Altor BioScience

Protocol QUILT-1.004 (CA-ALT-803-03-17)

A Single Center, Open-label, Pharmacokinetic Study of Subcutaneous ALT-803

Statistical Analysis Plan

Final

Version 3.0

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STATISTICAL ANALYSIS PLAN APPROVAL PAGE

Protocol No.:	**QUILT-1.004 (CA-ALT-803-03-17)**
Protocol Title:	**A Single Center, Open-label, Pharmacokinetic Study of Subcutaneous ALT-803**
Protocol Version/ Date:	**Version 1 / 09Nov2017**
Statistical Analysis Plan Authors:	**Megan Huang**
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By signing, I approve the Statistical Analysis Plan. The Statistical Analysis Plan outlined in this document is in accordance with the study/project requirements and is adequate to meet the needs for the study/project.

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-}inf}$	Area under the plasma concentration curve from time 0 extrapolated to infinite time
$AUC_{0\text{-}t}$	Area under the plasma concentration curve from time 0 through the last measurable concentration
CBC	Complete Blood Count
CI	Confidence Interval
CL/F	Apparent (extravascular) clearance
C_{max}	Maximum observed concentration
CMP	Complete Metabolic Panel
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Event
ECG	Electrocardiogram
IL	Interleukin
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System Organ Class
SRC	Safety Review Committee
subQ	Subcutaneous
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time of the observed maximum concentration
$t_{½}$	Half-life
V_z/F	Apparent (extravascular) volume of distribution

1. INTRODUCTION

This Statistical Analysis Plan (SAP) summarizes the planned presentation and safety analyses of protocol QUILT-1.004 (CA-ALT-803-03-17), Version 1/ 09Nov2017 "A Single Center, Open-label, Pharmacokinetic Study of Subcutaneous ALT-803". The main focus of this SAP is safety data analyses. The study safety endpoints, derived variables, and the corresponding planned statistical methodology are summarized in this SAP.

2. STUDY OBJECTIVES

Primary Objectives:

- To determine the pharmacokinetic (PK) profile after single dose subcutaneous (subQ) injection(s) of 10 µg/kg and 20 µg/kg ALT-803 at concentrations of 1.0 mg/mL or 2.0 mg/mL.

Secondary Objectives:

- To assess safety after single dose subQ injection(s) of 10 µg/kg and 20 µg/kg ALT-803 at concentrations of 1.0 mg/mL or 2.0 mg/mL.

3. STUDY OVERVIEW

3.1 Study Design

This is a single center, open-label, pharmacokinetic study of ALT-803 administered as a subQ injection to healthy volunteers.

Subjects meeting the entry criteria will be randomized in a 1:1 ratio (Groups A or B) to one of two ALT-803 drug concentrations. Subjects randomized to Group A will receive ALT-803 at a concentration of 1.0 mg/mL, and subjects randomized to Group B will receive ALT-803 at a concentration of 2.0 mg/mL. All subjects in Groups A and B will receive a single 10 µg/kg subQ dose of ALT-803 on Day 1 of study period 1. After a 6-day minimum rest period, subjects will receive a single 20 µg/kg subQ dose of ALT-803 on Day 1 of study period 2.

Blood samples to determine serum levels of ALT-803 will be collected prior to dosing, and at 1, 4, 24, 48, 72, 96, 120, 144, 168 and 192 hours after dosing.

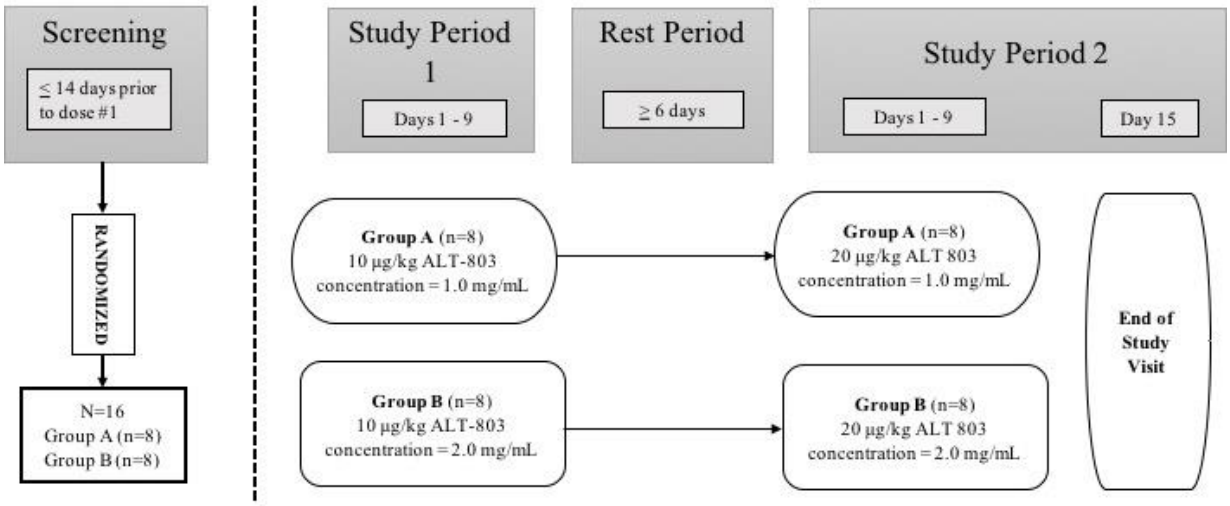
Vital signs (heart rate, blood pressure, respiration, temperature) will be monitored.

Safety will be assessed for all subjects and will include monitoring of vital signs, and incidence and severity of adverse events. Blood samples will be collected for hematology and chemistry, immune cell levels and activity, immune cell phenotype subsets, cytokine levels, and immunogenicity testing, which include assays for anti-ALT-803 antibodies.

After the completion of study period 2, subjects will be followed for additional 6 days and will have an End of Study visit on Day 15 which will include safety labs, immune cells, and cytokines.

Concomitant medications and adverse events will be collected throughout the study.

Figure 1: Study Schema



3.2 Number of Study Sites

This study will be conducted at a single study site in US.

3.3 Number of Subjects

The study population consists of healthy male and female volunteers, aged 18 - 65 years. A total of 16 evaluable subjects will be enrolled (8 in Group A and 8 in Group B).

Any subject who meets the following criteria will be replaced:

- Subjects who are enrolled but do not receive ALT-803
- Subjects who withdraw consent
- Subjects who have a positive alcohol or drug test after enrollment
- Subjects who miss more than one PK collection timepoint during study period 1 or study period 2 will be replaced.

3.4 Duration of Treatment

This study will consist of two study periods (9 days each) and a rest period (> 6 days). Subjects will receive a single 10 µg/kg subQ dose of ALT-803 on Day 1 of study period 1. After a rest period, subjects will receive a single 20 µg/kg subQ dose of ALT-803 on Day 1 of study period 2. In both study periods 1 and 2, blood sampling for PK and safety labs will commence on Day 1 and continue daily throughout the 9-day study period. After the completion of study period 2, subjects will be followed for additional 6 days and will have an End of Study visit on Day 15.

Subjects who are replaced will be followed for up to 14 days, following their last dose of ALT-803 for adverse events monitoring only.

3.5 Randomization and Blinding

Subjects meeting the entry criteria will be randomized in a 1:1 ratio (Groups A or B) to one of two ALT-803 drug concentrations.

This is an open-label study, so blinding is not applicable.

4. STUDY ENDPOINTS

4.1 Primary Endpoints

Serum concentration will be used to calculate the following PK parameters:

- half-life ($t_{½}$)

- apparent (extravascular) volume of distribution (V_z/F)
- apparent (extravascular) clearance (CL/F)
- maximum observed concentration (C_{max})
- time of the observed maximum concentration (T_{max})
- area under the plasma concentration curve from time 0 through the last measurable concentration (AUC_{0-t})
- area under the plasma concentration curve from time 0 extrapolated to infinite time (AUC_{0-inf})

4.2 Secondary Endpoint

- Safety, as assessed by the incidence and severity of adverse events.

4.3 Measures of Interest

- Blood samples will be collected for immune cell levels and activity, immune cell phenotype subsets, cytokine levels and immunogenicity testing, which include assays for anti-ALT-803 antibodies.
- General health as assessed by the RAND General Health Questionnaire (SF-36).

5. SAMPLE SIZE

A total of 16 patients will be enrolled (8 patients in Group A and 8 patients in Group B).

6. ANALYSIS POPULATIONS

Safety population: Safety population will include all enrolled subjects who received at least one dose of ALT-803.

Study results will be presented for each study group as well as all subjects combined.

7. STATISTICAL METHODOLOGY

7.1 Analysis Conventions

This section details general analysis conventions to be used for the statistical analyses. Departures from these general conventions may be given in the specific detailed sections of the SAP.

- Statistical analyses will be descriptive in nature. Descriptive statistics will consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, median, S.D., minimum, and maximum for continuous variables;

- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value;

- All percentages will be rounded to whole numbers. The number and percentage of responses will be presented in the form XX (XX%), where the percentage is in the parentheses;

- Confidence intervals (CIs) will be presented as 2-sided 95% CIs;

- All listings will be sorted for presentation in order of treatment cohort, study site, subject, and date of procedure or event;

- All analysis and summary tables will have the analysis population sample size (i.e., number of subjects);

- When necessary for analysis purposes, an adverse event or medication start or stop dates without a specific day of the month given (i.e., JAN1999) will be assigned the 15th day of the month and dates without a specific day or month (i.e., 1999) will be assigned the 30th day of June to complete the date. If the incomplete date is a start date and the above imputation inappropriately results in a date on or before the first dose date, then the incomplete date will be assigned to the day following the first dose date. If either imputation results in an imputed start date after the stop date, then the start date will be set to the day prior to the stop date;

- The day of the first dose of any study drug will be defined as Day 1;

- Baseline value will be defined as the last value before the first dose of any study drug is administered;

- Final Evaluation will be defined as the last on-treatment value;

- MedDRA version 19.1 will be used for adverse events coding and Health Organization (WHO) drug dictionary version DEC2016 for medications coding; and

- SAS® Version 9.4 (or later) will be used to analyze the clinical data and generate summary tables, listings, and figures.

7.2 Interim Analysis

No interim analysis is planned for the study.

7.3 Subject Disposition

Subject disposition will be summarized by the number and percentage of the subjects enrolled, in the Safety population, who discontinued the study prematurely, and the reasons for premature discontinuation.

Subject disposition, entry criteria violations, and subjects excluded from Safety population will be presented in a data listing.

7.4 Demographics and Baseline Characteristics

Summary statistics will be calculated for age, sex, ethnicity, race, height, and baseline body weight. Age is defined as the time from the subject's date of birth to date of informed consent in years.

7.5 Medical History

Medical history will be collected at screening and includes any relevant medical history findings which will be coded using MedDRA and classified by System Organ Class (SOC) and Preferred Term (PT). Coded medical history data will be summarized.

7.6 Prior and Concomitant Medication

The name, route of administration, duration of use, dose, unit, frequency, and indication for all prior and concomitant medications taken from screening through study termination will be collected. Prior and concomitant medications will be coded to therapeutic drug classes and generic drug names using the WHO drug dictionary.

A prior medication will be defined as any medication taken prior to the date and time of the first dose of ALT-803. A concomitant medication will be defined as any medication started on or after the first dose of ALT-803. Concomitant medications will be summarized by ATC level and preferred term. All available date information will be used in order to determine if a medication is concomitant. In the event of completely missing date information, the medication will be assumed concomitant.

7.7 Safety Analyses

7.7.1 Study Drug Exposure

Study drug exposure will be summarized as follows:

- Number and percentage of subjects who received doses in both study periods 1 and 2;

- Number and percentage of subjects who did not receive a dose in study period 1 and the reason(s) for that;

- Number and percentage of subjects who did not receive a dose in study period 2 and the reason(s) for that;

- Summary statistics for the dose received and percentage of protocol dose in each study period. Percentage of protocol dose will be calculated as the dose received divided by the protocol dose (i.e., prescribed dose) x 100%.

7.7.2 Adverse Events

Several summary tables will be presented for the incidence of treatment-emergent adverse events (TEAEs). TEAEs will be defined as any AE that begins or worsens in grade after the start of study drug until 30 days after the last dose of study drug or End of Study, whichever is later.

Summary tables will be tabulated alphabetically by SOC and PT based on the MedDRA version 19.1 coding dictionary. If a subject experiences multiple episodes of the same AE, the subject only will be counted once for that particular AE.

The following TEAE tables will be presented:

- All TEAEs,
- Grade 3 or higher TEAEs,
- Treatment-related TEAEs,
- Treatment-related grade 3 or higher TEAEs,
- Serious AEs,
- Treatment-related SAEs,
- TEAEs leading to discontinuation of study drug, and
- TEAEs leading to death.

Any AE with a missing onset date will be considered as treatment-emergent unless there is a non-missing end date information (i.e., month or year) that indicates it resolved prior to administration of study drug.

If a subject experiences multiple episodes of the same event, the event with the maximum severity or strongest relationship to study medication will be used for analysis. Missing severity or relationship will be presented as “Severe” or “Suspected”, respectively.

SAEs, deaths, and AEs leading to discontinuation of study drug will be presented in data listings. Any non-TEAEs will be presented in the data listings and indicated as non-TEAE.

7.7.3 Laboratory Assessments

The hematology including complete blood count (CBC) with differential and blood chemistry (Complete Metabolic Panel [CMP]) will be evaluated at baseline and through 2 study periods.

Laboratory data will be summarized at baseline and as change from baseline at each post-baseline visit for all laboratory tests.

7.7.4 Vital Signs and Physical Examinations

Vital signs (heart rate, blood pressure, respiratory rate, body temperature) will be collected at screening and at study visits per Schedule of Assessments as described in Section 4.3 of the study protocol. Vital signs will be performed prior to, and one hour post-ALT-803 subQ injection. On PK sample collection days, vital signs are to be collected prior to blood draw. Height will be measured at screening and body weight will be noted before each ALT-803 subQ injection.

A complete physical exam [head, eyes, ears, nose, throat, skin, heart, lungs, abdomen, extremities, and neurological (e.g. level of consciousness, pupils, motor and sensory responses, and reflexes)] will be performed at screening and a routine physical exam will be performed on all study visits.

Vital signs and body weight will be summarized at baseline and as change from baseline at each post-baseline evaluation time point.

Abnormal vital signs and physical examination findings will be reported as AEs.

7.7.5 Injection Site Reaction

The most common adverse event attributed to ALT-803 administered subcutaneously is an injection site reaction. Injection site reactions are localized rashes surrounding the ALT-803 injection site. Injection site reactions typically occur 3 days post ALT-803 subQ injection and resolve in less than one week.

The ALT-803 Injection Site Reaction Diary will be given to subjects on the day that the ALT-803 subQ injection is administered (Day 1 of study periods 1 and 2). The diary is to be completed by the subject daily until the resolution of symptoms. If any symptoms have not resolved by the next dose of ALT-803 (Day 1 of study period 2), the subject will need to complete two diaries. Each diary will address the individual injection sites and their corresponding symptoms until resolution. The subject will return the completed diaries to the study coordinator.

Any of the symptoms that represent an adverse event will be reported as an AE.

Injection site reaction data will be summarized for each injection diary as follows:

- Number and percentage of subjects who experienced redness at the injection site
- Number and percentage of subjects who experienced firmness or swelling at the injection site
- Number and percentage of subjects who experienced any pain or itching at the injection site
- Number and percentage of subjects who took or applied any medication for injection site pain or itching
- Number and percentage of subjects who experienced chills
- Number and percentage of subjects with at least one daily temperature higher than 101^{o}F
- For each occurred symptom, summary statistics will be presented for the symptom starting day, duration of the symptom, and the worst assessment over the study course if applicable.

7.7.6 General Health Questionnaire

The General Health Questionnaire, RAND 36-item Short Form Survey 1.0 (SF-36) will be completed by the subject at baseline on Day 1, study period 1, and at the Follow-up visit.

The RAND 36-Item Health Survey (Version 1.0) taps eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health.

Scoring the RAND 36-Item Health Survey in this study is a two-step process (Hays 1993). First, precoded numeric values are recoded per the scoring key given in Step 1. Note that all items are scored so that a high score defines a more favorable health state. In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are 0 and 100, respectively. Scores represent the percentage of total possible score achieved. In step 2, items in the same scale are averaged together to create the 8 scale scores. Step 2 lists the items averaged together to create each scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Hence, scale scores represent the average for all items in the scale that the respondent answered.

Step 1: Recoding Items

Item numbers	Change original response category *	To recoded value of:
1, 2, 20, 22, 34, 36	1 →	100

	2 →	75
	3 →	50
	4 →	25
	5 →	0
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1 →	0
	2 →	50
	3 →	100
13, 14, 15, 16, 17, 18, 19	1 →	0
	2 →	100
21, 23, 26, 27, 30	1 →	100
	2 →	80
	3 →	60
	4 →	40
	5 →	20
	6 →	0
24, 25, 28, 29, 31	1 →	0
	2 →	20
	3 →	40
	4 →	60
	5 →	80
	6 →	100
32, 33, 35	1 →	0
	2 →	25
	3 →	50
	4 →	75
	5 →	100

Step 2: Averaging Items to Form Scales

Scale	Number of items	After recoding per Table 1, average the following items
Physical functioning	10	3 4 5 6 7 8 9 10 11 12
Role limitations due to physical health	4	13 14 15 16
Role limitations due to emotional problems	3	17 18 19
Energy/fatigue	4	23 27 29 31

Emotional well-being	5	24 25 26 28 30
Social functioning	2	20 32
Pain	2	21 22
General health	5	1 33 34 35 36

General Health Questionnaire data will be summarized at baseline and as change from baseline at the follow-up visit. Eight summary scales in Step 2 will be derived and used in the analyses.

7.8 IMMUNOGENICITY (Anti-Drug Antibody) METHODOLOGY

Immunogenicity samples will be analyzed in all subjects who have received at least one dose of ALT-803. Samples will be collected at baseline (prior to any drug administration), prior to the start of Study Period 2, and at the End of Study visit. ADA (anti-drug antibody(s)) positivity will be listed for each subject for the screening, confirmatory and/or titer assays. Incidence of ADA formation will be summarized by cohort.

7.9 Deviations from Statistical Analyses Planned in Protocol

As of this date, there have been no deviations between the protocol-defined statistical analyses and those presented in this statistical plan.

8. REFERENCES

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3. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. 2010; http://evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed October 23, 2013.

4. Ron D. Hays, Cathy Donald Sherbourne, and Rebecca M. Mazel. The RAND 36-item Health Survey 1.0. Health Economics, Vol. 2:217-227, 1993.

9. SCHEDULE OF ASSESSMENTS

Tests & Procedures	**Screen**[1]	**BL**[2]	**Study Period 1**									**Rest Period**	**Study Period 2**									
Study Day		1	1	2	3	4	5	6	7	8	9	≥ 6d	1 (pre-dose)	1	2	3	4	5	6	7	8	9	End of Study, D15
Medical History & Demographics	X																						
Complete Physical Exam	X																						
Routine Physical Exam		X											X										X
HIV, Hepititis B/C	X																						
Serum/Urine Pregnancy Test[3]	X	X											X										X
Urine Drug Test[4]	X	X											X										
Alcohol Breath Test[5]	X	X											X										
Vital Signs, Height and Weight[6,7]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
CBC with differential	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
Blood Chemistry (CMP)	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
Blood Sampling for Immune Cells		X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
Blood Sampling Cytokines		X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
Blood Sampling for Immunogenicity Testing		X											X										X
Blood Sampling for ALT-803 Pharmacokinetics[8]		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	
General Health Questionnaire		X																					X
Drug Administration																							
ALT-803			X											X									
Safety Monitoring																							
Injection Site Reaction (ISR) Diary[9]		As applicable																					
Digital Photography of Injection Site and ISR[10]		X	As applicable										X	As applicable									
Adverse Events Monitoring		Continual																					
Concomitant Meds		Continual																					

[1]Screening evaluations performed ≤14 days prior to dose #1 unless otherwise specified.

[2]Baseline (BL) evaluations will be performed on Treatment Day 1 (pre-dose).

[3]For women with childbearing potential only. Screening test should be serum. Baseline test may be urine.

[5]A positive read (≥ 0.010% BAC) is an exclusion criteria during screening or will result in subject not being dosed while on study.

[6]Vital signs will be assessed prior to dosing with ALT-803 and 1 hour post-dose. On all other days, vital signs will be collected prior to sample collection.

[7]Height should only be measured at screening. Weight will be measured prior to ALT-803 dose, for study periods 1 and 2.

[8]Blood sampling for PK will be collected prior to ALT-803 dose, 1 and 4 hours post dose and at 24, 48, 72, 96, 120, 144, 168 a nd 192 hours after dosing for study periods 1 and 2.

[9]Injection site reaction diaries should be completed through Day 6 or resolution of symptoms, whichever is longer.

[10] A digital photograph of the Injection site will be taken prior to subQ injection of ALT-803. Photograph ISR's daily in 2 views through Day 6 or resolution, whichever is longer.