the QLQ-CR29 is identical in principle to that for the function and symptom scales/single-items of the QLQ-C30 (see Scoring algorithm

. All scoring information specific to the QLQ-CR29 is presented in Table .

Table 12: Scoring the QLQ-CR29

	Number of Items (n)	Item range*	QLQ-CR29 Items	Reverse Items
Symptom scales/items				
Urinary frequency	2	3	31,32	
Urinary incontinence	1	3	33	
Dysuria	1	3	34	
Abdominal pain	1	3	35	
Buttock pain	1	3	36	
Bloating	1	3	37	
Blood and mucus in stool	2	3	38, 39	
Dry mouth	1	3	40	
Hair loss	1	3	41	
Taste	1	3	42	
Flatulence[1]	1	3	49	
Faecal incontinence[1]	1	3	50	
Sore skin[1]	1	3	51	
Stool frequency[1]	2	3	52, 53	
Embarrassment[1]	1	3	54	
Stoma care problems[2]	1	3	55	
Impotence[3]	1	3	57	
Dyspareunia[4]	1	3	59	
Functional scales/items				
Anxiety	1	3	43	
Weight	1	3	44	
Body Image	3	3	45 – 47	
Sexual interest (men)[3]	1	3	56	56
Sexual interest (Women)[4]	1	3	58	58

* Item range is the difference between the possible maximum and the minimum response to individual items.

[1] When scoring scales or single-items that include questions 49 – 54, ensure the answers are taken from the relevant box of questions. Therefore, check the answer to question 48: 'Do you have a stoma bag (colostomy/ileostomy)?'

[2] This item is of relevance only if the answer to question 48 is 'Yes'.

[3] Items 56 and 57 are only applicable to men.

[4] Items 58 and 59 are only applicable to women.

12.4.5 EORTC LC13

The Lung Cancer Module is a supplementary questionnaire module to be employed in conjunction with the QLQ-C30. The QLQ-LC13 incorporates one multi-item scale to assess dyspnoea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis. The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales / single-items of the QLQ-C30 (see Scoring algorithm
All scoring information specific to the QLQ-LC13 is presented in Table .

Table 13: Scoring the QLQ-LC13

Symptom scales/items	Number of items (*n*)	Item range*	QLQ-LC13 Items range
Coughing	1	3	31
Haemoptysis	1	3	32
Dyspnoea [a]	3[a]	3	33 - 35
Dyspnoea when resting [a]	1	3	33
Dyspnoea when walking [a]	1	3	34
Dyspnoea when stairs [a]	1	3	35
Sore mouth	1	3	36
Dysphagia	1	3	37
Peripheral neuropathy	1	3	38
Alopecia	1	3	39
Pain in chest	1	3	40
Pain in arm or shoulder	1	3	41
Pain in other parts	1	3	42

* Item range is the difference between the possible maximum and the minimum response to individual item.

a The dyspnoea scale should only be calculated if all three items have been answered. Some respondents ignore question 35 because they never climb stairs; in this case, the score for the dyspnoea scale would be biased if it were based upon the other two items. Hence if item 35 is missing then items 33 and 34 should be used as single-item measures.

12.4.6 EORTC QLQ-OV28

The Ovarian Cancer Module is a supplementary questionnaire module to be employed in conjunction with the QLQ-C30. The QLQ-OV28 incorporates seven multi-item scales to assess body image, sexuality, attitude to disease or treatment, abdominal or gastro-intestinal symptoms, peripheral neuropathy, hormonal or menopausal symptoms and other chemotherapy side-effects. The scoring approach for the QLQ-OV28 is identical in principle to that for the [function and/or symptom scales / single items] of the QLQ-C30 (see Scoring algorithm

All scoring information specific to the QLQ-OV28 is presented in Table .

Table 14: Scoring the QLQ-OV28

Symptom scales/items	Number of items (*n*)	Item range*	QLQ-OV28 item numbers	Reverse scoring items
Abdominal/GI symptoms	7	3	31 - 37	
Peripheral Neuropathy	3	3	41 - 43	
Other chemotherapy side-effects [a, b]	7	3	38 - 40, 44 - 47	
Hormonal/menopausal symptoms	2	3	48, 49	
Body image	2	3	50, 51	
Attitude to disease/treatment	3	3	52 - 54	
Sexuality [c]	2 / 4	3	55 - 58	55, 56, 57

* Item range is the difference between the possible maximum and the minimum response to individual items

[a] The "other chemotherapy side effects" scale is composed of 7 items which may not be highly intercorrelated depending on the administered treatment. In case of doubt, it is advised to investigate these 7 items individually.

[b] Item 39 is conditional and must not be scored if the response to question 38: 'Have you lost any hair?' is 'not at all'.

[c] Items 57 and 58 are conditional and must not be scored if the response to question 56 ('To what extent were you sexually active?') is 'not at all'. If items 57 and 58 are not applicable, than the sexuality scale is composed only of items 55 and 56.

13.0 STATISTICAL METHODS

13.1 General Statistical Conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

No formal tests of hypotheses are planned for analyses described in this document. Nominal p-values may be computed for secondary or exploratory efficacy analyses as a descriptive measure of strength of results rather than for formal tests of hypotheses.

Unless otherwise stated, all summary tables and summary figures will be presented by cohort/dose level and scheduled visits (if applicable).

All specified visit assessments described in protocol section 6.1.4 will be included in the analyses. If more than one visit assessments (not labeled as unscheduled) are available, only consider the chronologically most recent assessment for the analyses.

All subject data, including unscheduled visit results and derived data, will be presented in listings sorted by cohort/dose level, scheduled visit, and subject number in chronological order (if applicable).

Efficacy data will be listed by patient. Continuous variables will be summarized using mean, standard deviation, median, minimum value, maximum value; categorical variables will be summarized using frequency counts and percentages; and time to event data will be summarized using the Kaplan-

Meier method. Where appropriate, estimates of the median and other quantiles, as well as individual time points (for time to event data) will be produced. The purpose of the efficacy summaries is to document the efficacy findings of this study to inform the design of subsequent studies. All summaries will be presented by cohort/dose levels and overall.

Emphasis will be on RP2D, highest dose, and combined RP2D and all higher doses for change from baseline and comparison to lowest dose.

13.2 Subject Disposition

Subject disposition information will be summarized for all screened subjects. The number and percent of subjects who were screened, screen failures, received study treatment, participated in immunization period, no dosing period, booster period, completed the treatment period, discontinued study treatment early along with the reasons for early discontinuation of study treatment, completed the study and discontinued the study early along with the reasons for early discontinuation of study, participated in the follow-up period.

Counts and percentages of subjects in each analysis population will also be summarized along with the reasons for exclusion from each analysis population.

By subject listing will also be provided.

13.3 Protocol Deviations

Major protocol deviations will be summarized. All protocol deviations will be listed.

13.4 Background Characteristics

13.4.1 Demographics and baseline disease characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics (for continuous variables) or counts and percentages of subjects (for categorical variables) as appropriate using all enrolled subjects. All demographic and baseline characteristics presented in CRF will be listed by subject.

The following demographic and baseline characteristics will be summarized:

- Age (years) at screening
- Sex
- Race
- Ethnicity
- Height at baseline
- Weight at baseline
- BMI at baseline
- Eastern Cooperative Oncology Group (ECOG) performance status
- Covid-19 test (Positive/Negative)
- Study disease

- Initial diagnosis disease
- Highest Stage achieved prior to resection
- Disease stage at screening
- Prior therapies (systemic therapies, radiation, and surgeries) (yes/no)

A by-subject listing will present genotype for HLA A, B, and C alleles. Due to expected heterogeneity at these loci, no summary table is planned for HLA type.

13.4.2 Other Therapies and procedures

By-subject listings will be provided for each of the following: prior anti-cancer therapy, prior-radiation therapy, subsequent cancer therapy, prior anti-cancer surgery and procedures and concomitant procedures.

Prior anti-cancer systemic therapies will be summarized using the count and percentage of subjects for FAS for different type of therapy, intent, and best response to therapy line, reason for discontinuation, and progressing during or after the treatment. Best response will not be evaluable for those subjects that previously received adjuvant therapy (versus total neoadjuvant therapy) since response to therapy is not assessed in the adjuvant setting.

Prior anti-cancer radiation therapy will be summarized using the count and percentage of subjects for radiation therapy type, intent, settings, and best response achieved with prior radiation therapy. Best response will not be evaluable for those subjects that previously received adjuvant therapy (versus total neoadjuvant therapy) since response to therapy is not assessed in the adjuvant setting.

Count and percentage of subjects with prior Anti-Cancer surgeries and procedure will be summarized for each cohort/dose levels. The Anatomical locations and the types will be presented in the listings.

Similarly, subsequent cancer therapies will be summarized using the count and percentage of subjects for therapy type and best response achieved with subsequent cancer therapies.

13.4.3 Medical history

A summary of medical history will be presented by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Affairs® (MedDRA) Version 23.1 or higher using the FAS.

A by-subject listing will be provided.

13.4.4 Prior and concomitant medications

Medications used in this study will be coded by using the latest available version of the World Health Organization Drug Dictionary Enhanced (WHODDE).

Prior medications: are defined as those medications with start date prior to the date of first dose of study treatment.

Concomitant medications: are defined as those medications with a start date on or after the first dose of study treatment or prior medication with an end date after the first dose of the study treatment.

Medications started prior to first dose and continued into the treatment phase will be considered as concomitant medication. Medications with missing start date but an observed end date after the first dose of study treatment, will be considered as concomitant medication.

A medication can be considered both prior and concomitant

Prior medications and concomitant medications will be summarized descriptively using frequency count tables by Anatomical Therapeutic Chemical (ATC) class and preferred name using the FAS and presented separately. Details for imputing missing or partial start and/or stop dates of medication are described in Section 7.3.2.

A by-subject listing will be provided for prior/concomitant medication.

13.4.5 Concomitant procedures

Concomitant procedures will be presented in a by-subject listing.

13.5 Extent of Exposure

Study treatment exposure and study treatment compliance will be summarized using the safety analysis set.

13.5.1 Duration of exposure to the study treatment

Exposure to study treatment will be defined as total number of days treated with study treatment during the study. The derivation of duration of exposure to the study treatment (in weeks) is given in Table 8. Study treatment exposure will be summarised on the Safety Analysis Set using descriptive statistics.

Exposure to study treatment will be summarized by cohort/dose level, and period (Immunization Period: Visit 3 to Visit 8, Booster Period: Visit 12 to Visit 15). The duration of exposure is based on non-missing dates from exposure CRF page.

The planned volume and number of planned doses are not collected in CRF. The total number of intended doses as per protocol is 10. The cumulative planned volume will be computed using the following information.

As per investigational product Manual the planned volume in cohort 1 through 3 is 1.64mL for 4 administrative locations. The planned volume of cohort 4 and cohort 5 is 2.2mL and 3.32mL respectively. Cumulative planned volume in mL will be derived using the formula in Table 8 and will be summarized based on Safety set.

The cumulative actual volume administered (mL) will be computed as the sum of actual volume administered in 4 locations from the study drug administration CRF page as mentioned in Table 8.

As per protocol the dose of ELI-002 Amph-Peptides 2P (mg) will be assumed as 1.4mg per 4 injections.

ELI-002 Amph-CpG-7909 dose will be the cohort dose levels 0.1mg, 0.5mg, 2.5mg, 5.0mg or 10.0 mg.

Expected dose will be calculated as the expected number of vaccinations multiplied by assigned dose in mg.

Compliance (%), Dose intensity (DI) for ELI-002 Amph-Peptides 2P, Dose intensity (DI) for ELI-002 Amph-CpG-7909, Duration of treatment in weeks, Relative dose intensity will be derived (see Table 8). The Number of Injections Received, Expected Doses, Reason Dose Not Administered, Administration Locations, and Amph-Peptides 2P dose will be summarized.

The summary will be based on Safety set.

Drug administration details including derived variables will be provided in listings.

13.5.2 Treatment compliance

The calculation for the cumulative planned volume, cumulative actual volume administered and treatment compliance is given in Table 8 will be summarized for the Safety Analysis Set. Compliance will also be summarized using descriptive statistics.

13.6 Efficacy Analyses

Continuous variables of efficacy endpoints will be summarized using descriptive statistics while categorical variables will be presented using counts and percentage of subjects. Kaplan-Meier (KM) estimates of the median and other quantiles, as well as individual time points (for time to event data) will also be provided as relevant. KM plots, waterfall, and swimmer plots will be presented as applicable. Once a subject's marker is selected for the waterfall plot, and the swimmer plots should use the same marker for the subjects.

13.6.1 Analysis methods and censoring

The statistical analysis methods for RFS, 1-Year RFS and OS are summarized in Table 15. Unless otherwise stated, the full analysis set (FAS) will be the primary analysis set for all efficacy endpoints.

Table 15: Statistical Method for Efficacy Endpoints

Endpoints	Analysis Set [#]	Type	Method
RFS [e]	FAS	Time to event	Kaplan-Meier
OS [e]	FAS		
1-Year RFS [e]	FAS		

[e] exploratory endpoint.
[#] FAS=Full Analysis Set.

The derivation and censoring rules for the efficacy endpoints described in the following table.

Table 16: Censoring Rules for RFS, 1-Year RFS and OS

Situation	Event or censored date	Event or Censored
Censoring Rules for RFS/Primary Analysis		
No subsequent anti-cancer therapy initiated or **lost to follow up/withdrawal of consent for follow up**: Death or recurrence **(iCPD)**	Date of recurrence **(iCPD)** or death, whichever occurs first	Event
No recurrence or death	Date of last evaluation CT/MRI visit, without documentation of recurrence of disease (iUPD or absence of progression)	Censor
Subsequent anti-cancer therapies initiated: Death or recurrence **(iCPD)** after no more than 1 consecutive missed **CT/MRI** evaluation (ie, ≤182 days (24 weeks + 2 weeks) after start of subsequent anti-cancer therapies	Date of recurrence **(iCPD)** or death, whichever occurs first, according to the following: If death occurs without recurrence, then event is the date of death If recurrence occurs prior to death, then the date of last evaluable CT/ MRI visit, without documentation of recurrence of disease **(iUPD or absence of progression)**, that is done before the start of subsequent anti-cancer therapy	Event
No recurrence or death after no more than 1 consecutive missed **CT/MRI** evaluation (ie, ≤182 days (≤24 weeks + 2 weeks) after start of subsequent anti-cancer therapy .	Date of last evaluable CT/ MRI visit, without documentation of recurrence of disease **(iUPD or absence of progression)**, that is done before the start of subsequent anti-cancer therapy	Censored
Incomplete or no baseline assessment	Date of start of treatment (censored on Day 1)	Censored
No post baseline CT/MRI scans	Date of start of treatment (censored on Day 1)	Censored
Treatment discontinuation for undocumented progression or for toxicity	Date of last evaluation CT/MRI visit, without documentation of recurrence of disease (iUPD or absence of progression)	Censored
Censoring Rules for RFS/Secondary Analysis		

Situation	Event or censored date	Event or Censored
No subsequent anti-cancer therapy initiated or **lost to follow up/withdrawal of consent for follow up**: Death or recurrence **(iCPD)** No recurrence or death	 Date of recurrence **(iCPD)** or death, whichever occurs first Date of last evaluation CT/MRI visit, without documentation of recurrence of disease (iUPD or absence of progression)	 Event Censor
Subsequent anti-cancer therapies initiated: Death or recurrence **(iCPD)** after no more than 1 consecutive missed **CT/MRI** evaluation No recurrence or death after no more than 1 consecutive missed **CT/MRI** evaluation	 Date of recurrence **(iCPD)** or death, whichever occurs first, according to the following: If death occurs without recurrence, then event is the date of death If recurrence occurs prior to death, then the date of last evaluable CT/ MRI visit, without documentation of recurrence of disease **(iUPD or absence of progression)** Date of last evaluable CT/ MRI visit, without documentation of recurrence of disease **(iUPD or absence of progression)**	 Event Censored
Incomplete or no baseline assessment	Date of start of treatment (censored on Day 1)	
No post baseline CT/MRI scans	Date of start of treatment (censored on Day 1)	Censored
Treatment discontinuation for undocumented progression or for toxicity	Date of last evaluation CT/MRI visit, without documentation of recurrence of disease (iUPD or absence of progression)	Censored
Censoring Rules for OS		
Death	Date of death	Event
No event prior to data cut-off date	Last known date that the subject was alive.	Censored
No event due to lost to follow-up	Last known date that the subject was alive.	Censored

13.6.2 Analysis of Median RFS

Relapse-free survival (RFS), defined as time from first dose of ELI-002 2P until recurrence/ death. RFS (in months) is calculated as:

[(date of recurrence/death – date of first ELI-002 dose2P dose) + 1)]/30.4375

Censoring details are described in Table .

Median RFS will be estimated using the Kaplan-Meier method. Number of subjects with events (recurrence/death) and number of subjects censored and reason of censoring will be presented along with an estimate for median time (days), Q1, and Q3. A Kaplan-Meier plot for time to event will also be provided by cohort. Tables and figures will be created for each of the two censoring rules presented in Table 16 for RFS.

13.6.3 Analysis of Overall Survival (OS)

The OS (in months) is defined as time from first dose of ELI-002 2P until death from any cause.

[(date of death or last known alive – date of first ELI-002 2P dose) + 1)]/30.4375

Subjects who are lost to follow-up or do not have a date of death at the time of data cut-off will be censored at the last date that they were known to be alive. Censoring details are described in Table 16.

Median OS will be estimated using the Kaplan-Meier method. The number of subjects with events (recurrence / death) and number of subjects censored and reason of censoring will be presented along with estimate for Q1, Q2 along with median time (days). Kaplan-Meier plot for time to event will also be provided by cohort in each phase.

13.7 Safety Analyses

All summaries of safety data will be conducted for the safety analysis set using actual treatment received. Safety measurements will include

- Adverse Event (AEs)
- Clinical laboratory evaluations
- Vital sign measurement
- Physical examinations
- 12-lead ECG
- ECOG performance status.

No statistical test will be performed on these safety endpoints above.

13.7.1 Adverse events

All Adverse events (AEs) will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 or higher.

AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. For CRS/ICANs (Immune effector Cell-Associated Neurotoxicity syndrome), AEs will be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) criteria.

In summaries by SOC and PT, the SOC terms will be presented alphabetically, and PTs within each SOC will be sorted by decreasing frequency within the overall column. In summaries by PT, AEs will be sorted by decreasing frequency in the overall column.

TEAE: any events not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment. Details for imputing missing or partial start dates of adverse events are described in Section 7.3.1.

AE summary tables will be presented for the following categories using counts and percentage of subjects (i.e., number and percentage of subjects with an event):

Table 7: Planned Summaries of Adverse Events

Summarize by / AE Type	Overall Summary [*]	By Cohort and Overall, SOC & PT	Additional Summary
TEAEs	X	X	By Cohort and Overall/Maximum CTCAE grade/SOC/PTBy Cohort/ PT By Cohort and Overll leading to study discontinuation
Serious TEAEs	X	X	By Cohort and Overall/relationship to study treatment/SOC/PT
Leading to study treatment discontinuation	X	X	By Cohort and Overall/relationship to study treatment/SOC/PT By Cohort and Overall/PT
Leading to death	X	X	
DLT (Phase 1A only) [#]	X	X	
Related TEAE	X	X	By Cohort and Overall/ leading to study discontinuation
Related TEAEs leading to study treatment discontinuation	X	X	
Cytokine Release Syndrome	X	X	
ICANS		X	
Reactogenicity event	X		By Reactogenicity type, events and toxicity grade

Note: all summary tables will be by Phase, Cohort/Overall.

[*] All types of AEs with "X" sign will be summarized in one overall summary table of TEAE, including outcome and action taken.
[#] Dose Limiting Toxicities (DLTs) are defined in the Protocol Section 6.7.3. The percentage of subjects having a DLT is based on all treated subjects in each cohort. DLT flag may be added to selected listings of adverse events as appropriate.

Where a subject has the same adverse event, based on PT reported multiple times, the subject will only be counted once at that PT level. Where a subject has multiple adverse events within the same system organ class, the subject will only be counted once at that SOC level.

Any AE with a missing severity based on CTCAE grading, or ASTCT in the case of CRS or ICANS, will be presented in the summary table under the category of "Missing" and will not be imputed. Any AE with a missing relationship to study treatment will be imputed as "Related". Any AE with a missing "Serious" evaluation will be imputed as "Serious".

For all AE data captured in the study by the Case Report Form (CRF), by-subject listings will be provided for all AEs, serious TEAEs, TEAEs leading to dose reduction or interruption, DLT and death, respectively.

Cytokine Release Syndrome, ICANS, and reactogenicity to the vaccine data captured in the CRF will be provided in a by-subject listing.

13.7.2 Clinical laboratory evaluations

Laboratory assessments comprise safety laboratory tests (hematology, blood chemistry and coagulation), serum cytokines, pregnancy and viral laboratory screening tests. For the purposes of summarization in both tables and listings, all laboratory values will be presented in SI units If a lab value is reported using a nonnumeric qualifier e.g., less than (<) a certain value, or greater than (>) a certain value, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

Laboratory test results and change from baseline of serum cytokine, worst on treatment hematology and chemistry results will be summarized using descriptive statistics by cohort/dose level, scheduled, and unscheduled visits.

For all clinical laboratory result listed in the protocol and captured by the CRF, by-subject, by-visit listings will be provided and abnormal flags (low or high) will be provided.

13.7.3 Vital signs

All vital sign measurements will also be presented in a by-subject listing.

13.7.4 Physical examinations

All abnormal physical examination data will be presented in a by-subject listing.

13.7.5 Electrocardiograms (ECG)

Observed values and change from baseline for continuous ECG parameters (ECG Heart Rate (beats/min), QRS Duration (ms), PR Interval (ms), RR Interval (ms), QT Interval (ms), QTc Interval

(ms)) will be listed by cohort, and scheduled visit. The listing will include overall ECG interpretation categorized as "Normal", "Abnormal, not clinically significant", and "Abnormal, clinically significant". Since post-baseline values are collected only at the discretion of the Investigator, no summary table is planned.

13.7.6 Eastern Cooperative Oncology Group (ECOG) performance status

Shift tables of ECOG performance status from baseline to worst post-baseline values, and to each post-baseline visit will be summarized by cohort/dose level and scheduled visits.

A by-subject listing of ECOG results will also be provided.

13.8 Other Analysis

13.8.1 Pharmacokinetics analysis

Not applicable.

13.8.2 Pharmacodynamics/immunogenic response analysis

The pharmacodynamic response to ELI-002 2P will be assessed by evaluation of immunogenic responses to the vaccine. PD (Pharmacodynamic) /Biomarker Evaluable Set will be used for tumor biomarker and PD endpoints. Safety analysis set will be used for other summary tables.

A subject level listing will be provided for all immunogenic responses listed in Table . Summary tables will be provided for the Safety Analysis Set, unless otherwise specified.. In addition a waterfall plot of subject's best tumor responses on percent change from baseline among ctDNA, and all serum biomarkers CA19-9and CEA will be presented.

Additional analyses of Immunogenicity are beyond the scope of this Statistical Analysis Plan and is specified in a separate addendum attached as an appendix in this document.

Table 18: Planned Analyses of PD and Immunologic Response Variables

Assessment	Summary Variables
High Resolution HLA	HLA type will be listed by subject in the demographics and baseline characteristics section
Serum cytokines (IL-2, IFNγ, IL-6, IL-10, and TNFα)	Observed results/change from baseline

13.8.3 Patient Reported Outcomes (PRO)

Patient Reported Outcomes will be assessed by European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC), QLQ-C30 and QLQ-PAN26, QLQCR29, QLQ-OV28, QLQ-BIL21 or QLQ-LC13.

A by-subject listing will also be provided.

13.8.3.1 EORTC QLQ-C30

The European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) is a tool for assessing the quality of life (QoL) of cancer subjects participating in clinical trials. The EORTC QLQ-C30 incorporates 9 multi-item scales are provided in Table . These scales are scored using the algorithm specified in the section 12.4.1.

13.8.3.2 Tumor type-specific PROs

Tumor type-specific PROs are intended to supplement the EORTC QLQ-C30 with questions appropriate for the symptoms experienced by subjects with each tumor type. PRO responses will be listed by subject and visit. Tumor type-specific PROs will include:

- QLQ-PAN26: pancreatic cancer
- QLQ-BIL-21: biliary cancer
- QLQ-CR-29: colorectal cancer
- QLQ-LC-13: lung cancer
- QLQ-OV-28: ovarian cancer

For QLQ-PAN26 symptoms/functional scales are provided in Table and the corresponding scale scores will be calculated (see section 12.4.2).

As per Table and section 12.4.3 QLQ-BIL-21 scales, and the scores will be computed

The QLQ-CR-29 scales are presented in per Table . These scale scores will be derived as specified in section 12.4.4.

The scales for QLQ-LC-13 and QLQ-OV-28 are provided in Table and Table respectively. The corresponding scale scores are computed referring to the sections 12.4.5 and 12.4.6.

14.0 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

The protocol has indicated that statistical testing and confidence intervals would be computed for the efficacy analyses; however, since the sample sizes are small and efficacy data from this trial are exploratory and not powered to elicit statistically significant treatment effects, no formal statistical testing will be computed except for RFS and OS endpoints. ctDNA and Immunogenicity analyses are beyond the scope of this document and are specified in a separate addendum which is attached here as an appendix.

Additional exposure outcomes namely Dose Intensity (DI) and Relative Dose Intensity (RDI) not mentioned in the protocol will be summarized for better clarity on the treatment exposure.

The protocol has requested that summary statistics be presented for patient reported outcomes, however, due to the early termination of the long term follow up of the study, only by-subject listing will also be provided for these endpoints.

The protocol has requested the use of the Disease Response Evaluable Set population, however, as no outputs in the SAP/shells are based on this set, it was dropped from the SAP.

15.0 REFERENCES

- Clinical Study Protocol (Version 2.0, Dated 2 Sep 2020) First in Human Phase 1/2 Trial of ELI-002 Immunotherapy as Treatment for Subjects with Kirsten Rat Sarcoma (KRAS) Mutated Pancreatic Ductal Adenocarcinoma and Other Solid Tumors.
- ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).
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- Whistance RN, Conroy T, Chie W, et al. Clinical and Psychometric Validation of the EORTC QLQ-CR29 Questionnaire Module to Assess Health-Related Quality of Life in Patients with Colorectal Cancer. Eur J Cancer 45:3017-3026, 2009.
- Greimel E, Bottomley A, Cull A, et al. on behalf of the EORTC Quality of Life Group and the Quality of Life Unit. An International Field Study of the Reliability and Validity of a Disease-Specific Questionnaire Module (the QLQ-OV28) in Assessing the Quality of Life of Patients with Ovarian Cancer. Eur J Cancer 39:1402-1408, 2003.

16.0 APPENDIX

STATISTICAL ANALYSIS PLAN
APPENDIX: Immunogenicity and ctDNA Analysis Plan

Protocol Number: **Protocol Version and Date:**	*Protocol Number: ELI-002-001* *Protocol Name: AMPLIFY-001* *First in Human Phase 1 Trial of ELI-002 Immunotherapy as Treatment for Subjects with Kirsten Rat Sarcoma (KRAS) Mutated Pancreatic Ductal Adenocarcinoma and Other Solid Tumors*
Name of Test Drug:	ELI-002
Phase:	1
Methodology:	open-label, Phase 1 trial
Sponsor:	Elicio Therapeutics, Inc
Sponsor Representative:	Lisa McNeil
Analysis Plan Date:	February 6, 2023
Analysis Plan Version:	Version 1.0

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
% CV	Coefficient of Variation
AMP-CpG	Amphiphile – Cytosine phosphoguanine
CD4	Clusters of Differentiation 4
CD8	Clusters of Differentiation 8
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CSV	Comma-Separated Values
DFR	Distribution Fee Resampling
FS	Fluorospot
ICS	Intracellular Cytokine Staining
IFN	Interferon
IFNg	Interferon Gamma
IVS	In vitro simulated
LOQ	Limit of Quantification
mL	milliliter
MTM/mL	Mean Tumor Molecules per mL
NS	Non-stimulated
TNFa	Tumor Necrosis Factor alpha
VAF	Variant Allele Frequency

1. BACKGROUND

Please refer to Protocol ELI-002-001 and Statistical Analysis Plan.

1.1. Objective

The objectives of this analysis are:

- To assess reduction in ctDNA
- To assess immune response at each timepoint based on
  - Ex vivo Intracellular cytokine staining (ICS)
  - Ex vivo Fluorospot
  - In vitro stimulated (IVS) Fluorospot
  - IVS ICS
  - Ex vivo Dextramer
  - IVS Dextramer.

The objectives will be assessed at up to five dose levels (0.1, 0.5., 2.5, 5 and 10 mg AMP-CpG).

1.2. Study Design, Sample Size, Dosing and Sample Collection

Please refer to Protocol ELI-002-001 and Statistical Analysis Plan.

A table of sample collection is below:

Table 1-1 Collection of Immunogenicity and ctDNA Samples

Visit	Week	Immunogenicity	ctDNA
2	Baseline	X (Baseline)	X
3 (First dose)	0		X (Baseline)
4	1		
5	2	X	
6	3		X
7	5	X	
9	9	X	
11	17	X	X
12	20		X
14	22	X	
16	25	X	X
17	29		X
18	37		X
19	49		X
20	61		X
21	73		X
22	85		X
23	97		X
24	105		X

Visits labeled “unscheduled”, or the equivalent may be collected,

1.3. Data Format

Data will be transmitted electronically for analysis in either Excel/CSV or SAS datasets. All files will be archived onto the computer system where the analysis will be performed. A working copy of these files will be created for analysis. Each file will be scanned for viruses, successfully opened, and content confirmed. Any electronic record issues will be reported to the provider.

1.4. Data Analysis Methods

1.4.1. General Methods

Analyses will be conducted using SAS version 9.4 or higher or R version 4.1.2 or later. Tabulations will summarize for the immunogenicity parameter over time and treatment group for data collected during the dose escalation phase, and by dose and tumor type for the expansion phase.

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation (SD), minimum, and maximum values will be presented. In addition, geometric mean and % CV will be presented. Summary statistics will be presented, as well as confidence intervals (CIs) on selected parameters, as described in the sections below. Tables will display dose cohorts in the column headings.

This study is primarily descriptive in nature; therefore, formal statistical hypothesis testing will be limited. Data will be presented by patient in data listings and summarized by dose cohort.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Except if noted, listings will be presented by dose cohort. Within each dose cohort, patients will be ordered by patient ID number, mutation (mKRAS / mNRAS) and within each patient, the data will be ordered by ordinal visit / week.

1.5. Population Definitions

The following patient populations will be evaluated and used for presentation and analysis of the immunogenicity or ctDNA biomarker data:

- Immunogenicity Population: All patients who receive any amount of study treatment and contribute any immunogenicity data.
- ctDNA Population: All patients who receive any amount of study treatment and contribute any ctDNA data.

1.6. Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug. For immunogenicity analyses, this will be the sample collected on Visit 2. For ctDNA, this will be the sample collected at Visit 3. If results are missing at Visit 3 but available for Visit 2, Visit 2 results may be used as baseline.

1.7. Multiple Comparisons/Multiplicity

No adjustments for multiplicity will be made in a study with a descriptive interpretation.

1.8. Timing of Analyses

Analyses will occur after the completion of each cohort including completion of immunologic and ctDNA assays.

1.9. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points.

For all assays, the limit of quantification (LOQ) will be used if available.

2. STUDY ANALYSES

2.1. Immunogenicity Analysis

Cellular responses will be characterized by:

- Ex vivo Intracellular cytokine staining
- In Vitro stimulated Intracellular cytokine staining
- Ex vivo Fluorospot
- In vitro stimulated Fluorospot
- Ex vivo Dextramer
- In vitro stimulated Dextramer

Response will be determined in two ways

- Method 1 – For subjects who are negative (below the limit of quantification) at baseline and have a detectable post baseline value (above the limit of quantification) will be considered at responder. For subjects who have detectable baseline values, a two-fold increase from baseline will be considered a responder.
- Method 2 (Fluorospot only)– distribution free resampling (DFR) will be applied using the methods described by Moodie et al 2010. A minimum threshold value of 2-fold difference between control and experimental wells will be assessed.

2.1.1. Intracellular Cytokine Staining

Actual and increase from baseline values for ex vivo and in vitro stimulated (IVS) Intracellular Cytokine (ICS) staining results will be presented at each timepoint by dose level and antigen. In addition to each cytokine, the sum of CD4 and CD8 cytokines will be summed and summarized with descriptive statistics. Non-stimulated (NS) results will be included in data listings but not tabulated.

Listings will include actual value and absolute and fold-change from baseline.

2.1.2. Fluorospot

Actual and increase from baseline values for ex Vivo and in vitro stimulated (IVS) Fluorospot (FS) results will be presented at each timepoint by dose level, assay, and antigen. In addition, the sum of results (IFNg, Granzyme B, and IFN+/Granzyme B for Ex vivo FS and IFNg, TNFa, IFNg+TNFa for IVS) will be calculated for each antigen. Non-stimulated (NS) results will be included in data listings but not tabulated.

Ex vivo (normalized to 1x10^6) and IVS FS data (non-normalized) will use the background subtracted values for analysis.

Listings will include actual value and absolute and fold-change from baseline and response status according to Method 1 (Section 2.1).

2.1.3. Dextramer

The frequency (%) of antigen-specific CD8 T-cells will be assessed using ex vivo and IVS dextramer based assays. Results will be presented by timepoint, dose-level, and dextramer.

2.2. ctDNA

ctDNA response is defined as the absence or reduction of circulating tumor DNA post-baseline. Analysis of ctDNA will be based on results from two laboratories and will be performed separately.

Duration of response is defined as the time in weeks from reduction until the date of increase or presence of ctDNA.

Any patient with detectable ctDNA at baseline whose post-baseline result is less than the baseline value or undetectable will be considered a responder. The number and percentage of responders will be reported.

Doubling will be calculated as the number of weeks between visits where ctDNA first doubles.

Doubling time and response will be based on the tumor molecules per mL (MTM/mL) and Variant Allele Frequency (VAF).

ctDNA levels over time will be summarized using descriptive statistics.

Data listings will present ctDNA values (VAF and MTM/mL) over time, ctDNA response, and duration of response, and time until doubling of ctDNA.

3. REFERENCES

- Z Moodie*, L Price*, C Gouttefangeas, A Mander, S Janetzki, M Lower, MJ Welters, C Ottensmeier, SH van der Burg, CM Britten. Response definition criteria for ELISpot assays revisited. Cancer Immunol Immunother, 59(10):1489-501, 2010. *Shared first authorship
- Z Moodie, L Price, S Janetzki, CM Britten. Response determination criteria for ELISPOT: toward a standard that can be applied across laboratories. Methods Mol Biol. 792:185-96, 2012.

4. CLINICAL STUDY REPORT APPENDICES

4.1. Statistical Tables and Figures to be Generated

Table 1 Summary and Change from Baseline for ex Vivo Fluorospot

Table 2 Summary and Change from Baseline for In vitro stimulated (IVS) Fluorospot

Table 3 Summary and Change from Baseline for Ex Vivo Intracellular cytokine staining

Table 4 Summary and Change from Baseline In Vitro stimulated Intracellular cytokine staining

Table 5 Summary and Change from Baseline for Ex Vivo Dextramer

Table 6 Summary and Change from Baseline for In Vitro stimulated Dextramer

Table 7 Summary and Change from Baseline for ctDNA (ctDNA Population)

Figure 1 Scatter and Box Plot of ex Vivo Fluorospot by Cohort Over Time

Figure 2 Scatter and Box Plot of In Vitro Stimulated Fluorospot by Cohort Over Time

Figure 3 Scatter and Box Plot of Ex Vivo Intracellular cytokine staining by Cohort Over Time

Figure 4 Scatter and Box Plot of In Vitro Stimulated Intracellular cytokine staining by Cohort Over Time

Figure 5 Scatter and Box Plot of ex Vivo Dextramer by Cohort Over Time

Figure 6 Scatter and Box Plot of In Vitro Stimulated Dextramer by Cohort Over Time

4.2. Data Listing to be Generated

Listing 1 Ex Vivo Fluorospot

Listing 2 In Vitro stimulated Fluorospot

Listing 3 Ex Vivo Intracellular Cytokine Staining

Listing 4 In Vitro stimulated Intracellular Cytokine Staining

Listing 5 Ex Vivo Dextramer

Listing 6 In Vitro stimulated Dextramer

Listing 7 ctDNA – Signatera Assay

Listing 8 ctDNA – Sysmex Assay

Table 1

Summary and Change from Baseline for ex Vivo Fluorospot

(Immunogenicity Population)

Analyte	Antigen	Visit	Value	Statistic	(N=xx)	(N=xx)	(N=xx)	Cohort 1	Cohort x	Cohort x
IFNg		[see programming note]	Baseline (1)	Actual			N [2]	x		
							Mean (SD)	xx.x	--	
							Median	(xx.xx)		
							Min,Max	xx.xx		
							N Undetectable [3]	xx.x, xx.x x		
			Visit x	Actual	N			xx xx.x		
							Mean (SD)	(xx.xx)		
							Median	xx.xx		
							Min,Max	xx.x, xx.x x		
							N Undetectable [3]			
				Fold Change from Baseline			N			
							Mean (SD)			
							Median			
							Min,Max			
				Response 1 [4,5]			N(%)			
				Response 2 [4,6]			N(%)			
Repeat for GrB										
IFNg+/GRB+										
Total [7]										

Results are summarized using the mean of normalized, background subtracted replicates
[1] Baseline is based on Visit 2 result
[2] N reflects the number of patients with detectable result.
[3] Number of subjects with results below the limit of detection. [4] Denominator is number of subjects with results at visit
[5] Response is defined as having a two-fold increase from baseline.
[6] Response is based on bootstrap method described by Moodie [2010] testing for 2-fold difference from the control wells
[7] Total Analyte is the sum of IFN, GrB, and IFN/GrB results for each analyte.
Programming note: For each analyte, antigens will include G12R, G12D, G12V, G12C, G12A, G12S, G13D, total mKRAS (sum of G12R, G12D, G12V, G12C, G12A, G12S and G13D antigens), Master mix NS will not be included in table but will be in the listing.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 2

Summary and Change from Baseline for In vitro stimulated (IVS) Fluorospot

(Immunogenicity Population)

Repeat layout for table 1.

Footnote: Results are summarized using the mean of background subtracted replicates
Programming note : Antigens will include G12R, G12D, G12V, G12C, G12A ,G12S, G13D , WT , master mix, and total mKRAS (sum of G12R, G12D, G12V, G12C, G12A, G12S and G13D antigens). Analytes will include IFNg, TNFa,IFNg+TNFa , and the sum of IFNg TNFa, and IFNg+TNFa
NS and CD3 will not be included in Table but should be in Listing.

Table 3

Summary and Change from Baseline for Ex Vivo Intracellular cytokine staining

(Immunogenicity Population)

Antigen	Cytokine	Visit	Value	Statistic	Cohort 1 (N=xx)	Cohort x (N=xx)	Cohort x (N=xx)	N [2]
[see programming note]			Baseline (1)	Actual	Mean (SD) Median Min,Max N Undetectable [3,4] N	x xx.x (xx.xx) xx.xx xx.x, xx.x x	--	
			Visit x	Actual	Mean (SD) Median Min,Max N Undetectable (3)	xx xx.x (xx.xx) xx.xx xx.x, xx.x x		
				Fold Change from Baseline	N Mean (SD) Median Min,Max			

[1] Baseline is based on Visit 2 result

[2] N reflects the number of patients with detectable result.
[3] Number of subjects with results below the limit of detection.
[4] Denominator is number of subjects with results at visit
[5] Total CD4 Response is the sum of CD4: IFNg+ IL2+ TNFa+, IFNg+ IL2+ TNFa-, IFNg+ IL2- TNFa+ , IFNg+ IL2- TNFa-,,IFNg- IL2+ TNFa+,IFNg- IL2+ TNFa-,IFNg- IL2- TNFa+. Total CD8 Response is the sum of CD8: IFNg+ IL2+ TNFa+, IFNg+ IL2+ TNFa-, IFNg+ IL2- TNFa+, IFNg+ IL2- TNFa-,,IFNg- IL2+ TNFa+,IFNg- IL2+ TNFa-,IFNg- IL2- TNFa+.

Programming note: For each analyte, antigens will include Antigens will include, total mKRAS (sum of G12R, G12D, G12V, G12C, G12A, G12S and G13D antigens), G12R, G12D, G12V, G12C, G12A

G12S,G13D,WT,, Master Mix . Each antigen will be have the following cytokines : CD4 IFNg,CD4 IL2,CD4 TNFa,CD4 IFNg+ IL2+ TNFa+,CD4 IFNg+ IL2+ TNFa-,CD4 IFNg+ IL2- TNFa+,CD4 IFNg+ IL2- TNFa-,CD4 IFNg- IL2+ TNFa+,CD4 IFNg- IL2+ TNFa-,CD4 IFNg- IL2- TNFa+,Total CD4 cytokine response [5],CD8 IFNg,CD8 IL2,CD8 TNFa,CD8 IFNg+ IL2+ TNFa+,CD8 IFNg+ IL2+ TNFa-,CD8 IFNg+ IL2- TNFa+,CD8 IFNg+ IL2- TNFa-,CD8 IFNg- IL2+ TNFa+,CD8 IFNg- IL2+ TNFa-,Total CD8 cytokine response [5]

Repeat layout by Analyte, Cytokine, and Visit.

Table 4

Summary and Change from Baseline In Vitro Intracellular cytokine staining

(Immunogenicity Population)

IVS Antigen	Antigen	Cytokine	Visit	Value	Statistic	(N=xx)	(N=xx)	(N=xx)		Cohort 1	Cohort x	Cohort x
		[See programming note]	(See Programming Note_		Baseline (1)		Actual		N [2]	x		
									Mean (SD)	xx.x (xx.xx)	--	
									Median	xx.xx		
									Min,Max	xx.x, xx.x		
									N Undetectable [3,4]	x		
					Visit x		Actual		N	xx		
									Mean (SD)	xx.x (xx.xx)		
									Median	xx.xx		
									Min,Max	xx.x, xx.x		
									N Undetectable (3)	x		
							Fold Change from Baseline		N			
									Mean (SD)			
									Median			
									Min,Max			

[1] Baseline is based on Visit 2 result
[2] N reflects the number of patients with detectable result.
[3] Number of subjects with results below the limit of detection.
[4] Denominator is number of subjects with results at visit
[5] Total CD4 Response is the sum of CD4: IFNg+ IL2+ TNFa+, IFNg+ IL2+ TNFa-, IFNg+ IL2- TNFa+, IFNg+ IL2- TNFa-,IFNg- IL2+ TNFa+,IFNg- IL2+ TNFa-,IFNg- IL2- TNFa+. Total CD8 Response is the sum of CD8: IFNg+ IL2+ TNFa+, IFNg+ IL2+ TNFa-, IFNg+ IL2- TNFa+, IFNg+ IL2- TNFa-,IFNg- IL2+ TNFa+,IFNg- IL2+ TNFa-,IFNg- IL2- TNFa+.

Programming note: For each analyte, antigens will include G12R, G12D, G12V, G12C, G12A, G12S, G13D, Master Mix, and total mKRAS (sum of G12R, G12D, G12V, G12C, G12A, G12S and G13D antigens). Each antigen will have the following cytokines:
CD4 IFNg,CD4 IL2,CD4 TNFa,CD4 IFNg+ IL2+ TNFa+,CD4 IFNg+ IL2+ TNFa-,CD4 IFNg+ IL2- TNFa+,CD4 IFNg+ IL2- TNFa-,CD4 IFNg- IL2+ TNFa+,CD4 IFNg- IL2+ TNFa-,CD4 IFNg- IL2- TNFa+,Total CD4 cytokine response [*],CD8 IFNg,CD8 IL2,CD8 TNFa,CD8 IFNg+ IL2+ TNFa+,CD8 IFNg+ IL2+ TNFa-,CD8 IFNg+ IL2- TNFa+,CD8 IFNg+ IL2- TNFa-,CD8 IFNg- IL2+ TNFa+,CD8 IFNg- IL2+ TNFa-,Total CD8 cytokine response [*] Repeat layout by Analyte, Cytokine, and Visit

Table 5

Summary and Change from Baseline for Ex Vivo Dextramer (Immunogenicity Population)

Programming Note: repeat layout for table 3. Replace Antigen column with "Dextramer" and remove IVS antigen and cytokine columns. Only CD8+ dextramer + column from source data will be included.

Table 6

Summary and Change from Baseline for In Vitro Dextramer (Immunogenicity Population)

Programming Note: repeat layout for table 3. Replace Antigen column with "Dextramer" remove IVS antigen and cytokine columns. Only CD8+ dextramer + column from source data will be included.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Table 7

Summary and Change from Baseline for ctDNA (ctDNA Population)

			Cohort 1 (N=xx)	Cohort 1 (N=xx)	Cohort 1 (N=xx)
Baseline	Baseline (1)				
		N (2)	xx	--	
		Mean (SD)	xx.x (xx.xx)		
		Median Min,	xx.xx xx.x		
		Max	xx.x		
		N Undetectable (3)	xx.x, xx.x xx		
Visit 6					
		N (2)	xx	xx	
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Fold Change Mean	xx.xx	xx.xx	
		Fold Shange SD- SD	xx.x	xx.x	
		Median	xx.x	xx.x	
		Min, Max	xx.x, xx.x	xx.x, xx.x	
		N Undetectable (3)	xx	xx	
		<repeat for remaining visits with at least 3 subjects			
Doubling Time	N(4)				
		Mean (SD)			
		Median			
		Min, Max			
Clearance Duration (weeks)	N(5)				
		Mean (SD)			
		Median			
		Min, Max			
Response Rate	n%				

[1] Baseline is based on Visit 3 result or Visit 2 if Visit 3 is missing
[2] N reflects the number of patients with detectable concentrations of ctDNA .

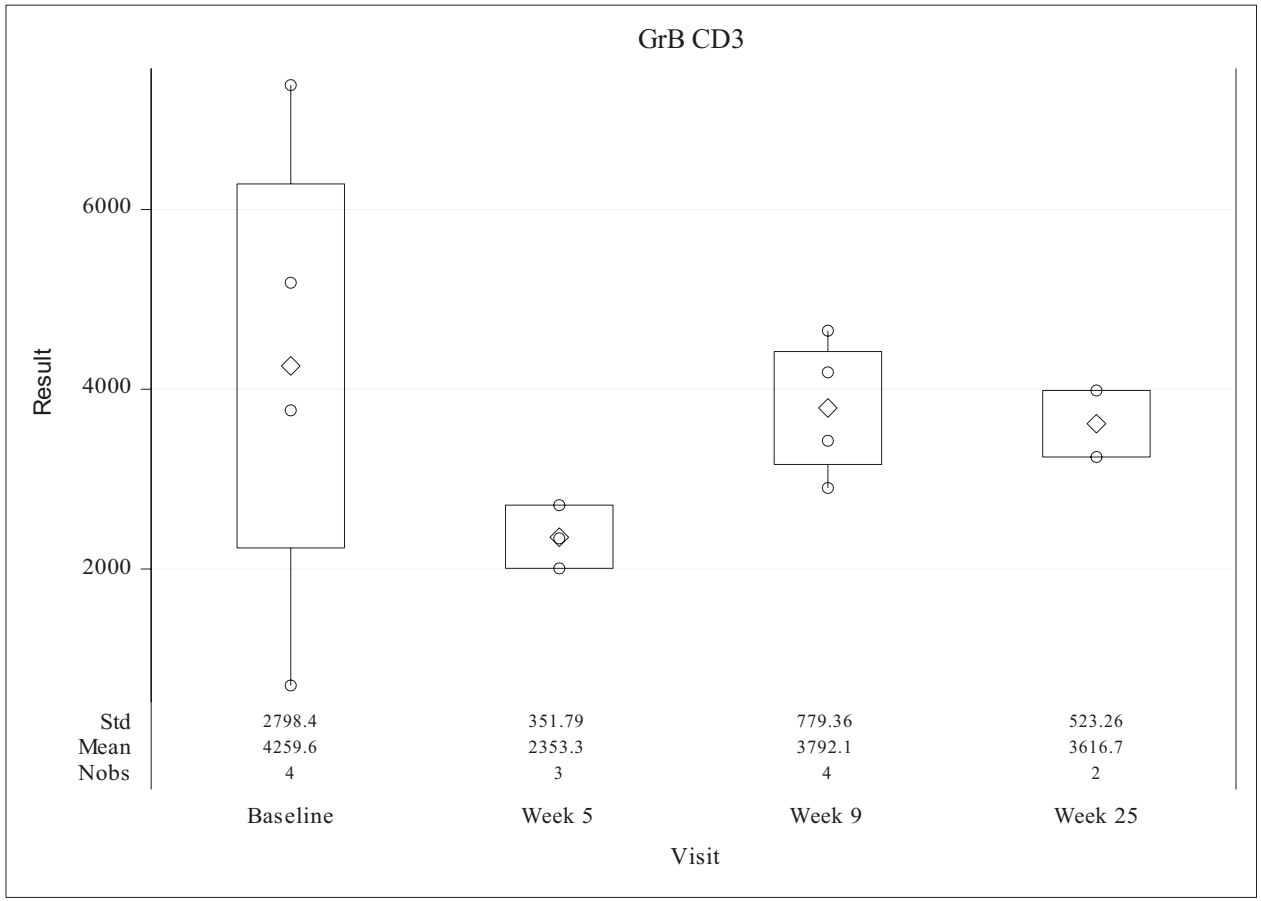
[3] Number of subjects with results below the limit of detection. [4] N reflects the subjects whose ctDNA doubled.
[5] N reflects subjects whose ctDNA was undetectable or decreased post-baseline.
[REPEAT univariate statistics For VAF + MTM/ML by Assay]

Notes for programming: Timepoints –
- Visits 2, 3 (pre-vaccination)
- Visits 6, 11, 12, 16, 17, 18, 19, 20, 21, 22, 23, 24 (post-vaccination)

Figure 1

Ex vivo Fluorospot

EXAMPLE
Repeat layouts for all figures. Each cohort will be identified by different colors on the scatter plot. All parameters included in summary tables should be graphed.



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Listing 1

Ex vivo Fluorospot

Dose Cohort:

Patient ID	KRAS / NRAS	Visit/ Week (1)	Date	Antigen	Analyte	Result(2)	Change from baseline	Fold change from baseline	Response Based on DFR

(1) Relative to first dose date.
(2) Response is based on bootstrap method described by Moodie (2010) testing for 2-fold difference from the control wells
(3) IVS Fluorospot results reflect the mean of background-subtracted replicate results. Ev Vivo Fluorospot results reflect the average of normalized background-subtracted replicate results.

Programming note - NS antigen is not included in the table but should be included in listing.

Listing 2

In Vitro Fluorospot

Repeat Listing 1 layout using data from IVS Fluorospot.

Listing 3

Ex Vivo Intracellular Cytokine Staining

Patient ID	KRAS / NRAS Mutation	Visit	Date	Antigen	Test	Result	Change from baseline	Fold change from baseline
						Live cells		
						Lymphocytes		
						CD3 T cells		
						CD4 T cells		
						CD4 IFNg		
						CD4 IL2		
						CD4 TNFa		
						CD4 Cm		
						CD4 Cm IFNg		
						CD4 Cm IL2		
						CD4 Cm TNFa		
						CD4 Em		
						CD4 Em IFNg		
						CD4 Em IL2		
						CD4 Em TNFa		
						CD4 Naive		
						CD4 Naive IFNg		
						CD4 Naive IL2		
						CD4 Naive TNFa		
						CD4 TEMRA		
						CD4 TEMRA IFNg		
						CD4 TEMRA IL2		
						CD4 TEMRA TNFa		
						CD4 IFNg-		
					DMSO	CD4 IL2-		
						CD4 TNFa-		
					G12R	CD4 IFNg+ IL2+ TNFa+		
					G12D	CD4 IFNg+ IL2+ TNFa- CD4		
					G12V	IFNg+ IL2- TNFa+ CD4		
					G12C	IFNg+ IL2- TNFa- CD4		
					G12A	IFNg- IL2+ TNFa+ CD4		
					G12S	IFNg- IL2+ TNFa- CD4		
					G13D	IFNg- IL2- TNFa+ CD4		
					WT	IFNg- IL2- TNFa- CD8 T cells		
					Positive control Master Mix			

Patient ID	KRAS / NRAS Mutation	Visit	Date	Antigen	Test	Result	Change from baseline	Fold change from baseline
					CD8 IFNg			
					CD8 IL2			
					CD8 TNFa			
					CD8 Cm			
					CD8 Cm IFNg			
					CD8 Cm IL2			
					CD8 Cm TNFa			
					CD8 Em			
					CD8 Em IFNg			
					CD8 Em IL2			
					CD8 Em TNFa			
					CD8 Naïve			
					CD8 Naive IFNg			
					CD8 Naive IL2			
					CD8 Naive TNFa			
					CD8 TEMRA			
					CD8 TEMRA IFNg			
					CD8 TEMRA IL2			
					CD8 TEMRA TNFa			
					CD8 IFNg-			
					CD8 IL2-			
					CD8 TNFa-			
					CD8 IFNg+ IL2+ TNFa+			
					CD8 IFNg+ IL2+ TNFa-			
					CD8 IFNg+ IL2- TNFa+			
					CD8 IFNg+ IL2- TNFa-			
					CD8 IFNg- IL2+ TNFa+			
					CD8 IFNg- IL2+ TNFa-			
					CD8 IFNg- IL2- TNFa+			
					CD8 IFNg- IL2- TNFa-			
					CD4 1+			
					CD4 2+			
					CD4 3+			
					CD4 % 1+			
					CD4 % 2+			
					CD4 % 3+			
					CD8 1+			
					CD8 2+			
					CD8 3+			
					CD8 % 1+			
					CD8 % 2+			
					CD8 % 3+			

Listing 4

In Vitro Intracellular Cytokine Staining

Repeat Layout used in listing 3 with IVS ICS.

Listing 5

Ex Vivo Dextramer + T cell

Patient ID	KRAS / NRAS (1)	Visit/ Week Date	Dextramer	Test	Result(2)	Change from baseline see note	Fold change from baseline
				% Viable cells			
				% Lymphocytes			
				% CD3 T cells			
				% CD8 T cells			
				% CD8+ Dextramer+ cells			
				% CD4 T cells			
				% CD4+ Dextramer+ cells			

Dextramers will include:
A11:01 G12V-10, A11:01 G12V-9, A11:01 G12D-10
A11:01 G12D-9, A03:01 G12V-10, A03:01 G12D-10, C08:02 G12D-10
C08:02 G12D-9, B07:02 G12R-10, A02:01 G12D-10, A02:01 G12V-10

Listing 6 In Vitro Dextramer

Repeat layout for listing 6 using IVS dextramer.

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Listing 7

ctDNA – Signaterra Assay

Dose Cohort

Patient ID	Mutation	Visit	Date	Status	Type	Result	Result baseline	Change from baseline	Fold change from previous*	Time	Fold change from e (1)	Response	Doubling	Respons	Duration of
						Negative/ Positive / Not performed	MTM/mL VAF								
										--	--	--			

Abbreviation: VAF = Variant Allele Frequency, MTM= mean Tumor Molecules
*Indicates 2-fold or greater change.

(1) response is defined as decrease from baseline or undetectable value. (2) Duration is calculated as the date of the first response until the date where the ctDNA is detectable or greater than baseline value. (3) Doubling time is the time until the ctDNA has increase 2-fold from nadir.

Listing 8

ctDNA – Sysmex Assay

Patient ID	Mutation	Visit	Date	GENE	Status	Type	Result	Change from previous	Fold change from baseline	Fold change from	Doubling Time	Response (1)	Duration of
				KRAS NRAS		MD=Mutation Detected NMD=No Mutation detected	MAF TM						

Abbreviation: VAF = Variant Allele Frequency, MTM= mean Tumor Molecules
*Indicates 2-fold or greater change.

(1) response is defined as decrease from baseline or undetectable value. (2) Duration is calculated as the date of the first response until the date where the ctDNA is detectable or greater than baseline value. (3) Doubling time is the time until the ctDNA has increase 2-fold from nadir

5. R CODE FOR DFR(2X)

```
require(DT)
require(readxl)
require(ggplot2)
require(dplyr)
X13 <- read_excel("<filename .xlsx",
                  sheet = "Sheet4")
#View(X13May2022_Preliminary_ex_vivo_FS_data_for_Veristat_Dataset_to_R_)

 datatable(X13,extensions = 'Buttons', filter='top',
           options = list(dom='Bfrtip',
                          lengthMenu = list(c(15, -1), c('15', 'All')),
                          buttons=c('copy', 'csv', 'excel', 'print', 'pdf')))

GRb=subset(X13, assay=='GrB'&Antigen != 'CD3'   )
 IFN=subset(X13, assay=='IFNg'&Antigen != 'CD3'   )
#p=ggplot(IFN, aes(x=Visit, y=Mean, color=Antigen ))

 IFN = rename(IFN, id=Subject, day = Visit, antigen = Antigen, a1=Rep_1, a2=Rep_2, a3=Rep_3)
 elsdfr2x(IFN, 3,3, "NS", ho.c=log10(2))
 d=elsdfr2x (GRb, 3, 3, "NS", ho.c=log10(2), alpha=0.1, B=1000 )
```

```
impose.mono <- function(x, dir){
    # Function to impose monotonicity on elements of the vector, x
    # dir="incr" gives increasing monotonicity
    # dir="decr" gives decreasing monotonicity

    if(dir=="decr"){ x <- rev(x) }
    for(i in 2:length(x)){
            idx <- is.na(x[(i-1):i])
            if (sum(idx)==1){
                    x[i] <- x[(i-1):i][!idx]
            } else {
                    x[i] <- max(x[i-1],x[i])
            }
    }
    if(dir=="decr"){ x <- rev(x) }
    x
}

perm <- function(dat, nExp, nCtl){
    N <- nExp+nCtl          # total number of exp and neg ctl wells
    k <- NROW(dat)      # number of peptide pools
    B <- choose(N,nExp) # number of perms needed for complete enumeration

    if(B < 20) stop("Too few replicates to use this method (B < 20).")

    mu.e <- rowMeans(dat[,1:nExp], na.rm=TRUE)        # vector of peptide pool means
    mu.c <- rowMeans(dat[,nExp+(1:nCtl)], na.rm=TRUE) # vector of neg ctl means
```

```
# test statistic for observed data
t <- mu.e-mu.c
t.sort <- sort(t)
index <- order(t)

# samp matrix contains all possible permutations of columns of dat matrix:
samp <- expand.grid(rep(list(0:1),N))
samp <- samp[apply(samp,1,sum)==nExp,]
samp <- as.matrix(samp)

tPerm <- matrix(0,nrow=k,ncol=B)

# calculate test statistics for each perm sample in samp:
for(i in 1:B){
        perm.dat <- dat[,order(samp[i,])]
        mu.exp <- rowMeans(perm.dat[,(1:nExp)+nCtl], na.rm=TRUE)
        mu.ctl <- rowMeans(perm.dat[,1:nCtl], na.rm=TRUE)
        tPerm[,i] <- mu.exp-mu.ctl
}

# order rows of tPerm to correspond with sorted test statistics in t.sort:
if(k==1){ tPerm.mono <- tPerm.sort <- tPerm }
if(k>1){
        tPerm.sort <- tPerm[index,]
        tPerm.mono <- apply(tPerm.sort,2,impose.mono,dir="incr")
}

# calculate adjusted p-values:
tpvalue <- apply(tPerm.mono>=t.sort, 1, mean, na.rm=TRUE)
```

```
    # enforce monotonicity on adjusted p-values in tpvalue:
    if(k>1){ tpvalue <- impose.mono(tpvalue, dir="decr") }

    list(tstat=t, tadjp=tpvalue[order(index)])
}


elsdfreq <- function(data, nExp, nCtl, nameCtl, alpha=0.05){
    data <- as.data.frame(data)
    data <- data[order(data[,1],data[,2]),]
    ncdat <- data[data[,3]==nameCtl,]
    dat <- data.frame(matrix(NA,nrow=NROW(data[data[,3]!=nameCtl,]),ncol=3+nExp+nCtl))
    dat[,1:(3+nExp)] <- data[data[,3]!=nameCtl,]
    names(dat) <- c(names(data)[1:(3+nExp)],paste("c",1:nCtl,sep=""))
    for(id in unique(data[,1])){
    for(day in unique(data[,2])){
            dat[dat[,1]==id & dat[,2]==day,3+nExp+(1:nCtl)] <- ncdat[ncdat[,1]==id & ncdat[,2]==day,-(1:3)]
    }}

    ### dat = a data.frame with ptid, day, antigen in cols 1 to 3,
    ### peptide replicates in col4:(3+nExp), control replicates in
    ### col(4+nExp):col(3+nExp+nCtl)
    ### Same control replicates are repeated for each peptide per unique ptid

    ### nExp = no. of experimental wells per peptide
    ### nCtl = no. of negative control wells
    ### Use alpha=0.05 as default
```

```
ind <- unique(dat[,1:2])
adjp <- teststat <- pos.call <- NULL

# perform permutation test on each unique ptid*day combination with
# multiplicity adjustment for the number of peptide pools

for(i in 1:NROW(ind)){
        temp.dat <- as.matrix(dat[dat[,1]==ind[i,1] & dat[,2]==ind[i,2],-(1:3)])
        temp.id <- ind[i,1]
        temp.day <- ind[i,2]
        temp.pep <- dat[dat[,1]==ind[i,1] & dat[,2]==ind[i,2],3]
        if (length(temp.pep)==1) temp.dat <- t(temp.dat)
        temp.adjp <- temp.teststat <- rep(NA, NROW(temp.dat))

        nas <- is.na(temp.dat)
        nCtlc <- nCtl - sum(nas[1,nExp+(1:nCtl)]) # observed number of neg ctl reps
        nExpC <- nExp - apply(nas[,1:nExp],1,sum) # observed numbers of exp reps
        idx <- (nExpC>=3 & nCtlc>=3) | (nExpC>=2 & nCtlc>=4)
        if (sum(idx)>0){
                temp.dat <- as.matrix(temp.dat[idx,])
                if (sum(idx)==1 & length(idx)>1) temp.dat <- t(temp.dat)
                out <- perm(dat=temp.dat, nExp=nExp, nCtl=nCtl)
                temp.teststat[idx] <- out$tstat
                temp.adjp[idx] <- out$tadjp
        }
        teststat <- c(teststat, temp.teststat)
        adjp <- c(adjp, temp.adjp)
```

```
            if (nCtlc<nCtl) warning(paste("ptid", temp.id, "has", nCtl-nCtlc, "missing value(s) for negative controls", "on day",
temp.day))
            if (min(nExpC)<nExp){
                  for (j in 1:sum(nExpC<nExp)){
                        warning(paste("ptid", temp.id, "has", nExp-nExpC[nExpC<nExp][j], "missing value(s) for",
temp.pep[nExpC<nExp][j], "on day", temp.day))
                  }
            }
    }
    pos.call <- ifelse(adjp <= alpha,1,0)

    output <- data.frame(cbind(dat,round(teststat,5),round(adjp,5),pos.call))
    colnames(output)[(ncol(dat)+1):(ncol(dat)+3)] <- c("t-stat","adjp","pos")
    output
}
```

 # The following code will use the above R function to apply the DRF (eq) Method

```
method1 <- elsdfreq(data=data1, nExp=3, nCtl=6, nameCtl="negctl")
method1
```

 # Where nExp = number of experimental wells
nCtl = number of negative control or mock wells
nameCtl = name of negative control exactly as it appears in data file

	id	day	antigen	a1	a2	a3	c1	c2	c3	c4	c5	c6	t-stat	adjp	pos
1	1	1	tyr	23	22	24	9	5	8	3	5	7	16.83333	0.01190	1
2	1	1	flu	11	7	8	9	5	8	3	5	7	2.50000	0.10714	0
3	2	1	tyr	12	17	14	9	11	12	8	13	6	4.50000	0.03571	1
4	2	1	flu	24	28	22	9	11	12	8	13	6	14.83333	0.01190	1
5	3	1	tyr	22	19	15	17	13	8	10	11	9	7.33333	0.02381	1
6	3	1	flu	3	8	9	17	13	8	10	11	9	-4.66667	0.98810	0
7	4	1	tyr	100	120	110	7	13	10	9	8	8	100.83333	0.01190	1
8	4	1	flu	9	16	15	7	13	10	9	8	8	4.16667	0.04762	1
9	5	1	tyr	21	15	13	14	13	10	9	11	12	4.83333	0.03571	1
10	5	1	flu	12	15	16	14	13	10	9	11	12	2.83333	0.05952	0
11	6	1	tyr	15	9	10	14	7	9	8	13	11	1.00000	0.34524	0
12	6	1	flu	36	43	41	14	7	9	8	13	11	29.66667	0.01190	1

Note that the output shows eight of the 12 hypotheses show a positive response.

6. SAMPLE CODE FOR FIGURES

```
title '#byval1 #byval2 ';
proc sgplot data=_data_  noautolegend ;
by  analyte antigen;
  vbox result /  nomedian nocaps category=Visit noFill  DISPLAYSTATS
 scatter y=reult x=Visit / jitter transparency=0.5
        markerattrs=(symbol=Circle size=7) group=cohort  ;
  xaxis discreteorder=data ; yaxis grid ;
run;
```