

Inozyme Pharma, Inc.
Protocol #: INZ701-101

**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
ENPP1 Deficiency**

Statistical Analysis Plan

Version v2.0

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List of Abbreviations

Abbreviation	Definition/Expansion
%AUC _{ex}	Percentage of AUC _{inf} obtained by extrapolation
%Fluct	Percent fluctuation
ADA	Anti-Drug Antibody
AE	Adverse Events
AESI	Adverse Events of Special Interest
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

Abbreviation	Definition/Expansion
CT	Computed Tomography
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
eCRF	Estimated Glomerular Filtration Rate
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
ENPP1	Ectonucleotide pyrophosphatase/phosphodiesterase 1
FIH	First-in-Human
E _{max}	Maximum effect observed, taken directly from the observed serum ENPP1 activity-time profile.
HFA	High Frequency Audiometry
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
NQ	Non-quantifiable
PD	Pharmacodynamic
PGI-I	Patient Global Impression of Improvement
PGI-S	Patient Global Impression of Status/Severity
PK	Pharmacokinetics
PROMIS	Patient Reported Outcomes Measurement Information System

Abbreviation	Definition/Expansion
PT	Posterior Tibial
PCS	Potentially clinically significant
PT	Preferred Term
PTA	Pure tone audiometry
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
sec	Seconds
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 activity-time profile
TmP	Tubular Maximum Reabsorption of Phosphate
ULN	Upper Limit of Normal
US	United States of America
V _z /F	Apparent volume of distribution following subcutaneous dosing
WPAI	Work Productivity and Activity Impairment Questionnaires
WHO	World Health Organization

I. Introduction

A. Background

Study INZ701-101 is a Phase 1/2, open-label, multicenter, first-in-human (FIH), multiple ascending dose (MAD) dose-finding study followed by a long-term open-label Extension Period in adult subjects (18 to <65 years of age at screening) with ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) deficiency. Study INZ701-101 will evaluate general safety and immunological parameters to determine the risk-benefit profile of INZ-701 in ENPP1 deficiency and will identify the INZ-701 dose for further clinical development in ENPP1 deficiency.

B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on version 8.0 of Protocol INZ701-101.

Version	Approval Date	Salient Changes, if any*
Protocol v4.0	24 May 2021	N/A
Protocol v5.0	16 August 2021	<ul style="list-style-type: none">-Holter Monitoring and/or Cardiac Telemetry and/or repeat ECGs (if required per site specific procedures and/or Investigator discretion) were added to the safety endpoints.-Efficacy endpoints were revised as “exploratory” to align with study objectives.-The 6-hour post-dose samples for ENPP1 activity, INZ-701 PK, and PPi were deleted at Days 8, 11, 15, 18, 22, and 25 in the Dose Evaluation Period.-Serology tests for HIV, hepatitis B and hepatitis C at Screening were added
Protocol v5.1 (UK specific)	18 August 2021	
Protocol v5.2 (France Specific)	04 November 2021	<ul style="list-style-type: none">-The PROMIS assessment for upper extremity has been updated.
Protocol v6.0	03 March 2022	N/A
Protocol v7.0	08 August 2022	N/A
Protocol v8.0 and Protocol Administrative Change	20 June 2023	<ul style="list-style-type: none">-Addition of Cohort 4-Update definition of AESI-Update schedule of events

Letter #1 dated 27 July 2023		<ul style="list-style-type: none">-Extend certain assessments beyond Week 48 (incorporated as part of SAP v1.0.-Remove interim analysis (while the amendment stated an interim analysis would be performed, a formal analysis was not performed).
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* Changes expected to require accommodation in analysis plan.

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

II. Protocol Objectives and Study Endpoints

Objective	Endpoint (Assessment)
Primary:	
<ul style="list-style-type: none">Assess the safety and tolerability of multiple ascending subcutaneous (SC) doses of INZ-701	<ul style="list-style-type: none">Adverse events (AEs), vital signs, physical examinations, laboratory tests, incidence of dose-limiting toxicities (DLTs), electrocardiograms (ECG)
<ul style="list-style-type: none">Assess the immunogenicity of multiple ascending SC doses of INZ-701	<ul style="list-style-type: none">Incidence of anti-drug antibody (ADA)Changes from baseline in the ENPP1 enzyme activity and neutralizing ADA
<ul style="list-style-type: none">Study the pharmacokinetics (PK) of multiple ascending SC doses of INZ-701	<ul style="list-style-type: none">INZ-701 plasma concentration-time profiles and determination of noncompartmental PK parameters (including but not limited to time to maximum plasma concentration [T_{max}], maximum plasma concentration [C_{max}], area under the concentration time curve to the last quantifiable concentration [AUC_{last}], area under the plasma concentration time curve over the dosing interval [AUC_{tau}], area under the plasma concentration-time curve from time zero to infinity [AUC_{inf}], elimination half-life [$T_{1/2}$], minimum plasma concentration [C_{min}], clearance [CL/F], and apparent volume of distribution [V_z/F])Linearity between ascending INZ-701 SC doses and PK parameters
<ul style="list-style-type: none">Study the long-term safety and pharmacodynamic (PD) changes from baseline in PPI and associated biomarkers of ENPP1 Deficiency after administration of multiple SC doses of INZ-701	<ul style="list-style-type: none">Summary of the PPI levels, phosphate, FGF23 levels, and tubular maximum reabsorption of phosphate/glomerular filtration rate (TmP/GFR)Changes from baseline of blood and urine biomarkers as available

Exploratory:

- Assess changes in calcification of arteries and organs
- Assess changes in clinical measures associated with underlying ENPP1 Deficiency, including skeletal, cardiac, vascular, and renal parameters
- Assess changes in physical function
- Assess changes in patient, clinician, and caregiver reported outcomes and quality of life
- Results of Na¹⁸F-PET/CT or low dose CT (full body) without contrast, echocardiogram, and renal ultrasound assessments
- Results of Na¹⁸F-PET/CT or low dose CT (full body) without contrast, X-ray, dual energy X-ray absorptiometry (DEXA), echocardiogram, ECG, and renal ultrasound assessments
- Results of walking ability, dynamometry, grip strength dynamometry and range of motion assessments
- Results of Patient Reported Outcomes Measurement Information System (PROMIS), global impression scales and Work Productivity and Activity Impairment Questionnaires (WPAI) assessments

III. Study Design

A. Design Overview

Study INZ701-101 is a Phase 1/2, open-label, multicenter first-in-human (FIH), multiple ascending dose (MAD), dose-finding study followed by a long-term open-label Extension Period conducted in adults with ENPP1 deficiency. 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) in subjects deficient in ENPP1 for further clinical development. No placebo/control arm or reference therapies will be used in the study.

Subject participation consists of a Screening Period of up to 30 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 where the subject resides or until an alternative study for subjects to continue receiving study drug is available. During the Extension Period, visits will be every 4 weeks until Week 48, followed by every 12 weeks until the subject

leaves the study. Subjects who continue in the study beyond 48 weeks will receive a phone call for safety follow-up approximately 30 days after their last dose. Subjects who discontinue treatment or the study will be asked to complete the End of Study (EOS) Safety Follow-up Safety Monitoring Visit 30 days after their last dose of INZ-701.

The study design during the Dose Evaluation Period is a MAD 3 + 3 with 4 dose cohorts. Based on nonclinical findings and nonclinical pharmacology modeling, the planned doses will be 0.2 mg/kg twice weekly, 0.6 mg/kg twice weekly, 1.8 mg/kg twice weekly, and 1.2 mg/kg once weekly.

Escalation to the next dose cohort will proceed after review of all available safety and PK/PD data from all subjects in the current dose cohort through Day 32 and recommendation from an independent Data Safety Monitoring Board (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 of the DSMB. Enrollment in the next dose cohort will not begin until the decision to dose has been sent to each participating site in writing.

After completion of the Day 29 Visit, the Investigator will assess the subject's safety data to confirm if the subject may continue dosing. The Investigator and subject will discuss available options to enable the subject to continue receiving INZ-701 in the Extension Period. The subjects will be required to provide written informed consent to participate in the Extension Period and may do so during the initial consenting process or at any time during the Dose Evaluation Period. In the event the subject provides written informed consent prior to the subject's safety data assessment through Day 29, the Investigator will reconfirm and document the subject's affirmation to continue in the study.

B. Cohort Stopping Criteria for the Dose Evaluation Period

A DLT is defined as a Grade ≥ 3 event (apart from fatigue) deemed related to INZ-701. Investigators must report an occurrence of a DLT to the Sponsor or designee immediately and no later than within 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) with consideration to the following:

- Stop enrollment at that dose level
- Declare maximum tolerated dose (MTD) at 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 in accordance with the protocol 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. 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

The study population includes adults (18 to <65 years of age at Screening) with a confirmed genetic diagnosis of ENPP1 Deficiency and biochemical evidence of hypopyrophosphatemia (ie, PPi <1300 nM at Screening).

See Section 7.1 and 7.2 of the protocol for a complete list of the inclusion/exclusion criteria.

D. Sample Size Predictions

Anticipated enrollment in the Phase 1 portion of this study 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 in 1 or more existing cohorts 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

For details regarding the schedule of assessments with timing and other requirements, refer to protocol Table 1, Table 2, Table 3, Table 4, and Table 5 plus Protocol Administrative Change Letter #1 dated 27 July 2023.

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. INZ-701 will be administered by SC injection on Day 1, on Day 8 the subject will receive study drug once or twice weekly as assigned per the dosing cohort. During the Extension Period, eligible subjects will be administered INZ-701 once or twice weekly at the dose assigned in the Dose Evaluation Period.

The administered dose for a subject may change once the selected dose has been determined upon completion of the Dose Evaluation Period for all subjects. At which time all subjects in the Extension Period may be assigned to the selected dose. If the selected dose is higher than what the subject received in the Dose Evaluation Period, the first administration of the higher dose will be at the clinical site under medical supervision. The Investigator will determine how long the subject will receive the higher dose in the clinic and when they may return to off-site administration. The change to the higher dose may coincide with the subject's next in-clinic visit.

Cohort Dose Level	INZ-701 Dose Cohorts
1	0.2 mg/kg twice weekly
2	0.6 mg/kg twice weekly
3	1.8 mg/kg twice weekly
4	1.2 mg/kg once 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 12 of the protocol provides additional detail for data recording, retention, and monitoring.

B. Definition of Baseline

Unless otherwise specified, the baseline value for each quantity being analyzed is defined as the last non-missing value prior to 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%

C. Study Day and On-study Treatment Flag

Study Day will be calculated from the reference start date and will be used to show 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 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

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 longer than the table described above, the additional analysis visits will be applied in a similar manner.

For the radiography and 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 radiography and imaging data:

Analysis Visit	Target Day	Analysis Window (inclusive)
Week 24	169	Post-screening - 210
Week 48	337	211 - 420
Week 96	673	421 - 756
Week 144	1009	757 - 1092
Week 192	1345	1093 - 1428

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:

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 6 hour Post-Treatment	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 and within an 8-hour window post dose, using 6 hours post dose as the target timepoint.
Study Day 2-7	1	2-7	Map using the Study Day. If the assessment was collected on a dosing day this will not apply.
Day 8 Pre-Treatment	2	8	Assessments collected on the same day as the first dose of Week 2 with the time indicating prior to the dose.
Day 8 Post-Treatment	2	8	Assessments collected on the same day as the first dose of Week 2 with the time indicating after the dose.
Day 11 Pre-Treatment	2	11	Assessments collected on the same day as the second dose of Week 2 with the time indicating prior to the dose.
Day 11 Post-Treatment	2	11	Assessments collected on the same day as the second dose of Week 2 with the time indicating after the dose.

Analysis Visit	Study Week	Target Study Day	Algorithm for selection
Day 15 Pre-Treatment	3	15	Assessments collected on the same day as the first dose of Week 3 with the time indicating prior to the dose.
Day 15 Post-Treatment	3	15	Assessments collected on the same day as the first dose of Week 3 with the time indicating after the dose.
Day 18 Pre-Treatment	3	18	Assessments collected on the same day as the second dose of Week 3 with the time indicating prior to the dose.
Day 18 Post-Treatment	3	18	Assessments collected on the same day as the second dose of Week 3 with the time indicating after the dose.
Day 22 Pre-Treatment	4	22	Assessments collected on the same day as the first dose of Week 4 with the time indicating prior to the dose.
Day 22 Post-Treatment	4	22	Assessments collected on the same day as the first dose of Week 4 with the time indicating after the dose.
Day 25 Pre-Treatment	4	25	Assessments collected on the same day as the second dose of Week 4 with the time indicating prior to the dose.
Day 25 Post-Treatment	4	25	Assessments collected on the same day as the second dose of Week 4 with the time indicating after to the dose.
Day 29 Pre-Treatment	4	29	Assessments collected on the same day as the first dose of Week 5 with the time indicating prior to the dose.
Day 29 Post-Treatment	4	29	Assessments collected on the same day as the first dose of Week 5 with the time indicating after the dose.
Day 32 Pre-Treatment	4	32	Assessments collected on the same day as the second dose of Week 5 with the time indicating prior to the dose.
Day 32 Post-Treatment	5	32	Assessments collected on the same day as the second dose of Week 5 with the time indicating after the dose.
Week 8 Pre-Treatment	8		Use the recorded visit date in the EDC and map to the closest corresponding laboratory date recorded and indicate if Pre or Post Treatment

Analysis Visit	Study Week	Target Study Day	Algorithm for selection
Week 8 Post-Treatment	8		Use the assigned visit date in the EDC and map to the closest corresponding laboratory date recorded and indicate if Pre or Post Treatment
Continue every 4 weeks until Week 48			Similar approach as the Week 8 Pre-Treatment and Week 8 Post-Treatment

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.
 - If year and month is not the same as the first dose date, then the day will be imputed as "01".

If the imputed date is prior to the ICF date, then impute the date as the ICF date.

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.
- 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 10 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

The protocol specifies a formal full delivery interim analysis to be conducted when all subjects from dose cohorts 1 through 4 completed the Week 48 visit. Additional intermediate analyses or administrative looks may be conducted while subjects are participating in the Extension Period. Intermediate analyses were conducted at two timepoints throughout the study to assess safety, PK, PD, and clinical activity data. The final analysis will be conducted when the last subject leaves the study as defined in the protocol.

In addition, there were administrative looks performed for the purposes of safety assessments by the DSMB at the indicated timepoints below:

- Cohort 1 Dose Level#1 (0.2 mg/kg): Data Review Meeting 1 will occur after 3 subjects of the dose level 1 complete Day 32.
- Cohort 2 Dose Level#2 (0.6 mg/kg): Data Review Meeting 2 will occur after 3 subjects of the dose level 2 complete Day 32.
- Cohort 3 Dose Level#3 (1.8 mg/kg): Data Review Meeting 3 will occur after 3 subjects of the dose level 3 complete Day 32.

The sponsor may decide to call additional DSMB meetings (ad hoc meetings), should they be deemed necessary based on a safety issue(s) identified by the DSMB or the sponsor.

Analyses for the assessment of safety by the DSMB are not part of the scope of this SAP, and thus, are not described herein.

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 1 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).

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 carry.

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 ().

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
 - 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 completes 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 through Week 48 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)
- 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. ENPP1 Deficiency Diagnosis

The ENPP1 deficiency diagnosis characteristics will be collected on the “ENPP1 Deficiency Diagnosis” eCRF page. The number and percentage of subjects with various mutations will be presented by dose cohort and overall.

The ENPP1 deficiency diagnosis characteristics will be presented in a data listing.

F. ENPP1 Family History

The family history data will be collected on the “ENPP1 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
- 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 based on the Safety Analysis Set by dose cohort and overall. Protocol deviations will be categorized as major or minor.

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. Pharmacodynamic Analysis

Analyses of plasma inorganic pyrophosphate (PPi) and ENPP1 activity 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.

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

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

All pharmacodynamic analyses will be performed by a group separate from IQVIA Biotech and identified by the sponsor and provided in a separate report.

VIII. Exploratory Biomarkers

The following exploratory biomarkers will be collected (unit).

- Serum 25(OH)D (Vitamin D3) (pg/mL)
- Serum intact parathyroid hormone (pmol/L)
- Plasma osteopontin (ng/mL)
- Serum C-reactive protein (mg/L)
- Plasma intact FGF23 (RU/mL)
- Serum β 2-microglobulin (ug/L)
- Serum procollagen type 1 N-terminal propeptide (P1NP) (ug/L)
- Serum carboxy terminal cross-linked telopeptide of type I collagen (CTX) (ng/L)
- Serum bone specific alkaline phosphatase (BALP) (ug/L)
- Plasma adenosine triphosphate (ATP)

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. Additionally, spaghetti plots will be displayed for plasma FGF23 intact and BALP.

All data will be presented in a data listing.

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 walking ability assessment, hand-held dynamometry, grip strength dynamometry, range of motion, Patient Reported Outcomes Measurements Information System (PROMIS), Work Productivity and Activity Impairment Questionnaire (WPAI), clinical global impression scale, patient global impression scale (PGI-S), caregiver global impression scale (CaGI-S), ankle-brachial index, pulse wave velocity, spirometry, carotid ultrasound and bone histomorphometry are part of the clinical outcome assessments.

The X-ray, DEXA (exception is Germany), echocardiogram, low-dose-computed tomography (CT), positron emission tomography-computed tomography, and renal ultrasound are part of the radiographic and imaging assessments.

The following assessments are not required. However, if the site has the ability (i.e. resources, staff.) to conduct the assessments they are strongly recommended. For any non-required assessment not conducted by Day 1, the investigator may arrange to have it conducted within 2 months following the first dose, and if not conducted within the first 2 months following first dose, the subject will not have the assessment conducted at any time during the study. The exception to this is the walk test, which should be attempted by all subjects at the Week 48 visit and annual visits thereafter.

- 2-minute walk test
- 6-minute walk test
- Hand-held dynamometry
- Grip strength dynamometry
- Range of motion
- Patient Reported Outcomes Measurement Information System (PROMIS)
- Work Productivity and Activity Impairment Questionnaire (WPAI)
- Global impression scales
- DEXA
- X-ray
- Ankle-brachial pressure index
- Pulse Wave Velocity
- Carotid ultrasound
- Spirometry
- Bone histomorphometry using transiliac crest bone biopsy (optional)

A. Walking Ability Test

The walking ability test 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 following walking assessments will be collected for this study:

- Two-minute walking test (2-MWT)
 - Distance (meters)
 - Completion (yes, no)
 - Device (none, cane, walker other)

- Six-minute walking test (6-MWT)
 - Distance (meters)
 - Completion (yes, no)
 - Device (none, cane, walker other)

If needed, the conversion of meters to feet will use a multiplicative factor of 3.28084.

Table 1 is the average number of feet/meters walked according to the NIH Toolbox Technical Manual: 2-Minute Walk Endurance Test for English speakers by gender and age (Kallen et al., 2012).

Table 1: Average number of feet/meters walked in 2 minutes

Age (years)	Reference Value in Feet		Reference Value in Meters	
	Males	Females	Males	Females
18-29	700.37	614.47	213.47	187.29
30-39	677.64	608.38	206.54	185.43
40-49	653.01	623.85	199.04	190.15
50-59	623.64	598.93	190.09	182.55
60-69	600.04	547.51	182.89	166.88

Table 1 will be used as the reference value when calculating the percent predicted for the two-minute walking assessment in meters. The age as collected in the eCRF will be used to determine the reference value. The percent predicted will be calculated as follows:

$$\text{Percent predicted (\%)} = ([\text{actual meters walked}] / [\text{reference value in meters}]) * 100$$

Table 2 contains the formula to derive the reference value in meters walked in six minutes (Dourado, 2011). The age as collected in the eCRF and baseline weight and height will be used for the reference calculation.

Table 2: Formula for reference value of meters walked in 6 minutes

Age (years)	Gender	Formula to Obtain the Reference Value in Meters
5-19	Male	$196.78 + (39.81 \times \text{age years}) - (1.36 \times \text{age}^2) + (132.28 \times \text{height cm})$
5-19	Female	$188.61 + (51.50 \times \text{age years}) - (1.86 \times \text{age}^2) + (86.10 \times \text{height cm});$
20-50	Male	$518.853 + (1.25 \times \text{height cm}) - (2.816 \times \text{age years})$

20-50	Female	$518.853 + (1.25 \times \text{height cm}) - (2.816 \times \text{age years}) - (39.07)$
51-65	Male	$(7.57 \times \text{height cm}) - (5.02 \times \text{age years}) - (1.76 \times \text{weight kg}) - 309$
51-65	Female	$(2.11 \times \text{height cm}) - (2.29 \times \text{weight kg}) - (5.78 \times \text{age years}) + 667$

The meters walked in 2 minutes and 6 minutes will be summarized descriptively for the observed, change from baseline, and percent change from baseline by dose cohort and overall. The predictive percent will be summarized descriptively.

A spaghetti plot for the meters walked in 6 minutes by dose cohort will be provided.

The results of the walking ability assessment will be presented in a data listing.

B. Hand-held Dynamometry

The hand-held dynamometry 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 following dynamometry assessments will be collected:

- Right shoulder abduction (newtons)
- Left shoulder abduction (newtons)
- Right shoulder flexion (newtons)
- Left shoulder flexion (newtons)
- Right elbow flexion (newtons)
- Left elbow flexion (newtons)
- Right elbow extension (newtons)
- Left elbow extension (newtons)
- Right hip abduction (newtons)
- Left hip abduction (newtons)
- Right hip flexion (newtons)
- Left hip flexion (newtons)
- Right hip extension (newtons)
- Left hip extension (newtons)
- Right knee extension (newtons)
- Left knee extension (newtons)
- Right knee flexion (newtons)
- Left knee flexion (newtons)

Each dynamometry assessment will be normalized. The body weight coinciding with the assessment will be used for the normalization. If the coinciding body weight is missing, the baseline body weight will be used. The normalizing formula is as following:

Normalized value (%)=(Assessment (newtons)/ body weight (newtons)) x 100
Where newtons=9.80665*kg

Table 3 displays the average force (newtons)/body weight (newtons) (%) by gender, age and assessment (Bohannon, 1997). These values will be used as the reference values in the percent predicted calculation.

Table 3: Average force (newtons)/body weight (newtons) (%) by gender, age and assessment

Assessment	Age	Dominant/ Non-Dominant	Male Normalized Value (%)	Female Normalized Value (%)
Shoulder Adduction	20-29	Non-Dominant	31.4	23.4
Shoulder Adduction	20-29	Dominant	32.7	26.5
Shoulder Adduction	30-39	Non-Dominant	30.5	21.2
Shoulder Adduction	30-39	Dominant	31.9	21.8
Shoulder Adduction	40-49	Non-Dominant	29.1	21.4
Shoulder Adduction	40-49	Dominant	29.6	22.8
Shoulder Adduction	50-59	Non-Dominant	26.1	21.5
Shoulder Adduction	50-59	Dominant	28.2	22
Shoulder Adduction	60-69	Non-Dominant	24.9	17.1
Shoulder Adduction	60-69	Dominant	25.5	18.4
Elbow Flexion	20-29	Non-Dominant	35.5	26.5
Elbow Flexion	20-29	Dominant	36.4	26.8
Elbow Flexion	30-39	Non-Dominant	36.1	25.1

Assessment	Age	Dominant/ Non-Dominant	Male Normalized Value (%)	Female Normalized Value (%)
Elbow Flexion	30-39	Dominant	34.6	25.7
Elbow Flexion	40-49	Non-Dominant	32.5	26
Elbow Flexion	40-49	Dominant	33.3	25
Elbow Flexion	50-59	Non-Dominant	31.6	25.2
Elbow Flexion	50-59	Dominant	33.8	24.9
Elbow Flexion	60-69	Non-Dominant	30.8	22
Elbow Flexion	60-69	Dominant	32.6	21.4
Elbow Extension	20-29	Non-Dominant	31.1	20
Elbow Extension	20-29	Dominant	30.8	20.2
Elbow Extension	30-39	Non-Dominant	29.5	18.4
Elbow Extension	30-39	Dominant	27.6	18.2
Elbow Extension	40-49	Non-Dominant	25.8	18.5
Elbow Extension	40-49	Dominant	25.3	18.1
Elbow Extension	50-59	Non-Dominant	21.9	17.5
Elbow Extension	50-59	Dominant	23.3	17.9
Elbow Extension	60-69	Non-Dominant	20.7	15.5
Elbow Extension	60-69	Dominant	21.1	14.8
Hip Abduction	20-29	Non-Dominant	40.2	32.7
Hip Abduction	20-29	Dominant	40.2	33.7
Hip Abduction	30-39	Non-Dominant	42.7	33.1
Hip Abduction	30-39	Dominant	42	35.5
Hip Abduction	40-49	Non-Dominant	38.4	33.3
Hip Abduction	40-49	Dominant	37.3	36
Hip Abduction	50-59	Non-Dominant	35.7	33.4
Hip Abduction	50-59	Dominant	36.2	34.7
Hip Abduction	60-69	Non-Dominant	33.1	26.7

Assessment	Age	Dominant/ Non-Dominant	Male Normalized Value (%)	Female Normalized Value (%)
Hip Abduction	60-69	Dominant	32.8	28.2
Hip Flexion	20-29	Non-Dominant	26.5	22.9
Hip Flexion	20-29	Dominant	27	24.3
Hip Flexion	30-39	Non-Dominant	28.9	18.7
Hip Flexion	30-39	Dominant	28.5	19.2
Hip Flexion	40-49	Non-Dominant	22.4	20.6
Hip Flexion	40-49	Dominant	23.2	20.6
Hip Flexion	50-59	Non-Dominant	24	18.8
Hip Flexion	50-59	Dominant	23.1	18.9
Hip Flexion	60-69	Non-Dominant	21.1	16.3
Hip Flexion	60-69	Dominant	21.4	17.1
Knee Extension	20-29	Non-Dominant	74	80.5
Knee Extension	20-29	Dominant	73.7	80.8
Knee Extension	30-39	Non-Dominant	73.7	63.8
Knee Extension	30-39	Dominant	73.6	63.3
Knee Extension	40-49	Non-Dominant	70.6	59.7
Knee Extension	40-49	Dominant	69.8	62.6
Knee Extension	50-59	Non-Dominant	55.1	51.2
Knee Extension	50-59	Dominant	55.7	53.7
Knee Extension	60-69	Non-Dominant	47.7	43.3
Knee Extension	60-69	Dominant	48.9	44.6

Each dynamometry assessment and normalized value will be summarized descriptively for the observed and change from baseline by dose cohort and overall for the dominant and the non-dominant side. If the subject is

ambidextrous, the right will be identified as the dominant side for the summary. The predictive percent will be summarized descriptively.

A spaghetti plot for each hand-held dynamometry assessment by dose cohort will be provided. The results of the dynamometry assessments will be presented in a data listing.

C. Grip Strength Dynamometry

The grip strength dynamometry 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 following grip strength assessments will be collected:

- Right hand, maximum force (pounds)
- Left hand, maximum force (pounds)
- Dominant hand (right, left, ambidextrous)

The grip strength results will be converted from pounds to newtons using the following conversion:

- $\text{Newtons} = \text{Pounds} * 4.44822$

Table 4 presents the average pounds of force as presented in the NIH Toolbox Technical Manual: Grip-Strength Test (Kallen et al, 2012), for English speakers by gender and age for the dominant hand. The age as collected on the eCRF will be used for the reference value.

Table 4 : Grip Strength average pounds of force

Age (years)	Average Force (pounds) in Males	Average Force (pounds) in Females
18-29	109.88	67.39
30-39	111.25	65.19
40-49	108.56	66.29
50-59	97.56	61.25
60-69	89.01	53.34

Each grip strength dynamometry assessment in newtons will be summarized descriptively for the observed and change from baseline by dose cohort and

overall for the dominant and the non-dominant hand. If the subject is ambidextrous, the right hand will be identified as the dominant hand for the summary. The number and percentage for the dominant hand will be presented as captured on the eCRF. The predictive percent will be summarized descriptively.

A spaghetti plot for each grip strength assessment by dose cohort will be provided.

The results of the grip strength dynamometry will be presented in a data listing.

D. Range of Motion

Range of motion 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.

Range of motion information is collected on the “Performance Outcomes” eCRF page.

The range of motion assessments will also be categorized as follows according to the percent change from baseline:

- Improve ($> 5\%$)
- No Change (-5% to 5% , inclusive)
- Worsen ($< -5\%$)

Range of motion assessments will be summarized descriptively for the observed, change from baseline, and percent change from baseline by dose cohort and overall. Improved, no change, and worsen will also be summarized at each visit for each joint.

Range of motion results will be presented in a data listing.

E. 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 summary of responders for each scale will be produced. A responder will be defined as a subject with improvement from baseline in the raw or t-score in >50% of their visits. Improvement in Pain Interference, Pain Intensity, and Fatigue will be defined as a decrease from baseline in the t-score. Improvement in Physical Function – Mobility and Cognitive Function will be defined as an increase in baseline in the t-score. An improvement in Physical Function-Upper Extremity will be defined as an increase in baseline in the raw score.

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.

F. 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.

G. 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. Spaghetti plots will be provided for the improvement scale. All data will be provided in a data listing.

H. 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.

The findings will be summarized by counts and percentages at each scheduled visit by dose cohort and overall. Spaghetti plots will be provided for the improvement scale. All data will be provided in a data listing.

I. 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 dose cohort and overall. Spaghetti plots will be provided for the improvement scale. All data will be provided in a data listing.

J. 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)
- 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.

All data will be presented in data listings.

K. 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.

L. Spirometry

The spirometry will be collected at Screening, Day 15 of the Dose Evaluation period, Day 32 of the Dose Evaluation Period, 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 spirometry assessments will be collected:

- Vital capacity (L)
- Forced vital capacity (L)
- Forced expiratory volume in 1 second (L)
- Forced expiratory flow 25–75% (L/sec)
- Maximal voluntary ventilation (L/min)

Spirometry assessments will be summarized descriptively for the observed, change, and percent change from baseline by dose cohort and overall.

All data will be presented in data listings.

M. Radiography and Imaging

Radiographic and imaging assessments will be performed at screening and scheduled time points during the Extension Period. The echocardiogram, low dose-computed tomography, positron emission tomography-computed tomography, and renal ultrasound are required. The carotid ultrasounds, DEXA and X-ray are not required.

i. 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 the 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.

All data will be presented in data listing.

ii. Low Dose-Computed Tomography (CT)

Low dose CT (full body) without contrast will be used to analyze skeletal endpoints and arterial and organ calcification endpoints.

Low dose CT (full body) without contrast will be performed in those not receiving Na¹⁸F-PET/CT and will identify skeletal abnormalities as well as quantify areas of calcification in joints, ligaments, soft tissue/organs and arteries. This assessment will be collected at Screening and Week 48 of the Extension Period and every 48 weeks after Week 48 of the Extension Period.

Data will be presented in a data listing.

Calcium volume (mm³) of calcifications will be calculated from the CT (full body) scans. Assessments will be made for the following locations (laterality): abdominal aorta, ascending and descending thoracic aorta, kidney (left), kidney (right), iliac arteries (left), iliac arteries (right), liver, renal arteries, and spleen. Total calcium volume will be calculated by visit for each location (laterality) by adding the volume across calcifications. Change from baseline and percent change from baseline in total volume will be listed and summarized.

iii. Positron Emission Tomography – Computed Tomography

Baseline Na¹⁸F-PET/CT will be performed in those not receiving low dose CT (full body) without contrast. It is a full body scan which also measures calcification of arteries and organs and skeletal abnormalities as well as microcalcifications and newly developing calcium deposits. This assessment will be collected at Screening and Week 48 of the Extension Period and every 48 weeks after Week 48 of the Extension Period.

Data will be presented in a data listing.

iv. 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)
- 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.

v. Carotid Ultrasound

The carotid ultrasound will be collected at Screening (or within 2 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)
- Area (mm²) 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.

All data will be presented in a data listing.

vi. DEXA

The DEXA will be collected at Screening (or within 2 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.

DEXA will be used to evaluate changes in bone mineral density and changes in surrounding mineralization by body area and location as following:

Body Area	Body Location
Spine	Adjusted Total Spine
	Total Spine
Hip	Femoral Neck
	Total Hip
Forearm	Radius 13 Distal
	Radius Ultra Distal
Whole Body	Adjusted Total Body
	Total Body
	Trunk

The following parameters will be summarized as applicable for each body area and location:

- Bone Mineral Density (BMD) (g/cm^2)
- Corrected Bone Mineral Density (BMD) (g/cm^2)
- Bone Mineral Content (BMC) (g)
- Fat (g)
- Percent Fat (%)
- Lean Mass (g)
- Total Mass (g)
- Visceral Adipose Mass (VATMASS) (g)
- Visceral Adipose Volume (VATVOL) (cm^3)
- T Score
- Corrected T Score
- Z-Score
- Corrected Z Score
- Z Score

Data will be summarized by observed, change and percent change and all data will be presented in a data listing.

vii. X-Ray

The X-Ray will be collected at Screening (or within 2 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.

Standard X-rays will be obtained to detect skeletal deformities. Images will be obtained of the standing long legs and upper extremities, including hand and wrist.

The following hand/wrist parameters will be summarized:

- Presence of fractures (Yes, No) for the following body parts:
 - Femur (Left, Right)
 - Fibula (Left, Right)
 - Hand/Wrist (Left, Right)
 - Humerus (Left, Right)

- Tibia (Left, Right)
 - Forearm (Left, Right)
- Presence of calcifications (Yes, No) for the following body parts:
 - Femur (Left, Right)
 - Fibula (Left, Right)
 - Hand/Wrist (Left, Right)
 - Humerus (Left, Right)
 - Tibia (Left, Right)
 - Forearm (Left, Right)
- Rachitic Deformities in Hand or Wrist
- Other Deformities in Hand or Wrist

The following spine parameters will be summarized:

- Presence of spinal fractures (Yes, No) for the following body parts:
 - Lumbar spine (L1- L5)
 - Thoracic spine (T4-T12)
- Presence of aortic calcifications (Yes, No) for the following body parts:
 - Spine (L1-L5, T4-T12)
- Aortic grade (0,1,2,3) or the following body parts:
 - Spine (L1-L5, T4-T12)
- Presence of joint calcifications (Yes, No) for the following body parts:
 - Lumbar spine (L1-L5)
 - Thoracic spine (T4-T12)
- Presence of Spinal Deformatities (Yes, No)
- Spinal Deformities (Kyphosis, Scoliosis)

Data will be summarized by counts and percentages. All data will be presented in a data listing.

N. Bone Histomorphology and Transiliac Crest Bone Biopsy

Bone biopsies are optional and will be collected at Screening and Week 48 of the Extension Period. Bone biopsies will be performed on any subject consenting to the procedure.

Data will be presented in a data listing.

O. Hearing Test

Hearing test data may include the following:

- Physical exam and otoscopy (Normal, Abnormal)
- Immittance audiometry (commonly called tympanometry) (Normal, Abnormal)
- Pure tone audiometry (PTA) with frequencies up to 8 kHz (Normal, Abnormal)
- High frequency audiometry (HFA), with frequencies up to 16 kHz (Normal, Abnormal)

All hearing data will be presented in a data listing.

P. Ophthalmologic Examinations

Ophthalmologic exam data may include the following: optical coherence tomography, color fundus photography, and best corrected visual acuity.

While ophthalmologic exams were removed as an exploratory endpoint from Protocol v7.0, examinations were performed prior to the amendment. Results of the ophthalmologic examinations that were performed will be presented in a data listing.

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 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, 14.4 mg/kg and 4.8 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.

Pre-treatment AEs are defined as AEs with an onset date prior to the first 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 (i.e. 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.

Systemic hypersensitivity reactions, including anaphylaxis, and seizures will be considered as Adverse Events of Special Interest (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
- 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.

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
- TEAE 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 TEAE will be summarized by the maximum grade by week. The injection site 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 serum chemistry, hematology, and urinalysis. 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

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

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

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

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:

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

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

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

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. Laboratory assessments performed on unscheduled visits will not be

summarized. Additionally, spaghetti plots for TmP/GFR 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.

Table 5: 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 /mm ³	>16 x 10 ³ /mm ³
Hemoglobin	Adult ≥18y																	<10 g/dL	>16.0 g/dL
Hematocrit	Adult ≥18y																	<34%	>54%
Platelet count	Adult ≥18y																	<70 x 10 ³ /mm ³	>400 x 10 ³ /mm ³

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 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°), 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 new onset PCS 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.

Table 6: 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 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 1 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 first dose of study drug. Concomitant procedures are defined as any procedure 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.

Table 7: 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
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 new onset PCS 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. Maximum ADA titers will be presented 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. Samples may also be used to assess and further establish assays for specificity confirmation (i.e., 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 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)
- Plasma histamine (pg/mL)
- Complement activation (C3, C4) (g/L)
- C-Reactive protein (mg/L)
- Erythrocyte sedimentation rate (mm/Hr)

All hypersensitivity data will be presented in a data listing.

K. Holter Monitoring and/or Cardiac Telemetry

Holter Monitoring and/or Cardiac Telemetry and/or 2 repeat post-dose ECGs will be collected if required per site specific procedures and/or Investigator discretion.

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.

XI. Pharmacokinetic Analysis

A. General Considerations

Derivation of the PK parameters for INZ-701 in serum will be the responsibility of a group separate from IQVIA Biotech and identified by the sponsor. In general, the serum concentration, PK, and PD tables, figures, and data listings as well as the statistical analysis of the PK variables will be the responsibility of this separate group. The clinical pharmacokinetics group at IQVIA will, however, provide descriptive summary tables and associate data listings for the observed values of serum concentrations (PK) and PD parameters.

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

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 subject listing of PK blood sample collection times and corresponding serum concentration values will be provided by the clinical pharmacokinetics group at IQVIA.

Serum concentrations will be summarized using descriptive statistics by Cohort and Day. Concentrations that are below the limit of quantification (BLQ) will not be used for the computation of descriptive statistics. Samples that are collected outside predetermined windows as specified below will be excluded from the concentration-time summaries 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,b} See Protocol Administrative Change Letter #1 dated 27 July 2023 for further details.

C. Serum Pharmacokinetic 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.

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. Calculated on Day 29 only.
C_{avg}	Average concentration over the dosing interval τ , calculated as AUC_{τ} divided by the dosing interval, τ . 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 $[(C_{max}-C_{min})/C_{avg}] \times 100\%$. Calculated on Day 29 only.
AUC_{last}	Area under the concentration-time curve from zero (predose) to time of last quantifiable concentration. <ul style="list-style-type: none">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_{τ}	Area under the concentration-time curve during a dosing interval “ τ ” (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_{τ} , calculated using the actual dose administered (mg). Calculated on Day 29 only
AUC_{inf}	Area under the concentration-time curve from zero (predose) extrapolated to infinite time, calculated as AUC_{last} and extrapolated to infinity by addition of the last quantifiable observed concentration divided by the apparent terminal rate constant: $AUC_{last} + C_{last}/k_z$. Calculated on Day 1 only.
$AUC_{inf}/Dose$	Dose-normalized AUC_{inf} , calculated using the actual dose administered (mg). Calculated on Day 1 only.

AUC_{0-72}	Area under the concentration-time curve from 0 (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). Calculated on Day 1 only.
RAUC	Accumulation ratio, calculated for AUC_{τ} 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.
$T_{1/2}$	Apparent terminal half-life, determined as $\ln 2/\lambda_z$.
CL/F	Apparent systemic clearance after SC dosing, calculated as <ul style="list-style-type: none"> ▪ Dose divided by AUC_{inf} on Day 1 ▪ Dose divided by AUC_{τ} on Day 29
V_z/F	Apparent volume of distribution following SC dosing, calculated as CL/F divided by λ_z . Calculated on Day 1 only.
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 $[(AUC_{inf} - AUC_{last})/AUC_{inf} \times 100]$. If the %AUC _{ex} is > 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.

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

Assessment of Dose Proportionality

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:

$$\log(\text{parameter}) = a + b * \log(\text{dose})$$

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.

XII. Changes in Analyses Planned Compared with Protocol

In the protocol, an interim analysis is planned when all subjects have completed the Week 48 visit.

In this SAP, the interim analysis is removed per Sponsor's decision. The Sponsor decided not to conduct the formal interim analysis after all subjects finished their Week 48 visit as many subjects transferred to the extension study prior to Week 48. However, intermediate analyses or administrative looks may be conducted while subjects are participating in the Extension Period.

XIII. Reference

Bohannon, R.W. (1997) Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years. *Archives of Physical Medicine and Rehabilitation*, 78 (1), 26-32

Dourado, V.Z. (2011) Reference Equations for the 6-Minute Walk Test in Healthy Individuals . *Arquivos Brasileiros de Cardiologia*, 96 (6).

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Appendix 1- Clinical Safety Laboratory Assessments

Chemistry (SI) (US conventional unit if applicable)

Alanine aminotransaminase (ALT) (SI unit U/L)
Aspartate aminotransaminase (AST) (SI unit U/L)
Gamma glutamyl transferase (GGT) (SI unit U/L)
Bilirubin (SI unit $\mu\text{mol/L}$) and (Conventional unit mg/dL)
Direct bilirubin (SI unit $\mu\text{mol/L}$) and (Conventional unit mg/dL)
Albumin (SI unit g/L) and (Conventional unit g/dL)
Lipase (SI unit U/L)
Amylase (SI unit U/L)
Creatine kinase (CK) (SI unit U/L)
Creatinine (SI unit $\mu\text{mol/L}$) and (Conventional unit mg/dL)
Urea Nitrogen (SI unit mmol/L) and (Conventional unit mg/dL)
Sodium (SI unit mmol/L)
Potassium (SI unit mmol/L)
Chloride (SI unit mmol/L)
Bicarbonate (SI unit mmol/L)
C Reactive Protein (SI unit mg/L) and (Conventional unit mg/dL)
Lactate dehydrogenase (LDH) (SI unit U/L)
Cholesterol (SI unit mmol/L) and (Conventional unit mg/dL)
Triglycerides (SI unit mmol/L) and (Conventional unit mg/dL)
Random Blood Glucose (SST) (SI unit mmol/L) and (Conventional unit mg/dL)
Protein (SI unit g/L) and (Conventional unit g/dL)
Uric acid (Urate) (SI unit $\mu\text{mol/L}$) and (Conventional Unit mg/dL)
Tryptophan (SI unit mg/dL)

Hematology (SI) (US conventional unit if applicable)

Absolute basophils count (SI unit x10E9/L)
Basophils/Leukocytes (%)
Absolute eosinophils count (SI unit x10E9/L)
Eosinophils /Leukocytes (%)
Erythrocyte (RBC) count total (SI unit x10E12/L)
Hematocrit (SI unit %)
Hemoglobin (SI unit g/L) and (Conventional unit g/dL)
Leukocytes (WBC) count total (SI unit x10E9/L)
Absolute lymphocyte count (SI unit x10E9/L)
Lymphocyte /Leukocytes (%)
Absolute monocyte count (SI unit x10E9/L)
Monocyte /Leukocytes (%)
Absolute neutrophils count (SI unit x10E9/L)
Neutrophils /Leukocytes (%)
Platelet count (SI unit x10E9/L)
Estimated glomerular filtration rate (eGFR) (mL/min/1.73m2)
Erythrocyte Sedimentation Rate (SI unit mm/hr)

Urine Chemistry

24 Hour Calcium (SI unit mmol/24hr) and (Conventional unit mg/24hr)
24 Hour Creatine (SI unit mmol/24hr) and (Conventional unit mg/24hr)
24 Hour Phosphorus (SI unit mmol/24hr) and (Conventional unit g/24hr)
24 Hour Volume (SI unit L)
Phosphorus, Random Urine (SI unit mmol) and (Conventional unit mg/dL)
Calcium, Random Urine (SI unit mmol) and (Conventional unit mg/dL)
Creatine, Random Urine (SI unit mmol) and (Conventional unit mg/dL)
TMP/eGFR (SI unit mmol/L) and (Conventional Unit mg/dL)

Mineral Metabolism

25-Hydroxyvitamin D (pg/mL)
Parathyroid hormone, Intact (pmol/L)
Calcium (SI unit mmol) and (Conventional unit mg/dL)
Phosphate (SI unit mmol) and (Conventional unit mg/dL)
Alkaline Phosphatase (SI unit U/L)
Alkaline Phosphatase, Bone specific (SI unit ug/L)

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 as 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

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

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/m ²)
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/m ²)
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/m ²)
LV Diastolic minor axis Dimension (mm)
LV Diastolic minor axis Dimension Index (mm/m ²)
LV End Diastolic Volume (mL)
LV End Diastolic Volume Index (mL/m ²)
LV End Systolic Volume (mL)
LV End Systolic Volume Index (mL/m ²)
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/m ²)
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
 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)