Inozyme Pharma, Inc.
Protocol #: INZ701-201

A Phase 1/2, Open-Label, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of INZ-701 Followed by an Open-Label Long-Term Extension Period in Adults with ABCC6 Deficiency Manifesting as *Pseudoxanthoma elasticum* (PXE)

Statistical Analysis Plan

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List of Abbreviations

Abbreviation	Definition/Expansion
$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
$\%AUC_{ex}$	Percentage of AUC_{inf} obtained by extrapolation
%Fluct	Percent fluctuation
ABCC6	ATP-binding cassette sub-family C member 6
ADA	Anti-Drug Antibody
AE	Adverse Events
ATC	Anatomical Therapeutic Class
AUC	Area under the concentration-time curve
AUC_{0-72}	Area under the concentration-time curve from zero (predose) until 72 hours postdose
AUC_{0-72}/Dose	Dose-normalized AUC_{0-72}
AUC_{inf}	Area under the concentration-time curve from zero (predose) extrapolated to infinite time
AUC_{inf}/Dose	Dose-normalized AUC_{inf}
AUC_{last}	Area under the concentration-time curve from zero (predose) to time of last quantifiable concentration
AUC_{last}/Dose	Dose-normalized AUC_{last}
AUC_{tau}	Area under the concentration-time curve from zero (predose) during a dosing interval
AUC_{tau}/Dose	Dose-normalized AUC_{tau}
AUEC	Area under the effect-time curve. Calculated using the linear trapezoidal rule.
BLQ	Below the limit of quantification
CaGI-I	Caregiver Global Impression of Improvement
CaGI-S	Caregiver Global Impression of Status/Severity
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Status/Severity
cm	Centimeter
C_{avg}	Average concentration over the dosing interval
CL/F	Apparent systemic clearance after subcutaneous dosing
C_{max}	Maximum concentration
C_{max}/Dose	Dose-normalized C_{max}
C_{min}	Minimum concentration after multiple dosing
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography

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Abbreviation	Definition/Expansion
CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DLT	Dose Limiting Toxicity
DP	Dorsalis Pedis
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
E_{max}	Maximum effect observed, taken directly from the observed serum ENPP1 specific activity-time profile.
ENPP1	Ectonucleotide pyrophosphatase/phosphodiesterase 1
EOS	End of study
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
HR	Heart Rate
kg	Kilogram
λ_z	Apparent terminal rate constant
L	Liters
LI	Linearity index
LLOQ	Lower limit of quantification
m	Meter
MAD	Multiple Ascending Doses
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
MTD	Maximum Tolerated Dose
n	Number of observations
nAB	Neutralizing Anti-Drug Antibody
PD	Pharmacodynamic
PET	Positron emission tomography
PGI-I	Patient Global Impression of Improvement
PGI-S	Patient Global Impression of Status/Severity
PK	Pharmacokinetics
PPi	Inorganic pyrophosphate
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Posterior Tibial
PCS	Potentially clinically significant
PT	Preferred Term

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Abbreviation	Definition/Expansion
PTH	Parathyroid hormone
PXE	Pseudoxanthoma elasticum
RAUC	Accumulation ratio for AUC_{tau}
RC_{max}	Accumulation ratio for C_{max}
Rsq_adj	Goodness of fit statistic for calculation of λ_z
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SDTM	Study data tabulation model
SI	Standard units
SOC	System Organ Class
$T_{½}$	Apparent terminal half-life
T_{lag}	Lag time before observation of quantifiable concentration
T_{max}	Time of maximum concentration
TEAE	Treatment-Emergent Adverse Events
tE_{max}	Time to maximum observed effect, taken directly from the observed serum ENPP1 specific activity-time profile
TmP	Tubular Maximum Reabsorption of Phosphate
TmP/GFR	Tubular maximum reabsorption rate of phosphate adjusted for glomerular filtration rate
ULN	Upper Limit of Normal
US	United States of America
V_z/F	Apparent volume of distribution following subcutaneous dosing
WHO	World Health Organization
WOCBP	Women of child-bearing potential
WPAI	Work Productivity and Activity Impairment Questionnaire

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I. Introduction

A. Background

Study INZ701-201 is a multiple ascending dose (MAD) dose-finding study followed by a long-term Extension Period in adult subjects (18 to <70 years of age) with ATP-binding cassette sub-family C member 6 (ABCC6) deficiency manifesting as PXE. Study INZ701-201 will evaluate general safety and immunological parameters to determine the risk-benefit profile of INZ-701 in ABCC6 deficiency and will identify the INZ-701 dose for further clinical development in ABCC6 deficiency.

B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on version 8.0 of Protocol INZ701-201.

This SAP will govern the analysis of data from this study. Any deviations from the SAP, including any after the time of database lock, will be documented as such in the study report.

II. Protocol Objectives and Study Endpoints

Objective	Endpoint (Assessment)
Primary:	
• Assess the safety and tolerability of multiple ascending SC doses of INZ-701	• Safety, tolerability measures and exploratory biomarkers
Secondary:	
• Assess the immunogenicity of multiple ascending SC doses of INZ-701	• Incidence of anti-drug antibody (ADA) • Changes from baseline in the ENPP1 enzyme activity and presence of neutralizing antibodies
• Study the pharmacokinetics (PK) of INZ-701 administered as multiple SC doses	• INZ-701 plasma concentration-time profiles and determination of noncompartmental PK parameters (including but not limited to time to maximum plasma concentration [Tmax], maximum plasma concentration [Cmax], area under the concentration time curve to the last quatifiable concentration [AUClast], area under the plasma concentration time curve over the dosing interval [AUCtau], area under the plasma concentration-time curve from time zero to infinity [AUCinf], elimination half-life [T1/2], minimum plasma concentration [Cmin], clearance [CL/F], and apparent volume of distribution [Vz/F])

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	• Linearity between ascending INZ-701 SC doses and PK parameters
• Study the long-term safety and pharmacodynamic (PD) changes from baseline in PPi after administration of multiple SC doses of INZ-701	• Change from baseline in PPi levels, phosphate, calcium, alkaline phosphatase, and intact parathyroid hormone (PTH) • Changes from baseline of blood and urine biomarkers as available
Exploratory:	
• Assess changes in calcification of arteries and organs (including the eye)	• Results of $Na^{18}F$-PET/CT, echocardiogram, renal ultrasound, carotid ultrasound
• Assess changes in clinical measures associated with underlying ABCC6 Deficiency, including cardiac, vascular, ophthalmologic, and renal parameters	• Results of echocardiogram, electrocardiogram (ECG), ophthalmologic examination and renal ultrasound assessments
• Assess changes in physical function	• Results of Pulse Wave Velocity, Ankle-Brachial Pressure Index and Edinburgh Claudication Questionnaire (ECQ) assessments
• Assess changes in patient, clinician, and caregiver reported outcomes and quality of life	• Results of Patient Reported Outcomes Measurement Information System (PROMIS), global impression scales and Work Productivity and Activity Impairment Questionnaires (WPAI) assessments, Clinical Global Impression Scales, Patient Global Impression Scales, Vision Function Questionnaire and Edinburgh Claudication Questionnaire

III. Study Design

A. Design Overview

Study INZ701-201 is a Phase 1/2, multicenter, open-label, MAD, dose-finding study followed by a long-term Extension Period conducted in adults with ABCC6 deficiency manifesting as PXE. This study is designed to assess the safety, tolerability, PK, and PD of multiple ascending doses of INZ-701. The goal of the study is to identify a dose and dose schedule (number of doses per week) for further clinical development in ABCC6 Deficiency. No placebo will be used in the study.

Subject participation consists of 3 parts, a Screening Period of up to 60 days, a 32-day Dose Evaluation Period, and an Extension Period during which subjects may continue to receive INZ-701 until it is approved and available in the country

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where the subject resides or until an alternative study for subjects to continue receiving study drug is available.

Subjects may participate in the Dose Evaluation Period only. Participation in the Extension Period is not a requirement. To participate in the Extension Period, the Investigator must assess the subject's safety data through Day 29 of the Dose Evaluation Period to confirm that dosing may continue; the subject must be willing and able to comply with the study and Investigator's requirements for dosing and must provide written informed consent to continue in the study.

The study design during the Dose Evaluation Period is a MAD 3 + 3 with 3 dose cohorts. Based on nonclinical findings and nonclinical pharmacology modeling, the planned doses will be 0.2 mg/kg, 0.6 mg/kg, and 1.8 mg/kg SC, with a twice weekly dose regimen. The maximum exposure level, based on no-observed-adverse-effect level (NOAEL) values from chronic GLP toxicology studies, is set at [redacted] µg/mL and [redacted] hr*µg/mL for Cmax and AUClast, espectively. Escalation to the next dose cohort will proceed after review of all safety and available PK/PD data from all subjects in the current dose cohort through Day 32 and recommendation from an independent DSMB. The decision to escalate to the next dose cohort will be made by the Sponsor in collaboration with the Investigators based upon the recommendation from the DSMB. The recommendation from the DSMB will be communicated by the Sponsor in writing to the Investigators, who will have 48 hours to communicate agreement or any concerns. Escalation to the next dose level will occur after resolution of any concerns, if needed. Enrollment in the next dose cohort will not begin until the decision to dose has been sent to each participating site in writing.

In the Extension Period, INZ-701 administration will initially be at the dose and dose schedule assigned in the Dose Evaluation Period. After all subjects in the Dose Evaluation Period complete Day 32, a cumulative review of all safety and PK/PD data will be conducted to select a dose regimen for the remainder of the study. All subjects in the Extension Period will be prescribed the selected dose regimen, as applicable. In-clinic visits will be every 4 weeks until Week 48 and then every 24 weeks until the subject leaves the study. Between the in-clinic visits, subjects will undergo a remote or in-clinic visit at the Investigator's discretion every 12 weeks.

Subjects will complete an End of Study (EOS) Visit (Safety Follow-up Visit) 30 days after their last dose of INZ701.

The dose and dosing regimen selected for the Extension Period may change based on an ongoing review of cumulative safety and PK/PD data, including population PK. The selected dose regimen may include a flat dose (non-weight based) regimen or a once weekly weight-based dose regimen that will not exceed the highest dose determined to be safe by the Sponsor and DSMB. The selected dosing regimen may be applied on an individual cohort basis at the discretion of the Sponsor once all subjects in the specific cohort complete Week 48.

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B. Cohort Stopping Criteria for the Dose Evaluation Period

A dose limiting toxicity (DLT) is defined as any Grade ≥3 event (apart from fatigue) deemed related to INZ-701. Investigators must report the occurrence of a DLT to the Sponsor or Sponsor's designee immediately and no later than 24 hours of awareness.

For each dose level, if at any time during the Dose Evaluation Period 1 DLT is observed, dosing and further enrollment in that dose cohort will pause and the DSMB will convene to make recommendation(s) as follows:

- Stop enrollment at that dose level
- Declare maximum tolerated dose (MTD) at the next lower dose level
- Resume cohort enrollment. If no other DLTs are observed in the 3 subjects after completing the 32-day Dose Evaluation Period, the cohort will be expanded by 3 subjects
- De-escalate to an existing lower dose level and enroll up to 3 new subjects for a maximum of 6 subjects in the dose cohort
- Add a lower dose level, enroll, and dose 3 new subjects in that dose cohort
- De-escalate current subjects in this cohort to a lower dose

At the completion of an expanded cohort with only 1 DLT, the DSMB will convene to review data to make dosing and dose level recommendations.

For each dose level, if at any time during the Dose Evaluation Period 2 or more DLTs are observed, irrespective of cohort expansion, enrollment and dosing at that dose level will be stopped and the DSMB will convene to make recommendation(s) as follows:

- Stop enrollment at that dose level
- Declare MTD at the next lower dose level
- Resume cohort enrollment. If no other DLTs are observed in the 3 subjects after completing the 32-day Dose Evaluation Period, the cohort will be expanded by 3 subjects
- De-escalate to an existing lower dose level and enroll up to 3 new subjects for a maximum of 6 subjects in the dose cohort
- Add a lower dose level, enroll, and dose 3 new subjects in that dose cohort
- De-escalate current subjects in this cohort to a lower dose

The decision on how to proceed will be made in collaboration with the Sponsor following DSMB recommendation.

The Sponsor in collaboration with the Investigators may declare MTD at any time and stop enrollment.

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The planned DSMB data analyses will be re-run at the end of the study and matched for quality purposes to the corresponding summary tables as described in this statistical analysis plan. Where appropriate, graphs created as a part of the DSMB package will be made available for use in the clinical study report (CSR).

C. Study Population

Subjects will be 18 to <70 years of age at Screening, with a confirmed clinical diagnosis of PXE, genetic evidence of biallelic mutation of the ABCC6 gene, and biochemical evidence of low levels of pyrophosphate (ie, PPi <1300 nM at Screening).

See Section 8.1 and 8.2 of the protocol for a complete list of the inclusion/exclusion criteria.

D. Sample Size Predictions

Anticipated enrollment is 9 subjects, assuming 3 cohorts are enrolled with no cohort expansion.

The maximum number of subjects that may be enrolled in the study is 24. This assumes cohort expansion by up to 3 additional subjects at each dose level as determined by a review of available safety data by the Data Safety Monitoring Board (DSMB) in collaboration with the Sponsor. In addition, once all subjects in Cohort 3 complete Day 32, the Sponsor may choose to add a cohort to evaluate an alternate dosing regimen and/or enroll up to 6 additional subjects to further evaluate and corroborate the PK and PD of INZ-701 at an existing dose level.

E. Treatment Randomization and Blinding

Randomization and blinding are not applicable in this single-arm, open-label study.

F. Assessment Schedule

See protocol table 1, table 2, table 3, table 4 and table 5 for study schedules of assessments.

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IV. Interventions

A. Clinical Trial Material

During the Dose Evaluation Period, all subjects will receive open-label INZ-701 as a single agent according to the table below. For each subject, the first dose of INZ-701 will be administered on Day 1. On Days 8 to 29, subjects will receive the proposed doses twice weekly, with a final dose on Day 29. If possible, the dose should be administered at approximately the same time on each dosing day.

During the Extension Period, eligible subjects will be administered INZ-701 at the dose and dose schedule assigned in the Dose Evaluation Period. After all subjects in the Dose Evaluation Period complete Day 32, a cumulative review of all safety and available PK/PD data will be conducted to select a dose regimen (ie, dose level and dose schedule) for the remainder of the study. All subjects in the Extension Period will be prescribed the selected dose regimen, as applicable.

During the Extension Period, if applicable, the prescribed dose regimen for a subject may change once the selected dose and dose schedule has been determined upon completion of the Dose Evaluation Period, at which time all subjects in the Extension Period will be assigned to the selected dose regimen. For any single period of interruption in dosing lasting <2 weeks, the subject may resume dosing at the Investigator's discretion. For any repeat multiple-interruptions or an interruption ≥2 weeks, the Investigator must consult with the Sponsor prior to resuming dosing.

Cohort Dose Level	INZ-701 Dose Cohorts (n=3 per cohort with an optional 3 subject expansion)
1	0.2 mg/kg twice weekly
2	0.6 mg/kg twice weekly
3	1.8 mg/kg twice weekly

V. General Analytical Considerations

A. Data Sources

All information requested in the protocol will be recorded on the electronic Case Report Forms (eCRFs) provided by the Sponsor or its designee (or via other data collection methods, e.g., electronic laboratory data transfer).

Section 13 of the protocol provides additional details for data recording, retention, and monitoring.

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B. Definition of Baseline

Baseline value for each quantity being analyzed is defined as the last non-missing value prior to the first dose of study drug. If a baseline value is missing, no change from baseline will be calculated. The change from baseline and percent change from baseline will be calculated as following:

- Change from baseline = Test value at post-baseline visit – Baseline value
- Percent change from baseline (%) = (Change from baseline at post-baseline visit / Baseline value) * 100

Baseline for all imaging data will include the following definition; if a baseline is not identified prior to first dose, then the date for visit windowing at baseline should be extended to 28 days after first dose.

C. Study Day and On-study Treatment Flag

Study Day will be calculated from the reference start date and will be used to show the start/stop day of assessments and events. Reference start date is defined as the day of first dose (Day 1).

Study Day will be computed as follows:

- Study Day = (date of event – date of first dose) + 1 if the date of the event is on or after the date of first dose.
- Study Day = (date of event – date of first dose) if the date of the event is prior to the date of first dose.

A lab assessment will be considered on-treatment if the subject was administered at least one dose seven days prior to the clinical lab assessment. For example, if a subject completes the Week 12 lab assessment on study day 86, they will be considered on-treatment if they received at least 1 dose between study day 79 - 85, inclusive.

D. Analysis Windows for Non-Laboratory Data

Unless stated otherwise, data collected during the Dose Evaluation and Dose Extension Period up to Week 48 will be analyzed according to the nominal visits (i.e., assigned visit) as collected in the EDC. After Week 48 the visits will be re-numbered to an analysis visit based on their windowed visits defined by actual study day. If more than one visit or assessment (scheduled or unscheduled) occurs within a single visit window, then the analysis will take the one closest to the target day. If the 2 visits are equidistant from the target day, the visit with later date and time will be used.
The following analysis visit windows will apply.

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Analysis Visit	Target Day	Analysis Window (inclusive)
Week 60	421	379-462
Week 72	505	463-546
Week 84	589	547-630
Week 96	673	631-714
Week 108	757	715-798
Week 120	841	799-882
Week 132	925	883-966
Week 144	1009	967-1050
Week 156	1093	1051-1134

If subjects are followed for a longer period of time than the table described above, the additional analysis visits will be applied in a similar manner.

For the imaging data, all post-screening visits will be re-numbered to an analysis visit based on their windowed visits defined by actual study day. If more than 1 visit or assessment (scheduled or unscheduled) occurs within a single visit window, then the analysis will take the one closest to the target day. If the 2 visits are equidistant from the target day, the visit with later date and time will be used.

The following analysis visit windows will apply for the imaging data:

Analysis Visit	Target Day	Analysis Window (inclusive)
Week 24*	169	29 - 210
Week 48	337	211 - 505
Week 96	673	506 - 756
Week 144	1009	757 - 1092
Week 192	1345	1093 - 1428
*Renal Ultrasound is not scheduled for Week 24 visit		

For the PROMIS, WPAI, impression scales and the exploratory biomarkers data all post-screening visits will be re-numbered to an analysis visit based on their windowed visits defined by actual study day. If more than 1 visit or assessment (scheduled or unscheduled) occurs within a single visit window, then the analysis will take the one closest to the target day. If the 2 visits are equidistant from the target day, the visit with later date and time will be used.

The following analysis visit windows will apply for the PROMIS, WPAI, impression scales and the exploratory biomarker data:

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Analysis Visit	Target Day	Analysis Window (inclusive)
Week 12	85	post-screening - 126
Week 24	169	127 - 210
Week 36	253	211 - 294
Week 48	337	295 - 378
Week 72	505	379 - 588
Week 96	673	589 - 756
Week 120	841	757 - 924
Week 144	1009	925 - 1092
Week 168	1177	1093 - 1260
Week 192	1345	1261 - 1428

E. Analysis Windows for Safety Laboratory Data excluding PK/PD Sample

Laboratory samples (blood draws and urine samples) should be linked using the intended visit date (per the study schedule) to the date the sample was collected. Below is the window algorithm for the Dose Evaluation Period.

Analysis Visit	Study Week	Target Study Day	Algorithm for selection
Baseline			Assessment collected closest to and prior to the time of first dose
Study Day 1 Post-Trt	1	1	Assessment collected on the same day as the first dose, however the time indicates it was collected after the time of the first dose.
Study Day 2 - 6	1	2 - 6	Map using the Study Day. If the assessment was collected on a dosing day this will not apply.
Day 7	1	7	Assessments collected on the same day as the first dose of Week 1.
Day 8 Pre-Trt	2	8	Assessments collected on the same day as the first dose of Week 2 with the time indicating prior to the dose.
Day 15 Pre-Trt	3	15	Assessments collected on the same day as the second dose of Week 3 with the time indicating prior to the dose.
Day 15 Post-Trt	3	15	Assessments collected on the same day as the first dose of Week 3 with the time indicating after the dose
Day 22 Pre-Trt	4	22	Assessments collected on the same day as the second dose of Week 4 with the time indicating prior to the dose.
Day 22 Post-Trt	4	22	Assessments collected on the same day as the first dose of Week 4 with the time indicating after the dose

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Analysis Visit	Study Week	Target Study Day	Algorithm for selection
Day 29 Pre-Trt	5	29	Assessments collected on the same day as the second dose of Week 5 with the time indicating prior to the dose.
Day 29 Post-Trt	5	29	Assessments collected on the same day as the first dose of Week 5 with the time indicating after the dose
Day 32 Pre-Trt	5	32	Assessments collected on the same day as the second dose of Week 5 with the time indicating prior to the dose.

Below is the window algorithm for the Extension Period Through Week 48.

Analysis Visit	Target Day	Analysis Window (inclusive)
Week 8 Pre-Trt	56	50 - 70
Week 12 Pre-Trt	84	78 - 98
Week 16 Pre-Trt	112	106 – 126
Week 20 Pre-Trt	140	134 - 154
Week 24 Pre-Trt	168	162 – 182
Week 28 Pre-Trt	196	190 – 210
Week 32 Pre-Trt	224	218 – 238
Week 36 Pre-Trt	252	246 – 266
Week 40 Pre-Trt	280	274 – 294
Week 44 Pre-Trt	308	302 – 322
Week 48 Pre-Trt	336	330 – 350

Below is the window algorithm for the Extension Period Post-Week 48.

Analysis Visit	Target Day	Analysis Window (inclusive)
Week 72 Pre-Trt	504	379 - 588
Week 96 Pre-Trt	672	589 - 756
Week 120 Pre-Trt	840	757 - 924
Week 144 Pre-Trt	1008	925 - 1092
Week 168 Pre-Trt	1176	1093 - 1260

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Analysis Visit	Target Day	Analysis Window (inclusive)
Week 192 Pre-Trt	1344	1261 - 1428

F. Missing Data

Unless stated otherwise, missing data will not be replaced with imputed values. When relevant, sections below will address how missing data will be handled for the particular analyses.

Missing PK concentrations will be handled as described in Section XI.

Partial dates will be imputed with the following convention to calculate the relative study day or duration.

Missing or Partial AE, Medication and Procedure start or stop date:

For partial start dates:

- If the year is unknown, no imputation will occur.
- If the year is known and the month and day is unknown, then:
  - If the year matches the year of the first dose date, then impute the month and the day the same as first dose date.
  - If the year is not the same year of the first dose, then month and day will be imputed as 01 January.
- If the month and year is known and the day is unknown, then:
  - If the month and year match the month and year of the first dose date, then impute the day the same as first dose date.
  - Otherwise, the day will be imputed as "01".

For partial end-dates:

- If the year is missing, no imputation will be performed, and the AE/CM will be assumed as ongoing.
- If the year is present and both month and day are missing and the year is not the same as the last study date, then the month and day will be imputed as the last day of the year, 31 December.
- If the year is present and both month and day are missing and the year is the same as the last study date, then the month and day will be imputed as the last study date.
- If the year and month are present and only the day is missing, and the year and month is not the same as the last study day then the day will be imputed as the last day of the month.

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- If the year and month are present and only the day is missing, and the year and month is the same as the last study day then the day will be imputed as the last day of the study.

G. Multiple Study Centers

The study is a multicenter trial that will be conducted at approximately 4 sites globally. Data from all study sites will be pooled for the purpose of analyses. No adjustment for study center is planned.

H. Covariate Adjustment in Primary Analysis

No covariate adjustments are planned for the analysis.

I. Interim Analysis

An interim analysis will be conducted when all subjects have completed the Week 48 visit. Additional interim analyses may be conducted based upon Sponsor decision.

The final analysis will be conducted when the last subject completes the study.

J. Analysis Sets

Four analysis sets are defined for this study.

1. Screened Analysis Set

All subjects entered into the eCRF system who have signed an informed consent.

2. Safety Analysis Set

All subjects who were enrolled and received at least 1 dose of INZ-701.

3. Pharmacokinetic Analysis Set

All subjects who receive at least one dose of INZ-701 and have at least 1 measured concentration for INZ-701 at a scheduled PK time point after the start of dosing without protocol violations or events with potential to affect the serum PK concentration. Subjects in this analysis set will be used for all PK summaries and statistical analyses.

4. Pharmacodynamic Analysis Set

All subjects who receive at least 1 dose of INZ-701 and have at least 1 post-dose plasma inorganic pyrophosphate (PPi).

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K. Data Display Characteristics

Data displays produced for this study will include summary tables, data listings, and figures.

Data listings will be produced for all recorded data. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes.

Summary tables and figures will be produced as specified in the following sections. The summary statistics displayed will be a function of the type of data associated with the summarized assessment. Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of non-missing values (n), mean, standard deviation (SD), standard error (SE) if applicable, minimum, median, and maximum. Categorical data will be summarized with the number of missing, non-missing values and the numbers of values equal to each of the possible values. Percentages of subjects with each of the possible values will be calculated from the number of subjects in the corresponding analysis set, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

Geometric mean and geometric coefficient of variation (CV) will be included for serum PK parameters, where applicable. For the PK parameter T_{max}, only n, median, minimum, and maximum will be presented.

L. Precision

Safety and efficacy variables and PD results including derivations will be reported to the same precision as the source data.

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carries. Derived PK parameters will be rounded for reporting purposes in by-subject listings. Summary statistics and inferential analysis of derived PK parameters will be performed by using the unrounded values exported into study data tabulation model (SDTM) and the statistical results will be rounded for reporting purposes.

For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure for reporting, with the following exceptions:

- Parameters directly derived from source data (e.g. C_{max} and C_{min}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g. T_{max}) will be reported with a precision of 2 decimal places.

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For the reporting of descriptive statistics for the PK analysis, the mean and SD will be presented to 1 digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation will always be reported to 1 decimal place.

M. Software Versions

All derivations, statistical analyses, summaries, and listings will be generated using SAS version 9.4 (64-bit).

Non-compartmental PK and PD parameter calculations will be performed using Phoenix® WinNonlin® 8.3 or higher ([redacted]). PK graphics may be prepared using the same versions of SAS. Graphics may be prepared with Phoenix WinNonlin or with SigmaPlot 12.5, or higher ([redacted]) for preliminary (i.e., DSMB) PK analyses.

VI. Subject Accountability

A. Disposition

The number of subjects who screened and screen failed will be presented. The number of subjects in the Safety Analysis Set, PK Analysis Set, and PD Analysis Set will be presented by dose cohort and overall (all patients).

Number and percentages of subjects who completed/discontinued Dose Evaluation Period (including reason), completed/discontinued Treatment (including reason), and who completed/discontinued early from the study (including reason) will be provided by dose cohort and overall based on the Safety Analysis Set.

- Completed Dose Evaluation Period
- Discontinued Treatment during Dose Evaluation Period
  - Adverse event
  - Physician decision
  - Pregnancy
  - Study terminated by sponsor
  - Subject non-compliance/protocol violations(s)
  - Withdrawal of consent
  - Other
- Complete Treatment
- Discontinued Treatment
  - Adverse event
  - Physician decision
  - Pregnancy
  - Study terminated by sponsor

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  - Subject non-compliance/protocol violations(s)
  - Withdrawal of consent
  - Other
- Complete Study
- Subject Discontinued the Study Early
  - Adverse event
  - Death
  - Lost to follow-up
  - Physician decision
  - Study terminated by sponsor
  - Subject non-compliance/protocol violations(s)
  - Withdrawal of consent
  - Other

A subject is considered to have completed the Dose Evaluation Period if the subject completed the assessments and dose administration through Day 29 and the PK/PD and safety assessments (Day 30-32). A subject is considered to have completed the study if the subject completed the Dose Evaluation Period, including PK/PD and safety assessment (Day 30-32) full treatment period, Extension Period visits and the Long-Term Follow-Up visit. Long-Term Follow-Up visit is not expected if the subject rolls over into the extension study.

A listing of subject disposition and a listing showing inclusion and exclusion of each subject from each analysis set, including reason for exclusion, will also be provided.

B. Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be presented by dose cohort and overall using the Safety Analysis Set:

Demographics

- Age (years)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported)
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Multiple)
- Dominant side (Right, Left, Ambidextrous)

Baseline characteristics

- Age at menarche (if applicable)
- Baseline weight (kg)
- Baseline Body Mass Index (BMI) (kg/m^2)

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- Baseline height (cm)

C. Medical History

Medical history events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.1. Coded medical history will be summarized by system organ class (SOC) and preferred term (PT) by dose cohort and overall based on the Safety Analysis Set. A subject having more than 1 reported medical diagnosis within the same SOC/PT will be counted only once for that SOC or PT.

All medical history will be presented in a data listing.

D. Disease History

Disease history characteristics captured on the "Disease History" eCRF page will be summarized for the Safety Analysis Set by dose cohort and overall.

All disease history will be listed as it pertains to each study participant.

E. ABCC6 Deficiency Diagnosis

The ABCC6 deficiency diagnosis characteristics will be collected on the "ABCC6 Deficiency Diagnosis" eCRF page. The number and percentage of subjects with various mutations will be presented by dose cohort and overall.

The ABCC6 deficiency diagnosis characteristics will be presented in a data listing.

F. ABCC6 Family History

The family history data will be collected on the "ABCC6 Deficiency Diagnosis" eCRF page.

The family history will be presented in a data listing.

G. Medicinal Treatment History, Physical Therapy, Occupational Therapy, and Assistive Devices

Medicinal treatment history, physical therapy, occupational therapy, and assistive devices history will be collected on the "Medicinal Treatment History, Physical Therapy, Occupational Therapy, and Assistive Devices" eCRF page.

Number and percentages will be provided by dose cohort and overall based on the Safety Analysis Set for the following:

- Subjects with any physical therapy history

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- Subjects with any occupational therapy history
- Subjects with any assistive device use history
  - Subjects with hearing aides
  - Subjects with glasses
  - Subjects with walker
  - Subjects with crutches
  - Subjects with cane
  - Subjects with other

All data will be presented in data listings.

H. Protocol Deviations

A summary table will be provided to summarize the number of major deviations and COVID related major protocol deviations based on the Safety Analysis Set by dose cohort and overall. Protocol deviations will be categorized as major or minor and flagged if COVID-19 related.

Changes to the procedures or events which may impact the quality of the PK data will be considered major protocol deviations or events and will be described within the CSR body text. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples of deviations/events for PK include, but may not be limited to, inaccurate dosing on the day of PK sampling.

Important deviations/events may potentially affect an entire concentration-time profile (e.g. mis-dosing) or as little as a single data record (e.g. sample processing error). In the case of an important protocol deviation or event with impact on PK, the affected PK data will be excluded from the study results. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered important protocol deviations. A common example of a protocol deviation which is not considered to be important is a missed blood sample or deviations from blood collection times at a non-critical time in the profile.

A listing of protocol deviations will be provided.

VII. Efficacy and Pharmacodynamic Analysis

Analyses of plasma inorganic pyrophosphate (PPi) and ENPP1 will be performed for the Pharmacodynamic (PD) analysis set and will be summarized descriptively for the observed, change from baseline and percent change from baseline by dose cohort and overall. Values of "<X" or not quantifiable will be included in the summary with the value of 0.

PPi and ENPP1 PD data will be presented in a data listing.

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Analysis of Serum ENPP1 Specific Activity

All statistical analyses and descriptive summaries of ENPP1 specific activity will be performed on the PD Analysis Set. A listing of serum ENPP1 specific activity sample collection times by individual, as well as derived sampling time and time deviations, will be provided. Serum ENPP1 specific activity (observed and baseline-adjusted) will be listed for all subjects by dose cohort and day; ENPP1 specific activity values excluded from the PD analysis will be flagged within the listing. Samples that are collected outside the specified time windows will be included in the PD analysis but excluded from the concentration summary.

Baseline is defined as the pre-dose sample on Day 1.

Serum ENPP1 specific activity level below the lower limit of quantification (LLOQ) will be taken as 0 for calculation of baseline-adjusted specific activity. Baseline correction is calculated as follows:

PD baseline-adjusted specific activity = observed specific activity – baseline.

Negative specific activity levels after baseline correction will be set to the LLOQ.

Observed and baseline-adjusted levels for serum ENPP1 specific activity will be summarized by dose cohort, day, and nominal time point. Plots of individual and mean (± SE) for serum ENPP1 specific activity (observed and baseline-adjusted) over time by dose cohort and day will be provided. Mean plots will include standard error bars (±SE) when plotted on a linear scale.

For each subject in the PD Analysis Set, the following observed PD parameters will be calculated for the Dose Evaluation Period on Day 1 and Day 29 for serum ENPP1 specific activity, where appropriate:

Symbol	Definition
E_{max}	Maximum effect observed, taken directly from the observed serum ENPP1 specific activity-time profile.
AUEC	Area under the effect-time curve. Calculated using the linear trapezoidal rule.
tE_{max}	Time to maximum observed effect, taken directly from the observed serum ENPP1 specific activity-time profile.

Pharmacodynamic parameters for serum ENPP1 specific activity will be calculated for the Dose Evaluation Period on Day 1 and Day 29 using standard noncompartmental methods with Phoenix WinNonlin using observed data. Pharmacodynamic parameters will be calculated using the actual elapsed time (rounded to 2 decimal places) since dosing. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.

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Pharmacodynamic serum ENPP1 specific activity parameters will be evaluated and listed for all subjects who provide sufficient specific activity-time data. At least 3 valid, post-dose ENPP1 specific activity points will be required in the PD profile to obtain any PD parameter estimate.

VIII. Exploratory Biomarkers

The exploratory biomarkers in Appendix 1 will be collected (unit).

Observed values, change from baseline and percent change from baseline will be presented in table summaries by dose cohort and overall for the Safety Analysis Set.

All data will be summarized and listed similarly as the clinical safety laboratory results.

IX. Exploratory Efficacy Analyses

Exploratory efficacy analyses will be performed on the Safety Analysis Set by dose cohort and overall. In general, the observed, change from baseline and percent change from baseline will be displayed if appropriate.

The positron emission tomography – computed tomography (PET/CT), echocardiogram, renal ultrasound, and carotid ultrasound are part of the imaging assessments.

The optical coherence tomography, color fundus photography, autofluorescence photography, and best corrected visual acuity are part of the ophthalmologic assessments.

Pulse wave velocity, ankle-brachial index, clinical global impression scale, patient global impression scale, caregiver global impression scale, Patient Reported Outcomes Measurements Information System (PROMIS), Vision Function Questionnaire (VFQ), Work Productivity and Activity Impairment Questionnaire (WPAI), and Edinburgh Claudication Questionnaire (ECQ) are part of the clinical outcome assessments.

The following assessments are not required. However, if the site has the ability (ie, resources, staff, etc.) to conduct them they are strongly recommended. For any nonrequired assessment not conducted by Day 1, the subject will not have the assessment conducted at any time during the study. Baseline Na18F-PET/CT imaging may be performed within 2 months after the first dose of INZ-701; if not conducted within the first 2 months after the first dose, the subject will not have the imaging assessment conducted at any time during the study.

- $Na^{18}F$-PET/CT

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- Pulse Wave Velocity (PWV)
- Ankle-Brachial Pressure Index (ABI)
- Global Impression Scales
- Patient Reported Outcomes Measurement Information System (PROMIS) Pain Inference, Fatigue, and Physical Functions – Upper Extremity
- Vision Function Questionnaire
- Work Productivity and Activity Impairment Questionnaire (WPAI)
- Edinburgh Claudication Questionnaire

A. Imaging

Imaging assessments will be performed at screening and scheduled time points during the Extension Period. The echocardiogram, renal ultrasound, and carotid ultrasound are required. The Na18F-PET/CT is a recommended assessment.

1. Echocardiogram

The echocardiogram will be used to measure heart function (left ventricular ejection fraction (LVEF), blood flow), calcification of heart and valves, arterial stiffness, and to identify any other abnormalities. A full list of all assessments is found in Appendix 3 of this document.

An echocardiogram should be performed at Screening, Week 24 of the Extension Period, Week 48 of the Extension Period and every 48 weeks after Week 48 of the Extension Period.

Continuous variables will be summarized by observed, change from baseline and percent change from baseline. Categorical variables will be presented by counts and percentages.

A spaghetti plot for select continuous echocardiogram assessment by dose cohort will be provided.

All data will be presented in data listing.

2. Renal Ultrasound

Bilateral renal ultrasounds will be performed to assess for nephrocalcinosis, nephrolithiasis, or other abnormalities. This assessment will be collected at Screening, Week 48 of the Extension Period and every 48 weeks after Week 48 of the Extension Period.

The following renal ultrasound assessment will be summarized:

- Nephrolithiasis presence (Yes, No)
- Nephrolithiasis location (Right kidney, Left kidney, N/A)

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- Nephrocalcinosis grade left kidney (0 = No echogenicity, 1 = Mild echogenicity around medullary pyramid borders, 2 = Moderate echogenicity around and inside pyramids, 3 = Severe echogenicity of entire pyramids)
- Nephrocalcinosis grade right kidney (0 = No echogenicity, 1 = Mild echogenicity around medullary pyramid borders, 2 = Moderate echogenicity around and inside pyramids, 3 = Severe echogenicity of entire pyramids.
- Urolithiasis presence (Yes, No)
- Urolithiasis location right kidney (Renal pelvis, Ureter, N/A)
- Urolithiasis location left kidney (Renal pelvis, Ureter, N/A)

Data will be summarized by count and percent. Shifts from baseline will be additionally summarized for the nephrocalcinosis grade. All data will be presented in a data listing.

3. Carotid Ultrasound

The carotid ultrasound will be collected at Screening (or within two months following the first dose), Week 24 of the Extension Period, Week 48 of the Extension Period and every 48 weeks after Week 48 of the Extension Period. If the assessment is not conducted within the first 2 months following the first dose, the subject will not have the assessment conducted at any time during the study.

Carotid ultrasound will be used to identify intimal medial thickness or other abnormalities.

The following carotid ultrasound assessment will be summarized:

- Average intimal medial thickness far wall (mm) for the following body parts:
    - Posterior (Left, Right)
    - Lateral (Left, Right)
    - Anterior (Left, Right)
- Maximum intimal medial thickness far wall (mm) for the following body parts:
    - Posterior (Left, Right)
    - Lateral (Left, Right)
    - Anterior (Left, Right)
- Minimum intimal medial thickness far wall (mm) for the following body parts:
    - Posterior (Left, Right)
    - Lateral (Left, Right)
    - Anterior (Left, Right)

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- Area (mm^2) for the following body parts:
  - Bulb (Left, Right)
  - Common (Left, Right)
  - Internal (Left, Right)
- Length (mm) for the following body parts:
  - Bulb (Left, Right)
  - Common (Left, Right)
  - Internal (Left, Right)

Data will be summarized by observed, change from baseline and percent change from baseline.

Additional derived variables maybe created for analysis purposes and will include, but not be limited to the following:

Right IMT Average as the average of the 90 posterior right, 120 lateral right and 150 anterior right

Left IMT Average as the average of the 210 anterior left, 240 lateral left and the 270 posterior left

A spaghetti plot for carotid ultrasound assessment by dose cohort will be provided.

All data will be presented in a data listing.

4. Na18F-PET/CT

Na18F-PET/CT will be a full body scan with radioactive tracer that measures neointimal proliferation and calcification in arteries as well as organ calcifications. Subjects will complete up to 3 PET/CTs during the study: at Baseline, Week 48, and EOS, if a PET/CT was not performed within 48 weeks of the EOS Visit.

Data will be presented in a data listing.

B. Ophthalmologic Assessments

An ophthalmological examination will be conducted by study staff qualified in Optical Coherence Tomography, Color Fundus Photography, and Autofluorescence Photography. These will be assessed centrally for abnormalities including but not limited to angioid streaks, choroidal and subretinal neovascularization, and breaks in Bruch's membrane. The BCVA will be determined locally.

The ophthalmologic examination will be collected at Screening, within 1 month of or concurrent with the Week 48 Visit. If conducted outside the context of this

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study, results that meet study requirements in the opinion of the Sponsor within the correct timeframe may be submitted for the Week 48 assessment, and every 48 weeks after Week 96 of the Extension Period.

Results of the ophthalmologic examinations will be presented in a data listing.

1. Optical Coherence Tomography

Optical coherence tomography is an imaging modality that is analogous to ultrasound imaging that uses light instead of sound. Cross-sectional images are generated by measuring the echo time delay and intensity of light that is reflected or backscattered from internal structures in tissue. En face images generated by OCT also allow one to study the spatial relationships between vasculature and adjacent retinal/choroidal layers with precision.

2. Color Fundus Photography

Color fundus photography uses a fundus camera to record color images of the condition of the interior surface of the eye in order to document the presence of disorders and monitor their change over time. A fundus camera or retinal camera is a specialized low power microscope with an attached camera designed to photograph the interior surface of the eye, including the retina, retinal vasculature, optic disc, macula, and posterior pole (ie, the fundus).

3. Autofluorescence Photography

Autofluorescence photography uses the naturally occurring fluorescence from the retina to provide an indicator of RPE (layer of the retina) health. Illuminating the retina with blue light causes certain cellular components to "glow" without injecting any dye. This glow (fluorescence) returning from the retina can be used to create a black-and-white image which can be interpreted by recognizing characteristic patterns.

4. Best Corrected Visual Acuity

Best Corrected Visual Acuity rates an examinee's ability to recognize small details with precision. This assessment will be performed locally using Early Treatment Diabetic Retinopathy Study letter charts.

C. Cardiovascular and Peripheral Vascular Reactivity Assessments

PXE patients are at high risk of vascular disease, especially peripheral artery disease and cerebrovascular disease, which is thought to be the result of a proposed unique type of arterial wall disease. Baseline assessments of vascular

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disease will include the following: arterial stiffness as measured by carotid-femoral PWV, carotid ultrasound for intimal media thickness, lower limb intermittent claudication using ABI, and the Edinburgh Claudication Questionnaire (ECQ).

1. Pulse Wave Velocity

Pulse wave velocity (PWV) is a non-invasive method to measure the degree of arterial wall stiffness by determining the rate at which the pulse pressure propagates down the vessel (typically carotid to femoral velocity). Arterial stiffness measured by PWV is a predictor of future cardiovascular events and all-cause mortality independent of conventional cardiovascular risk factors.

The pulse wave will be collected at Screening, Week 24 of the Extension Period, Week 48 of the Extension Period and every 24 weeks after week 48 of the Extension Period.

The pulse wave velocity assessment will be summarized descriptively for the observed, change and percent change from baseline by dose cohort and overall.
A spaghetti plot for each pulse wave assessment by dose cohort will be provided.

All data will be presented in data listings.

2. Ankle-Brachial Pressure Index

The Ankle-Brachial Pressure Index will be performed by measuring the systolic blood pressure from both brachial arteries and from both the dorsalis pedis and posterior tibial arteries to compare blood pressure in the upper and lower extremities and identify areas of diminished blood flow.

The ankle-brachia pressure index will be collected at Screening, Week 24 of the Extension Period, and Week 48 of the Extension Period and every 24 weeks after Week 48 of the Extension Period.

The following ankle-brachial pressure index assessments will be collected for this study:

- Systolic blood pressure of the right dorsalis pedis (DP) artery (mmHg)
- Systolic blood pressure of the right posterior tibial (PT) artery (mmHg)
- Systolic recumbent blood pressure of right brachial artery (mmHg)
- Systolic blood pressure of the left dorsalis pedis (DP) artery (mmHg)

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- Systolic blood pressure of the left posterior tibial (PT) artery (mmHg)
- Systolic recumbent blood pressure of left brachial artery (mmHg)
- Ankle-Brachial Pressure Index Result

The ankle brachial pressure index assessments will be summarized descriptively for the observed, change and percent change from baseline by dose cohort and overall.

A spaghetti plot for each ankle-brachial pressure index assessment by dose cohort will be provided.

All data will be presented in data listings.

D. Patient, Clinician, and Caregiver Reported Outcomes

All patient reported outcomes will be completed by the subject without assistance unless the subject has visual impairment, which necessitates that the assessment be administered verbally by qualified site staff.

1. Clinical Global Impression Scales

The clinical global impression scales will be collected at Screening, Weeks 12, 24, 36, 48 of the Extension Period and every 24 weeks after Week 48 of the Extension Period.

The Clinical Global Impression of Status/Severity (CGI-S) will be completed by the Investigator at Screening. During the Extension Period, the Investigator will complete the Clinical Global Impression of Improvement (CGI-I) at scheduled time points.

The findings will be summarized by counts and percentages at each scheduled visit by dose cohort and overall. All data will be provided in a data listing.

2. Patient Global Impression Scales

The clinical global impression scales will be collected at Screening, Weeks 12, 24, 36, 48 of the Extension Period and every 24 weeks after Week 48 of the Extension Period.

The Patient Global Impression of Status/Severity (PGI-S) will be completed by the subject at Screening. During the Extension Period, the Patient Global Impression of Improvement (PGI-I) will be completed at scheduled time points.

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The findings will be summarized by counts and percentages at each scheduled visit by dose cohort and overall. All data will be provided in a data listing.

3. Caregiver Global Impression Scales

The clinical global impression scales will be collected at Screening, Weeks 12, 24, 36, 48 of the Extension Period and every 24 weeks after Week 48 of the Extension Period.

The Caregiver Global Impression of Status/Severity (CaGI-S) will be completed by the subject's caregiver at Screening, if applicable. During the Extension Period, the Caregiver Global Impression of Improvement (CaGI-I) will be completed at scheduled time points.

The findings will be summarized by counts and percentages at each scheduled visit by cohort and overall. All data will be provided in a data listing.

4. Patient Reported Outcomes Measurement Information System (PROMIS)

The PROMIS will be collected at Screening, Week 12 of the Extension Period, Week 24 of the Extension Period, Week 36 of the Extension Period, Week 48 of the Extension Period and every 24 weeks after Week 48 of the Extension Period.

PROMIS scales will include the Pain Interference, Pain Intensity, Physical Function-Upper Extremity, Physical Function-Mobility, Fatigue, and Cognitive Function. These assessments will be completed by the subject without assistance. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. The derivation of the PROMIS scales Physical Function-Upper Extremity and Pain Intensity will follow the directions as outlined in Appendix 2. The t-score for the Physical Function-Upper Extremity will not be produced nor analyzed.

Each scale of the PROMIS assessment will summarize the raw score, t-score and change from baseline of the raw and t-score by dose cohort and overall as applicable.

A spaghetti plot for each PROMIS assessment with a t-score by dose cohort will be provided.

The raw and standardized results of the PROMIS will be presented in a data listing.

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5. Vision Function Questionnaire

The VFQ-25 will be collected at Screening, Week 12 of the Extension Period, Week 24 of the Extension Period, Week 36 of the Extension Period, Week 48 of the Extension Period and every 24 weeks after Week 48 of the Extension Period.

The sub-scales target vision specific challenges and include the following: global vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral and color vision and ocular pain. There is also a single question that asks the respondent to rate their overall health. Scores range from 0 to 100, with higher scores representing higher functioning.

The Vision Function Questionnaire assessments will be summarized descriptively for the observed, change and percent change from baseline by dose cohort and overall.

The VF-25 Composite Global Score is calculated by taking the average of the 11 vision targeted sub-scale scores where the General Health Sub-Scale is not included.

The categorical result will be summarized by dose cohort and overall.

All data will be provided in data listings.

6. Work Productivity and Activity Impairment (WPAI) Questionnaire

The WPAI questionnaire will be collected at Screening, Week 12 of the Extension Period, Week 24 of the Extension Period, Week 36 of the Extension Period and Week 48 of the Extension Period, and every 24 weeks after Week 48 of the Extension Period.

The WPAI will assess the impact of ENPP1 deficiency on a subject's employment status and ability to work and will be collected at scheduled timepoints. This data will be summarized descriptively by dose cohort and overall.

All data will be provided in data listings.

7. Edinburgh Claudication Questionnaire (ECQ)

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The ECQ will be collected at Screening, Week 12 of the Extension Period, Week 24 of the Extension Period, Week 36 of the Extension Period and Week 48 of the Extension Period, and every 24 weeks after Week 48 of the Extension Period.

Patient assessment of the symptoms of lower limb intermittent claudication are detected using the ECQ administered by the Investigators and scored as "asymptomatic" or "symptomatic."

Number and percentages will be provided by dose cohort and overall.

All data will be provided in data listings.

X. Safety Analyses

Analysis of the safety data will be performed on the Safety Analysis Set. Data will be summarized by dose cohort and overall. In general, analysis by timepoint will only be performed on scheduled assessment visits. Unscheduled assessments will only be included for the derivation of baseline where applicable.

A. Tolerability and Exposure

Tolerability and exposure to INZ-701 will be determined using the dosing data entered on the "Drug Administration - INZ-701" and "Study Drug Self Administration" eCRF page and will be summarized by dose cohort and overall and presented in data listing for the Safety Analysis Set.

The following exposure measures will be summarized for the Dose Evaluation Period, Extension Period and overall:

- Total cumulative dose (mg/kg), defined as the sum of the doses administered. Presented only for the Dose Evaluation Period.
- Total cumulative dose (mg), defined as the total cumulative dose (mg/kg) multiplied by the subject's weight (kg) at Day 1. Presented only for the Dose Evaluation Period.
- Duration of dosing (weeks), defined as (date of last dose of study drug – date of first dose of study drug + 1)/7.
- Total exposure (weeks) defined as (Last date of study period-first dose date +1)/7.
- Total volume of dose administered (mL), defined as the sum of the doses administered.
- Dose intensity (mg/kg/week), defined as (sum of total cumulative dose (mg/kg))/ (duration of dosing (week)). Presented only for the Dose Evaluation Period.
- Compliance for Dose Evaluation Period (%) = (Total cumulative dose of

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the Dose Evaluation Period/Total dose planned to be received) * 100. The planned dose for the Dose Evaluation Period is 1.6 mg/kg, 4.8 mg/kg, and 14.4 mg/kg for the cohorts respectively. Presented only for the Dose Evaluation Period.

Compliance will be summarized as a continuous variable as well as a categorical variable for the categories of <80% and ≥ 80%.

INZ-701 administration, including dose modifications will be summarized and listed by dose cohort and overall for the Dose Evaluation Period.

- Number and percentage of subjects with any dose held by reason.
- Number and percentage of subjects with drug permanently withdrawn by reason.

Details of study drug administration will be presented in data listings.

B. Adverse Events

Adverse Events (AEs) will be documented on the 'Adverse Event' eCRF page and monitored continuously throughout the study from the time of informed consent until 30 days after the subject's last dose of INZ-701.

Treatment-Emergent AEs (TEAEs) are defined as AEs with an onset date on or after the first dose of INZ-701, and within 30 days of the last dose of INZ-701.

The AEs will be coded using MedDRA (Version 23.1).

Severity of AEs are graded using National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. AE summaries includes by the maximum CTCAE grade for the item being summarized (ie, System Organ Class [SOC] or Preferred Term [PT]). In these cases, the outputs will include a row for 'All Grades' as well as rows for the 5 potential CTCAE grades, 'Grade 1 (Mild)', 'Grade 2 (Moderate)', 'Grade 3 (Severe)', 'Grade 4 (Life threatening or disabling)', or 'Grade 5 (Death)'. AEs missing a severity grade will be imputed as 'Grade 3 (Severe)' unless the outcome is fatal in which case it will be imputed as 'Grade 5 (Death)'. An AE reported by a subject more than once will be represented in the most severe category.

TEAEs will be categorized as 'Related' or 'Not Related' to study drug. AEs missing relationship status will be imputed as 'Related' in the related TEAE tables and listings.

Based on experience with other enzyme replacement therapies, hypersensitivity reactions, including anaphylaxis, and injection site reactions determined to be

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related to hypersensitivity will be considered as AESI. Additionally, seizure will be considered an AESI.

The determination of hypersensitivity will be identified by a list of preferred terms that will be finalized prior to the database lock.

An overall summary of number and percentage of subjects with at least 1 of the categories described below will be provided by dose cohort and overall.

- All AEs
- All TEAEs
  - TEAEs related to study drug
  - TEAEs with CTCAE grade 3 or higher
  - TEAEs with dose limiting toxicity
  - TEAEs leading to study drug discontinuation
  - TEAE of special interest
  - TEAE associated with hypersensitivity
  - TEASs associated with injection site reactions
- TEAEs by maximum relationship to study drug
  - Related
  - Not Related
- TEAEs by maximum CTCAE grade
  - Grade 1 - mild
  - Grade 2 - moderate
  - Grade 3 - severe
  - Grade 4 - potentially life threatening
  - Grade 5 – death
- Treatment-related TEAEs by maximum CTCAE grade
  - Grade 1 - mild
  - Grade 2 - moderate
  - Grade 3 - severe
  - Grade 4 - potentially life threatening
  - Grade 5 – death
- All serious AEs (SAEs)
  - SAEs related to study drug
  - SAEs with outcome fatal
- All serious TEAEs
  - Serious TEAEs related to study drug
  - Serious TEAEs with outcome fatal

The counts and percentages will be summarized for each PT and SOC by cohort and overall. Additional summaries will also be provided by relationship to study drug and CTCAE grade. A subject reporting multiple cases of the same TEAE will be counted once within each system organ class, preferred term and will be counted once under the strongest relationship to study drug or worst severity grade.

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Below is a list of the AE summary tables:

- All TEAEs
- TEAEs leading to permanent study drug discontinuation
- TEAEs of special interest
- Treatment-related TEAEs
- TEAEs associated with hypersensitivity
- TEAEs associated with injection site reactions
- TEAEs with dose interruption
- TEAEs by maximum relationship to study drug
- TEAEs by maximum CTCAE grade
- Treatment-emergent serious adverse events

The counts and percentages of injection site reaction TEAE will be summarized by the maximum CTCAE grade by week. The injection site reaction TEAE will be identified by the text "Injection" in the verbatim term.

The following listings will be produced:

- All AEs
- Treatment-related TEAEs
- TEAEs of special interest
- TEAEs with dose interrupted or discontinued study drug.
- SAEs leading to death

C. Clinical Laboratory Results

Laboratory tests will include the results of following categories:

- Hematology
- Chemistry, Liver Function and Metabolism
- Electrolytes and Kidney Function
- Urinalysis
- Urine Chemistry
- Mineral Metabolism
- Serology
- Exploratory Biomarkers

The ratio of tubular maximum reabsorption of phosphate (TmP) to GFR is used to evaluate renal phosphate transport. TMP/GFR derivation includes serum and urine test where the serum creatinine and phosphate are collected less than 2 hours from the time the urine creatinine and phosphate samples have been collected. The derivation of TMP/GFR is as following:

Step 1: Calculate the ratio of phosphate clearance to creatinine clearance

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$$\frac{Cp}{CCR} = \frac{Serum\ Creatinine * Urine\ phosphate}{Urine\ creatine * Serum\ phosphate}$$

Step 2: Subtract this fraction from 1.0 to give the fractional tubular reabsorption of phosphate (TRP)

$$TRP = 1 - \frac{Serum\ Creatinine * Urine\ phosphate}{Urine\ creatine * Serum\ phosphate}$$

Step 3: If TRP is ≤ 0.86 then phosphate reabsorption is maximal and there is a linear relationship between plasma phosphate concentration and excretion and TmP/GFR which is calculated by:

$$\mathrm{TmP/GFR} = \mathrm{TRP} * \mathrm{serum\ phosphate}$$

Step 4: If TRP is > 0.86 relationship between plasma phosphate concentration and excretion is curvilinear and TmP/GFR is defined as follows:

$$\mathrm{TmP/GFR} = \alpha * \mathrm{serum\ phosphate}$$

Where

$$\alpha = \frac{0.3 * TRP}{1 - (0.8 * trp)}$$

Summaries of on-treatment observed, change from baseline and percent change from baseline will be presented by dose cohort and overall for each assessment time point. Change from baseline will be calculated as the post-baseline measurement minus the baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary. The count and percentages will be presented for the categorical urinalysis parameters by dose cohort and overall for each assessment timepoints. Additionally, spaghetti figures for TmP/GFR, serum calcium and serum phosphate will be provided.

Clinical laboratory values will be converted to US conventional and SI units (Appendix 1). Potentially clinically significant (PCS) values are defined as abnormal values according to predefined criteria/thresholds. The incidence of PCS, and specifically new-onset, will be summarized by dose cohort and overall for each visit as well as across all post-baseline visits. New onset of PCS is defined as an assessment that meets the PCS criteria, yet the previous non-missing assessment did not.

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PCS criteria for Laboratory Parameters

Test/Panel	Age	Sex	Client-Defined Alerts- Conventional			Client-Defined Alerts- SI			Suggestions for labs not included in the Lab Alert Manual	
			Alert Low	Alert High	Units	Alert Low	Alert High	Units	PCS Low	PCS High
Alanine aminotransferase (ALT)	Adult >=18y	M	N/A	89**	U/L	N/A	89**	U/L		
		F	N/A	67**	U/L	N/A	67**	U/L		
Alkaline phosphatase	Adult >=18y	M	N/A	259**	U/L	N/A	259**	U/L		
		F	N/A	197**	U/L	N/A	197**	U/L		
Aspartate aminotransferase (AST)	Adult >=18y	M	N/A	79**	U/L	N/A	79**	U/L		
		F	N/A	69**	U/L	N/A	69**	U/L		
Bicarbonate	Adult >=18y	M/F	14**	41**	mmol/L	14**	41**	mmol/L		
Bilirubin, total	Adult >=18y	M/F	N/A	2.5**	mg/dL	N/A	41.1**	umol/L		
Creatinine	Adult >=18y	M	N/A	1.59**	mg/dL	N/A	140**	umol/L		
		F	N/A	1.25**	mg/dL	N/A	110**	umol/L		
Glucose, Fasting	Adult >=18y	M/F	31**	400**	mg/dL	1.6**	20.1**	mmol/L		
Phosphate	Adult >=18y	M/F	0.6**	9.5**	mg/dL	0.22**	3.05**	mmol/L		
White blood cells	Adult >=18y	M/F	1.9**	22.1**	10^3/uL	1.9**	22.1**	10^9/L		
Parathyroid hormone, intact	Adult >=18y	M/F	14.7**	105.1**	pg/mL	1.56**	11.3**	pmol/L		
Vitamin D 25 Hydroxy Total	Adult >=18y	M/F	N/A	123**	ng/mL	N/A	300.1**	nmol/L		
Vitamin D, 1,25 (OH)2, Total	Adult >=18y	M/F	N/A	89**	pg/mL	N/A	89**	pg/mL		
Amylase	Adult >=18y								N/A	3 x ULN
Lipase	Adult >=18y								N/A	3 x ULN
Total thyroxine (T4)	Adult >=18y								<4.0 mcg/dL	>13.0 mcg/dL
Total cholesterol	Adult >=18y								N/A	>300 mg/dL
Triglycerides	Adult >=18y								N/A	>400 mg/dL
White blood cell (WBC) count	Adult >=18y								<4.0 x 10^3/mm3	>16 x 10^3/mm3
Hemoglobin	Adult >=18y								<10 g/dL	>16.0 g/dL
Hematocrit	Adult >=18y								<34%	>54%
Platelet count	Adult >=18y								<70 x 10^3/mm3	>400 x 10^3/mm3

Listings will be provided for the PCS laboratory assessments.
If there are observations meeting Hy's Law criteria, the evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) graphs of the Hy's law will be presented

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across all dose cohort with the maximum total bilirubin in y-axis vs. maximum ALT, AST, or combined ALT and AST in the x-axis.

Results from pregnancy, COVID-19 test, HIV, Hepatitis B and Hepatitis C will be collected at screening and provided in data listings.

D. Vital Signs

Vital signs (including height (cm), weight (kg), temperature (method oral or tympanis) (C^o), heart rate (beats/min), respiratory rate (breaths/min), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg)) will be presented in summary tables as observed and change from baseline for each dose cohort at each scheduled assessment. The change from baseline will be calculated as the post-baseline measurement minus the baseline measurement. If either the baseline or post-baseline value is missing, then the observation will not be included in the change from baseline summary.

The incidence of PCS and specifically new-onset, will be summarized by dose cohort and overall for each visit as well as across all post-baseline visits.

Listings will be provided for PCS vital signs.

PCS criteria for Vital Signs

Vital Sign	PCS Low	PCS High
Sitting SBP (mm Hg) Ages >18 years	<100 mm Hg OR a decrease of 20 mm Hg or more from baseline	>180 mm Hg OR an increase of 25 mm Hg or more from baseline
Sitting DBP (mm Hg) Ages >18 years	<40 mm Hg OR a decrease of 20 mm Hg or more from baseline	>110 mm Hg OR an increase of 25 mm Hg or more from baseline
Heart rate	<40 bpm	>120 bpm

E. Physical Examination

All physical examination data will be listed.

F. Prior and Concomitant Medications

All medications including any drug (investigational, prescription, or over-the-counter), biological product (such as vaccines, blood, or blood components), herbal remedies or preparations, and supplements received 4 weeks prior to first dose of INZ-701 and throughout the study will be coded using the Sep2020 version of WHO Drug. Prior medications are defined as any medication that stopped before the date of first dose of study drug. Concomitant medications are

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defined as any medication that were ongoing or ended at the date of first dose, or any medication that started on or after the date of first dose.

Concomitant medications will be summarized by Anatomical Therapeutic Class (ATC) level 2 and preferred drug name by dose cohort and overall based on the safety analysis set. A subject having more than one medication within the same ATC Level 2 or preferred drug name will be counted only once for that ATC Level 2 or preferred drug name.

All medications (prior and concomitant) will be listed.

G. Prior and Concomitant Procedure

Prior and concomitant procedures will be collected on the "Concomitant Procedures" eCRF page and coded using MedDRA (Version 23.1). Prior procedures are defined as any procedure that stopped before the date of the first dose of study drug. Concomitant procedures are defined as any procedures that were ongoing or ended at the date of first dose, or any procedure that started on or after the date of first dose.

Concomitant procedures will be summarized by System Organ Class (SOC) and preferred term by dose cohort and overall based on the Safety Analysis Set. A subject having more than one procedure within the same SOC or PT will be counted only once for that SOC or PT.

All procedures (prior and concomitant) will be listed.

H. Electrocardiogram (ECGs)

ECG aggregate parameters (PR interval, RR interval, QRS interval, QT interval, QTcB interval, QTcF interval) and mean heart rate (HR) will be summarized as observed and change from baseline for each assessment timepoints by dose cohort and overall. All ECG results will be presented in data listing.

PCS criteria for ECG parameters

Parameter	**PCS Low**	**PCS High**
PR Interval	None	1) >200 ms only OR 2) increase from baseline ≥20 ms only OR 3) >200 ms and increase from baseline ≥20 ms
QRS Interval	None	1) >100 ms only OR 2) increase from baseline ≥10 ms only OR 3) >100 ms and increase from baseline ≥10 ms

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Parameter	PCS Low	PCS High
QT Interval	None	1) >450 ms only OR 2) increase from baseline ≥60 ms only OR 3) >450 ms and increase from baseline ≥60 ms
QTcF and QTcB Interval	None	1) >450 ms only OR 2) increase from baseline ≥60 ms only OR 3) >450 ms and increase from baseline ≥60 ms

The incidence of PCS and specifically new-onset, will be summarized by dose cohort and overall for each visit as well as across all post-baseline visits.

I. Immunogenicity

Anti-Drug antibody (ADA) results and Neutralizing Anti-Drug Antibody (nAb) status will be presented in a summary table by dose cohort and overall. Data listings will also be presented.

Immunogenicity testing will utilize a multi-tiered approach; if ADAs are detected in the initial screen, a confirmatory test will be run to determine specificity and subtypes. Samples may also be used to assess and further establish assays for specificity confirmation (ie, titer) and neutralizing antibodies.

Summary ADA results will be presented categorically by dose cohort for key immunogenicity parameters according to the definition below:

Category Definitions

- **Evaluable Subjects**: the percentage of subjects who had at least 1 baseline and 1 post dose sample analyzed.
- **Unevaluable Subjects**: percentage of patients with no ADA sample or no post-treatment sample.
- **ADA Positive Subjects**: percentage of subjects who had at least 1 confirmed ADA positive sample.
- **Neutralizing ADA Positive Subjects:** percentage of patients with at least 1 nAb positive sample.
- **Subjects with Pre-Existing ADA**: percentage of subjects with an ADA positive baseline sample.
- **Treatment Induced ADA Response**: percentage of subjects with an ADA negative baseline and at least 1 ADA positive post-treatment sample.
- **Transient ADA Response**: percentage of subjects with a treatment induced ADA response detected at only one sampling time point during

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treatment or follow-up period. If the single sampling time point was the last sampling timepoint, it cannot be defined as conclusively transient in nature and will not be counted as a transient ADA response.

- **Persistent ADA Response**: percentage of subjects with a treatment induced ADA response detected at 2 or more sampling time points during treatment.

J. Hypersensitivity

In the event of severe hypersensitivity reactions, including anaphylaxis, blood samples will be collected for the following assessment:

- IgE (IU/mL)
- IgG (g/L)
- Serum tryptase (mcg/L)
- Serum histamine (pg/mL)
- Complement activation (C3, C4) (g/L)
- Acute phase reactants (to include, at minimum C-reactive protein (mg/L))

All hypersensitivity data will be presented in a data listing.

K. Holter Monitoring and/or Cardiac Telemetry

Holter Monitoring and/or Cardiac Telemetry should be obtained if required per site specific procedures and/or Investigator discretion. If collected, they will be interpreted locally. Cardiac telemetry, if performed, will be collected on Day 1, beginning pre-dose and continuing through 24 hours post-dose.

The findings will be summarized by counts and percentages at each scheduled visit by cohort and overall. All data will be provided in a data listing.

XI. Pharmacokinetic Analysis

A. General Considerations

Derivation of the PK parameters for INZ-701 in serum will be the responsibility of the clinical pharmacokineticist at an external vendor contracted to perform the analyses. This data will be transferred to be include in PK, PD, and safety summaries, figures, and data listings.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

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B. Serum Concentration Data

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters. A minimum of 3 quantifiable concentration-time data points will be required for calculation of PK parameters.

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided.

Serum concentrations will be summarized using descriptive statistics by Cohort and Day. Concentrations that are below the limit of quantitation (BLQ) will be treated as 0 for the computation of descriptive statistics. Samples that are collected outside predetermined windows as specified below will be excluded from the concentration summary but included in the calculation of PK parameters.

Study Day	**Sampling Time Point**	
	ENPP1 specific activity and INZ-701 PK (serum sample)[b]	**PPi [a, b] (plasma sample)**
Screening (Day -30 to -1)	Not Applicable	Single sample
1 to 7 **Note: Days 2 to 7 are not treatment days**	Pre-dose (Day 1 only) Post-dose (Days 1 to 7): 1 hour (±15 min), 2 hours (±15 min), 3 hours (±15 min), 6 hours (±30 min), 12 hours (±30 min), 24 hours (±1 hour), 48 hours (±1 hour), 72 hours (±3 hours), 96 hours (±3 hours), 120 hours (±3 hours), and 144 hours (±3 hours)	Day 1: Pre-dose and 6 hours (± 30 min) post-dose Days 2 to 7: Single sample
8, 11, 15, 18, 22, 25	Pre-dose	Pre-dose
29 to 31 **Note: Days 30 to 31 are not treatment days**	Pre-dose (Day 29) Post-dose (Days 29 to 31): 1 hour (±15 min), 3 hours (±15 min), 6 hours (±30 min), 12 hours (±30 min), 24 hours (±1 hour), 48 hours (±1 hour)	Day 29: Pre-dose and 6 hours (± 30 min) post-dose Days 30 to 31: Single sample
Day 32	Single sample	Single sample
For Subjects Participating in the Extension Period		
Through Week 48	Single sample at Weeks 8, 12, 24, 36, and 48	Single sample at Weeks 8, 12, 24, 36, and 48
After Week 48		Single sample every 12 weeks (for in clinic visits only)

A subject listing of all concentration-time data for each treatment will be presented. Figures of arithmetic mean concentration-time data (±SD on linear scale, as appropriate) will be presented by Day on linear and semi-logarithmic scales. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales. Individual concentrations which are BLQ

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will be displayed as 0 in the graphic presentations on linear scale; but will not be plotted on semi-logarithmic scale. Means which fall below the lower limit of quantitation (LLOQ) will not be displayed.

C. Serum Pharmacokinetic Parameters

For PK parameter calculations, pre-dose samples that are BLQ or missing will be assigned a numerical value of 0. Any other BLQ concentrations will be assigned a value of 0 if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of 0 makes sense, or if exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be treated as 0. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration-time curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile. Any missing concentrations post-dose will not be imputed.

Any anomalous concentration values observed at predose on Day 1 of the Dose Evaluation Period will be identified in the CSR and used for the computation of PK parameters. If the anomalous concentration is greater than 5.00% of C_{max} (when rounded to 3 significant digits), the PK parameters for the affected subject profile will be calculated and reported in the listing. The affected profile will be evaluated to determine whether exclusion of the derived PK parameters from summary or inferential statistics is warranted. The PK concentrations of the affected profile will be handled in the same manner as the calculated PK parameters.

The following serum PK parameters will be estimated for INZ-701 for the Dose Evaluation Period on Day 1 and Day 29 by non-compartmental methods using actual elapsed time from dosing (rounded to 2 decimal places), whereas nominal times will be used in the DSMB PK analysis. The derived dose in mg will be used for calculation of INZ-701 dose-dependent PK parameters (CL/F and V_z/F, etc.).

C_{max}	Maximum concentration obtained directly from the observed concentration versus time data.
C_{max}/Dose	Dose-normalized C_{max}, calculated using the actual dose administered (mg).
T_{max}	Time of maximum concentration, obtained directly from the observed concentration versus time data.

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T_{lag}	Lag time before observation of quantifiable concentrations, obtained directly from the observed concentration versus time data.
C_{min}	Minimum concentration after multiple dosing, obtained directly from the observed concentration versus time data.
C_{avg}	Average concentration over the dosing interval tau, calculated as AUC_{tau} divided by the dosing interval, tau. Actual elapsed time at the end of the dosing interval will be used for the calculation. Calculated on Day 29 only
%Fluct	Percent fluctuation, calculated as $[(C_{max}-C_{min})/C_{avg}]\times100$. Calculated on Day 29 only
AUC_{last}	Area under the concentration-time curve from zero (predose) to time of last quantifiable concentration. • On Day 1, AUC_{last} is calculated up to the Day 8 pre-dose (168 hours post Day 1 dose) sample. • On Day 29, AUC_{last} is calculated up to the Day 32 pre-dose (72 hours post Day 29 dose) sample.
AUC_{last}/Dose	Dose-normalized AUC_{last}, calculated using the actual dose administered (mg).
AUC_{tau}	Area under the concentration-time curve during a dosing interval "tau" (= 72 hours). Actual elapsed time at the end of the dosing interval will be used for the calculation. Calculated on Day 29 only.
AUC_{tau}/Dose	Dose-normalized AUC_{tau}, calculated using the actual dose administered (mg).
AUC_{0-72}	Area under the concentration-time curve from zero (predose) until 72 hours postdose. Calculated on Day 1 only.
AUC_{0-72}/Dose	Dose-normalized AUC_{0-72}, calculated using the actual dose administered (mg).
RAUC	Accumulation ratio, calculated for AUC_{tau} as $[AUC_{tau,Day\ 29}/AUC_{0-72,Day\ 1}]$.
RC_{max}	Accumulation ratio, calculated for C_{max} as $(C_{max,Day\ 29}/C_{max,\ Day\ 1})$.
λ_z	Apparent terminal rate constant, determined by linear regression of the terminal points of the log-linear concentration-time curve. Phoenix best fit method combined with visual assessment will be used to identify the terminal linear phase of the concentration-time profile.

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$T_{1/2}$	Apparent terminal half-life, determined as ln2/λ_z.
CL/F	Apparent systemic clearance after subcutaneous dosing, calculated as ▪ Dose divided by AUC_{inf} on Day 1 ▪ Dose divided by AUC_{tau} on Day 29
V_z/F	Apparent volume of distribution following subcutaneous dosing, calculated as CL/F divided by λ_z.
LI	Linearity index, calculated as [$AUC_{tau,Day\ 29}$/$AUC_{inf,Day\ 1}$].

Area under the concentration-time curve will be calculated by linear up/log down trapezoidal summation.

The following PK parameters will be calculated for diagnostic purposes and listed but will not be summarized.

$T_{1/2}$, Interval	The time interval (h) of the log-linear regression to determine λ_z.
$T_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z. A minimum of 3 data points will be used for determination.
Rsq_adj	Goodness of fit statistic for calculation of λ_z. If the Rsq_adj value is less than 0.800 (when rounded to 3 significant figures), λ_z and related parameters will be listed but not included in descriptive and inferential statistics.
$\%AUC_{ex}$	Percentage of AUC_{inf} obtained by extrapolation, calculated as [(AUC_{inf} - AUC_{last})/AUC_{inf}×100]. If the $\%AUC_{ex}$ is greater than 20.0% of AUC_{inf} (when rounded to 3 significant figures), then AUC_{inf} and related parameters will be listed but not included in summary and inferential statistics.

Pharmacokinetic parameters will be summarized by dose cohort and day using descriptive statistics. A subject listing of individual PK parameters for each cohort will be provided.

Scatter plots of dose-normalized AUC_{last} and C_{max} versus dose will be presented. Steady state evaluation will be performed based on visual inspection of the mean INZ-701 serum trough concentration versus time plot. Additionally, graphical presentations of PK data may be added at the discretion of the PK pharmacokineticist, if further illustration of the PK results is deemed appropriate.

Primary PK variables include AUC_{last} and C_{max}. All other parameters are secondary variables.

Assessment of Dose Proportionality

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The dose proportionality of the primary PK parameters AUC_{last} and C_{max} over the administered dose range on Day 1 and Day 29 will be investigated using the following power model:

log (parameter) = a + b * log (dose)
where ‘a’ is the intercept and ‘b’ is the slope.

The intercept ‘a’ and the slope ‘b’ together with 90% confidence intervals will be estimated using least-squares (LS) regression or an equivalent method and presented for each primary PK parameter. A minimum of 3 values per dose must be available for a given parameter to estimate dose proportionality with the power model. Dose proportionality analysis will not be performed for the secondary PK parameters.

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Appendix 1- Clinical Safety Laboratory Assessments

Chemistry, Liver Function and Metabolism (SI) (US conventional unit if applicable)

Alanine Aminotransferase (ALT) (SI unit IU/L)
Albumin (ALB) (SI unit g/L) and (Conventional unit g/dL)
Amylase (AMYLASE) (SI unit IU/L)
Aspartate Aminotransferase (AST) (SI unit IU/L)
Bilirubin (BILI) (SI unit umol/L) and (Conventional unit mg/dL)
Cholesterol (CHOL) (SI unit mmol/L) and (Conventional unit mg/dL)
Creatine Kinase (CK) (SI unit IU/L)
Direct Bilirubin (BILDIR) (SI unit umol/L) and (Conventional unit mg/dL)
Ferritin (FERRITIN) (SI unit ug/L)
Gamma Glutamyl Transferase (GGT) (SI unit IU/L)
Iron (IRON) (SI unit umol/L)
Lactate Dehydrogenase (LDH) (SI unit IU/L)
Lipase (LIPASET) (SI unit IU/L)
Protein (PROT) (SI unit g/L) and (Conventional unit g/dL)
Transferrin (TFERRIN) (SI unit g/L)
Transferrin Saturation (TFRRNSAT) (SI unit %)
Triglycerides (TRIG) (SI unit mmol/L) and (Conventional unit mg/dL)
Urate (URATE) (SI unit umol/L) and (Conventional unit mg/dL)

Urine Chemistry (SI) (US conventional unit if applicable)

24hr Urine Calcium (UCA) (SI unit mmol/day) and (Conventional unit mg/24hr)
24hr Urine Creatinine (URCR) (SI unit mmol/day) and (Conventional unit mg/24hr)
24hr Urine Phosphate (UPHO) (SI unit mmol/day) and (Conventional unit g/24hr)
24hr Urine Volume (UVOL) (SI unit mL/day) and (Conventional unit mL/24hr)
Calcium, Random Urine (CARAUR) (SI unit mmol/L) and (Conventional unit mg/dL)
Creatinine, Random Urine (CREARAUR) (SI unit mmol/L) and (Conventional unit mg/dL)
Phosphorus, Random Urine (PHOSRAUR) (SI unit mmol/L) and (Conventional unit mg/dL)
TMP/GFR (TMP) (SI unit mmol/L) and (Conventional unit mg/dL)
TMP/GFR TPR (TMPTRP) (SI unit mL/min/1.73m2)

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Electrolytes and Kidney Function (SI) (US conventional unit if applicable)

Bicarbonate (BICARB) (SI unit mmol/L)
Chloride (CL) (SI unit mmol/L)
Creatinine (CREAT) (SI unit umol/L) and (Conventional unit mg/dL)
Glomerular Filtration Rate, Estimated (GFRE) (SI unit mL/min/1.73m2)
Potassium (K) (SI unit mmol/L)
Random Blood Glucose (SST) (TGL) (SI unit mmol/L) and (Conventional unit mg/dL)
Sodium (SODIUM) (SI unit mmol/L)
Urea Nitrogen (UREAN) (SI unit mmol/L) and (Conventional unit mg/dL)

Exploratory Biomarkers (SI) (US conventional unit if applicable)

Beta-2 Microglobulin (B2MICG) (SI unit mg/L) and (Conventional unit mg/dL)
C Reactive Protein (CRP) (SI unit mg/L) and (Conventional unit mg/dL)
C-Terminal Telopeptide (CTX) (SI unit ng/L) and (Conventional unit pg/mL)
Calcium, Ionized (CAION) (SI unit mmol/L) and (Conventional unit mg/dL)
Complement C3 (C3) (SI unit g/L) and (Conventional unit mg/dL)
Complement C4 (C4) (SI unit g/L) and (Conventional unit mg/dL)
Fibroblast Growth Factor 23, C-Terminal (FGF23C) (SI unit RU/mL)
Fibroblast Growth Factor 23, Intact (FGF23I) (SI unit ng/L) and (Conventional unit pg/mL)
Immunoglobulin E (IGE) (SI unit IU/mL)
Immunoglobulin G (IGG) (SI unit g/L) and (Conventional unit mg/dL)
Osteopontin (OPN) (SI unit ug/L) and (Conventional unit ng/mL)
Procollagen 1 N-Terminal Propeptide (P1NP) (SI unit ug/L) and (Conventional unit ng/mL)
Tryptase (TRYPTASE) (SI unit mcg/L)

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Hematology (SI) (US conventional unit if applicable)

Basophils (BASO) (SI unit 10^9/L) and (Conventional unit 10^3/uL)
Basophils/Leukocytes (BASOLE) (SI unit %)
Blasts (BLAST) (SI unit %)
Eosinophils (EOS) (SI unit 10^9/L) and (Conventional unit 10^3/uL)
Eosinophils/Leukocytes (EOSLE) (SI unit %)
Erythrocyte Sedimentation Rate (ESR) (SI unit mm/h)
Erythrocytes (RBC) (SI unit 10^12/L) and (Conventional unit 10^6/uL)
Hematocrit (HCT) (SI unit %)
Hemoglobin (HGB) (SI unit g/L) and (Conventional unit g/dL)
Leukocytes (WBC) (SI unit 10^9/L) and (Conventional unit 10^3/uL)
Lymphocytes (LYM) (SI unit 10^9/L) and (Conventional unit 10^3/uL)
Lymphocytes/Leukocytes (LYMLE) (SI unit %)
Metamyelocytes (METAMY) (SI unit %)
Monocytes (MONO) (SI unit 10^9/L) and (Conventional unit 10^3/uL)
Monocytes/Leukocytes (MONOLE) (SI unit %)
Myelocytes (MYCY) (SI unit %)
Neutrophils (NEUT) (SI unit 10^9/L) and (Conventional unit 10^3/uL)
Neutrophils Band Form/Leukocytes (NEUTBLE) (SI unit %)
Neutrophils, Segmented/Leukocytes (NEUTSGLE) (SI unit %)
Neutrophils/Leukocytes (NEUTLE) (SI unit %)
Nucleated Erythrocytes (RBCNUC) (SI unit %)
Percent Unclassified Cells (PERUNCLC) (SI unit %)
Platelets (PLAT) (SI unit 10^9/L) and (Conventional unit 10^3/uL)
Promyelocytes (PROMY) (SI unit %)

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Mineral Metabolism (SI) (US conventional unit if applicable)

1,25-DihydroxyvitD2+1,25-DihydroxyvitD3 (VTD23125) (SI unit ng/L) and (Conventional unit pg/mL)
1,25-Dihydroxyvitamin D2 (VTD2125) (SI unit ng/L) and (Conventional unit pg/mL)
1,25-Dihydroxyvitamin D3 (VTD3125) (SI unit ng/L) and (Conventional unit pg/mL)
25 OH Vitamin D (VIDT) (SI unit nmol/L) and (Conventional unit ng/mL)
Alkaline Phosphatase (ALP) (SI unit IU/L)
Bone Specific Alk Phos (BNSPALP) (SI unit ug/L)
Calcium (CA) (SI unit mmol/L) and (Conventional unit mg/dL)
Calcium - Phosphorus Product (CAPHOSPD) (SI unit mmol2/L2) and (Conventional unit mg2/dL2)
Parathyroid Hormone, Intact (PTHI) (SI unit pmol/L) and (Conventional unit pg/mL)
Phosphate (PHOS) (SI unit mmol/L) and (Conventional unit mg/dL)

Urinalysis (SI)

Bacteria (BACT) (SI unit /HPF)
Calcium Oxalate Crystals (CYCAOXA) (SI unit /HPF)
Erythrocytes (RBC) (SI unit /HPF)
Granular Casts (CSGRAN) (SI unit /LPF)
Hyaline Casts (CSHYAL) (SI unit /LPF)
Leukocytes (WBC) (SI unit /HPF)
RBC Casts (CSRBC) (SI unit /LPF)
Renal Epithelial Cells (EPIRCE) (SI unit /HPF)
Squamous Epithelial Cells (EPISQCE) (SI unit /HPF)
Transitional Epithelial Cells (EPITCE) (SI unit /HPF)
Triple Phosphate Crystals (CYTRPHOS) (SI unit /HPF)
Uric Acid Crystals (CYURIAC) (SI unit /HPF)
WBC Casts (CSWBC) (SI unit /LPF)
Waxy Casts (CSWAX) (SI unit /LPF)
Yeast Cells (YEAST) (SI unit /HPF)

Serology (SI)

Tryptophan (TRP) (SI unit mg/dL)

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Appendix 2- PROMIS Scoring

The PROMIS data will be provided from an external data source. The PROMIS Upper Extremity raw score and PROMIS Pain Intensity 3a raw score, t-score and SE will be derived in the analysis dataset.

PROMIS Upper Extremity

Step 1: Update the score for the "pour liquid" question in the SDTM QS

For the 'pour liquid" question for the "PROMIS Upper Extremity" the variable SDTM.QS.QSORRES which stores the verbatim text will remain as is since it is correctly mapped from the value reported from the external vendor data. The standardized variable in the SDTM QS.QSSTRESC/ QS.QSSTRESN will be mapped below.

External data source reported value	QS.QSORRES	QS.QSSTRESC / QS.QSSTRESN
5	Without any Difficulty	4
4	With a little Difficulty	3
3	With some difficulty	2
2	With much Difficulty	1
1	Unable to do	1

Step 2: Calculate the raw score

The raw score for the "PROMIS Upper Extremity" is the summation of the QS.QSSTRESN variable in the SDTM for the following questions:

- Heavy object
- Wash dishes
- Dress yourself
- Pour liquid
- Fingernails
- Shampoo your hair
- Open a can
- Light bulb
- Opened jar

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PROMIS Pain Intensity 3a

Step 1: Calculate the raw score

The raw score for the "PROMIS Pain Intensity 3a" is the summation of the variable QSSTRESN in the SDTM QS for the following questions:

- Worst Pain
- Average Pain
- Pain Right Now

Step 2: Map the T-score and SE

The table below will be used to map the T-score and SE

RAW SCORE	TSCORE	SE
0	0	0
1	0	0
2	0	0
3	36.3	5.4
4	43.1	3.9
5	47.5	3.7
6	51.4	3.8
7	54.8	3.9
8	58.5	3.9
9	61.9	3.8
10	64.9	3.9
11	68.4	4.1
12	72	4.2
13	75.1	4.8
14	77.8	5
15	81.8	4.2

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Appendix 3- Echocardiogram Assessments

Below is a list of the assessment from the Echocardiogram test.

Test (unit)
Annular Plane Systolic Excursion (mm)
Aortic Valve Comment
Aortic Valve HR (HB)/min)
Aortic Valve Thickening/Calcification (Yes, No, Not Assessable)
AR Regurgitation (Absent, Trace, Mild, Moderate, Severe, Not Assessable)
Cardiac Index (l/min/m2)
Cardiac Output (l/min)
Inferior Vena Cava Expiration Diameter (mm)
Inferior Vena Cava Inspiration Diameter (mm)
LA End Systolic Volume (mL)
LA End Systolic Volume Index (mL/m2)
Left Ventricle Global Longitudinal Strain endocardial (%)
Left Ventricle Systolic minor axis Dimension (mm)
Left Ventricular Ejection Fraction (%)
Left ventricular -Ejection Fraction-2D mode-Teichholz (%)
Left Ventricular Fractional Shortening (%)
Left Ventricular Mass Index (g/m2)
LV Diastolic minor axis Dimension (mm)
LV Diastolic minor axis Dimension Index (mm/m2)
LV End Diastolic Volume (mL)
LV End Diastolic Volume Index (mL/m2)
LV End Systolic Volume (mL)
LV End Systolic Volume Index (mL/m2)
LV Interventricular Septum Thickness End Diastole (mm)
LV Interventricular Septum Thickness End Systole (mm)
LV Mass (g)
LV Outflow Tract Cardiovascular Orifice Diameter (mm)
LV Outflow Tract Mean Gradient Antegrade Flow (mm[Hg])
LV Outflow Tract Mean Velocity Antegrade Flow (m/s)
LV Outflow Tract Peak Gradient Antegrade Flow (mm[Hg])
LV Outflow Tract Peak Velocity Antegrade Flow (m/s)
LV Outflow Tract Stroke Index (ml/m2)
LV Outflow Tract Velocity Time Integral (cm)
LV Peak Diastolic Tissue Velocity During Atrial Systole Lateral Mitral Annulus (m/s)
LV Peak Diastolic Tissue Velocity During Atrial Systole Medial Mitral Annulus (m/s)
LV Peak Early Diastolic Tissue Velocity Lateral Mitral Annulus (m/s)
LV Peak Early Diastolic Tissue Velocity Medial Mitral Annulus (m/s)
LV Peak Tissue Velocity E-Wave Lateral Mitral Annulus

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LV Posterior Wall Thickness End Diastole (mm)
LV Posterior Wall Thickness End Systole (mm)
LV Relative Wall Thickness (%)
LV Systolic minor axis Dimension Index (mm/m2)
LVEF < 45% (Yes, No, Not Assessable)
Mitral E/A Ratio
Mitral Valve A-Wave Peak Velocity (m/s)
Mitral Valve Comment
Mitral Valve E-Wave Peak Velocity (m/s)
Mitral Valve thickening/Calcification (Yes, No, Not Assessable)
Moderate or greater pericardial effusion (Yes, No, Not Assessable)
Moderate or greater valvular regurgitation (Yes, No, Not Assessable)
MR Regurgitation (Absent, Trace, Mild, Moderate, Severe, Not Assessable)
Other significant abnormality thrombus, vegetation, tumor, tamponade (Yes, No, Not Assessable)
Overall Quality
PR Regurgitation (Absent, Trace, Mild, Moderate, Severe, Not Assessable)
Pulmonary Artery Pressure - Systole (mm[Hg])
Pulmonary hypertension RV systolic pressure of 50 mm Hg or more (Yes, No, Not Assessable)
Pulmonic Valve Comment
Pulmonic Valve Thickening or Calcification (Yes, No, Not Assessable)
Ratio of MV Peak Velocity to LV Peak Tissue Velocity E-Wave Medial Mitral Annulus
Right Atrium – Pressure (Right Ventricles) (mm[Hg])
Right Atrium – Pressure (Valves) (mm[Hg])
Right Ventricle - Peak Gradient – Systole (mm[Hg])
Right Ventricle - Right Ventricular Fractional Area Change - 2D mode (%)
Right Ventricular Peak Systolic Tissue Velocity (m/s)
Stroke Volume (ml)
TR Regurgitation (Absent, Trace, Mild, Moderate, Severe, Not Assessable)
Tricuspid Valve Comment
Tricuspid Valve Peak Gradient Regurgitant Flow (mm[Hg])
Tricuspid Valve Peak Velocity Regurgitant Flow (m/s)
Tricuspid Valve Thickening/Calcification (Yes, No, Not Assessable)

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