STATISTICAL ANALYSIS PLAN

Trial ID: EXT608-101

EXT608 in Human Healthy Adults; A First-in-Human, Randomized, Double-blind, Placebo-controlled, Single Dose Escalation Study (Version 2.0)

Table of Contents

ABBREVIATION AND DEFINITIONS

- **λz**: Terminal rate constant
- **ADA**: Anti-drug Antibodies
- **AE:** Adverse Event
- **ANOVA:** Analysis of Variance
- **AUC:** Area under the curve
- **AVG:** Average
- **CMax:** Maximum Concentration
- **CL/F**: Clearance
- **DIABP:** Diastolic Blood Pressure
- **ECG:** Electrocardiogram
- **EDC**: Electronic Data Capture systems
- **EXT608**: Name of the study medication
- **FAS**: Faull Analyses Set
- **FIH**: First-in-human
- **LLOQ**: Lower limit of quantification
- **MedDRA**: Medical Dictionary for Regulatory Activities
- **Nab**: Neutralizing subset
- **PD**: Pharmacodynamics
- **PK**: Pharmacology
- **PP:** Per Protocol
- **PT:** Preferred Term
- **SAD**: Single Ascending Dose
- **SAE:** Serious Adverse Event
- **SAS**: Analyses Software by SAS institute
- **SOC:** System Organ Class
- **SYSBP:** Systolic Blood Pressure
- **TMax:** Time corresponding to the Maximum Concentration
- **tHalf,early**: Half-life Early
- **tHalf,late**: Half-life Late
- **VAS:** Visual Analogue Scale
- **Vz/F**: Volume Distribution
- **V**: Volume

1 OVERVIEW

1.1 INTRODUCTION

This documentation describes the planed data analyses for Extend Biosciences EXT608-101 clinical trial.

1.2 OBJECTIVES

1.2.1 Primary Objective

The primary objective is to characterize the safety and tolerability profile of escalating dose levels of EXT608 when administered to healthy adult participants as a single injection as assessed by:

- Incidence, nature, and severity of adverse events (AEs) and withdrawals due to treatment emergent AEs (TEAEs) [Time Frame: Day 0 up to Day 28]
- Frequency and severity of post-dose change from baseline in hematology, serum chemistries, urinalysis, electrocardiogram (ECG), vital signs, and physical examination (Exam) findings [Time Frame: Day 0 up to Day 28]
- Percentage of participants with injection or infusion site reactions [Time Frame: Day 0 to Day 7]

1.2.2 Secondary Objectives

The secondary objectives are to assess:

- Single dose PK including AUC0-24h, AUC0-48h, AUC0-28d, AUC0-≈, Cmax, Tmax, T½, ƛz, Cl/F and Vz/F.
- Single dose PD by post-dose change from baseline in serum chemistries with particular attention to Se-Ca, phosphate, magnesium, and creatinine. Urinalysis will also be performed.

1.2.3 Exploratory Objectives

Furthermore, the exploratory objectives are to assess:

- Single dose Immunogenicity by anti-drug antibodies (ADA) and any neutralizing subset (NAb),
- Single dose effect on vitamin D metabolism by serum 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D concentrations.

1.3 ANALYSIS SOFTWARE

SAS 9.4 Windows

1.4 MODIFICATIONS FROM THE STATISTICAL SECTION IN THE PROTOCOL

None

2 INVESTIGATIONAL PLAN

2.1 STUDY DESIGN AND RANDOMIZATION

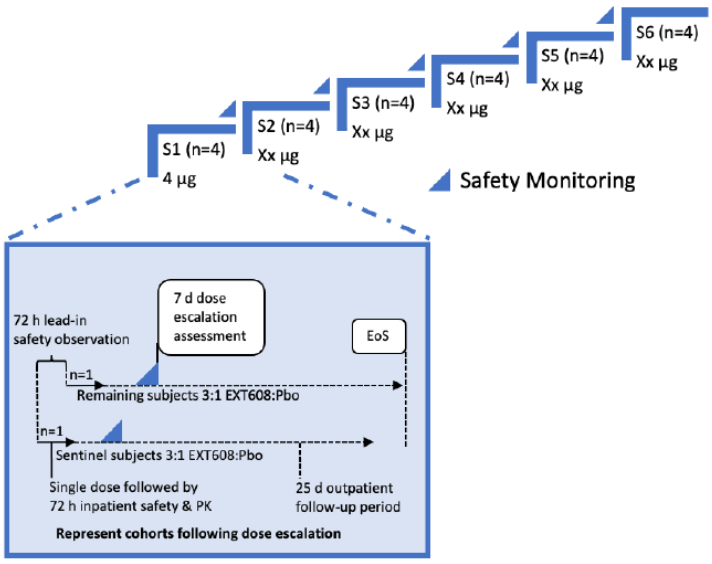
2.1.1 Study Design

This is a randomized, double-blind, first-in-human (FIH), placebo-controlled single ascending dose (SAD) study to study the safety, tolerability, PK, and PD of EXT608 in healthy adult participants.

This is a multiple cohort study. Participants will be enrolled into 1 of up to 6 planned single dose cohorts (designated as S1 through S6, respectively) in ascending fashion.

- Each cohort will consist of 4 participants randomized to receive either EXT608 or placebo, whereby 3 will receive a single injection of EXT608 and 1 will receive matching placebo.
- Up to approximately 30 participants may be enrolled to the study intervention such that approximately 24 evaluable participants complete the study.
- Participants who discontinue prematurely may be replaced at the discretion of the Sponsor.
- Additional participants and cohorts may be enrolled pending review of study data and recommendation by a Data Monitoring Board (DMB) and ratification by the Sponsor.

Figure 1 Study Design



2.1.2 Randomization

Treatment allocation is performed in the EDC in a manner that ensures only the unblinded pharmacist or unblinded monitoring person know the treatment code. The treatment assignment is computer generated by the EDC at the point of randomization.

- Participants are randomized 3:1 EXT608:Placebo in blocks of 4.
- A Pocock-Simon (Pocock and Simon 1975) allocation minimization procedure is implemented into the randomization process to ensure the balance between each treatment arm.
- The balance procedure is based on the serum calcium (mg/dL) obtained at visit Day -1 of each participant.
- Participants who discontinue prematurely may be replaced at the discretion of the Sponsor.

2.1.3 Sample Size Justification

The sample size is not determined for inferential testing purposes. The sample size of 4 participants per cohort (3 EXT608: 1 Placebo) is considered sufficient for evaluation of safety, tolerability, and PD of EXT608 prior to making a decision about dose escalation as Se-Ca is very tightly regulated and determination of effect based on simulations can therefore reliably be made with the small sample.

3 Statistical and analytical procedures

3.1 ANALYSIS POPULATIONS

Two participant populations are defined.

3.1.1 Safety or Full Analysis Set population (FAS)

The Safety or Full Analysis Set population (FAS) will be defined as all participants who are randomized.

- In the event of subjects having received treatments that different from those assigned according to the randomized schedule, then the safety analyses will be conducted according to the treatment received rather than according to the randomization groups.
- Participate who is replaced and received at least one study medication will also be included in this population.

3.1.2 Per-protocol (PP) Population

The Per-Protocol (PP) population will be a subset of the Safety/FAS population and only include participants for whom evaluable data to and including Day 7 is available and with no major protocol violations.

3.2 Data Handling Conventions

3.2.1 Missing Data

- Any blank value will be treated as missing (unknown)
- Blank value will be left as blank in the data listings.
- Missing data will not be estimated unless specified

3.2.2 Per Protocol Time Points Vs Actual Time Points

Unless specified in the analyses section, actual blood sampling times, if available, will be used for individual figures while protocol times will be used for grouping summary.

3.2.3 Repeated and Unscheduled Visit

A repeated visit is a visit planned, by the site, to replace a scheduled visit. Usually same data measurements as the scheduled visit will be collected.

Unscheduled visit is an unplanned visit which includes unexpected data collection.

- Whether a visit is repeated or unscheduled is determined by site and reported in the EDC.

3.2.3.1 Repeated Visit

The principle of last observation priority will be used to handle the situation of repeated visit. Some general recommendations are listed below:

- If a variable (except dates and all lab transferred data) is measured/collected at the repeated visit, the value from the repeated visit will be used for analyses.
- Dates and Lab transferred data will be determined case by case based on its scientifically meaningful and the date/time relative to the treatment date/time.
- If a variable is not measured / collected at the repeated visit, then the value from the original visit will be used for analyses.

3.2.3.2 Unscheduled Visit

Unscheduled visit usually includes data not scheduled to be collected or not required by protocol.

- Data from unscheduled visit will be listed but not used for analyses, except:
    - The data be used to substitute a missing data in the scheduled visit if it clinically meaningful and within a suitable visit window. This is usually determined by the Medical Monitor.

3.2.4 Major Protocol Violations and Minor Protocol Deviations

Towards the end of trial, the scientifically responsible contact (medical monitor) and the statistician will review all protocol deviations and decide if any fit the criteria of a Major Protocol Violation, for the purpose of determining if the participants satisfy the requirement of per protocol population.

- The decision should be documented
- For a blinded trial, the decision should be made before unblinding

3.2.5 Visit Window

The following visit window is defined based on protocol.

Table 1 Protocol Defined Visit Schedule

Procedure	Period:	Screening	Check-in[a]	Inpatient Observation	Outpatient Follow-up					
		Day -28 to Day-2	Day -1	Days 0-3	Day 5	Day 7	Day 14	Day 21	Day 28	Early Termination
Tolerance (days)			0	See In-patient sch.	0	1	1	2	2	

Table 2 Protocol Defined Sequestered Schedule for Day 0-3

Procedure	Period	Pre-Dose			Dose	Post-Dose											
	Day	Day 0													Day 1	Day 2	Day 3
	Time Unit	Minutes			Hour												
	Time	-120	-90	-30	0	0.25	0.5	1	1.5	2	4	8	12	18	24	36	48	72
+/- Tolerance (minutes)		15	10	5	0	1	2	5	5	5	10	15	30	30	60	60	60	60

Based on the above tables (Table 1 and Table 2), for convenience, the following visit name will be used for all analyses.

Table 3 Visit name used in the analyses

Screening	Day -1	Day 0-3	Day 5	Day 7	Day 14	Day 22	Day 28	Early Termination

3.3 ANALYSIS VARIABLES

This section describes any reformatting, calculation or transformation that might be applied to any variable before analyses.

- Unless specified, Unit will be kept as originally reported regardless if it is Metric or American system
- If a variable is reformatted, the new format will be displayed in the data listing.
- If a variable is calculated, both the original value and the calculated value will be displayed in the data listing.
    - This usually refers to the substitution of any missing value
- If a variable is transformed for analyses, only the original value will be will be displayed in the data listing, as the transformation is usually an intermediate step in analyses.

3.3.1 Demographic Characteristics Variables

Common Demographic variables include:

- Demographics
- Height weight
- Medical history
- Physical Exam

Reformatting maybe applied for display purpose but no additional calculation (except BMI) or transformation will be done before analyses.

- For Physical Exam and Medical history, if the Body system is “Other”, it will not be coded unless the “Other” category becomes the largest or 2nd to the largest category.
- Weight: Change from baseline will be calculated
    - Baseline is the weight at the beginning of visit Day -1.
- Physical Exam: Change from baseline will be evaluated
    - Baseline is Physical Exam status at screening
    - Change from baseline will be the status changes from screening to Day 28 or end of study. The following categorization will be used:
        - Normal -> Normal
        - Normal -> Abnormal
        - Abnormal -> Abnormal
        - Abnormal -> Normal
        - Unknown (if the status is missing as either of the time point)

3.3.1.1 Age

Since only the month and year of birth are collected in the EDC, we will use number 15 to substitute the day of birth.

Then the Age will be calculated by:

$$\text{Age} = \text{Floor}(\frac{(\text{Day } 0 - (\text{The approximated Date of Birth})}{365.25})$$

- Function floor means age will take the largest integer (e.g., age 50.8 will become age 50).
- For participant who is not advanced to Day 0, i.e. screening failure or randomized but not dosed, there will be no Age calculated.

3.3.1.2 Medical History

Reformatting maybe applied for display purpose but no additional calculation or transformation will be done before analyses.

3.3.2 Trial conduct variables

These include the visit dates and the study completion data of each participant. These variables are usually used for disposition or drug exposure summaries.

Reformatting maybe applied for display purpose but no additional calculation or transformation will be done before analyses unless specified in the analyses.

3.3.2.1 Day 0

Day 0 is anchor day used to define timeline. Based on the visit windows (section 3.2.5):

Day 0 = date of Dose (or IP administration in EDC)

3.3.2.2 Last date in study

Last date in study is determined by site and directly reported in EDC. However, in rare case when a participant lost to follow-up and site report unknown for “last date in study”, the last known day that the participant is in clinic will be used.

3.3.3 Efficacy Variables

3.3.3.1 Handling of (Possible) Multiple Peaks of PK Curve

We expect the PK curve to have a single peak. However, it is possible that multiple peaks or no peak will be observed. The following are ways to handle PK curves:

1. Determination of single peak/no peak/Multi-peak will be based on the plot of the PK curve

   a. The statistician will make the judgement based the visual observation of each plot of the PK curve
2. No peak. (i.e. the variables keep rising until the last PK measurement)
   a. The Maximum (CMax), Time to Maximum (TMax), Time to Half-Maximum (T-Half) will be set as missing. We will consider these variables as undefined.
   b. The AUC_{0-t} will be calculated but the $AUC_{0-\infty}$ will be set as missing.
3. Multi-peak.
   a. If the same Maximum value appears at two or more time point, the CMax, Time to T-Half (early) will be estimated based on the first occurrence and Time to T-Half (late)

3.3.3.2 PK values at baseline, infinity, and under Lower Limitation of Qualification (LLOQ)

PK is assumed to be 0 at baseline (i.e. prior to time 0) and at infinity.

Additionally, any PK value that is LLOQ between time 0 and infinity will be assumed to be:

- 1/2 of the value of LLOQ specification (specified in the comment for PK results by Lab), or
- 100pg/mL, if no LLOQ specification is given (default is 200 pg/mL)

3.3.3.3 Handling of missing PK time

If PK collection time is missing but PK result is available (include LLOQ), the collection time stamp will be estimated using the scheduled time and the time 0.

For example, if the value of PK at 24 hour post dose is not missing, but the collection Time of 24 hour post dose PK is unknown. Then the collection time 24 hour post dose PK will be estimated as: T0 + 24 hour.

3.3.3.4 PK Parameters

The following PK parameters will be developed directly from the PK data.

- PK parameters will only be calculated or evaluated for participants who receives EXT608 dose. PK parameters will not be calculated for placebo participants.

3.3.3.4.1 Time 0

Time 0 is defined as the date and time of IP Administration.

3.3.3.4.2 The Maximum (CMax)

CMax is the maximum PK readings from time 0 to the last PK measurement.

- In a “No Peak” case, this will be set as missing.

3.3.3.4.3 Time to Maximum (TMax)

Tmax is the minutes, from time 0, to the time when CMax is reached the first time.

- In a "No Peak" case, this will be set as missing.

3.3.3.4.4 Terminal rate constant λz

Terminal rate constant λz is needed before we estimate AUC_{0-t}. Since we are expecting the terminal PK will have an exponential decline, λz is estimated by:

a. Find the PK after TMax
    i. If there only 1 or 0 available PK readings after PK Tmax, then λz will be set as missing.
b. Do a regression of log-transformed PK vs Time
c. λz is -1 * (slope from this regression)
d. In a "No Peak" case, λz will be set as missing

3.3.3.4.5 AUC_{0-t}

The AUC_{0-t} of PK over time will be calculated using trapezoid rule and the actual time points. Missing data for the calculation of the AUC will be handled as followed:

1. If the reading for Time 0 is missing, it will be the assumed as 0.
2. If any reading between Time 0 and TMax is missing:
    a. It will be imputed with linear interpolation.
3. If any reading after CMax is missing:
    a. If λz is available, it will be imputed using the regression line obtained when estimate λz
    b. If λz is missing, AUC_{0-t} will be set as missing.

We will calculate the following AUC_{0-t}

Table 4 AUC_{0-t}

AUC 0-24 Hour
AUC 0-48 Hour
AUC 0-7 Day
AUC 0-14 Day
AUC 0-21 Day
AUC 0-28 Day

3.3.3.4.6 $AUC_{0-\infty}$

$AUC_{0-\infty}$ is estimated as:

$AUC_{0-\infty} = AUC_{0-last} + AUC_{last}$, where $AUC_{last} = PK_{last}/\lambda z$, and PK_{last} is the last available PK reading

- If λz is missing, then $AUC_{0-\infty}$ is set as missing.

3.3.3.4.7 Time to Half-Maximal PK, Both Early and Late ($t_{Half,early}$ & $t_{Half,late}$)

$T_{half,early}$ is the time in minutes, from time 0, to the time when PK rises to half way to the maximum. It is calculated as followed:

- $T_{half,early}$ = Time corresponding to $\frac{\text{CMax}}{2}$ - t_0, linear interpolation may be used if needed.
- If CMax is missing, $T_{half,early}$ will also be set as missing.

$T_{half,late}$ is the # of days, from TMax, to the time when PK reduced to half way to the maximum. Since we assume the PK is exponential decline, $T_{half,late}$ is calculated as followed

- $T_{half,late} = \frac{Ln(2)}{\lambda z}$
- If λz is missing, $T_{half,late}$ will also be set as missing.

3.3.3.4.8 Clearance (CL/F)

Clearance is calculated as the dose divided by the $AUC_{0-\infty}$:

- $CL/F = \frac{Dose}{AUC_{0-\infty}}$
- If is missing, then CL/F is set as missing.

3.3.3.4.9 Volume Distribution (Vz/F)

Volume Distribution is calculated as:

- $Vz/F = \frac{Dose}{\lambda z * AUC_{0-\infty}}$
- If λz is missing, then Vz/F is set as missing.

3.3.3.5 PD Parameters

The PD variables include:

- Serum total calcium (corrected for albumin)(Se-Ca)
- Phosphate
- Magnesium
- Creatinine
- Serum PTH
- Creatinine with estimated GFR
- 25-hydroxy-vitamin D (25-OH-D)
- 1,25-dihydroxy-vitamin D (1,25-OH-D)

3.3.3.5.1 Change from baseline

Change from baseline will be calculated for all numeric variables where baseline is the measurement at Day -1.

- Baseline will be the measurements collected on Day 0 Pre-Dose.

- If the measurements on Day 0 Pre-dose is not available, the measurements collected on day -1 will be used.

3.3.3.5.2 Change of severity status along time

Additionally, the change of severity (normal/abnormal) status along time will also be categorized. The severity is determined by lab and reported to IMD directly.

In the EDC, the abnormal status is defined as:

- L = Low
- H = High
- A = Abnormal
- If the abnormal status variable is blank, then it is considered as Normal.

The change between two consecutive time points will be categorized based on the reported severity starting from baseline. The following category will be evaluated:

- Normal -> Normal
- Normal -> High
- Normal -> Low
- Normal -> Abnormal
- High -> High
- High -> Normal
- High -> Low
- Low -> Low
- Low -> Normal
- Low -> High
- Abnormal -> Abnormal
- Abnormal -> Normal
- Unknown (if lab test results at any of the consecutive time points is missing)

3.3.3.6 Urine PD Volume

The Urine Volume is reported in the EDC along with starting and ending date/time. The volume will be normalized for the volume per hour (V_{upd}):

$$V_{upd} = \frac{Reported\ Volume}{\frac{Ending\ Datetime - Starting\ Datetime}{60 \times 60}}$$

The 4-hour Urine PD volume on Day 0 will then be estimated as $V_{upd}\ x\ 4$

The 12-hour Urine PD volume on Day 1-3 will then be estimated as $V_{upd}\ x\ 12$

Note: Assuming the value of datetime variable is in seconds. If either the date, time or volume is missing, this variable will also be set as missing. No imputation will be done.

3.3.4 Safety Variables

3.3.4.1 Adverse Events (AE)

All observed or volunteered adverse events regardless in the treatment group or suspected causal relationship to the investigational device are captured in the EDC.

For all AEs, reformatting maybe applied and necessary transformation/Substitution may be needed as specified below:

- If an AE has known onset date but unknown onset time, then 12:00 will be used to substitute the onset time
    - The purpose of this substitution is for the determination of the TEAE
- If an AE has unknown onset date, no substitution will be done.

Treatment-emergent adverse event (TEAE) is defined as a post-baseline adverse event with onset date and time after the initiation of study treatment.

- Baseline is the IP administration date and time
- In this study, TEAE are the AEs that occur after the first successful IP administration.
    - If the AE has an unknown onset date, it will be assumed to be non-TEAE unless the investigational site confirms it is an TEAE

AE Coding:

- AE will be coded with latest available, at the time of coding, MedDRA code.

3.3.4.2 Vital Signs

Change from baseline will be calculated for vital sign from Day 0 to Day 28.

- Baseline will be the vital signs collected at Day 0 -90 pre-dose
- If Day 0 -90min vital signs are missing, then the vital signs on Day -1 will be considered as baseline. If the vital sign on Day -1 is also missing, then the change from baseline will be set as missing.

3.3.4.3 ECG

Change from baseline will be calculated for ECG from Day 1 to Day 3.

- Baseline will be the ECG collected at Day -1
- If Day -1 ECG is missing, then the ECG on Screening will be used as baseline.

3.3.4.4 Lab evaluations

Handling of the safety lab variables will be the same as the PD variables (section 3.3.3.5)

3.3.4.5 Injection site reaction

Injection site Assessment includes Tenderness, VAS pain score, Edema and Erythema.

- If Tenderness is “None” and VAS pain score is missing, then VAS pain score will be set as 0
- No substitution will be done for any missing VAS if Tenderness is not None.

Although the standard VAS line is 100mm, the actual VAS line printed on paper could be deviate from 100mm due to printer settings. Thus, all reported VAS will be normalized to 100mm scale for analyses.

The normalized VAS (VAS_{nom}) score is calculated as below:

$$\mathrm{VAS}_{nom} = \frac{Measured\ VAS(mm) \times 100}{Total\ VAS(mm)}$$

The following describes the handling of Edema and Erythema related variables.

- If “none” reported for edema or Erythema, then the following variables will be substitute as 0 for analyses only
  - Shortest length (Edema or Erythema)
  - Longest length (Edema or Erythema)
  - Tallest height (Edema)
  - Grade (Erythema)
- If “not done” reported, there is no substitution

Edema and Erythema is assumed to be Ellipse, and the area will be calculated as:

$$Area\ of\ Edema\ or\ Erythema = \frac{(3.14159 \times shortest\ length \times longest\ length)}{4}$$

The Grade of Erythema is expected to be the following:

- 1: very faint, 2: faint, 3: bright, 4: very bright
- If a non-integer number is reported, it will be rounded to the nearest integer.

The tallest height of Edema will be used directly.

3.3.4.6 Immunogenicity variables

Immunogenicity variables include anti-drug antibodies (ADA) and any neutralizing subset (NAb). These are variables for exploratory analysis. Handling of these variables will not be pre-defined in this analyses plan.

3.4 STATISTICAL METHODS

3.4.1 General Considerations for all analyses

Unless specified, the following will apply to all summary tables:

- Continuous variable descriptive summary will include N, Mean, median, standard deviation, maximum and minimum.
- Categorical variable descriptive summary will include Total, count, and percentage.

3.4.2 Disposition of Participants

Descriptive summaries of participants' disposition will be provided. It will show the count and percentage.

The following will be presented for all screened participants:

- Screen failed
- Enrolled (qualified)
- Randomized

The following will be presented for all randomized participants:

- Cohorts
- Fully completed
- Early terminated
- Safety/FAS Population
- PP Population
- Treatment Randomized
- Treatment Received

3.4.3 Demographic Characteristics analyses

The demographic characteristics analyses will be done for Safety/FAS population.

3.4.3.1 Demographics

Descriptive summaries of the following will be provided:

- Age
- Race
- Ethnicity
- BMI

3.4.3.2 Medical History

Descriptive summaries of Body System will be provided.

3.4.3.3 Physical Exam

Descriptive summaries of Body System will be provided.

Additionally, change from baseline of the status of each Physical Exam will be summarized for each treatment arm.

3.4.3.4 Height, Weight and BMI

Height, weight and BMI will be summarized descriptively for each treatment arm at screen visit.

Additionally, weight will be summarized at each time point for each treatment arm from baseline.

3.4.3.5 Medication

Only a listing of the medication used by each participant will be provided.
It will be done for safety population only.

3.4.3.6 Protocol Compliance

The protocol compliance summary can be inferred from the disposition summary in section 3.4.2. Thus, there is no separated analysis.

3.4.4 Efficacy Analysis

All Efficacy analyses will be done for Safety/FAS population unless specified.

3.4.4.1 PK Analyses

All PK parameters (section 3.3.3.2) will be presented descriptively for each treatment arm.

A simple ANOVA model with treatment arm as the factor will be applied to each PK parameter to compare the active treatment arms to the pooled placebo group. The estimated mean difference and 95% Confidence Interval between each treatment arm and the placebo group will be presented. The corresponding p-value will also be reported although we do not expect it to be significant given the small sample size.

Additionally, a statistical model will be attempted to model the dose response of each PK parameters. The mode will not be pre-defined. We will plot the mean of each PK parameter against the dose and find an appropriate model if any.

- In additional to the Safety/FAS population, it will also be done with the PP population

3.4.4.2 PD Analyses

All PD parameters (section 3.3.3.5) including the change from baseline will be presented descriptively for each treatment arm.

Additionally, the change of severity (normal/abnormal) status along time will also be summarized for each treatment arm.

- In additional to the Safety/FAS population, it will also be done with the PP population

3.4.4.3 Urine PD Volume

The Urine PD volume will be summarized descriptively for each treatment arm.

3.4.5 Safety Analyses

All Safety analyses will be done for Safety/FAS population.

3.4.5.1 Adverse Event

All AE (including TEAE and non-TEAE) will be listed.

Unless there are less than or equal to 5 TEAE in the whole study period, TEAE will be summarized as followed:

All TEAE will be presented with the number and percentage of participants and events (counts only), by System organ class (SOC) and by Preferred Term (PT).

The same summary will also be presented for the following group:

- All TEAE that may have a relationship to the study medication (i.e., site categorize the relationship in EDC as either Related, Probable, Possible, or Unlikely)
- Intensity Categorization Groups: Mild, Moderate and Severe
- Serious TEAE (SAE)

An overview of the above summary with count and percentage of participants will also be provided.

Any non-TEAE will be provided as listing only.

3.4.5.2 Laboratory tests Results

This section will describe the summary of safety lab test results. Summary of PK and PD results are described in previous section (3.4.4.1 and 3.4.4.2).

All safety lab test results will be listed. Additionally, each Lab Test results of each subject at different time points will be plot against the time points to show the trend.

The change of baseline of any numeric safety lab results will be for each treatment arm.

The change of severity (normal/abnormal) status of each safety lab results along time will also be summarized for each treatment arm.

3.4.5.3 Vital Sign

Vital sign at each time point and the corresponding Change from (section 3.3.4.2) baseline will be presented descriptively by treatment arm.

3.4.5.4 ECG

ECG at each time point and the corresponding Change from (section 3.3.4.3) baseline will be presented descriptively by treatment arm.

3.4.5.5 Injection site reaction

Injection site reactions include VAS, tenderness, Edema and Erythema. The parameters defined in section 3.3.4.5 will be summarized descriptively by each treatment arm.

3.5 INTERIM ANALYSES FOR SAFETY REVIEW

Interim analyses are planned for the safety review after each cohort. Blinded Interim summaries of selected variables are generated for the safety review committee. Details of those analyses are specified in the safety monitoring plan.

4 List of planned listings, table and figures

Please see the attached Table of Contents Excel file.

Note that this is the planned Table of Contents, based on the actual data, table numbers, table names and structures may change.

5 Software documentation

PC SAS – Windows version 9.4 or higher.

[PC R - Windows version 12.0 or higher.]

[WinNonlin - Professional Version 5.2 or higher.]

Excel - Microsoft Excel 2007 or higher.

6 Reference

Pocock S J, Simon R, Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial, *Biometrics*. 1975 Mar; 31(1):103-15.

7 Revision History

Version	Summary
1.0	Initial Document
2.0	1.Add sections dealing with different LLOQ used by the PK Lab 2.Clarified how to handle missing values in PK 3.Corrected few typos