16.1.9 Documentation of Statistical Methods

The document listed below is provided in this section.

Statistical Analysis Plan (ALRN-6924-1-01) dated 13-March-2018

Statistical Analysis Plan

Sponsor Name:	Aileron Therapeutics, Inc.
Protocol Number and Title:	ALRN-6924-1-01 A Phase 1/2a Open-Label Study to Determine the Safety and Tolerability of ALRN-6924 in Subjects with Advanced Solid Tumors or Lymphomas Expressing Wild-Type p53 Protein
Protocol Version and Date:	Amendment 6: 20 Oct 2017 Amendment 5: 27 Mar 2017 Amendment 4: 08 July 2016 Amendment 3: 31 December 2015 Amendment 2: 18 February 2015 Amendment 1: 23 September 2014 (Submitted to FDA only) Version 1.1: 22 July 2014 (Submitted to IRBs for approval) Original: 16 June 2014 (Submitted in IND)
Author(s):	Scott Chasan-Taber, Ph.D. (etera Solutions, LLC)
SAP Version:	V.1
SAP Version Date:	13-Mar-2018

Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
V.1	13-Mar-2018	Scott Chasan-Taber etera Solutions, LLC	Original version

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
etera Solutions, LLC	
Scott Chasan-Taber, Ph.D. Biostatistician	04APR2018 Date (dd-Mmm-yyyy)
Allergon Therapeutics, Inc.	
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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ATC	anatomical therapeutic chemical
BOR	best overall response
C1D1	cycle 1, day 1
CI	confidence interval
CR	complete response
CTCAE	common terminology criteria for adverse events
DCB	duration of clinical benefit
DCR	disease control rate
DEP	dose escalation phase
DLT	dose-limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EXP	dose expansion phase
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
ORR	overall response rate
PD	progressive disease
PFS	Progression-free survival
PR	partial response
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SI	standard international system of units
SOC	system organ class
TEAE	Treatment-emergent adverse event

Abbreviation	Description
TLF	table, listing and figure
TTR	time to overall response

2. STUDY DESIGN

2.1. BRIEF DESCRIPTION

This is a Phase 1/2a open-label, multi-center, dose-escalation study designed to evaluate the safety, tolerability, PK, PD, and antitumor effects of ALRN-6924 in subjects with advanced solid tumors or lymphomas with WT TP53.

The Phase 1 portion of the study, referred to as the dose escalation phase (DEP), is a "3+3" dose escalation design to establish the MTD and OBD of ALRN-6924. Dose cohorts are delineated in the study protocol.

Two regimens are explored in the Phase 1 portion of the study:

- Dose Regimen A: once weekly for 3 consecutive weeks (Days 1, 8, and 15 of a 28-day cycle)
- Dose Regimen B: twice weekly for 2 consecutive weeks (Days 1, 4, 8, and 11 of a 21-day cycle)

The Phase 2a portion of the study, referred to as the dose expansion phase (EXP), will enroll up to 5 distinct groups of subjects with specific solid tumors and/or lymphomas to further investigate the clinical safety profile and potential efficacy of ALRN-6924 at the MTD or OBD. A third dosing regimen, Dose Regimen C, will also be explored during the EXP. Subjects assigned to this regimen will receive ALRN-6924 on days 1, 3, and 5 of a 21-day cycle.

Treatment of subjects in the dose escalation and the dose expansion phases of the study will continue until documentation of disease progression, unacceptable toxicity, or subject or physician decision to discontinue therapy. Subjects receiving clinical benefit may continue on study after a discussion between the Principle Investigator and Medical Monitor.

2.2. DETERMINATION OF SAMPLE SIZE

The total number of subjects enrolled in the study will depend on the number of dose levels and the number of subjects in each cohort before the MTD or OBD is established. Approximately 75 subjects, exclusive of replacements for subjects who discontinue for non-safety reasons, will be enrolled in the DEP, and approximately 20 additional subjects will be enrolled in each expansion cohort. Enrollment of a total of approximately 175

subjects is planned for the study. Approximately 15 to 25 clinical sites are planned.

2.3. TREATMENT ASSIGNMENT & BLINDING

This is an open-label study. Blinding is not applicable for this study.

3. GENERAL CONSIDERATIONS

3.1. GENERAL METHODS

- This Statistical Analysis Plan (SAP) addresses the analysis methodology for the Phase 1 (dose escalation) portion of this study.
- Separate analysis plans will be developed for analyses of
    - Phase 2a (dose expansion)
    - Pharmacokinetics
    - Pharmacodynamics
    - Cell-free DNA from blood
    - Immunogenicity
- All tabulations of data will be provided by dose cohort within each dose regimen, dose regimen overall, and overall for all subjects in the analysis set.
- Two versions of the 28-day dosing cycle (Dose Regimen A and Dose Regimen A2 as described in the protocol) were implemented in the study, but all analyses will combine these subjects.
- In addition to the tabulations delineated in analysis methods below, all data will be displayed in listings organized by regimen and dose cohort.
- The continuous variables will be summarized using number of observations (n), mean, standard deviation (SD), median, 95% confidence interval of the mean, minimum, and maximum, unless otherwise specified. All mean and median values will be formatted to 1 more decimal place than the measured value. All SD values will be formatted to 2 more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value.
- The categorical variables will be summarized using frequency counts and percentages of subjects. Percentages will be calculated using the study population, excluding subjects with missing values, as the denominator. All percentages will be rounded to 1 decimal place. Number and percentage values will be presented as xx (xx.x).

- P-values will be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999.

- Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless specified differently in specific analyses.

- All analyses will be performed using SAS® statistical software package, version 9.3 or higher.

3.2. KEY DEFINITIONS

3.2.1. Cycle 1 Day 1

Cycle 1 Day 1 (C1D1) is defined as the date of the first dose of ALRN-6924.

3.2.1.1. Baseline and Change from Baseline

Baseline value is defined as the last value obtained before the first dose of study treatment administration. This value could be the pre-dose assessment on C1D1 or an assessment obtained during screening. Change from baseline = (post-baseline value – baseline value).

3.2.2. Enrollment

A subject is considered enrolled onto the study after having received at least one dose of study treatment. The enrollment date is set to C1D1.

3.2.3. Study Day and Cycle Day

The study day is the number of days relative to C1D1, while the cycle day is the number of days relative to the first dose date in that cycle. The day of the first dose of ALRN-6924 in Cycle 1 is defined as study Day 1. The day prior to the first dose of ALRN-6924 is study Day -1. There is no study Day 0.

3.3. MISSING DATA

No imputation or extrapolation will be implemented for missing safety or clinical activity results. Partial start/end dates for AEs and medications will be handled as follows:

Adverse events:

Missing day of AE start date

- AE will be treated as treatment emergent unless the month/year are strictly before the month/year of first dose.

Missing day and month of AE start date

- AE will be treated as treatment emergent unless the year is strictly before the year of first dose.

Missing day, month, and year of AE start date

- AE will be treated as treatment emergent.

Missing any date component of AE end date

- No imputation is needed.

Medications other than study treatment:

Missing any date component of medication start date

- No imputation is needed.

Missing day of medication end date

- Medication will be treated as concomitant unless the month/year are strictly before the month/year of first dose.

Missing day and month of medication end date

- Medication will be treated as concomitant unless the year is strictly before the year of first dose.

Missing day, month, and year of medication end date

- Medication will be treated as concomitant.

3.4. VISIT WINDOWS

All collected lab, vital, and ECG data, including unscheduled visits, will be included in data listings and factored into data analyses though no relabelling of assessments based on visit windows will be instituted. Instead, for summaries by time point, only scheduled assessments will be tabulated according to the visit designations established by investigative sites and cleaned by data management. For shift analyses between baseline and maximum or minimum post-baseline assessments, all assessments, including unscheduled visits, will be included in the identification of extreme values.

3.5. POOLING OF CENTERS

Data from all study centers will be combined for analysis.

3.6. SUBGROUPS

There are no planned analyses by subgroups.

4. STUDY ENDPOINTS

4.1. SAFETY ENDPOINTS

- Treatment emergent adverse events (TEAEs)
    - Dose limiting toxicities (DLTs)
- Laboratory evaluations (hematology, coagulation, chemistry, urinalysis tests)
- Vital signs (systolic and diastolic blood pressure, pulse, respiratory rate, and oral body temperature)
- ECG parameters (overall assessment; heart rate; PR, QRS, QT, and QTc intervals)
- ECOG performance status

4.2. CLINICAL ACTIVITY ENDPOINTS

- Overall response - objective evidence of complete response (CR) or partial response (PR). The evaluation of overall response will be based on response, as determined by the investigator, in accordance with RECIST version 1.1, for subjects with solid tumors, or IWG 2014 criteria, for subjects with lymphomas.
    - Overall Response Rate (ORR) – proportion of subjects with overall response
    - Time to Response (TTR) - time from the date of the first dose of ALRN-6924 to the date of the first documentation of overall response. The TTR will be calculated as follows (in months):

      (date of first response (CR/PR) – first dose date + 1)/30

      Subjects who do not respond will be censored at their last tumor assessment.
    - Duration of Response (DOR) - time from the first documentation of overall response to the first documentation of objective or clinical disease progression or death due to any cause. This endpoint is only assessed among subjects who achieve overall response at some point during the study. The DOR will be calculated as follows (in months):

(date of disease progression/death – date of first response (either CR or PR) + 1)/30

Subjects who do not have disease progression (or death) will be censored at the last known time point that the subject was progression-free. Subjects with two or more consecutive missing response assessments prior to a visit with progression (or death) will be censored at the last date of tumor assessment when the subject was known to be progression free.

- Disease control - objective evidence of CR, PR, or stable disease (SD). The evaluation of disease control will be based on response, as determined by the investigator, in accordance with RECIST version 1.1, for subjects with solid tumors, and IWG 2014 criteria, for subjects with lymphomas.

    - Disease Control Rate (DCR) - proportion of subjects with objective evidence of disease control

    - Duration of Clinical Benefit (DCB) - time from the first documentation of disease control to the first documentation of objective or clinical disease progression or death due to any cause. This endpoint is only assessed among subjects who achieve disease control at some point during the study. The DCB will be calculated as follows (in months):

(date of disease progression/death – date of first response (either CR/PR/SD) + 1)/30

Subjects who do not have disease progression (or death) will be censored at the last known time point that the subject was progression-free. Subjects with two or more consecutive missing response assessments prior to a visit with progression (or death) will be censored at the last date of tumor assessment when the subject was known to be progression free.

- Best Overall Response (BOR) – the highest level of objective response recorded (complete response, partial response, stable disease, or progressive disease) for each subject

- Progression-free Survival (PFS), defined as the time from the date of the first dose of ALRN-6924 to the date of first evidence of objective or clinical disease progression or the date of death, due to any cause, whichever occurs first. The PFS will be calculated as follows (in months):

    (date of disease progression/death – first dose date + 1)/30

  Subjects who do not have disease progression (or death) will be censored at the last known time point that the subject was progression-free. Subjects with two or more consecutive missing response assessments prior to a visit with progression (or death) will be censored at the last date of tumor assessment when the subject was known to be progression free.

5. ANALYSIS SETS

5.1. SAFETY POPULATION

The Safety Population, defined as all subjects who receive at least 1 dose of ALRN-6924, will be used for safety analyses and summaries of demographics and baseline characteristics.

5.2. EFFICACY EVALUABLE POPULATION

The Efficacy Evaluable Population is defined as those subjects who meet all of the following criteria:

- Received at least one dose of ALRN-6924 at a dose level at least 0.8 mg/kg per infusion.
- Have at least one post-baseline evaluation or had clinical disease progression
- Are TP53 wild type or indeterminate (as assessed by the central lab; if not assessed by central laboratory, as assessed by the local laboratory)

This population will be used for analyses of clinical activity.

6. SUBJECT ACCOUNTING

6.1. SUBJECT DISPOSITION

The total number of subjects enrolled, treated, and discontinued from treatment will be summarized including reasons for discontinuation. Reasons for treatment discontinuation include:

- Adverse Event
- Objective Disease Progression
- Clinical Disease Progression
- Non-compliance
- Consent withdrawn
- Lost to follow-up
- Death
- Other

Inclusion/exclusion criteria that were not met will be listed by subject, including designation of whether a waiver was granted.

Important protocol deviations will be listed.

6.2. SUBJECT EVALUABILITY

Accounting for all enrolled subjects and their inclusion in analysis sets (Safety Population and the Efficacy Evaluable Population), along with reasons for exclusion from analysis sets, will be summarized.

7. DEMOGRAPHICS, OTHER BASELINE CHARACTERISTICS AND MEDICATIONS

7.1. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Age (years), height (cm), weight (kg), and BMI (kg/m^2) at baseline will be summarized descriptively. Gender, race, and ethnicity will be summarized by frequency counts. Age is calculated as follows (in years):

(date of informed consent for the full study – date of birth +1)/365.25

Body mass index is calculated based on weight and height at baseline.

7.2. GENERAL MEDICAL AND SURGICAL HISTORY

Medical history events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or later which will provide a System Organ Class (SOC) and preferred term (PT) for each relevant medical or surgical history reported by the investigator.

These data will be summarized by SOC and PT.

7.3. CANCER DIAGNOSIS AND PRIOR CANCER-DIRECTED THERAPIES

The following factors will be tabulated:

- P53 status
- The time from initial cancer diagnosis to the first dose of ALRN-6924 calculated as follows (in years):

  (date of first dose - diagnosis date + 1)/365.25
- Prior radiation therapy (yes, no)

- Prior cancer surgery (yes, no)

7.4. PRIOR AND CONCOMITANT MEDICATIONS

Concomitant medications are defined as medications ongoing or stopped on or after the date of the first dose of ALRN-6924. Prior and concomitant medications will be coded with World Health Organization Drug Dictionary (WHO DDE) Enhanced B2 Format September 1, 2016 or later.

Concomitant medications will be summarized. The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least 1 medication within each medication group and subgroup.

8. SAFETY ANALYSES

8.1. STUDY TREATMENT AND EXTENT OF EXPOSURE

The ALRN-6924 administration profile will be summarized with respect to treatment duration (Treatment duration (days) = last treatment date – first treatment date + 1), number of infusions, total ALRN-6924 dose received (mg), average dose per cycle, number of cycles, number of subjects with dose modification(s), and reason for dose modification(s).

8.2. DOSE-LIMITING TOXICITIES

The number and percent of subjects experiencing DLTs will be summarized by DLT category.

8.3. ADVERSE EVENTS

Treatment-emergent adverse events (TEAEs) are defined as AEs that are newly occurring or worsening on or after the date of the first dose of ALRN-6924. Reported AE terms will be coded using MedDRA version 19.1 or later.

The number and percent of subjects, and the number of events where relevant, will be summarized by SOC and PT for the following categories of TEAEs:

- All TEAEs
- Grade 3 or higher CTCAE grade TEAEs
- Related TEAEs defined as at least possibly related, as delineated by the investigator, or missing
- Serious TEAEs

- Serious related TEAEs
- TEAEs leading to discontinuation of study drug
- TEAEs leading to death

8.4. LABORATORY EVALUATIONS

Laboratory assessments include:

Hematology: complete blood count, reticulocytes, platelets and differential

Clinical chemistry: glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, phosphate, BUN [blood urea nitrogen], serum creatinine, uric acid, ALP, ALT, AST, LDH, CRP, and total and direct bilirubin

Coagulation: prothrombin time, INR, aPTT, fibrinogen.

Urinalysis: pH, specific gravity, protein, glucose, ketones, nitrite, leukocyte esteras

All clinical laboratory parameters will be converted to consistent units according to the International System of Units (SI) before summarization.

For numeric laboratory parameters, the observed values at each scheduled visit and change from baseline to post-baseline scheduled visits will be summarized. For numeric laboratory parameters that have an upper and/or lower reference range, all assessments (including unscheduled) will be categorized as low, normal, or high (i.e., below, within, or above reference range) and shift tables from baseline to max and min post-baseline values will be tabulated.

For categorical laboratory parameters, shift tables from baseline to max and min post-baseline values will be tabulated.

The incidence of grade 3 and 4 laboratory abnormalities will be summarized by CTCAE toxicity grade.

8.5. VITAL SIGNS

Vital signs (respiratory rate, temperature, blood pressure, and heart rate) are assessed periodically during and after each infusion. The data analysis of these data will consist of two phases:

- For cycles 1 and 2, each subject's values at each time point and the changes from pre-infusion to each follow-up assessment within the cycle will be summarized.

- For cycle 3 and beyond, the average of each subject's values for each time point across cycles and the changes from pre-infusion average to each follow-up time point average will be summarized.

Additionally, the changes from baseline to max and min post-baseline values will be summarized.

8.6. ECG

A summary of ECG parameters (heart rate, PR, QRS, QT, and QTc intervals) and change from baseline will be presented for each planned visit. When triplicate assessments were taken at a visit, the median value will be used for summary purposes.

The ECGs will be assessed by the investigator and deemed, from best to worst finding, "Normal", "Abnormal, not clinically significant" or "Abnormal, clinically significant". Shifts in this overall interpretation between baseline and the worst overall assessment will be tabulated.

8.7. ECOG PERFORMANCE STATUS

The ECOG performance status scores range from 0 to 5 as follows:

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al, 1982.

Shifts in ECOG performance status between baseline and the worst overall assessment will be summarized.

8.8. PHYSICAL EXAMINATION

Adverse physical examination findings with onset after the first dose of ALRN-6924 will be considered adverse events and tabulated accordingly.

9. CLINICAL ACTIVITY ANALYSES

ORR and DCR will be summarized by frequency counts, percentages, and the two-sided 95% CIs. The Wilson score method will be used to construct the confidence intervals.

The distribution of TTR and PFS will be summarized using Kaplan-Meier methodology grouped. The 25th, 50th (median), and 75th percentiles will be provided, along with their two-sided 95% CIs.

The distribution of DOR (among responders) and DCB (among subjects experiencing clinical benefit) will be summarized using Kaplan-Meier methodology grouped. The 25th, 50th (median), and 75th percentiles will be provided, along with their two-sided 95% CIs.

The best overall response (BOR) will be summarized by frequency counts and percentages of subjects achieving each possible category (complete response, partial response, stable disease, progressive disease).

10. INTERIM ANALYSES

No interim analysis is planned for this study.

11. CHANGE FROM ANALYSES PLANNED IN PROTOCOL

This statistical analysis plan is based on protocol Amendment 6, which was finalized on 20 October 2017. In addition to the endpoints outlined in the protocol, duration of clinical benefit has been included as an additional endpoint in this SAP.

12. REFERENCE LIST

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Nonclinical evaluation for anticancer pharmaceuticals. S9. Published October 29, 2009.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982:5(6):649-55.

US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. (v4.03 14 June 2010).