Clinical Study Protocol

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

Protocol Number:	EXT608-101
Version Number:	3.0; 24 October 2022
Compound:	EXT608
IND Number:	IND 146180
Study Phase:	Phase 1

Short Title: Safety and Tolerability Study of EXT608 in Healthy Participants

SPONSOR SIGNATURE PAGE

INVESTIGATOR SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulatory and ICH guidelines.

DESCRIPTION OF CHANGES to Protocol v.3.0

The protocol was amended per recommendation of FDA to state that all Injection Site Reactions, serious and non-serious, will be recorded as Adverse Events.

Changed text is indicated by ~~strikethrough~~ (deleted text).

Section. 6.4 Injection Site Assessment

Positive events will furthermore be recorded as AEs. ~~only if they are determined to be Serious Adverse Events.~~

DESCRIPTION OF CHANGES to Protocol v.2.0

The protocol was amended to clarify discrepancies between the schedule of procedures (Tables 7.1 and 7.1.1) and the text, to correct minor errors and to add a Visual Analog Scale for evaluation of injection site pain.

Changed text is indicated by **boldface** type (new text) or ~~strikethrough~~ (deleted text). In addition to the changes shown below, clarifications, minor editorial and formatting changes have been made.

Section 4.1 Participant inclusion criteria

3. Male or female between 18 and 55 years of age. Male subjects with female partners of child bearing potential must agree to use barrier contraception, e.g., condoms plus spermicide, from administration of the study drug until at least 3 months after administration of the study drug. Abstinence from heterosexual intercourse from administration of study drug until at least 3 months after administration of study drug is acceptable if it is in accordance with the subject's lifestyle. Female subjects should be surgically sterile (had a bilateral tubal ligation, hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or hysterectomy), postmenopausal (defined as 12 months with no menses prior to Screening and a serum follicle stimulating hormone in the postmenopausal range at Screening), or, if of child bearing potential, must be non-lactating and willing to use a highly effective method of birth control for 30 days prior to administration of study drug and agree to continued use of this method until at least 1 month after administration of study drug. Abstinence from heterosexual intercourse for 30 days prior to administration of study drug until at least 1 month after the administration of study drug is acceptable if it is in accordance with subject's lifestyle. ~~May also consider including wording on male sterilization (vasectomy) and sole male partner of female subject sterilization (vasectomy).~~

Reason for change: The deleted text was included in error in the original protocol.

Section 6.2.2 Medical History

The medical history will include: disorders of head, eyes, ears, nose and throat; neoplastic and hematological disorders; infectious diseases; disorders of the cardiovascular system including hypertension and hyperlipidemia, each with duration; disorders of the

respiratory system; disorders of the kidney and urinary tract; disorders of the gastrointestinal system; disorders of the immune system, connective tissue and joints; endocrinology and metabolism with a subcategory for diabetes including year of diagnosis, treatment, complications including nephropathy, neuropathy, and retinopathy; neurological disorders; and finally alcohol, illicit drug and smoking history including duration in years and ~~20 pack equivalents a day~~ **number of pack years.**

Reason for change: Correction

Section 6.4 Injection Site Assessment

A Visual Analog Scale (VAS) will be used for evaluation of injection site pain. A copy of the VAS is in Appendix 2.

Reason for change: To provide a standardized measurement of tenderness.

Positive events that are deemed clinically relevant will furthermore be recorded as AEs **only if they are determined to be Serious Adverse Events.**

Reason for change: Potential injection site reactions are of special interest and thus carefully assessed as described above. As asking participants to rate injection site pain is a form of solicitation, which results in biased reporting frequencies, non-serious injection site reactions will not additionally be reported as AEs in the present study.

Section 6.8.2.2 Urine PD

Additional pooled urine collections will take place at the following intervals:

- Day ~~1~~ **0**: a 4-hour urine collection will begin after dosing.
- Day ~~1~~ **0**: from 4 hours post-dose until bedtime. Participants will be instructed to empty their bladders prior to sleep. If the participant voids during the night, the urine will be collected and pooled with the first morning void. The time and volume of urine must be recorded.
- Day ~~2~~ **1** through Day 3: 12- hour urine collections.

Reason for change: To be consistent with the Schedule of Procedures with regards to naming conventions for study days.

Section 7.1.1: Sequestered Schedule- Footnote 4 and Section 7.2.5.3 Time 4 hours

~~C-telopeptide of type I collagen~~

Reason for change: This test is not required and was included in the original protocol in error.

Section 7.2.3.2 – 90 minutes prior to planned delivery of study product:

a. Clinical Chemistry panel **and Complete Blood Count**

Sections 7.2.6.1- Day 1, 7.2.6.3- Day 2 and 7.2.6.4- Day 3:

Added: **Review of concomitant medication**

Reason for change: To be consistent with the Schedule of Procedures in Table 7.1.1.

Added: **Appendix 2 Visual Analog Scale**

Synopsis

Protocol Title:

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

Study Center(s):

Pharmaceutical Research Associates, Inc.

9755 Ridge Drive, Lenexa KS, 66219

Investigational Product:

EXT608 dissolved in a buffered isotonic saline solution

Starting Dose and Dose Escalation Scheme:

The starting dose will be 4 μg in a volume of 10 ul. Up to 6 dosing cohorts are planned with no single dose escalation to exceed a 3-fold dose increment.

Route of Administration:

Subcutaneous (SC) injection

Objectives and Endpoints:

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:

1. Incidence, nature, and severity of adverse events (AEs) and withdrawals due to treatment emergent AEs (TEAEs) [Time Frame: Day 0 up to Day 28]
2. 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]
3. Percentage of participants with injection site reactions [Time Frame: Day 0 to Day 7]

The secondary objectives are to assess:

1. Single dose PK including $AUC_{0\text{-}24h}$, $AUC_{0\text{-}48h}$, $AUC_{0\text{-}28d}$, $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, $T½$, λz, Cl/F and Vz/F.
2. 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.

Furthermore, the exploratory objectives are to assess:

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

Number of Patients:

Up to approximately 30 participants may be enrolled to the study intervention, such that approximately 24 evaluable participants complete the study.

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.

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. Each participant will provide written informed consent and must meet all of the eligibility criteria prior to being randomized and administered study product. Participants who discontinue prematurely will be replaced at the discretion of the Sponsor.

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.

A safe clinical starting dose will be targeted to have a <10% of maximal effect (E_{max}) based on allometric scaling of pharmacokinetics (PK) and pharmacodynamics (PD), and will be less than the threshold derived from 1/10 of the human equivalent of the No Adverse Effect Level (NOAEL) established in GLP toxicology studies. Up to 6 dosing cohorts are planned with no single dose escalation to exceed a 3-fold dose increment.

Following a dose escalation, participant dosing for the second and third participant will be staggered at least 72 hours post-dosing pending review of safety data including Se-Ca and adverse events (AEs) by the Investigator and Medical Monitor.

A potential DLT is defined as any of the following EXT608 TEAEs that occurs during the DLT period, graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (2):

• Grade = 3 TEAE

• Grade = 3 anemia

• Grade = 3 AST/ALT elevation; and/or

• Grade = 2 AST/ALT elevation and Grade = 2 Bilirubin elevation

- Grade = 3 QTc prolongation
- Grade = 3 Hyper- and/or Hypotension
- Grade = 2 Hyperparathyroidism
- Grade = 2 Hyperthyroidism
- Grade = 3 Hypercalcemia
- Grade = 3 Hypocalcemia
- Grade = 3 Hypophosphatemia
- Grade = 3 Hypomagnesemia
- Grade = 3 Creatinine increased

Dose escalation decisions will be based on the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (2) and Se-Ca levels.

The DMB will review the seven-day safety data in each cohort before authorizing the initiation of the next cohort according to the following decision tree:

1. No Grade 3 AEs suspected related to study drug and no indication of effect observed from Se-Ca will result in the next dose at 3x the previous cohort dose.
2. No Grade 3 AEs suspected related to study drug and clear indication of effect on Se-Ca will result in the next dose at 2x the previous cohort dose.
3. A Grade 3 AE suspected related to study drug in a single (n=4) cohort and the absence of prohibitive effects on Se-Ca will result in an additional cohort at the same dose.
4. A single Grade 3 AE suspected related to study drug in 2 cohorts at the same dose (n=8) cohort and the absence of prohibitive indication of effects on Se-Ca will result in a dose escalation to 1.5x the previous dose.
5. Two or more of the same Grade 3 AE within the same cohort suspected related to study drug, or average peak Se-Ca > 1.5 mg/dl above the Upper Limit of Normal (ULN) range will terminate dose escalation.
    a. If the last dose escalation was 50% and by implication 2 cohorts received the previous dose for an n=8, the study will stop.
    b. If the last dose escalation was >50%, the next cohort should receive a dose 2/3x the previous dose.

Any DMB recommendation that deviates from the decision tree will be ratified by the Sponsor prior to implementation.

The study schematic is presented in Section 3.2.

Pending the outcomes of the GLP toxicology and other nonclinical pharmacology studies, planned dose levels will be administered by subcutaneous injection.

A screening visit will take place within 28 days of dosing.

Participants for each cohort will be admitted to the study unit 1 day prior to dosing and remain in the unit through at least 72 hours after dosing for safety and PK assessments before discharge. The total confinement period will be 4 nights, unless extended for management of AEs at the discretion of the Investigator. The schedule of events while inpatient is provided in Section 7.1.1. Follow-up visits to the clinic will occur on/about days 5, 7, 14, 21 and 28. Participants will be monitored closely during the duration of the

study for safety, PK, and PD assessments as described in Section 3.2. The total duration of follow-up period may be modified in the final study design based on safety and PK data from non-clinical studies, anticipated PK/PD response and extended in individual participants as needed to observe their calcium levels return to concentrations deemed not needing further follow up.

Additional/Alternative PK/PD time points may be implemented if the Sponsor determines this is necessary to fully characterize the PK profile of EXT608.

Eligibility Criteria

Inclusion Criteria:

Participants must meet each of the following inclusion criteria to be eligible for randomization:

1. Ability to personally provide written, signed, and dated informed consent to participate in the study.
2. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
3. Male or female between 18 and 55 years of age. Male subjects with female partners of child bearing potential must agree to use barrier contraception, e.g., condoms plus spermicide, from administration of the study drug until at least 3 months after administration of the study drug. Abstinence from heterosexual intercourse from administration of study drug until at least 3 months after administration of study drug is acceptable if it is in accordance with the subject's lifestyle. Female subjects should be either surgically sterile (had a bilateral tubal ligation, hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or hysterectomy), postmenopausal (defined as 12 months with no menses prior to Screening and a serum follicle stimulating hormone in the postmenopausal range at Screening), or, if of child bearing potential, must be non-lactating and willing to use a highly effective method of birth control for 30 days prior to administration of study drug and agree to continued use of this method until at least 1 month after administration of study drug. Abstinence from heterosexual intercourse for 30 days prior to administration of study drug until at least 1 month after the administration of study drug is acceptable if it is in accordance with subject's lifestyle.
4. Body mass index between 18.5 and 32 kilogram per square meter (kg/m^2), inclusive, with a body weight greater than or equal to (>=) 45 kg (99 pounds [lbs]). This inclusion criterion will only be assessed at the first screening visit.
5. The participant is in general good medical health with no clinically significant or relevant abnormalities, including medical history, physical exam, vital signs, ECG, and laboratory evaluations (hematology, chemistry, and urinalysis) as assessed by the Investigator.
6. Willing and able to consume standardized meals during the confinement period of the study. All participants will be required to consume the similar meals and

amounts as practicable on study days when serial pharmacokinetic (PK) and pharmacodynamic (PD) blood samples are collected.

7. A clinical safety laboratory parameter of hemoglobin greater than (>) 11.7 gram per deciliter (g/dl) (females) or 13.1 g/dl (males) and less than (<) 16 g/dl (females) or 17.4 g/dl (males) or, if out of this range, deemed not clinically significant by the Investigator.
8. Total Se-Ca within laboratory normal limits.
9. Serum parathyroid hormone (PTH) concentration within normal laboratory limits at the screening visit only.

Exclusion Criteria:

Participants are excluded from the study if any of the following exclusion criteria are met:

1. Participant has received any investigational compound within 30 days prior to the first dose of study product, or within 5 half-lives, whichever is greater.
2. Participant is a study site employee or an immediate family member of a study site employee.
3. Participant has evidence of clinically significant (CS) neurologic, cardiovascular, pulmonary, hepatic, hematopoietic disease, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, serious allergy, allergic skin rash, psychiatric disorder, or other abnormality that may impact the ability of the participant to participate or potentially confound the study results.
4. There is any finding in the participant's medical history, physical exam, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking EXT608, or a similar drug in the same class, or that might interfere with the conduct of the study.
5. Participant has a known hypersensitivity to any component of the formulation of EXT608.
6. Participant has a positive urine result for drugs of abuse at Screening or Inpatient Check-in (Day -1).
7. Participant has a history of drug abuse (defined as any illicit drug use) or alcohol abuse within 1 year prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
8. Participant is currently using any medication (including over-the-counter [OTC], herbal or homeopathic preparations), that, in the opinion of the Investigator, cannot be discontinued and avoided for 4 weeks (or other time period as noted below) prior to the first dose through 1 month after dose administration. Specifically:
    a. 14 days - thiazide diuretics
    b. 30 days - loop diuretics, lithium, systemic corticosteroids (medical judgment is required by the Investigator). Primarily high doses of systemic corticosteroids (i.e., prednisone) should be excluded
    c. 3 months - calcitonin, cinacalcet hydrochloride, treatment with rhPTH (1-84) or N-terminal PTH or PTH-related peptide fragments or analogs

   d. For females: changes in hormone replacement therapy within 3 months are excluded. Stable (>=3 months) hormone replacement therapy is acceptable
   e. 6 months - fluoride tablets, oral bisphosphonates, methotrexate, growth hormone, digoxin, raloxifene or similar selective estrogen receptor modulators (SERMs)
   f. 12 months - intravenous bisphosphonates
9. Participant is pregnant, nursing, or planning a pregnancy during the course of or within 3 months of completing this study.
10. Participant is male and intends to donate sperm before 90 days after study drug administration.
11. Participant has a history of cancer or other malignancy, with the exception of basal cell carcinoma that has been in remission for at least 5 years prior to Day -1.
12. Participant has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody or a human immunodeficiency virus (HIV) infection at Screening.
13. Participant has used nicotine-containing products (including but not limited to cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 28 days prior to Inpatient Check-in (Day -1) or a positive urine cotinine test at Screening or Inpatient Check-in (Day -1).
14. Participant has poor peripheral venous access.
15. Participant has donated or lost 450 mL or more of their blood volume (including plasmapheresis) or had a transfusion of any blood product, within 45 days prior to Day 0.
16. Participant has a Screening or Inpatient Check-in (Day -1) abnormal (CS) ECG. Entry of any participant with an abnormal (NCS) ECG must be approved and documented by signature by the Investigator or medically qualified sub-investigator.
17. Participant has a resting blood pressure outside the ranges of 90 to 140 mm Hg for systolic and 55 to 90 mm Hg for diastolic, confirmed with repeat per Investigator discretion, at the Screening Visit or Inpatient Check-in (Day -1).
18. Participant has a resting heart rate outside the range 40 to 90 bpm, confirmed with repeat per Investigator discretion, at the Screening Visit or Inpatient Check-in (Day -1).
19. Participant has increased CV proarrhythmic potential (3):
   a. Participant has a QT interval with Fridericia's correction method (QTcF) >450 ms or PR outside the range of 120 to 220 ms, confirmed with one repeat testing, at the Screening Visit or Inpatient Check-in (Day -1) Visit.
   b. A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).
   c. The use of concomitant medications that prolong the QT/QTc interval.
20. Participant has abnormal Screening or Inpatient Check-in (Day -1) laboratory values that suggest a CS underlying disease or participant with the following laboratory abnormalities: ALT and/or AST >1.5 the ULN, confirmed with one repeat testing.
21. Participant is at increased baseline risk for osteosarcoma such as participant with Paget's disease of bone or unexplained elevations of alkaline phosphatase, young

adult participants with open epiphyses, participants with hereditary disorders predisposing to osteosarcoma or participant with a prior history of external beam or implant radiation therapy involving the skeleton are excluded.

Study duration

Subject participation in the study includes:

• Up to a 4-week screening period

• Approximately a 5-day inpatient dosing period

• An additional outpatient monitoring of 25 days, for a total study duration of approximately 58 days

Statistical Methods

Sample Size

The sample size is not determined for inferential testing purposes. The sample size of 4 participants per cohort (3 active: 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.

Statistical Analyses

AEs will be presented in listings and TEAEs will be summarized. Individual results of laboratory tests (hematology, chemistry, and urinalysis) will be listed and change from baseline will be summarized using shift tables. Individual results of vital signs will be listed and observed values and changes from baseline will be summarized.

Individual results of quantitative ECG parameters from the 12-lead safety ECGs will be listed and observed values and changes from baseline will be summarized and analyzed consistent with the ICH E14 (3).

All summaries will be performed by placebo and each EXT608 dose level. Placebo data will be pooled across cohorts. Physical exam findings will be presented in data listings.

Concentrations of EXT608 will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing. PK parameters will be summarized by dose using descriptive statistics. Dose proportionality will be assessed graphically and using a power model. PD will be presented in listings and summarized by dose and time point.

Detection of ADA and NAbs will be presented in listings and summarized by dose and time point.

No formal hypothesis testing will be conducted as part of this study.

DMB data packages will be based on the FAS for safety and PP for PK/PD.

Table of Contents

Abbreviations and Definitions

ADA	Anti-drug antibody
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}24h}$	Area under the curve, zero to 24 hours
$AUC_{0\text{-}48h}$	Area under the curve, zero to 48 hours
$AUC_{0\text{-}28d}$	Area under the curve, zero to 28 days
$AUC_{0\text{-}\infty}$	Area under the curve, zero to infinity
BMI	Body Mass Index
bpm	Beats per minute
BUN	Blood urea nitrogen
Ca	Calcium
CBC	Complete Blood Count
Cl/F	Apparent clearance
CRA	Clinical Research Associate
(e)CRF	(Electronic) Case Report Form. Refers to the online form part of the EDC that directly reflects data that is manually entered by the investigational site staff.
CRU	Clinical Research Unit
CS	Clinically significant
CTCAE	NCI Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DLT	Dose limiting toxicity
DMB	Data Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture (application). In addition to the eCRF, the EDC may include other items including uploaded files, treatment allocation and supply management.
EDTA	Ethylenediaminetetraacetic acid
eID	Electronic ID
Emax	Estimated maximal value of drug levels in an Emax model
EoS	End of Study
Exam	Examination
F	Bioavailability
FAS	Full Analysis Set (statistical analysis population)
FIH	First-in-human

GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
Hg	Mercury; a measurement of pressure
HIV	Human immunodeficiency virus
ICMJE	Internal Committee of Medical Journal Editors
IRB	Institutional Review Board
ITT	Intent to Treat (statistical analysis population)
iv	Intravenous
λz	Elimination constant
NAb	Neutralizing antibody
NCS	Non-clinically significant
NOAEL	No Adverse Effect Level
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over the counter
PD	Pharmacodynamics
PDF	Portable Document Format
Pbo	Placebo
PK	Pharmacokinetics
PP	Per Protocol (statistical analysis population)
PR	A measurement on an ECG of the conduction of the impulse from the upper part of the atrium to the ventricle
PTH	Parathyroid hormone - amino acids 1-84 (full length)
QRS	A measurement on an ECG of ventricular depolarization
QTc	A measurement on an ECG of the duration of ventricular depolarization
QTcF	QTc measurement using Fridericia's formula
RBC	Red Blood Cell count
RR	A measurement on an ECG of the function of the intrinsic properties of the sinus node (the time between heart beats)
SAD	Single Ascending Dose
SAE	Serious Adverse Event
sc	Subcutaneous
Se-Ca	Serum calcium
SERM	Selective estrogen receptor modulator

Study product	The formulated product as delivered to the participant containing either test (active) drug or control (placebo). The term may refer to either.
$T_{1/2}$	Serum half-life of a drug; the time it takes for the concentration of the drug to be reduced by half
TEAE	Treatment Emergent Adverse Event
TdP	Torsade de pointes; refers to a specific abnormal heart rhythm
T_{max}	The time it takes to reach maximum drug concentration
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
Vz/F	Apparent distribution volume
WBC	White Blood Cell count with differential count

1 Background Information

1.1 Hypoparathyroidism

Hypoparathyroidism is a rare clinical syndrome that results from reduced or absent parathyroid gland function and is characterized by low serum calcium (Se-Ca) levels, elevated serum phosphorus levels, and absent or inappropriately low levels of parathyroid hormone (PTH) in circulation. Hypoparathyroidism is most often caused by inadvertent removal or destruction (i.e., radiation treatment) of the parathyroid glands, the presence of autoimmune or congenital diseases, or low blood plasma magnesium levels. The low production of PTH in hypoparathyroidism patients leads to abnormally low calcium levels in blood, and an increase of phosphorus in the blood.

PTH is secreted in response to low blood Se-Ca levels. To release more ionic calcium into the blood, PTH indirectly stimulates bone matrix turnover, enhances renal tubular calcium reabsorption, as well as intestinal calcium absorption.

Patients with hypoparathyroidism most often present with paresthesia, cramps, or tetany, but the disorder may also manifest acutely with seizures, bronchospasm, laryngospasm, or cardiac rhythm disturbances. In the postsurgical setting, the presentation can be acute with tetany, cramping, tachycardia, and altered mental status predominating. Affected individuals are most often diagnosed with low blood calcium, magnesium and PTH levels, but high phosphorus levels, and frequently show increased urinary calcium excretion, which can lead to nephrocalcinosis and kidney stones. Hyperphosphatemia can be associated with deposition of calcium-phosphate complexes in other soft tissues.

1.1.1 Hypoparathyroidism standard of care

Current standard of care for hypoparathyroidism includes oral calcium carbonate supplements and active forms of vitamin D. Under restrictions, alternative treatment with once-daily injections of Parathyroid hormone (rhPTH (1-84), Natpara®) has been approved by the FDA only for patients whose calcium levels can't be controlled with calcium and vitamin D supplements.

1.2 Extend Biosciences' EXT608

EXT608 is under development as an extended half-life hPTH(1-34), covalently attached to a derivative of vitamin D using the D-VITylation® technology, which results in an extended half-life and improved absorption and bioavailability of PTH, aimed at reducing the rate and/or doses of injections. For more information refer to the Investigator's Brochure (1).

The purpose of this study is to characterize the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of EXT608 when administered as a single dose to healthy adult participants. EXT608 has undergone a full non-clinical testing program as recommended by the FDA and is therefore ready to be studied in humans to further its development. Data from this study are intended to identify and select pharmacologically active dose levels for subsequent dose ranging and other studies in patients with hypoparathyroidism.

1.3 Rationale for Dose Selection

[redacted]

2 Trial Objectives and Purpose

The purpose of this first-in-human study is to obtain initial safety, tolerability, PK, and PD information about EXT608 to facilitate optimal design of the first clinical study conducted in participants with the target indication.

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:

1. Incidence, nature, and severity of adverse events (AEs) and withdrawals due to treatment emergent AEs (TEAEs) [Time Frame: Day 0 up to Day 28]
2. 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]
3. Percentage of participants with injection or infusion site reactions [Time Frame: Day 0 to Day 7]

2.2 Secondary Objectives

The secondary objectives are to assess:

1. Single dose PK including $AUC_{0\text{-}24h}$, $AUC_{0\text{-}48h}$, $AUC_{0\text{-}28d}$, $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, $T½$, λz, Cl/F and Vz/F.
2. 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.

2.3 Exploratory Objectives

Furthermore, the exploratory objectives are to assess:

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

3 Trial Design

3.1 Design Description

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. Each participant will provide written informed consent and must meet all of the eligibility criteria prior to being randomized and administered study product. Participants who discontinue prematurely will be replaced at the discretion of the Sponsor.

3.1.1 Numbers of Cohorts and Participants, and Treatment Allocation

Up to approximately 30 participants may be enrolled to the study intervention such that approximately 24 evaluable participants complete the study.

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.

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.

3.1.2 Starting Dose

The starting dose will be 4 µg in a volume of 10 ul. Up to 6 dosing cohorts are planned with no single dose escalation to exceed a 3-fold dose increment.

3.1.3 Staggering of Participants after Dose Escalation (Sentinel Participants)

For the first cohort, one participant will be dosed initially. A review of safety data, including Se-Ca and adverse events (AEs) for the first 72 hours post-dose will be conducted by the Investigator and Medical Monitor. If there are no safety concerns, a second participant will be dosed and the same safety review will be conducted to review data up to 72-hrs post-dose. If there are no safety concerns, the last two participants in the cohort will be dosed.

For subsequent cohorts, this staggering requirement only applies to cohorts for doses higher than previously experienced in the study.

3.1.4 Dose Limiting Toxicity (DLT) Criteria

A potential DLT is defined as any of the following EXT608 TEAEs that occurs during the DLT period, graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (2):

- Grade = 3 TEAE
- Grade = 3 anemia
- Grade = 3 AST/ALT elevation; and/or
- Grade = 2 AST/ALT elevation and Grade = 2 Bilirubin elevation

- Grade = 3 QTc prolongation
- Grade = 3 Hyper- and/or Hypotension
- Grade = 2 Hyperparathyroidism
- Grade = 2 Hyperthyroidism
- Grade = 3 Hypercalcemia
- Grade = 3 Hypocalcemia
- Grade = 3 Hypophosphatemia
- Grade = 3 Hypomagnesemia
- Grade = 3 Creatinine increased

3.1.5 Dose Escalation

Dose escalation decisions will be based on the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (2) and Se-Ca levels.

The DMB will review the seven-day safety data in each cohort before authorizing the initiation of the next cohort according to the following decision tree:

1. No Grade 3 AEs suspected related to study drug and no indication of effect observed from Se-Ca will result in the next dose at 3x the previous cohort dose.
2. No Grade 3 AEs suspected related to study drug and clear indication of effect on Se-Ca will result in the next dose at 2x the previous cohort dose.
3. A Grade 3 AE suspected related to study drug in a single (n=4) cohort and the absence of prohibitive effects on Se-Ca will result in an additional cohort at the same dose.
4. A single Grade 3 AE suspected related to study drug in 2 cohorts at the same dose (n=8) cohort and the absence of prohibitive indication of effects on Se-Ca will result in a dose escalation to 1.5x the previous dose.
5. Two or more of the same Grade 3 AE within the same cohort suspected related to study drug, or average peak Se-Ca > 1.5 mg/dl above the Upper Limit of Normal (ULN) range will terminate dose escalation.
    a. If the last dose escalation was 50% and by implication 2 cohorts received the previous dose for an n=8, the study will stop.
    b. If the last dose escalation was >50%, the next cohort should receive a dose 2/3x the previous dose.

Any DMB recommendation that deviates from the decision tree will be ratified by the Sponsor prior to implementation.

The study schematic is presented in Section 3.2.

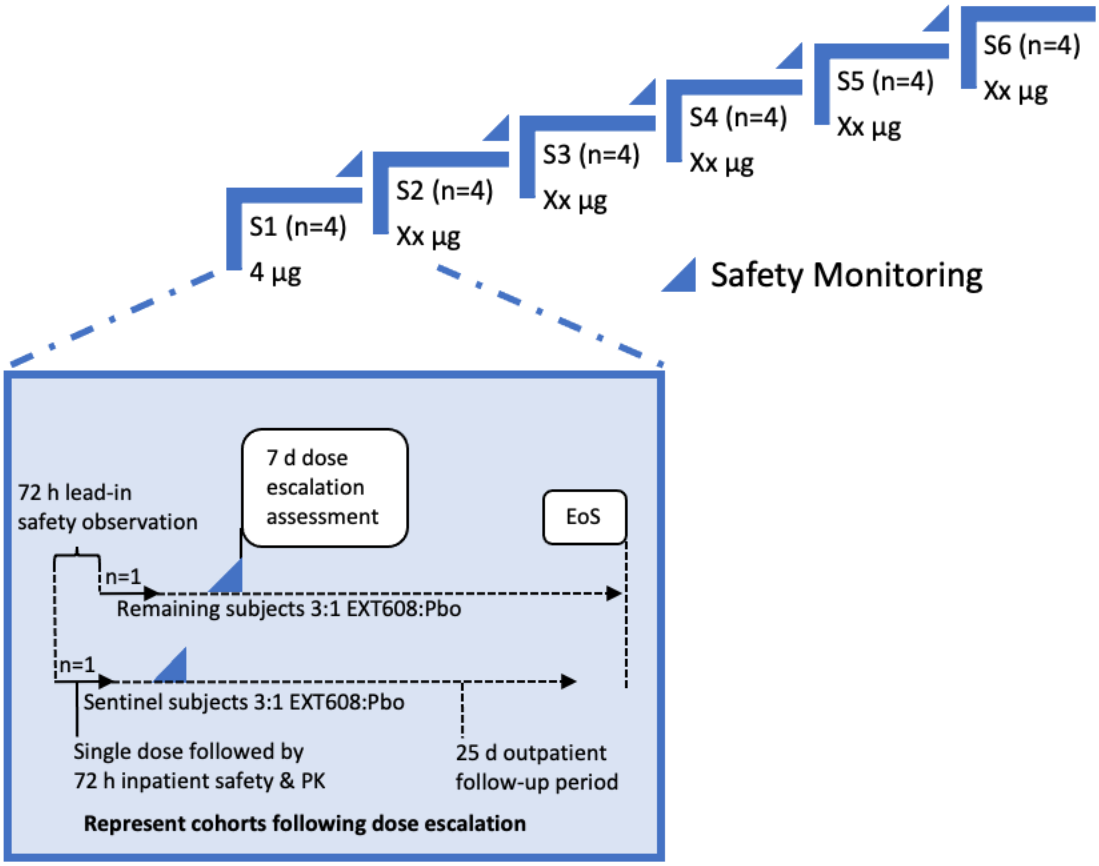
3.1.6 Individual Participant Schedule

A screening visit will take place within 28 days of dosing. Eligible participants for each cohort will be admitted to the Clinical Research Unit (CRU) 1 day prior to dosing and remain in the CRU through at least 72 hours after dosing for safety and PK assessments before discharge. The total confinement period will be 4 nights, unless extended for management of AEs at the discretion of the Investigator. The schedule of events while

inpatient is provided in Section 7.1.1. Follow-up visits to the CRU will occur on/about days 5, 7, 14, 21 and 28. Participants will be monitored closely during the duration of the study for safety, PK, and PD assessments as described in Section 3.2. The total duration of follow-up period may be modified in the final study design based on safety and PK data from non-clinical studies, anticipated PK/PD response and extended in individual participants as needed to observe their calcium levels return to concentrations deemed not needing further follow up.

Additional/Alternative PK/PD time points may be implemented if the Sponsor determines this is necessary to fully characterize the PK profile of EXT608.

3.2 Trial schematic



3.3 Design rationale

3.3.1 Population

PK modeling of various approaches to extend the half-life of compounds in animals is generally not a good predictor of half-life in humans. Knowledge of single dose PK and indications of PD in humans are usually sufficient to model multiple dose PK accurately and with reasonable precision, and can give good indications of plasma drug concentrations. This enables the accurate determination of target dose range for therapeutic effect and therefore guides optimal design choice for studies in patients with hypoparathyroidism.

The safest population in which to obtain the single dose PK is healthy participants.

3.3.2 Control

To study the PD, the most appropriate comparator is placebo, and as the participants do not have a parathyroid hormone deficiency, there are no concerns associated with that.

3.3.3 Intervention

EXT608 is the compound under development.

3.3.4 Stratification, randomization and adaptive treatment allocation based on baseline covariates with strata

In the modest planned cohort size, the DMB needs evaluable data up to and including Day 7 for a reliable dose escalation decision. Any participants for whom such data are not available will be replaced with a new participant receiving the same treatment assignment as the original participant to ensure the 3:1 ratio of active compound to control.

3.3.5 Blinding

The primary outcome is safety and tolerability. The assessment relies partly on adverse events evaluations that are prone to reporting bias and can be effectively mitigated with the double-blind design.

3.3.6 Endpoint

Dose limiting toxicity is routinely determined by AEs related to the intervention under investigation. Acute effects of parathyroid hormone analogues can be monitored by changes Se-Ca, which is tightly regulated in normal physiology with a narrow normal range. Furthermore, the relationship between elevated Se-Ca and adverse effects is well established. The combination of the limiting toxicity guided by PD therefore appears optimal in this situation.

4 Selection and Withdrawal of Participants

4.1 Participant inclusion criteria

Participants must meet each of the following inclusion criteria to be eligible for randomization:

1. Ability to personally provide written, signed, and dated informed consent to participate in the study.
2. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
3. Male or female between 18 and 55 years of age. Male subjects with female partners of child bearing potential must agree to use barrier contraception, e.g., condoms plus spermicide, from administration of the study drug until at least 3 months after administration of the study drug. Abstinence from heterosexual intercourse from administration of study drug until at least 3 months after administration of study drug is acceptable if it is in accordance with the subject's lifestyle. Female subjects should be surgically sterile (had a bilateral tubal ligation, hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or hysterectomy), postmenopausal (defined as 12 months with no menses prior to Screening and a serum follicle stimulating hormone in the postmenopausal range at Screening), or, if of child bearing potential, must be non-lactating and willing to use a highly effective method of birth control for 30 days prior to administration of study drug and agree to continued use of this method until at least 1 month after administration of study drug. Abstinence from heterosexual intercourse for 30 days prior to administration of study drug until at least 1 month after the administration of study drug is acceptable if it is in accordance with subject's lifestyle.
4. Body mass index between 18.5 and 32 kilogram per square meter (kg/m^2), inclusive, with a body weight greater than or equal to (>=) 45 kg (99 pounds [lbs]). This inclusion criterion will only be assessed at the first screening visit.
5. The participant is in general good medical health with no clinically significant or relevant abnormalities, including medical history, physical exam, vital signs, ECG, and laboratory evaluations (hematology, chemistry, and urinalysis) as assessed by the Investigator.
6. Willing and able to consume standardized meals during the confinement period of the study. All participants will be required to consume similar meals and amounts as practicable on study days when serial pharmacokinetic (PK) and pharmacodynamic (PD) blood samples are collected.
7. A clinical safety laboratory parameter of hemoglobin greater than (>) 11.7 gram per deciliter (g/dl) (females) or 13.1 g/dl (males) and less than (<) 16 g/dl (females) or 17.4 g/dl (males) or, if out of this range, deemed not clinically significant by the Investigator.
8. Total Se-Ca within laboratory normal limits.
9. Serum parathyroid hormone (PTH) concentration within normal laboratory limits.

4.2 Participant exclusion criteria

Participants are excluded from the study if any of the following exclusion criteria are met:

1. Participant has received any investigational compound within 30 days prior to the first dose of study product, or within 5 half-lives, whichever is greater.

2. Participant is a study site employee or an immediate family member of a study site employee.
3. Participant has evidence of clinically significant (CS) neurologic, cardiovascular, pulmonary, hepatic, hematopoietic disease, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, serious allergy, allergic skin rash, psychiatric disorder, or other abnormality that may impact the ability of the participant to participate or potentially confound the study results.
4. There is any finding in the participant's medical history, physical exam, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking EXT608, or a similar drug in the same class, or that might interfere with the conduct of the study.
5. Participant has a known hypersensitivity to any component of the formulation of EXT608.
6. Participant has a positive urine result for drugs of abuse at Screening or Inpatient Check-in (Day -1).
7. Participant has a history of drug abuse (defined as any illicit drug use) or alcohol abuse within 1 year prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
8. Participant is currently using any medication (including over-the-counter [OTC], herbal or homeopathic preparations), that, in the opinion of the Investigator, cannot be discontinued and avoided for 4 weeks (or other time period as noted below) prior to the first dose through 1 month after dose administration. Specifically:
    a. 14 days - thiazide diuretics
    b. 30 days - loop diuretics, lithium, systemic corticosteroids (medical judgment is required by the Investigator). Primarily high doses of systemic corticosteroids (i.e. prednisone) should be excluded
    c. 3 months - calcitonin, cinacalcet hydrochloride, treatment with rhPTH (1-84) or N-terminal PTH or PTH-related peptide fragments or analogs
    d. For females: changes in hormone replacement therapy within 3 months are excluded. Stable (>=3 months) hormone replacement therapy is acceptable
    e. 6 months - fluoride tablets, oral bisphosphonates, methotrexate, growth hormone, digoxin, raloxifene or similar selective estrogen receptor modulators (SERMs)
    f. 12 months - intravenous bisphosphonates
9. Participant is pregnant, nursing, or planning a pregnancy during the course of or within 3 months of completing this study.
10. Participant is male and intends to donate sperm before 90 days after study drug administration.
11. Participant has a history of cancer or other malignancy, with the exception of basal cell carcinoma that has been in remission for at least 5 years prior to Day -1.
12. Participant has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody or a human immunodeficiency virus (HIV) infection at Screening.
13. Participant has used nicotine-containing products (including but not limited to cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch or

nicotine gum) within 28 days prior to Inpatient Check-in (Day -1) or a positive urine cotinine test at Screening or Inpatient Check-in (Day -1).

14. Participant has poor peripheral venous access.
15. Participant has donated or lost 450 mL or more of their blood volume (including plasmapheresis) or had a transfusion of any blood product, within 45 days prior to Day 0.
16. Participant has a Screening or Inpatient Check-in (Day -1) abnormal (CS) ECG. Entry of any participant with an abnormal (NCS) ECG must be approved and documented by signature by the Investigator or medically qualified sub-investigator.
17. Participant has a resting blood pressure outside the ranges of 90 to 140 mm Hg for systolic and 55 to 90 mm Hg for diastolic, confirmed with repeat per Investigator discretion, at the Screening Visit or Inpatient Check-in (Day -1).
18. Participant has a resting heart rate outside the range 40 to 90 bpm, confirmed with repeat per Investigator discretion, at the Screening Visit or Inpatient Check-in (Day -1).
19. Participant has increased CV proarrhythmic potential (3):
    a. Participant has a QT interval with Fridericia's correction method (QTcF) >450 ms (males) or >450 ms (females) or PR outside the range of 120 to 220 ms, confirmed with one repeat testing, at the Screening Visit or Inpatient Check-in (Day -1) Visit.
    b. A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).
    c. The use of concomitant medications that prolong the QT/QTc interval.
20. Participant has abnormal Screening or Inpatient Check-in (Day -1) laboratory values that suggest a CS underlying disease or participant with the following laboratory abnormalities: ALT and/or AST >1.5 the ULN, confirmed with one repeat testing.
21. Participant is at increased baseline risk for osteosarcoma such as participant with Paget's disease of bone or unexplained elevations of alkaline phosphatase, young adult participants with open epiphyses, participants with hereditary disorders predisposing to osteosarcoma or participant with a prior history of external beam or implant radiation therapy involving the skeleton are excluded.

4.3 Participant withdrawal criteria

4.3.1 Originator of withdrawal request

4.3.1.1 Participant choice

Study participants are free to withdraw from the study at any time at their own initiative. Participants should be instructed in the importance of notifying the site of such a decision.

4.3.1.2 Investigator determination

The Investigator may withdraw the participant at his or her discretion should further participation for medical reasons not be in the participant's best interest, or for non-

compliance with the CRU rules and requirements. If possible, the Medical Monitor for the study should be contacted to discuss the individual case before withdrawal.

4.3.1.3 Data Monitoring Board Recommendation

Potential DLTs as listed in Section 3.1.4 are evaluated by the DMB per the procedures outlined in the Safety Plan.

4.3.1.4 Sponsor request

The Sponsor may request discontinuation of any participant for non-compliance with study procedures or other significant protocol violations, and may discontinue the study in the case that significant new information becomes available that renders the study unsafe or of questionable medical and scientific value to continue.

4.3.2 Withdrawal documentation

In case of withdrawal, the end of study Case Report Form (CRF) must be filled out including the reasons for the withdrawal, and if possible, a full end of study visit should be completed, and as a minimum the Investigator must evaluate that the participant is clinically stable for release from the study.

4.3.3 Follow up on withdrawn participants

Early discontinuation does not nullify the need to follow adverse events up until resolution or stabilization.

4.4 Non-completer replacement policy

Any participants who do not complete and deliver data for a reliable Day 7 assessment for review by the DMB for dose escalation decisions will be replaced with a new participant receiving the same treatment assignment as the original participant after discussion and approval by the Sponsor's Medical Monitor.

5 Treatment of Participants

5.1 Lifestyle

Participants will be instructed to continue to lead their normal lifestyle except they should refrain from high intensity aerobic and anaerobic exercise for the duration of the study.

5.2 Concomitant medications

5.2.1 Medications for the investigated condition

Not applicable.

5.2.2 Other concomitant medications and dietary supplements

Except as noted in Section 5.2.3, and Section 4.2 (Exclusion criterion #8) all medication and dietary supplements should be discontinued at least 4 weeks prior to investigational product dosing, and if possible, no new medications should be started. If any changes of

products or doses occur, the Investigator must be notified by the participant to ensure adequate documentation.

5.2.3 Prohibited medications

To the degree possible, NSAIDs should be avoided due to their effect on coagulation.

5.3 Test and control product

The test and control products are dissolved in a buffered isotonic saline and have indistinguishable appearances. EXT608 injectable solution is stored frozen (-20°C) and thawed when ready to use. Thawing should take place at room temperature (~25°C), but no higher than body temperature (~37°C), protected from light if possible. It is supplied as a clear solution in a ready-to-use concentration, single use, glass vial at a concentration of 0.4 mg/mL (pH 4.8-6.2). The vehicle/placebo solution consists of sterile saline.

EXT608 is provided as a single dose, glass vial containing a sterile, clear injectable solution in one strength of 0.4 mg/mL.

5.3.1 General principles

Storage is frozen at -20 ºC or less.

5.3.2 Test treatment

EXT608 dissolved in a buffered isotonic saline solution.

5.3.3 Control treatment

Buffered isotonic saline solution.

5.3.4 Drug Accountability

Accountability for the study drug at the CRU is the responsibility of the Investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the CRU, inventory at the CRU, use by each subject, and return to the Sponsor (or destruction, if approved by the Sponsor) will be maintained by the CRU. These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all study drug received from the Sponsor or its designee. Accountability records will include dates, quantities, batch/serial numbers, and subject identification numbers. The site monitor will review drug accountability at the site on an ongoing basis during monitoring visits.

5.3.5 Disposal, Return or Retention of Study Drug

All unused and used study drug will be retained at the CRU until inventoried by the site monitor. All used, unused or expired study drug will be returned to the Sponsor or if authorized, disposed of at the study site in accordance with governing regulations and documented.

5.4 Blinding

5.4.1 Treatment blinding

Two Unblinded pharmacy staff members including at least one pharmacist trained to prepare sterile injectables will prepare the doses. The pharmacy staff can have no other role in the study. The doses will be administered by qualified staff trained to administer subcutaneous injections.

With the exception of the DMB members, all other parties remain blinded to the treatment results, until periodic reviews are performed by the DMB.

5.4.2 Endpoint blinding

For safety reasons, no outcomes are blinded.

5.4.3 Breaking the blind

In case of a medical emergency for a participant, the Investigator and Medical Monitor have the capability to obtain the treatment code from the EDC. The reason for this action must be documented in the EDC.

5.5 Treatment assignment, stratification, and randomization

Treatment allocation is performed in the EDC in a manner that ensures only the unblinded pharmacist or equivalent knows the treatment code.

The treatment assignment is computer generated by the EDC at the point of randomization. Participants are randomized 3:1 active:control in blocks of 4.

5.6 Supply, storage and accountability

5.6.1 Test and Control Treatment and Labeling

Extend Biosciences, Inc. will supply test and control product. The products will be supplied bulk in 2 ml vials each labeled individually with a label that includes:

1. Product identity
2. Lot no. and manufacturing date
3. Recommended storage (protect from light)
4. The text: “Caution – for Investigational Use Only.”
5. Manufacturer and address.

Storage for both is frozen at -20ºC or less.

The products will be logged by the site pharmacy or equivalent, and accounting of all dispensed product will be performed.

5.6.2 Study Product Preparation

Study product is thawed in a room temperature water bath and has to be administered within 4 hours of thawing.

5.6.3 Concomitant medications

No concomitant medications are supplied.

5.6.4 Ancillary supplies

Not applicable.

5.7 Participant Compliance

Participant compliance will be assessed by planned versus delivered medication, and completeness of data acquisition.

6 Procedures and Assessments Description

This section describes how to collect and transfer the individual data to the Sponsor/CRO. The tables in Section 7.1 describe what data has to be collected when, and Section 7.2 outlines the activities in a logical but not mandatory sequence for ease of execution.

6.1 Collection Methodology and Data Flow

6.1.1 Case Report Form (CRF)

An electronic CRF (eCRF) will be supplied to the investigational site for collection of information. The eCRF is not considered source information and the investigational site must have the information available in source documentation.

6.1.2 Electronically uploaded data

6.1.2.1 Participant Files and Documents

Participant files are uploaded in the EDC under the specific participant ID. These files may include:

1. photographs of the injection sites or
2. lesion from other AEs, or
3. files from other data collection devices, or
4. requested copies of source documents for remote source document verification (SDV)

6.1.2.2 Laboratory Data

Data from the local laboratory will be uploaded to the Sponsor/CRO directly. A test report will be sent to the site for inclusion in the participant chart; this will be considered source data.

6.2 Demographic Variables

Demographic variables including the medical history and current medications will be obtained at the screening visit. All demographic data are entered into the EDC.

The data to be collected include:

6.2.1 Participant identification

Participant sex, month and year of birth, and ethnic origin with the categories Caucasian, African-American, Hispanic, Asian and "other" with a text input field.

6.2.2 Medical History

A medical history will be taken at screening. While serious conditions in the past have to be recorded, the emphasis will be on conditions within the last two years including completeness of currently ongoing conditions.

The medical history will include: disorders of head, eyes, ears, nose and throat; neoplastic and hematological disorders; infectious diseases; disorders of the cardiovascular system including hypertension and hyperlipidemia, each with duration; disorders of the respiratory system; disorders of the kidney and urinary tract; disorders of the gastrointestinal system; disorders of the immune system, connective tissue and joints; endocrinology and metabolism with a subcategory for diabetes including year of diagnosis, treatment, complications including nephropathy, neuropathy, and retinopathy; neurological disorders; and finally alcohol, illicit drug and smoking history including duration in years and number of pack years.

6.2.3 Concomitant medication

A complete listing of current medications within the last three months including vitamins, herbal and dietary supplements with dose and frequency will be obtained at screening. Any medications taken throughout the study must be recorded in the eCRF. Acetaminophen may be given at the discretion of the Investigator.

6.3 Physical Exam

6.3.1 Complete Physical Exam

A complete physical exam will be performed at the screening and the last visit either when the participant has completed the full study or at an early termination. The physical exam will include: general appearance; head, eyes, ears, nose, throat, chest, lungs, heart, abdomen, musculoskeletal, skin neurological including reflexes. At the screening exam, any abnormalities found will be recorded in the eCRF under the medical history in the appropriate category. Any new findings at the last visit will be captured as an adverse event on the CRF for adverse events. The eCRF will thus not include any specific pages for physical exam.

6.3.2 Directed Physical Exam

A directed physical exam based on reported symptoms will be conducted at the scheduled time points except for the first and last visit with the complete physical exam described above. Any new findings at the last visit will be captured as an adverse event on the CRF for adverse events.

6.4 Injection Site Assessment

The intended injection site in the abdomen will be photographed prior to injection.

The injection site assessment includes evaluation of erythema, edema and any tenderness. The size of any erythema is measured with shortest and longest size in mm, and edema similarly in size and in addition the tallest height above surrounding skin. The measurement data are recorded in the EDC.

Any positive finding will photographed with clear labeling next to the lesion of participant ID, date and time.

Following a positive finding the injection site will be photographed daily in the inpatient period, and subsequently at the clinics visits until resolved.

Minimally, the photographs

1. prior to injection,
2. when the event is at highest intensity, and
3. when resolved or stabilized

will be uploaded in the EDC.

A Visual Analog Scale (VAS) will be used for evaluation of injection site pain. A copy of the VAS is in Appendix 2.

Positive events will furthermore be recorded as AEs.

6.5 Vital Signs: Pulse, Blood Pressure, Respiratory Rate and Temperature

Pulse, diastolic and systolic blood pressure are measured sitting after five minutes rest. Automated instruments may be used.

Respiratory rate will be measured over at least 30 seconds if regular, if irregular, at least 1 minute.

Temperature will be measured orally.

These data are recorded in the EDC.

6.6 Weight, Height and Body Mass Index (BMI)

Weight is measured with empty pockets and normal indoor clothes without shoes. Weight is measured at several time points according to the schedule and entered in the EDC.

Height is measured without shoes and is only measured at screening and entered in the EDC.

The BMI is calculated by the EDC.

6.7 Electrocardiogram (ECG)

Equipment for recording the ECG should be recently serviced and calibrated. Machine calibration records and performance data should be maintained on file.

A standard 12-lead ECG will be obtained in supine position after at least 5 minutes at rest. A copy of the recording will be made available for the Sponsor.

At screening, any abnormalities or normal variants will be assessed for clinical relevance and recorded in the medical history. Subsequent changes will be recorded in the EDC description text field and deemed clinically relevant or not (separate files). Changes that are deemed clinically relevant are furthermore recorded as AEs.

In addition to the description above, the ECG intervals PR, QRS, RR and QT will be measured and recorded in the eCRF for QTc assessment.

6.8 Urine Sample Laboratory Variables

Tests on urine are conducted on a fresh midstream urine sample obtained from the participant.

6.8.1 Urine Pregnancy Test

All females irrespective of reproductive potential will be tested for pregnancy.

The tests at screening and end of study will be sent to the local laboratory with the sample for urinalysis described in Section 6.8.2.

The test at Day -1 is performed in the CRU using a commercially available pregnancy kit and documented with a photograph. The binary negative/positive result will be recorded in the EDC. Alternatively, if the turnaround time allows, the test may be sent to the local lab.

6.8.2 Urinalysis

The sample for urinalysis will be sent to the local laboratory for testing.

6.8.2.1 Screening

At screening, at Day -1, and at the end of study, a complete urinalysis will be done including visual inspection of color and clarity, chemical testing for specific gravity, pH, bilirubin, urobilinogen, protein, glucose, ketones, blood, leukocytes, nitrite, and creatinine.

6.8.2.2 Urine PD

Participants will be instructed to empty their bladder prior to sleep. If the participant voids during the night, the urine will be collected and pooled with the first morning void. The time and volume of urine must be recorded. On Day 0 a first morning void will be collected prior to dosing, and pooled with any urine collected during the night. An aliquot will be sent for urine PD. The time on collection and total volume must be recorded.

Additional pooled urine collections will take place at the following intervals:

- Day 0: a 4-hour urine collection will begin after dosing.
- Day 0: from 4 hours post-dose until bedtime. Participants will be instructed to empty their bladders prior to sleep. If the participant voids during the night, the urine will be collected and pooled with the first morning void. The time and volume of urine must be recorded.
- Day 1 through Day 3: 12- hour urine collections.

For each collection period an aliquot of the pooled samples will be collected and tested for concentration of u-calcium, u-phosphate, u-magnesium, u-bicarbonate, u-sodium, and u-chloride and u-creatinine. The times of each void and total volume collected for each collection period must be recorded.

Participants will be provided with a 12-hr. urine collection container and instructed to collect all urine for 12 hours leading up to the out-patient visits on Days 5, 7, 14 and 28.

Results will be sent to the CRU and transferred periodically to data management.

6.9 Blood Sample Laboratory Variables

6.9.1 Blood Sample Draw

Blood is drawn either from a phlebotomy, or an indwelling catheter during the inpatient period after drawing out minimally 1 ml blood that is discarded per the investigational site's procedures.

Samples are drawn into appropriate sample container and processed according to the laboratory's instructions.

6.9.2 Total Amount of Blood Drawn for Sampling

The total amount drawn from screening to last visit, which is a period of time of approximately 60 days, is well under 500 ml, including potentially discarded blood from the indwelling catheter sampling procedure described in Section 6.9.1.

6.9.3 Screening and Safety Laboratory Tests

See Sections 7.1 and 7.1.1 for timing of lab tests.

1. Serum PTH at screening.
2. Complete blood count (CBC) including RBCs, hemoglobin, hematocrit, WBC, and platelets, at all scheduled time points.
    a. At screening and end of study, the CBC will also include a differential count.
3. Clinical chemistry comprehensive metabolic panel including serum glucose, calcium, albumin, total protein, sodium, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, alkaline phosphatase, alanine amino transferase (ALT), aspartate aminotransferase (AST), total bilirubin.
4. Hepatitis B, C and HIV will be tested for at screening.
    a. Hepatitis B surface antigen
    b. Hepatitis C antibody screening test
    c. HIV-1 and HIV-2 antigen and antibody routine screen.

Anti-Drug Antibody and Neutralizing Antibody development Lab reports will be reviewed by the investigator for clinical relevance and possible clinical laboratory adverse event reporting.

6.9.4 Pharmacokinetics (PK)

One 5 ml serum sample will be collected at the time points noted in Section 7.1.1 and divided into 2 aliquots of 1ml each for determination of EXT608 concentrations. Samples will be shipped to the laboratory in batches, with one of the samples retained at the site in case of transfer problems.

6.9.5 Pharmacodynamic (PD) variables

See Sections 7.1 and 7.1.1 for timing PD labs. Laboratory PD variables include:

[redacted]

See Section 6.8.2.2 for urine PD variables.

6.10 Safety Variables and Safety Reporting

6.10.1 Adverse Events

6.10.1.1 Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered related to the medicinal product.

Adverse events will be collected from the time informed consent is signed and until the Follow-Up or Early Termination visit.
All participants will be queried, using non-leading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms should be identified as one overall event or diagnosis. All AEs for randomized subjects will be recorded in the eCRF and the subject's source documents. Adverse events for subjects who are screened but not subsequently randomized in the study will be recorded only in the subject's source documents. The following data should be documented for each AE:

- Description of the events
- Classification of “serious” or “not serious”
- Date of first occurrence and date of resolution (if applicable)
- Severity
- Causal relationship to study drug
- Action taken
- Outcome
- Concomitant medication or other treatment given

Adverse events will be rated a mild, moderate or severe intensity using the following definitions:

- Mild: “Mild” events are usually transient and do not interfere with the participant’s daily activities.
- Moderate: “Moderate” events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities.
- Severe: “Severe” events interrupt the participant’s usual daily activities.

The causality will be rated in the following categories:

- Unlikely: An "unlikely" relationship suggests that only a remote connection exists between the investigational study product and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the reported AE.
- Possible: A "possible" relationship suggests that the association of the AE with the investigational study product is unknown; however, the AE is not reasonably supported by other conditions.
- Probable: A "probable" relationship suggests that a reasonable temporal association of the AE with study product functionality exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the study product's functionality and the AE, and other conditions (concurrent illness, progression or expression of disease state or concomitant medication reactions) do not appear to explain the AE.

6.10.1.2 Adverse Event Outcome

An AE should be followed until the Investigator has determined and provided the final outcome. The outcome should be classified according to the following categories:

- Recovered/resolved: Resolution of an AE with no residual signs or symptoms
- Recovered/resolved with sequelae: Resolution of an AE with residual signs or symptoms
- Not recovered/not resolved (continuing): Either incomplete improvement or no improvement of an AE, such that it remains ongoing
- Fatal: Outcome of AE is death. "Fatal" should be used when death is at least possibly related to the AE
- Unknown: Outcome of an AE is not known (e.g., subject lost to follow-up)

6.10.1.3 Serious Adverse Events

A serious adverse event is any adverse event that:

- Results in death
- Is life-threatening (the term "life-threatening" here refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might cause death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Would in the opinion of the Investigator jeopardize the participant
- May require medical or surgical intervention to prevent one of the outcomes listed above

6.10.1.4 SAE Reporting Procedure

Serious adverse events will be collected over the same time period as stated above for AEs. All SAEs must be reported regardless of the relationship to the drug. The initial report should include at least the following information:

- Subject's study ID number
- Protocol number
- Description of the event
- Criterion for categorizing the AE as serious
- Preliminary assignment of causality to study drug

Any new information should be provided as it becomes available. Copies of discharge summaries, consultant reports, autopsy reports, and any other relevant documents may also be requested.

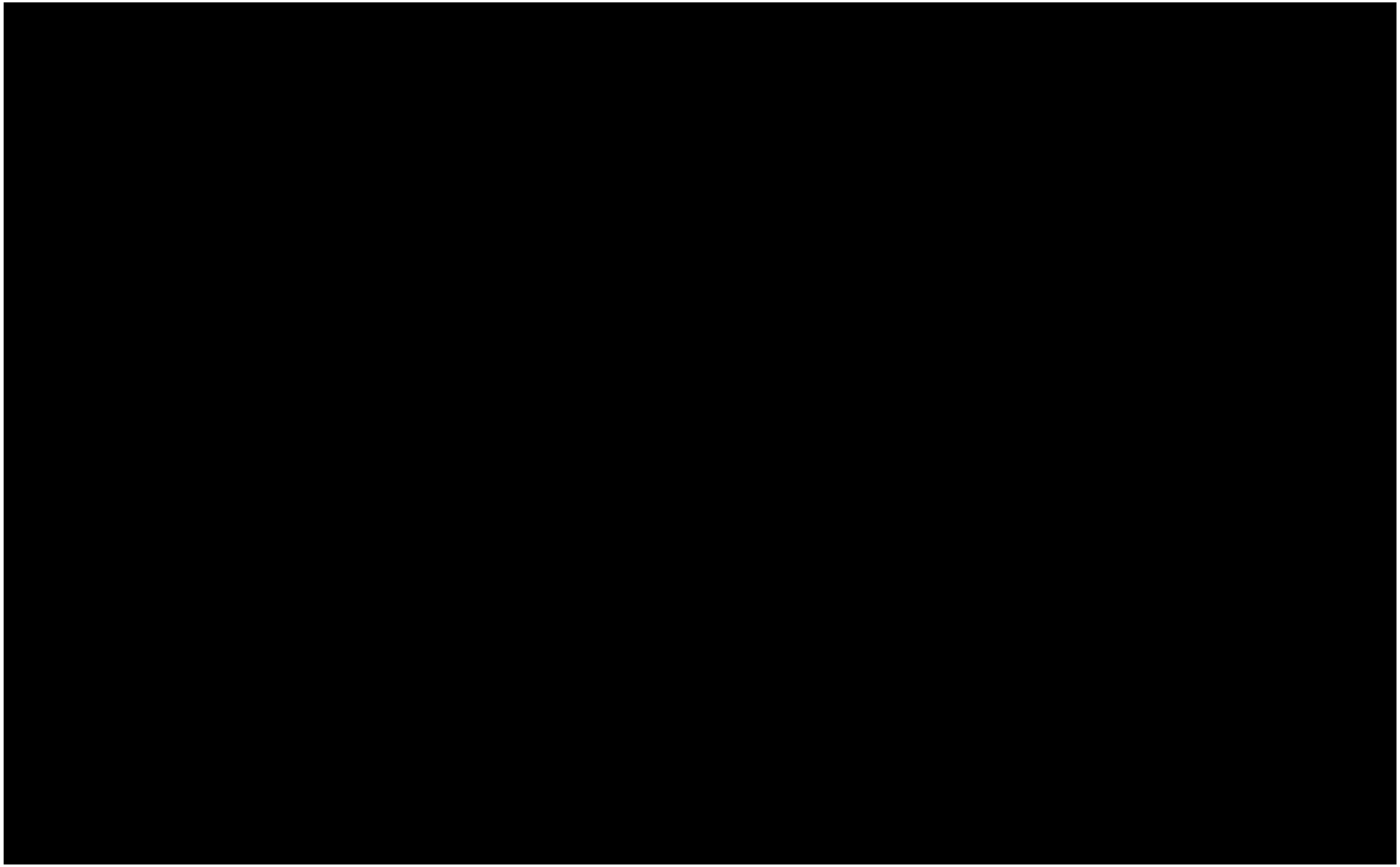
Appropriate remedial measure should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the subject's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

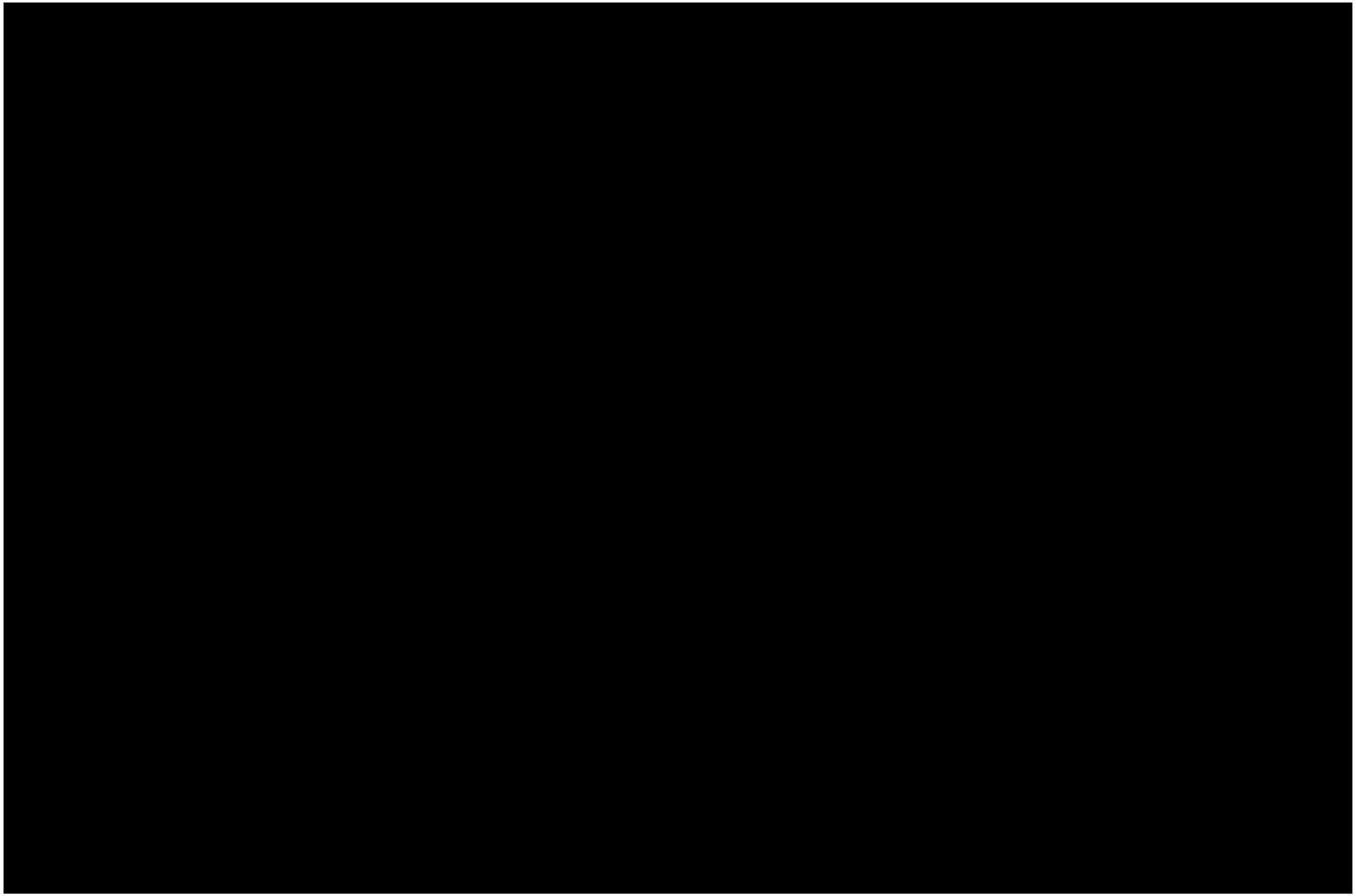
The Investigator will be responsible for reporting all SAEs to the Institutional Review Board (IRB)/Ethics Committee (EC). The Sponsor will be responsible for reporting to the regulatory authorities.

Serious adverse events must be reported to the Sponsor within 24 hours of coming to the Investigator's attention Any serious adverse event that occurs any time after the participant has signed the informed consent form for the study, up to the participant's final study visit, inclusive, is to be reported to Product Safety within 24 hours following when the event was first recognized, discovered, or reported, regardless of severity or relationship to the study product. If unable to enter the SAE information in the EDC (e.g., internet connection is down), the report may be reported by telephone to the Medical Monitor directly [redacted]

Serious adverse events must be followed up by the Investigator until resolution or stabilization.

7 Study Procedures





7.2 Chronological Description of Study Activities

This section describes the schedule of activities per assessment time point. Details of each procedure may be found in Section 6.

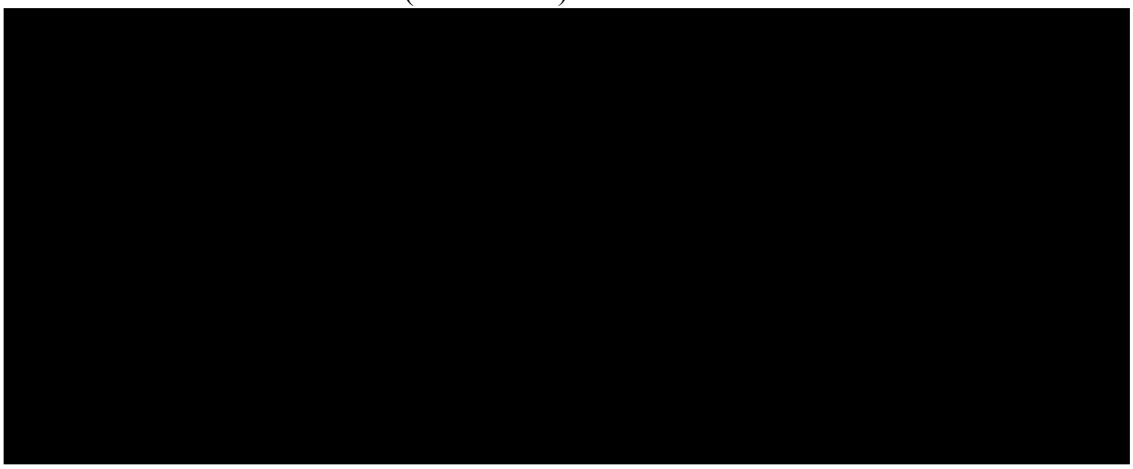
The timing of all activities for a specific participant are counted in minutes, hours or days relative to the receipt of the study product on minute, hour, Day 0. Unless otherwise noted, the maximal time tolerances on task execution is noted in the Schedules in Sections 7.1 and 7.1.1. Priority will be for the PK and PD assessments to be as close to the target time as possible. Deviation from this time window is not considered sufficient to disqualify the participant from per protocol analysis.

The sequence of activities within each visit as described below is not fixed, but may be modified to optimize clinic workflow.

7.2.1 Screening

Prior to screening for the protocol, the potential participant must be screened for SARS-CoV-2 per investigational site procedures.

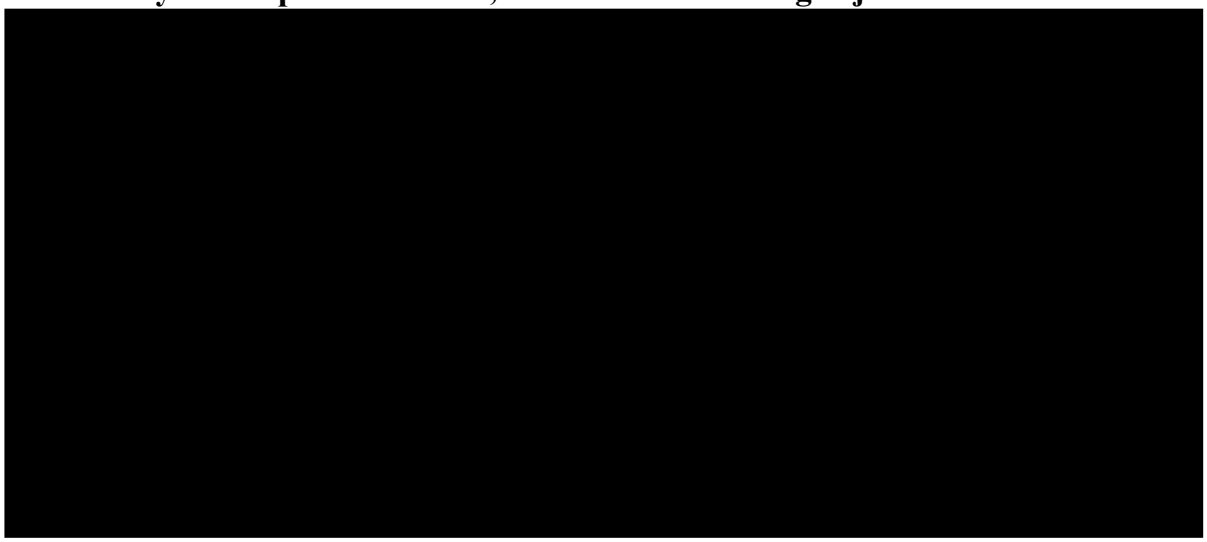
1. Informed consent including a signed IRB-approved informed consent form must be obtained before any other study procedures involving the participant are undertaken. The nature of the risks involved and the tasks the participant will do will be explained.
2. Throughout the screening process as outlined below, preliminary assessments of eligibility are performed whenever new information is available and further screening abandoned, if the participant is no longer eligible.
3. The participant's medical history including current conditions will be obtained. For females of current reproductive potential, the history will include current or plans of pregnancy, and for males of current reproductive potential, plans of conceiving or donating sperm during the course of or within 3 months of completing this study.
4. The participant's complete use of concomitant medications including vitamins, herbal supplements and illicit substances will be obtained (Section 6.2.3).
5. A physical exam including temperature, vital signs, weight and height will be performed (Sections 6.3.1, 6.5, and 6.6).
6. An ECG will be obtained (Section 6.7).



9. The next visit for the check in to the Inpatient Period will be scheduled when all the screening data are anticipated to be available. If the site's procedures for mitigating risk of contagious diseases, including SARS-CoV-2, require additional screening and visits prior to the check-in day -1, these are scheduled at the site's discretion.

7.2.2 Day -1, Check-in for Inpatient Period

7.2.3 Day 0 of Inpatient Period, before and including Injection



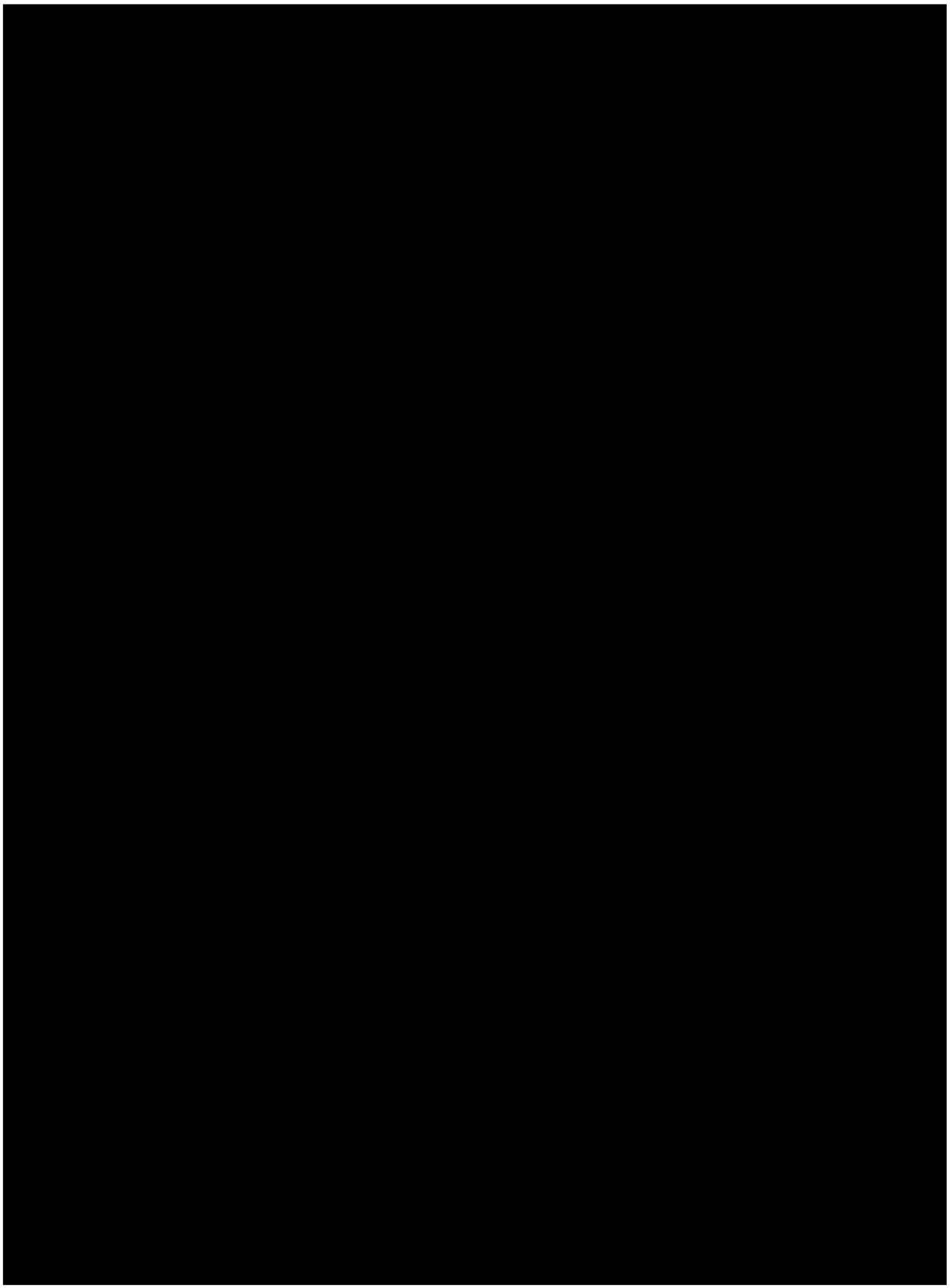
[redacted]

7.2.4 Day 0, the First Hour after Injection

[redacted]

7.2.5 Day 0 from 1 Hour after Injection

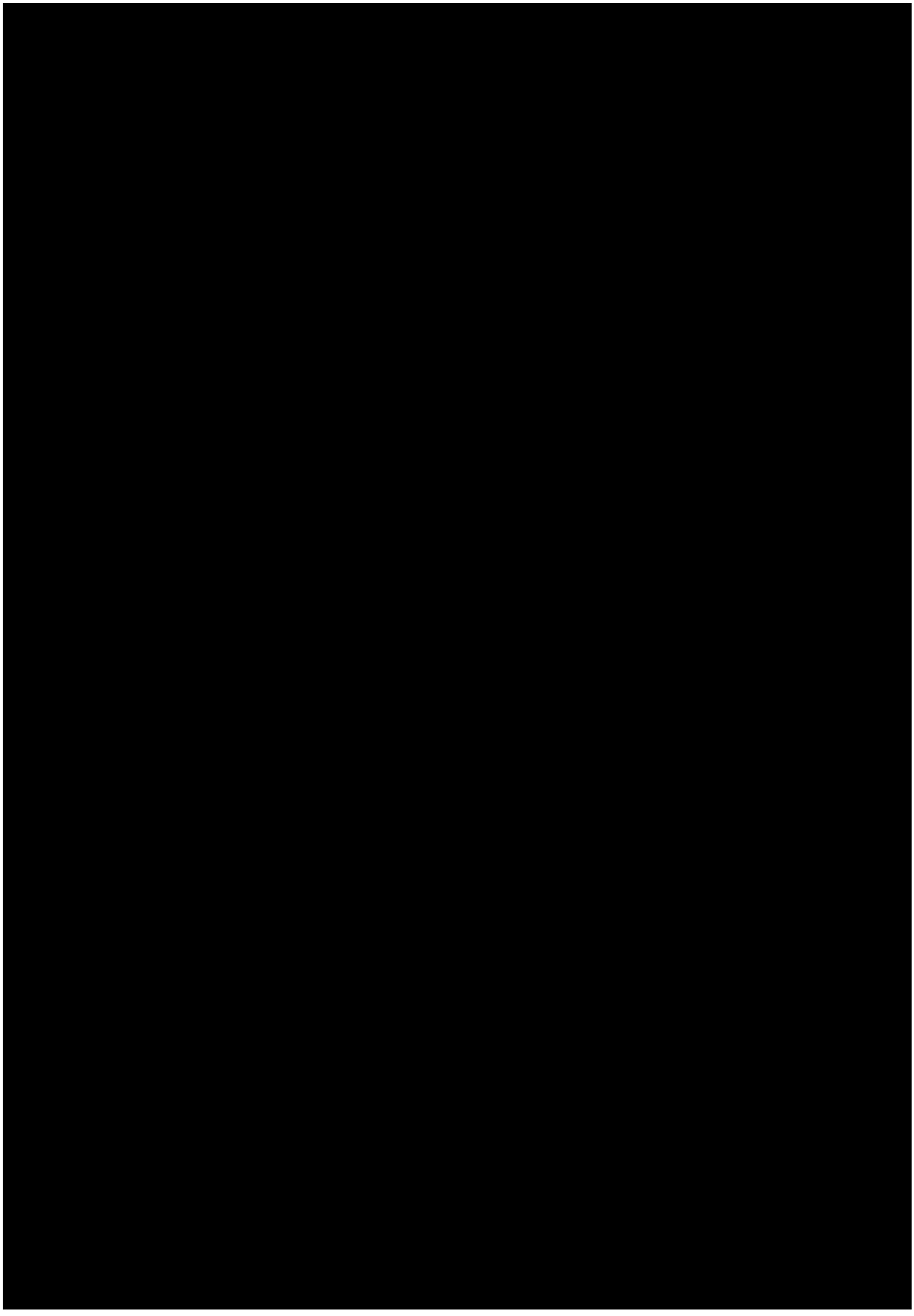
7.2.6 Days 1 through 3 of the Inpatient Period

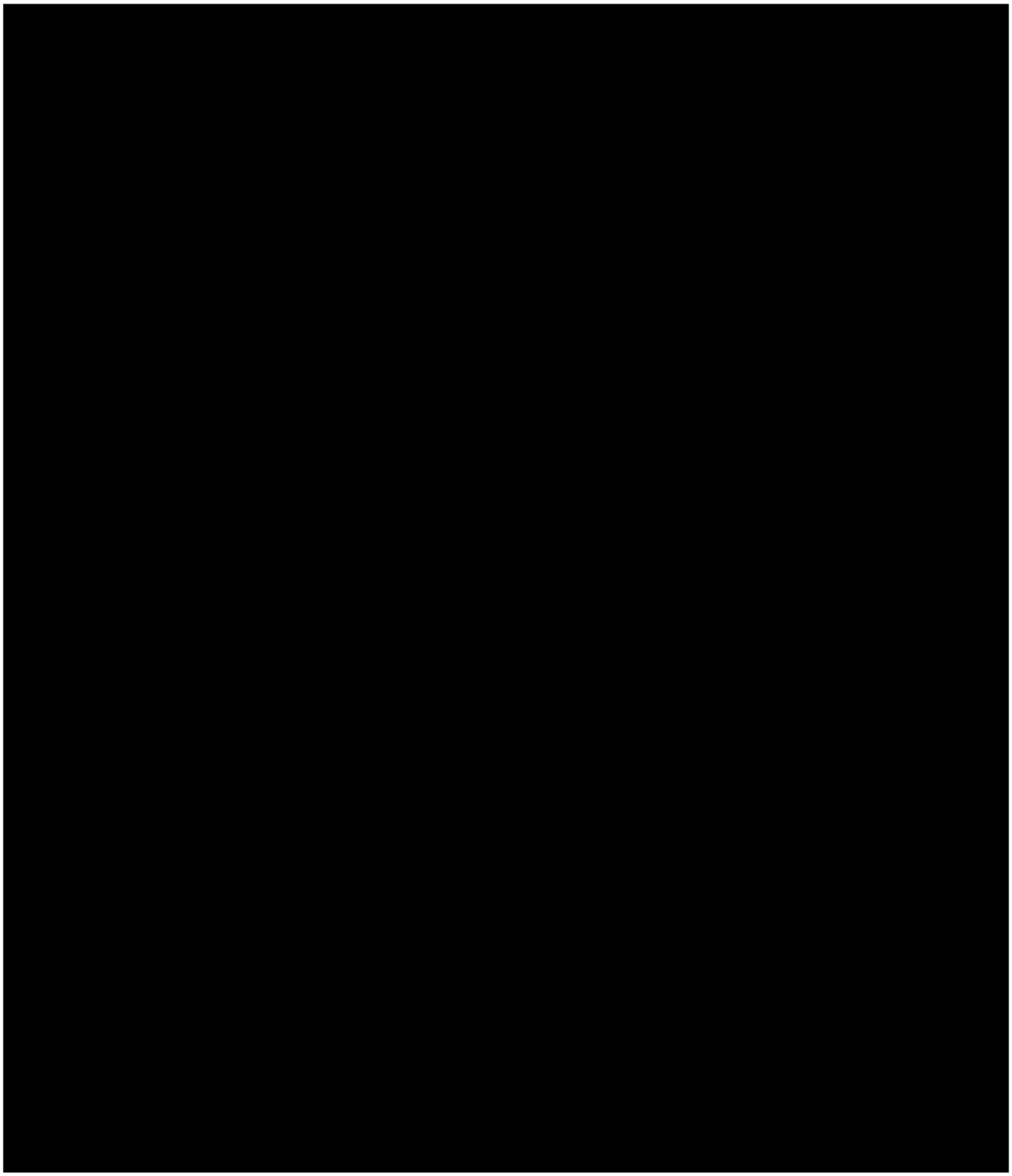


[redacted]

7.2.7 Outpatient Follow-up

[redacted]





7.2.8 Early Termination from Study

In case of early termination from the study, the last visit to the CRU will include the same assessment as the Day 28 visit plus a careful assessment of the reason for the early termination.

7.3 Data Monitoring Board and Dose Escalations

7.3.1 Data Monitoring Board

A DMB will be formed to monitor safety and dose cohort choices and provide recommendations to the Sponsor for implementation in the study. The DMB will minimally include an independent Safety Monitor, the Medical Monitor, the Investigator(s), and an independent statistician as voting members, as well as a non-voting coordinator. Operational details will be described in a Safety Plan.

7.3.2 Dose Escalations

When the last participant of a cohort has completed Day 7 and evaluable data are available, statistics will provide a data summary of the cohort data for the DMB. The DMB will meet and decide further actions as described in the Safety Plan.

8 Statistical Methods

8.1 Sample size

The sample size is not determined for inferential testing purposes. The sample size of 4 participants per cohort (3 active: 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.

8.2 Analysis populations

Two participant populations will be defined. The Safety of Full Analysis Set population (FAS) will be defined as all participants who are randomized. The Per-Protocol (PP) population will be participants for whom evaluable data to and including Day 7 is available and with no major protocol violations.

8.3 Data Analysis

AEs will be presented in listings and Treatment Emergent Adverse Events (TEAEs) will be summarized. Individual results of laboratory tests (hematology, chemistry, and urinalysis) will be listed and change from baseline will be summarized using shift tables. Individual results of vital signs will be listed and observed values and changes from baseline will be summarized.

Individual results of quantitative ECG parameters from the 12-lead safety ECGs will be listed and observed values and changes from baseline will be summarized and analyzed consistent with the ICH E14 (3).

All summaries will be performed by placebo and each EXT608 dose level. Placebo data will be pooled across cohorts. Physical exam findings will be presented in data listings.

Concentrations of EXT608 will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing. PK parameters will be summarized by dose using descriptive

statistics. Dose proportionality will be assessed graphically and using a power model. PD will be presented in listings and summarized by dose and time point.

Detection of ADA and NAbs will be presented in listings and summarized by dose and time point.

No formal hypothesis testing will be conducted as part of this study.

DMB data packages will be based on the FAS for safety and PP for PK/PD.

Further details are described in the Statistical Analysis Plan.

9 Direct Access to Source Data/Documents

Extend Biosciences, Inc. or agents thereof, the reviewing IRB/EC, and health authorities from the US or other countries will have access to source documents at the investigational site for monitoring, auditing or inspection purposes.

10 Quality Control and Quality Assurance

10.1 Monitoring

The study will be monitored by qualified site monitors approved by the Sponsor. Monitoring will be done via on-site visits by the site monitor, who will review the eCRFs and source documents, and via remote review of eCRF entries. The site monitor will make sure that the investigation is conducted according to protocol design, GCP, and regulatory requirements.

Alternatively, due to the ongoing SARS-CoV-2 pandemic, all monitoring may be remote using a combination of source documents uploaded to the EDC and other tools for viewing site documents, e.g., for signed ICFs, for SDV. Further details will be described in a Clinical Monitoring Plan.

10.2 Data Management

Data will be entered in the electronic data capture (EDC) system at the investigational site.

The data management plan will describe the methods used to collect, check, validate, and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process.

AEs and medical/surgical history will be classified according to the terminology of the Medical Dictionary for Regulatory Activities (MedDRA; version specified in the Data Management Plan). Medications will be classified according to the latest World Health Organization (WHO) Drug Dictionary.

Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. When all data have been coded, validated, and locked, clean file will be declared. Any treatment-revealing data may thereafter be added and the final database will be locked.

10.2.1 Audits

In addition to monitoring, the Sponsor, Sponsor's representative, US or foreign regulatory authorities, and/or the reviewing IRB/ethics committee, may audit the conduct of the study. The auditors must have access to all study documents, the facilities where the study was conducted, and the study staff for interviews. The investigator will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at the center.

11 Ethics

The study will be performed in accordance with applicable regulatory requirements, the International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP), and the ethical principles that have their origins in the Declaration of Helsinki.

An IRB will approve the final study protocol, including the final version of the informed consent form and any other written information and/or materials to be provided to the subjects, before any subjects are enrolled. The investigator will ensure the distribution of these documents to the applicable IRB/EC and to the staff of the study site.

11.1 Informed Consent

Prior to performing any study procedures, written informed consent will be obtained from the subject. The method of obtaining and documenting the informed consent and the contents of the informed consent will comply with ICH-GCP and all applicable regulatory requirements.

12 Data Handling and Recordkeeping

The investigator must keep the study documentation for 15 years after the completion of the study.

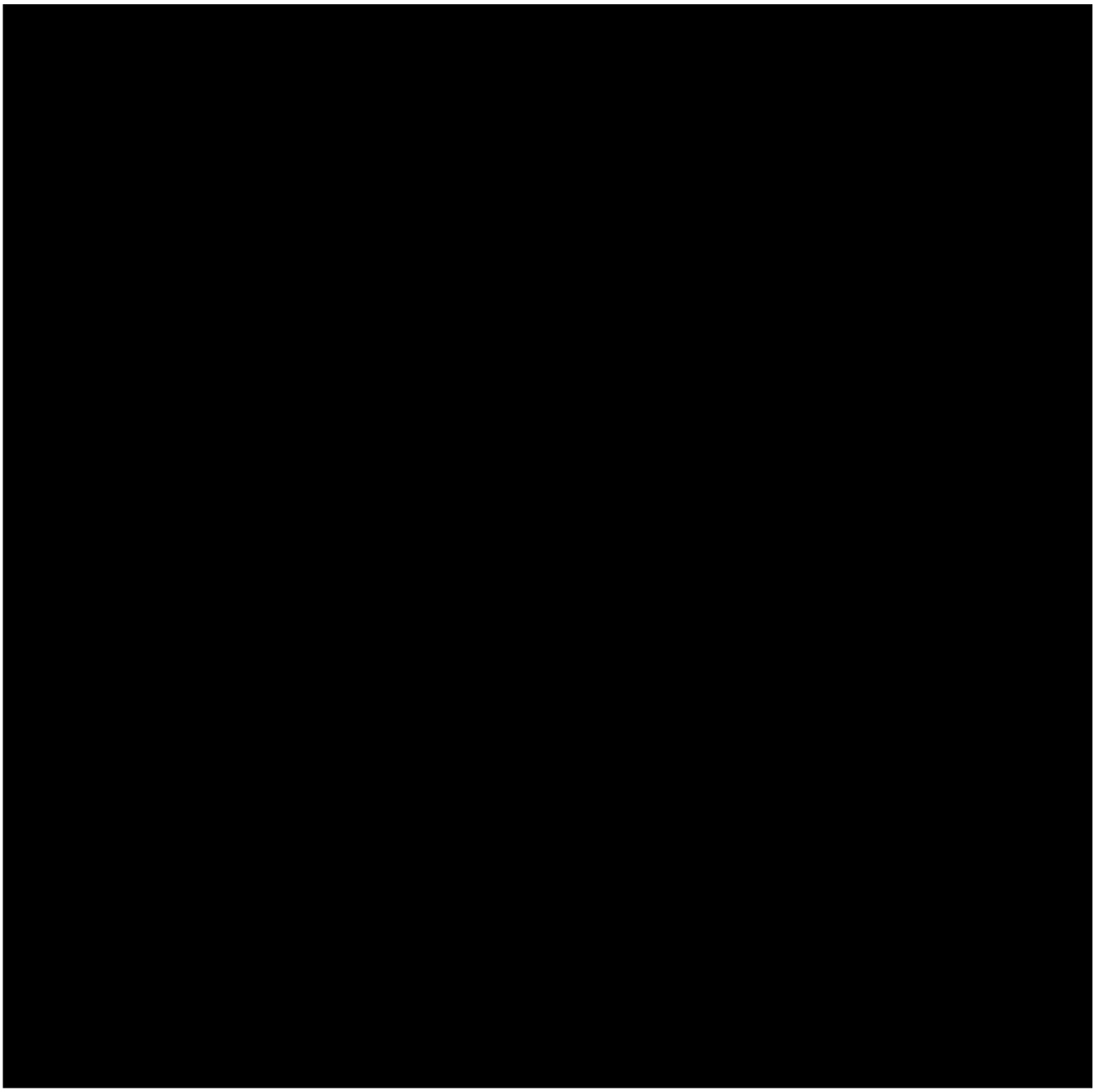
13 Publication Policy

The Sponsor intends to publish the findings of the study and in general follows the guidelines set forth by the Internal Committee of Medical Journal Editors (ICMJE) (6). The investigator may publish the data from the site one year after the last participant finished the study.

14 References

1. EXT608 Investigator's Brochure
2. NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf Accessed 23-Sep-2020.
3. ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. October 2005. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinical-evaluation-qtqtc-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-0 . Accessed 26-Sep-2020
4. American Association for Clinical Chemistry https://labtestsonline.org/tests-index
5. Mayo Clinic Laboratories https://www.mayocliniclabs.com/test-catalog/
6. ICMJE. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. www icmje org 2020 October 10; Available from: URL: www.icmje.org

15 Appendix 1



16 Appendix 2

Visual Analog Scale

Please draw a **single vertical line** through the scale below that corresponds to the intensity (severity) of any pain you are feeling **right now**.

To indicate “no pain” or “worst possible pain” please **circle** the words instead of marking on the line.