

CLINICAL STUDY PROTOCOL

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

Protocol Number:	INZ701-101
Investigational Product:	INZ-701 (recombinant human ectonucleotide pyrophosphatase/phosphodiesterase 1 [ENPP1] fused to the Fc fragment of IgG1; rhENPP1-Fc)
Indication:	ENPP1 Deficiency
Development Phase:	1/2
US IND Number:	142398
EudraCT Number:	2020-003716-27
ClinicalTrials.gov Identifier:	NCT04686175
Sponsor:	Inozyme Pharma, Inc. [REDACTED]
Sponsor's Responsible Signatory:	[REDACTED] Chief Medical Officer
Protocol Version:	8.0
Effective Date:	07 June 2023

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Investigational Product: INZ-701 (rhENPP1-Fc)
Protocol: INZ701-101: Version 8.0

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SPONSOR PROTOCOL APPROVAL PAGE

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Declaration of Sponsor:

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research that have their origin in the Declaration of Helsinki and the guidelines on Good Clinical Practices applicable to this clinical study.

This protocol has been approved by Inozyme Pharma. The following person is authorized on behalf of Inozyme Pharma to approve this protocol; the signature below documents this approval.



6/7/2023



Chief Medical Officer
Inozyme Pharma, Inc.

Date

INVESTIGATOR SIGNATURE PAGE

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I have read the foregoing protocol and agree to conduct this study in accordance with the current protocol. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Investigator Signature

Date

Investigator Name (Print)

Please sign, date, and return this form to your Study Monitor. Please retain a copy for your files.

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1. SYNOPSIS

Title 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
Development Phase Phase 1/2
Planned Number of Study Sites Approximately 10 sites globally
Planned Number of Subjects 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 additional cohorts to evaluate an intermediate dose level and/or alternative dosing regimen at an existing dose level, and/or enroll up to 6 additional subjects in one or more existing cohorts to further evaluate and corroborate the PK and PD of INZ-701 at an existing dose level.
Indication Ectonucleotide Pyrophosphatase/Phosphodiesterase 1 (ENPP1) Deficiency
Rationale for Treatment with INZ-701 <p>ENPP1 Deficiency is an ultra-rare, genetic disorder with an incidence of 1 in 64,000 pregnancies caused by inactivating mutations in the ENPP1 gene that encodes the ENPP1 enzyme. The ENPP1 enzyme hydrolyzes adenosine triphosphate (ATP) to generate either inorganic pyrophosphate (PPi) plus adenosine monophosphate (AMP) or inorganic phosphate (Pi) plus adenosine diphosphate (ADP). As a consequence, deficiency in this enzyme results in a decrease in PPi. PPi is an inhibitor of hydroxyapatite crystal deposition ie, mineralization, and therefore a reduction in PPi leads to mineralization in tissues that would normally not occur (since there is a loss of inhibition), resulting in a number of physiological changes and ultimately, clinical manifestations and pathological consequences which include: ectopic (especially arterial) calcification skeletal abnormalities, rickets, and osteomalacia. No targeted therapy exists for this disease. Thus, ENPP1 Deficiency has a high unmet medical need.</p> <p>The Sponsor is developing the investigational product, INZ-701, as an ERT for the treatment of ENPP1 Deficiency. Like endogenous ENPP1, the primary substrate for INZ-701 is ATP, which is cleaved to AMP and PPi, thereby increasing plasma PPi levels. Since ENPP1 Deficiency is caused by lack of sufficient or active ENPP1 enzyme, replacing the endogenous human enzyme with INZ-701 ERT should increase plasma PPi, and in turn, address the clinical manifestations of this disease.</p>

There is strong preclinical evidence to support the above concept that replacing the missing ENPP1 enzyme (ie, ERT) can restore circulating PPi levels and in turn, treat the tissue and organ abnormalities in this disease. The proof of concept for this therapeutic approach has been demonstrated in preclinical animal models of ENPP1 Deficiency. Treatment with recombinant ENPP1-Fc fusion proteins restored circulating PPi levels, reduced tissue/organ calcification, and significantly improved relevant clinical symptoms and signs. Inozyme has also evaluated INZ-701 in a mouse model of ENPP1 Deficiency. Administration of INZ-701 led to a significant increase in plasma PPi translating into prevention of soft tissue calcification and skeletal abnormalities. Further details regarding the nonclinical program, which elaborate on the proof of concept for the efficacy of INZ-701 as a treatment for ENPP1 Deficiency can be found in the INZ-701 Investigator's Brochure (IB).

Given the above, Study INZ701-101 is a 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) with ENPP1 Deficiency. Study INZ701-101 will evaluate general safety and immunological parameters to determine the risk-benefit profile of INZ701 in ENPP1 Deficiency and will identify the INZ-701 dose for further clinical development in ENPP1 Deficiency.

Objectives

Primary Objectives:

- Assess the safety and tolerability of multiple ascending subcutaneous (SC) doses of INZ-701
- Assess the immunogenicity of multiple ascending SC doses of INZ-701
- Study the pharmacokinetics (PK) of multiple ascending SC doses of INZ-701
- Study 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

Exploratory Objectives:

- 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

Study Design

Study INZ701-101 is a Phase 1/2, multicenter, open-label, FIH, and MAD 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) for further clinical development. No placebo will be used in the study. Subjects will be 18 to <65 years of age, with a confirmed genetic diagnosis of ENPP1

Deficiency and biochemical evidence of hypopyrophosphatemia (ie, PPi <1300 nM).

Safety events will be characterized and graded using the National Cancer Institute (NCI)-Common Terminology Criteria of Adverse Events (CTCAE) version 5.0 grading scale. Safety assessments, including assessments for dose limiting toxicities (DLTs), will be performed throughout the study. Dose limiting toxicity will be evaluated and managed per the pre-defined DLT criteria and rules specified in the protocol.

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. Subjects may participate in the Dose Evaluation Period only. Participation in the Extension Period is not a requirement. To participate in the Extension Period, the Investigator must assess the subject's safety data through Day 29 of the Dose Evaluation Period to confirm that dosing may continue; the subject must be willing and able to comply with the study and Investigator's requirements for dosing and must provide written informed consent to continue in the study. During the Extension Period, visits will be every 4 weeks until Week 48 and then every 12 weeks until the subject leaves the study. Subjects will complete an End of Study (EOS) Visit (Safety Follow-up Visit) 30 days after their last dose of INZ-701.

The study design of the Dose Evaluation Period is a MAD 3 + 3 with 3 dose cohorts. Additional cohorts may be added to evaluation an intermediate dose and/or an alternative dosing regimen at an existing dose level. Based on nonclinical findings and nonclinical pharmacology modeling, the initial planned doses will be 0.2 mg/kg, 0.6 mg/kg, and 1.8 mg/kg all twice weekly, not to exceed 3.6 mg/kg weekly.

Escalation to the next dose cohort will proceed after review of all safety and available PK/PD data from all subjects in the current cohort through Day 32 and recommendation from an independent DSMB. The decision to escalate to the next dose cohort will be made by the Sponsor in collaboration with the Investigators based upon the recommendation of the DSMB. The recommendation from the DSMB will be communicated by the Sponsor in writing to the Investigators, who will have 48 hours to communicate agreement or any concerns. Escalation to the next dose level will occur after resolution of any concerns, if needed. Enrollment in the next cohort will not begin until the decision to dose has been sent to each participating site in writing.

After the last subject in each cohort completes the Dose Evaluation Period, the Sponsor will conduct an ongoing review of cumulative safety and PK/PD data, including population PK, to determine if an alternative dosing regimen may be selected. This may include a flat dose (non-weight based) dosing regimen or a once weekly weight-based dosing regimen that will not exceed the maximum exposure level established by chronic GLP toxicology studies determined as safe by the Sponsor and DSMB. The selected dosing regimen can be applied on an individual cohort basis at the discretion of the Sponsor once all subjects in the individual cohort complete Week 48.

The first administration of the selected dose will be at the clinical site under medical supervision. The Investigator will determine how long the subject will receive the selected dose in the clinic and when they may return to off-site administration. The change to the selected dose may coincide with the subject's next in-clinic visit, and PK and PPi samples

will be collected.

Screening Period

During the Screening Period, assessments will be performed to determine eligibility. Screening procedures may be conducted over several days as necessary and assessments should be conducted in a manner and order to minimize the subject burden. A subject will be enrolled into the study if they meet all eligibility criteria. For subjects who do not meet eligibility criteria, certain assessments may be retested and/or the subject may be rescreened after consultation with the Sponsor.

Dose Evaluation Period

Subjects may be admitted to the clinical study site for all, or a portion(s) of the 32-day Dose Evaluation Period, at the discretion of the Investigator. Subjects must fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before the collection of pre-dose study samples. Subjects should also refrain from eating, drinking, and exercising during the 2 hours prior to the 6 hours post-dose blood sample collection. There are no additional restrictions on eating, drinking, or exercise for post-dose study sample collections. The Investigator will document the patient's compliance with fasting and no-exercise requirement as required per protocol.

Blood and urine samples will be collected. INZ-701 should be administered within 10 minutes of the pre-dose blood collection (may be extended up to 1 hour in case of challenges with the PPi sample processing). Subjects will be observed for at least 36 hours following the first administration of INZ-701 and for 6 hours after each subsequent dose for safety monitoring. Subjects will be observed for 24 hours after the dose on Day 29 to monitor for safety and collect study samples.

The Investigator or an appropriately qualified delegate will administer INZ-701 at the prescribed dose and dosing interval for each given cohort. For each subject, the first dose of INZ-701 will be administered on Day 1. On Days 8 to 29, subjects will receive the cohort-assigned dose. Dosing in each cohort between the first and second subject must be staggered by at least 8 days; the second subject in each cohort cannot receive INZ-701 until after the first subject has received their second dose of INZ-701 and completed the required 6-hour safety monitoring for that dose. The Investigator will assess the safety and tolerability data from the first subject to determine if dosing of the second subject may proceed and will inform the Sponsor accordingly. The third subject in each cohort cannot receive INZ-701 until after the second subject has received their first dose of INZ-701 and completed 6 hours of safety monitoring for that dose. The Investigator will assess the safety and tolerability data from the second subject to determine if dosing of the third subject may proceed and will inform the Sponsor accordingly.

The Dose Evaluation Period includes PK/PD sample collection and safety assessments on Days 30 to 32 following the Day 29 dose of INZ-701.

Extension Period

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

discuss available options to enable the subject to continue receiving INZ-701 (eg, off-site administration) and be monitored for safety in the Extension Period. In the event the subject provides consent to participate in the Extension Period prior to their safety data assessment through Day 29, the Investigator will reconfirm and document the subject's affirmation of consent to continue in the study.

Subjects may receive their first dose in the Extension Period on Day 32 only after completion of the Day 32 PK/PD sample collection and safety assessments. After the completion of Day 32 assessments, subjects who participate in the Extension Period will receive INZ-701 at the dose and dose schedule assigned in the Dose Evaluation Period. As described above, a subject's prescribed dosing regimen may change once the selected dose and dose schedule has been determined. The first administration of the selected dose will be at the clinical site under medical supervision. The Investigator will determine how long the subject will receive the selected dose in the clinic and when they may return to off-site administration. The change to a higher dose should coincide with the subject's next in clinic visit.

During the Extension Period (through to Week 48, and after Week 48), INZ-701 will be administered in the clinic by qualified site personnel until the Investigator determines that dosing may occur off-site (eg, at the subject's home) by the subject, the subject's caregiver(s), and/or delegated healthcare provider. The Investigator will ensure the subject, the subject's caregiver(s), and/or delegated healthcare provider(s) successfully complete dose administration training, including monitoring and management of signs and symptoms of hypersensitivity reactions, before the subject is transitioned to off-site dose administration. Off-site dose administration may be stopped or reinitiated at any time during the study as needed.

For those subjects who transition to self-administration or administration by a caregiver in the Extension Period, site staff will contact the subject at least weekly for the first 4 weeks to evaluate safety and compliance and address any questions the subject may have. The Investigator may choose to extend the duration and/or increase the frequency of these communications as needed.

The Investigator, following consultation with the Sponsor, will prescribe the required post-dose monitoring duration for each subject. For doses administered at the study site, the subject will be monitored by site staff. For doses administered away from the study site (eg, the subject's home) the subject will be monitored, as prescribed by the Investigator following consultation with the Sponsor, by the subject, the subject's caregiver(s), or by a qualified home healthcare professional (under the supervision of the Investigator) for a minimum of 1-hour post-dose. Subjects will be monitored for injection-site and hypersensitivity reactions.

Subjects should fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before the collection of pre-dose PPI blood samples. Blood and urine samples will be collected. INZ-701 should be administered as soon as possible after the pre-dose blood collection, as soon as the pre-dose samples have been processed and are confirmed to be acceptable.

End of Study Visit (Safety Follow-up Visit) – All Subjects

The End of Study (Safety Follow-up) Visit will be conducted 30 days after the last dose of INZ-701 (greater than 5 half-lives of INZ-701) for all subjects. This will include a urine

pregnancy test for women of child-bearing potential (WOCBP). Pregnancies for female partners of male subjects will also be reported.

Safety Monitoring

Study INZ701-101 will be supervised by qualified personnel, study monitors, and the Sponsor. Specific safety measures include formation of an independent, charter defined DSMB, staggered dosing of subjects during the Dose Evaluation Period, gated enrollment, individual subject early treatment discontinuation criteria, and protocol specified dose escalation, cohort stopping, and study stopping criteria.

Collection of safety data will be ongoing and reviewed at frequent intervals throughout the study. Immunogenicity will be monitored continuously during the study.

After all subjects in a cohort complete the Dose Evaluation Period, the Sponsor in collaboration with the Investigators will determine the minimum duration of post-dose monitoring for the Extension Period for each subject.

Subjects will be given instructions to contact the site and/or go to the nearest emergency room if they experience adverse events (AEs). Through Week 48 of the Extension Period, subjects will return to the clinic every 4 weeks for evaluation. After Week 48, subjects will undergo a remote or an in-clinic visit every 12 weeks until they leave the study. In addition, the study site will contact subjects minimally every 4 weeks to monitor for safety and compliance. All subjects will complete a safety follow-up visit approximately 30 days after the last dose.

Dose (mg/kg) Modifications

During the Dose Evaluation Period, no dose modifications are allowed for an individual subject. A cohort may be de-escalated to a lower dose based upon DSMB recommendation as per protocol.

During the Extension Period, the subjects' prescribed dose and dose schedule may change once the selected dosing regimen has been determined. This determination will be made based upon review of all safety and PK/PD data after all subjects have completed the Dose Evaluation Period. When the selected dosing regimen has been determined, all subjects in the Extension Period will be prescribed the selected dosing regimen.

Early Treatment and Study Discontinuation

Subjects may choose to terminate their participation in the study at any time for any reason or may be withdrawn by the Investigator. The Sponsor or its designee should be notified within 24 hours of the Investigator awareness of all early treatment discontinuations. Any subject who discontinues the study prior to completion of the Dose Evaluation Period will be asked to complete the PK/PD and safety assessments on Days 30 to 32.

Subjects who discontinue INZ-701 will be offered the opportunity to remain in the study for follow-up and assessment of their disposition. Such subjects will complete applicable study questionnaires for their duration on study.

All subjects who discontinue will be asked to complete the EOS (Safety Follow-up) Visit 30 days after their last dose of INZ-701.

Subjects who withdraw from the study for reasons other than safety reasons on or after Day 32 of the Dose Evaluation Period may re-enroll in the study at the Extension Period at the Investigator's discretion and following approval from the Sponsor. Subjects will be

required to re-consent in order to re-enroll, and subjects who re-enroll will initially receive the same dose regimen that they were receiving before withdrawing from the study for 4 weeks. After 4 weeks, the subject's dose may be modified if the dose regimen for the cohort in which the subject was originally enrolled has changed or if a new dose and schedule has been selected for all subjects.

Dose Escalation and Cohort Stopping Criteria for the Dose Evaluation Period

Escalation to the next dose cohort will proceed after review of all available safety and PK/PD data from all subjects in the current cohort and recommendation from an independent DSMB. The DLT period for dose evaluation assessment for each cohort will occur from Day 1 for the first subject in the cohort until the last subject in the cohort has completed Day 32. The rationale for this DLT period relies on the ability to observe and capture acute AEs leading to a DLT. In addition to traditional DLTs associated with biochemical and hematological serious adverse events (SAEs), DLT events in enzyme replacement therapy (ERT) are associated with acute hypersensitivity reactions. The last dose of the Dose Evaluation Period for each subject will be administered on Day 29 and the last PK/PD blood collection of the Dose Evaluation Period will occur on Day 32. Based on experience with other ERTs, this should be a sufficient period of observation to detect any event associated with a DLT.

Any change to increase the proposed maximum dose (3.6 mg/kg weekly) or maximum exposure level established by chronic GLP toxicology studies (C_{max} of [REDACTED] and AUC_{last} of [REDACTED]) will require regulatory authority approval via a substantial amendment before implementation.

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

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

- Stop enrollment at that dose level
- Declare 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) with consideration to the

following:

- Stop enrollment at that dose level
- Declare MTD at this next lower dose level
- 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.

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

Study Stopping Criteria

Dosing can be stopped for all subjects if suspected adverse drug reactions and/or changes in safety data (including but not limited to vital signs, electrocardiogram [ECG], cardiac telemetry, or clinical laboratory results) are observed and these changes pose a significant health risk. Additionally, dosing will also be stopped for all subjects for any single serious Grade ≥ 3 event deemed by the PI as related to INZ-701 unless inextricably linked to disease progression or some alternate cause.

The Sponsor will consider DSMB recommendations throughout the course of the study in accordance with the protocol. If safety considerations warrant, the Sponsor may stop the study at any time. The decision to stop the study will be reached only after review of all available safety, tolerability, PK, PD, and efficacy data.

The study will be stopped if the positive evaluation or the approval of the regulatory authority is canceled. The Sponsor also reserves the right to discontinue the study at any time for non-safety related reasons.

The Sponsor will inform the Investigators, the DSMB, and the regulatory authorities of the decision to stop the study. All participating sites will be informed without delay on the decision to stop dosing or stop the study via formal correspondence within 1 business day directly by the Sponsor or by the designated contract research organization. Subjects will be followed according to protocol and the final study visit will be planned according to the schedule of events to monitor safety in these subjects.

If the study stopping criteria are met, a decision to restart dosing will require regulatory authority approval via a substantial amendment.

Replacement of Subjects

Subjects who withdraw or are removed from the study after receiving INZ-701 and prior to completion of the Dose Evaluation Period may be replaced at the discretion of the Sponsor.

End of Study

The end of the study is defined as the date of the last protocol-specified visit/assessment for the last subject participating in the study.

INZ-701 Dosage and Formulation

INZ-701 is an investigational product being studied in patients with ENPP1 Deficiency. INZ-701 is supplied as a lyophilized powder intended for reconstitution and injection via the SC route.

INZ-701 will initially be administered SC twice weekly at doses of 0.2 mg/kg, 0.6 mg/kg, and 1.8 mg/kg. These doses bracket the efficacious dose extrapolated from a murine model of disease using an allometric conversion to human-equivalent doses; normalization of data was conducted with one half logarithm based on clinical pharmacology modeling of PPi and all nonclinical data.

Control Group

None

Estimated Duration of Subject Participation

Subject participation consists of a Screening Period of up to 30 days, a 32-day Dose Evaluation Period, and, for subjects who consent to continue on study, 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. All subjects will complete an EOS (Safety Follow-up) Visit 30 days after their last dose of INZ-701.

Population

Individuals eligible to participate must meet all of the following inclusion criteria:

1. Must provide written or electronic consent after the nature of the study has been explained, and prior to any research-related procedures, per International Conference on Harmonisation (ICH) Good Clinical Practice (GCP)
2. Clinical diagnosis of ENPP1 Deficiency supported by prior identification of biallelic *ENPP1* mutations (ie, homozygous or compound heterozygous)
3. Male or female, 18 to <65 years of age at Screening
4. PPi <1300 nM at Screening
5. WOCBP (as defined in Clinical Trials Facilitation and Coordination Group [CTFG 2020]) must have a negative serum pregnancy test at Screening
6. WOCBP and partners of fertile males who are WOCBP must be using or agree to use 1 highly effective form of contraception (per CTFG 2020) and a barrier method from at least 1 month before the first dose of INZ-701 through 30 days after the last dose of INZ-701 (greater than 5 half-lives of INZ-701). WOCBP and partners of fertile males who are WOCBP must also agree to not donate ova from the period following the first dose of INZ-701 through 30 days after last dose of INZ-701.
7. Males who are sexually active must agree to use condoms from the period following first dose of INZ-701 through 30 days after the last dose of INZ-701. Males must also agree to not donate sperm from the period following the first dose of INZ-701 through 30 days after last dose of INZ-701.
8. In the opinion of the Investigator, must be willing and able to complete the Dose Evaluation Period.
9. Agree to provide access to relevant medical records.

Individuals who meet any of the following exclusion criteria will not be eligible to participate:

1. In the opinion of the Investigator, presence of any clinically significant disease (outside of those considered associated with the diagnosis of ENPP1 Deficiency) that precludes study participation or may confound interpretation of study results, including known uncontrolled cardiovascular, thyroid, or unrelated connective tissue, bone, mineral, lipid, or muscle disease
2. Clinically significant abnormal laboratory result at Screening in the opinion of the Investigator, including but not limited to screening laboratory results demonstrating
 - a. estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] equation) $< 60 \text{ mL/min/1.73m}^2$,
 - b. 25-hydroxyvitamin D (25[OH]D) levels $< 12 \text{ ng/mL}$, or
 - c. Intact parathyroid hormone (iPTH) $> 40\%$ above the upper limit of normal
3. Known active fungal, bacterial, and/or viral infection including human immunodeficiency virus, hepatitis B virus, hepatitis C virus, or COVID-19 infection. In Germany and France, a negative COVID-19 test result is required within 5 days prior to the first dose of INZ-701.
4. Malignancy within the last 5 years, except non-melanoma skin cancers or cervical carcinoma in situ
5. Known intolerance to INZ-701 or any of its excipients
6. Unable or unwilling to discontinue the use of any prohibited medication (examples include 1,25-dihydroxy vitamin D, phosphate, anti-FGF23 [eg, burosumab], calcimimetics, calcium-containing antacids, systemic corticosteroids, PTH suppressors). Discontinuation should be undertaken only if considered not detrimental and indicated by the subject's treating physician (see [Appendix C](#) for guidelines on recommended washout periods).
7. Concurrent participation in another non-Inozyme interventional clinical study and/or receipt of any other investigational new drug within 5 half-lives of the last dose of the other investigational product or from 4 weeks prior to the first dose of INZ-701, whichever is longer, or use of an investigational device, through completion of participation in the study
8. Subjects who are pregnant, trying to become pregnant, or breastfeeding
9. Subjects who are trying to father a child

Study Procedures and Assessments

Assessments will be performed at each visit as indicated in the period-specific Schedule of Events in the protocol.

Criteria for Evaluation

Safety and Immunogenicity:

Safety assessments will be summarized at Baseline and at each observed time point. Safety variables include:

- Changes from baseline in the ENPP1 enzyme activity and neutralizing antibodies

- Incidence, frequency, and severity of AEs, treatment-related AEs, treatment-emergent AEs (TEAEs), TEAEs associated with hypersensitivity reactions, and serious adverse events (SAEs)
- Vital signs, weight and height
- Physical examinations
- Laboratory tests including chemistry with eGFR, hematology, and urinalysis, and additional biochemical parameters of interest
- Incidence of any anti-drug antibodies (ADA)
- Incidence of DLTs
- Concomitant medications
- ECG
- Holter Monitoring and/or Cardiac Telemetry and/or repeat ECGs (if required per site specific procedures and/or Investigator discretion)

Pharmacokinetic Endpoints:

- INZ-701 plasma concentration-time profiles and determination of noncompartmental PK parameters including INZ-701 plasma concentration-time profiles and determination of noncompartmental PK parameters including time to maximum plasma concentration (T_{max}), C_{max} , AUC_{last} , area under the 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 after extravascular administration of drug (CL/F), and apparent volume of distribution after extravascular administration of drug (V/F)
- Assess linearity between ascending INZ-701 SC doses and PK parameters

Pharmacodynamic Endpoints:

- Changes from baseline in 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 Efficacy Endpoints

Note: Na¹⁸F-positron emission tomography (PET)/computed tomography (CT) or low dose CT, X-rays, and dual-energy X-ray absorptiometry (DEXA) will not be performed in Germany.

- Skeletal assessment
 - X-rays and DEXA
- Arterial and organ calcification
 - Either Na¹⁸F-PET/CT or low dose CT (full body) without contrast
 - Echocardiogram
 - Renal ultrasound
- Cardiovascular function

○ Echocardiogram

The following assessments are not required. However, if the site has the ability (ie, resources, staff, etc.) to conduct them they are strongly recommended. For any non-required assessment not conducted by Day 1, the PI 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.

- 2-minute walk test, 6-minute walk test
- Hand-held dynamometry
- Grip strength dynamometry
- Range of motion
- Patient Reported Outcomes Measurement Information System
- Work Productivity and Activity Impairment Questionnaire
- Global Impression Scales
- DEXA
- X-ray of standing long legs and upper extremities, including hand and wrist
- Ankle-Brachial Pressure Index
- Pulse Wave Velocity
- Carotid ultrasound
- Spirometry
- Bone histomorphometry using transiliac crest bone biopsy (optional)

Statistical Considerations

A full description of the statistical evaluations, general considerations, and procedures for handling missing data will be provided in the Statistical Analysis Plan (SAP).

Timing of Analysis

Available data will be evaluated throughout the study for safety and observed changes from baseline in plasma PPi and other clinical intermediates.

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

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

Efficacy and Biomarker Analyses

Changes in blood and urine PD markers associated with ENPP1 Deficiency will be described as changes from baseline and in a time-dependent manner during each phase of the study and will be summarized by dose and time with descriptive statistics.

Safety Analyses

All subjects who were enrolled and received at least one dose of INZ-701 will be included

in the safety analysis. The primary safety endpoint will be evaluated by examining incidence and type of TEAEs.

PK, PD, Immunogenicity, and Exploratory Biomarker Analyses

Pharmacokinetic analysis will be performed on the PK population analysis set, and PK parameters of INZ-701 will be summarized by dose with descriptive statistics. Dose linearity of PK and PD parameters will also be assessed.

Determination of Sample Size

The minimum sample size of 9 subjects was determined empirically to evaluate dose escalation of INZ-701 and characterize initial safety, PK, and PD in the Dose Evaluation Period.

Sponsor

Inozyme Pharma, Inc.

SCHEDULE OF EVENTS

Table 1: Schedule of Events – Screening and Dose Evaluation Periods

Study Period	Screening ^a		Dose Administration									PK/PD and Safety Assessment ^b		
Day of Study	-30 to -2	-1	1	2-7	8	11	15	18	22	25	29	30	31	32
Visit Window			± 1 day ^c									+1 day ^c		
Informed Consent	X													
Informed Consent for Extension Period ^d														X
Inclusion/Exclusion Criteria ^e	X	X	X ^e											
HIV, Hepatitis B, and/or Hepatitis C tests ^f	X													
COVID-19 test (Germany and France only)	X													
Medical History, ENPP1 Deficiency Specific History, Demographics ^g	X													
Safety Evaluations														
Vital Signs ^h	X		X	X	X	X	X	X	X	X	X	X	X	X
Height	X													
Weight ⁱ	X		X											X
Physical Exam	X		X		X		X		X		X			X
Electrocardiogram ^j	X		X		X		X		X		X			X
Cardiac Telemetry and/or Holter monitoring and/or 2 repeat post-dose ECGs ^k	X		X	X ^k										
Clinical Safety Laboratory Evaluations ^{l, m}	X	X	X		X		X		X		X			X
24-hour Urine ⁿ			X								X			

Table 1: Schedule of Events – Screening and Dose Evaluation Periods

Study Period	Screening ^a		Dose Administration									PK/PD and Safety Assessment ^b		
Day of Study	-30 to -2	-1	1	2-7	8	11	15	18	22	25	29	30	31	32
Visit Window			± 1 day ^c									+1 day ^c		
Pregnancy test (WOCBP only) – serum at Screening, urine at additional assessments	X	X ^o	X ^o						X					X
Immunogenicity ^{l,p}			X		X		X		X		X			X
Adverse Event Monitoring	Throughout study													
Prior and Concomitant Medication/Therapy	Throughout study													
INZ-701 Administration														
INZ-701 Injection (SC) ^q			X		X	X	X	X	X	X	X			X ^p
Efficacy, Biomarker, PK-PD Evaluations														
Inorganic pyrophosphate (PPi) ^{l,s}	X		X	X	X	X	X	X	X	X	X	X	X	X
FGF23 ^l			X		X		X		X					X
INZ-701 PK and ENPP1 specific activity ^{l,t}			X	X	X	X	X	X	X	X	X	X	X	X
Exploratory Biomarkers (blood) - 25(OH)D and PTH only ^u	X													
Exploratory Biomarkers (blood) ^{l,u}			X											
Second Morning Urine (phosphate, calcium, creatinine) and serum phosphate and creatinine as part of the safety laboratory tests ⁿ			X								X			
Na ¹⁸ F PET/CT or low dose CT scan ^v (Note: not performed in Germany)	X													
Renal Ultrasound ^v	X													
Echocardiogram	X													

Table 1: Schedule of Events – Screening and Dose Evaluation Periods

Study Period	Screening ^a		Dose Administration									PK/PD and Safety Assessment ^b		
Day of Study	-30 to -2	-1	1	2-7	8	11	15	18	22	25	29	30	31	32
Visit Window			± 1 day ^c									+1 day ^c		
Not Required Exploratory Efficacy Evaluations ^u														
X-ray ^{v, w, x} (Note: not performed in Germany)	X													
2MWT/6MWT ^{w, y}	X													
Hand-held dynamometry, Grip strength, Range of motion ^w	X													
PROMIS, WPAI ^w	X													
Global Impression Scales ^{w, z}	X													
DEXA ^{v, w} (Note: not performed in Germany)	X													
Ankle-Brachial Pressure Index and Pulse Wave Velocity ^w	X													
Carotid Ultrasound ^w	X													
Spirometry ^w	X						X							X
Transiliac crest bone biopsy (optional) ^{w, aa}	X													
Demeclocycline prior to transiliac crest bone biopsy (if biopsy will be performed) ^{w, aa}	X													

Note: Subjects may be admitted to the clinical study site for all, or a portion(s) of the 32-day Dose Evaluation Period, at the discretion of the Investigator.

Subjects will be observed for at least 36 hours following the first administration of INZ-701 and for 6 hours after each subsequent dose for safety monitoring. Subjects will be monitored for 24 hours after the dose on Day 29 to monitor safety and collect study samples. All subjects will complete an End of Study (Safety Follow-up) Visit 30 days after their last dose if they do not wish to continue in the Extension Period of the study (Table 4).

- a **Screening:** The PI will confirm that the subject meets Inclusion Criterion No. 2 (clinical diagnosis of ENPP1 Deficiency supported by prior identification of biallelic ENPP1 mutations) before undergoing any Screening procedures. During the Screening Period, assessments will be performed to determine eligibility. For those subjects who have completed all Screening assessments and are deemed eligible but are unable to be dosed within 60 days from the start

of Screening (day of consent), a serum pregnancy test (WOCBP only) must be repeated within 30 days of dosing (can be done locally). In Germany and France only, COVID-19 test must be repeated within 5 days of dosing.

- b PK/PD and Safety Assessment Period: includes PK/PD sample collection and safety assessments on Days 30 to 32.
- c Visit Window: All assessments which don't otherwise have a specific time associated with them can be done on any day within the specified visit window even if on different days (eg, Day 1 weight can be obtained on Day -1).
- d Subject may consent to the Extension Period at any time during the Dose Evaluation Period. In the event the subject provides written informed consent prior to the Investigator's assessment of the subject's safety data through Day 29, the Investigator will reconfirm and document the subject's affirmation to continue in the study.
- e Inclusion/Exclusion Criteria: Eligibility must be confirmed prior to the first dose of INZ-701 on Day 1.
- f HIV, Hepatitis B, and Hepatitis C Tests: HIV, Hepatitis B, and Hepatitis C tests will be done at Screening where required per institutional policy.
- g Medical History includes date and method of ENPP1 Deficiency diagnosis. Each subject must have a documented historical genetic mutation analysis by a CAP/CLIA certified laboratory using a CE-marked assay.
- h Vital Signs should be obtained within 15 minutes prior to and after INZ-701 administration; and once per hour for 6 hours after dosing on days when INZ-701 is administered during visits on Days 1 to 15. After Day 15, record vital signs once per visit, prior to INZ-701 administration.
- i Weight obtained at Day 1 will be used to calculate the dose of INZ-701. If the subject's weight changes more than 10% of the Day 1 weight, the dose will be weight adjusted unless a flat dose is being used.
- j Electrocardiogram: Standard 12-lead ECGs obtained prior to dosing. Additional ECGs may be collected if clinically indicated.
- k Cardiac Telemetry and/or Holter monitoring and/or 2 repeat post-dose ECGs: if required per site specific procedures and/or Investigator discretion. Cardiac telemetry, if performed, will be obtained at Day 1 beginning pre-dose and continuing through 24 hours post-dose (Day 2).
- l Blood Collection: All blood draws should be collected, processed, and shipped (if applicable) as outlined in the Laboratory Manual. INZ-701 is to be administered as soon as possible after the pre-dose study samples have been processed and are confirmed to be acceptable. Subjects must fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before the collection of pre-dose study samples. Subjects are to refrain from eating, drinking, and exercising during the 2 hours prior to the 6 hours post-dose blood sample collection. If maximum allowed blood volume (per local guidance) may be reached for any given time-period, prioritize as follows: clinical safety laboratory evaluations, immunogenicity, PPi, ENPP1 specific activity, other biomarkers.
- m Clinical Safety Laboratory Evaluations: Obtain prior to dosing (if applicable); includes blood chemistry panel with liver function tests, hematology panel including CBC with differential, and urinalysis (see [Appendix A](#)). The requirement to obtain Day -1 safety labs is based on local site SOP and PI recommendation. On Day 1, clinical safety laboratories will also be collected 6 hours post-dose (± 30 min). Additional safety laboratory evaluations may be collected during the dose evaluation period to monitor safety at institutions where required. Cholesterol and triglycerides will be assessed at Screening only. Magnesium will be assessed at Day 1 and Day 29 only. Routine urinalysis required only at Screening and on Days 1 and 32/early termination; additional assessments may be performed if clinically indicated.
- n 24-hour Urine: 24-hour urine collection will be started on Days -1 and 28 and collected pre-dose at Days 1 and 29. On Day 1 and Day 29 Visit that includes 24-hour urine collection, a second morning urine will be collected to measure urine calcium, phosphate and creatinine. At the same time, blood sample for serum creatinine and phosphate will be collected as part of the safety laboratory tests. An aliquot of the 24-hour urine sample will be stored frozen for future urine biomarkers associated with ENPP1 Deficiency.
- o Pregnancy test required on Day -1 or Day 1, not both days.
- p Immunogenicity: All immunogenicity samples must be collected prior to dosing on indicated days. Additional samples may be obtained if clinically indicated (eg, suspected hypersensitivity reaction).

- q INZ-701 will be administered at the assigned dose level by SC injection. On Day 1 subjects will remain in the clinic for at least 36 hours and for 24 hours on day 29 after dosing for safety evaluation and sample collection. For all other doses during the Dose Evaluation Period, subjects will remain in clinic for 6 hours after each dose for safety evaluation. Dosing in each cohort between the first and second subject must be staggered by at least 8 days; the second subject in each cohort cannot receive INZ-701 until after the first subject has received their second dose of INZ-701 and undergone required 6-hour safety monitoring for that dose. The Investigator will assess the safety data from the first subject and will decide if dosing of the second subject in the cohort/dose level is well-tolerated and can proceed. Information regarding fasting, administration of INZ-701, and safety monitoring are provided in Section 8.1.2, Section 8.1.3, and Section 8.1.4. INZ-701 administration on Day 32 is the first dose of the Extension Period.
- r Dosing on Days 11, 18, and 25 is only for Cohorts 1-3.
- s PPi Sampling: Pre-dose sample must be collected in the morning. Follow PK-PD collection schedule (Table 5).
- t PK and ENPP1 Specific Activity samples will be obtained according to the PK-PD sampling schedule (Table 5).
- u Exploratory Biomarkers: include 25(OH)D, intact PTH, C-reactive protein, β 2-microglobulin, PINP, CTX, and BALP in serum and osteopontin, FGF23 (C-terminal), and ATP in plasma (Appendix A). Sample for 25(OH)D need not be collected at Day 1.
- v Na^{18}F -PET/CT or low dose CT, DEXA, X-rays, and renal ultrasound conducted within up to 6 months prior to study enrollment may be used as Baseline if they meet study requirements in the opinion of the Sponsor. Historical Na^{18}F -PET/CT, low dose CT, and/or X-rays that do not meet the specifications above may be considered for the study Baseline upon Investigator discretion in consultation with the Sponsor.
- w Exploratory Efficacy Assessments are not required. However, if the site has the ability (ie, resources, staff, etc.) to conduct them they are strongly recommended. For any non-required assessment not conducted by Day 1, the PI 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.
- x X-ray (standing long legs and upper extremities, including hand and wrist): Images will be read by a central imaging vendor.
- y 2MWT/6MWT: If the subject is unable to complete the 6MWT, they should attempt the 2MWT.
- z Global Impression Scales: At Screening, Investigators will complete the CGI-S and will administer the PGI-S and CaGI-S, if applicable.
- aa If a transiliac crest bone biopsy and Na^{18}F -PET/CT or low dose CT are performed, Na^{18}F -PET/CT or low dose CT must be performed first. Bone biopsies conducted within 6 months of study enrollment may be used as Baseline if they meet study requirements. Demeclocycline loading prior to baseline transiliac crest bone biopsy is required: two courses of demeclocycline (3 days each) separated by a 12-day (± 1 day) interim period ending 4 days (± 1 day) prior to biopsy. If demeclocycline is not available at the time of the first bone biopsy, tetracycline may be used.
- 2MWT=2-minute walk test; 6MWT=6-minute walk test; 25(OH)D=25-hydroxyvitamin D; ATP=adenosine triphosphate; BALP=bone specific alkaline phosphatase; CaGI-3=Caregiver Global Impression of Status/Severity; CAP/CLIA=College of American Pathologists/Clinical Laboratory Improvement Amendments; CBC=complete blood count; CGI-S=Clinical Global Impression of Status/Severity; COVID-19=Coronavirus 2019; CTX=carboxy terminal cross-linked telopeptide of type I collagen; DEXA=dual-energy X-ray absorptiometry; ECG=electrocardiogram; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; FGF23=fibroblast growth factor 23; HIV=human immunodeficiency virus; Na^{18}F -PET/CT=sodium fluoride positron emission tomography/computed tomography; PI=principal investigator; PINP=procollagen type 1 N-terminal propeptide; PD=pharmacodynamic; PGI-S=Patient Global Impression of Status/Severity; PET/CT=positron emission tomography/computed tomography; PK=pharmacokinetic; PPi=inorganic pyrophosphate; PROMIS=Patient Reported Outcomes Measurement Information System; PTH=parathyroid hormone; SC=subcutaneous; SOP=standard operating procedure; WOCBP=women of child-bearing potential; WPAI=Work Productivity and Activity and Impairment Questionnaire.

Table 2: Schedule of Events – Extension Period Through Week 48

Study Period	Extension Period											
Week of Assessment	8	12	16	20	24	28	32	36	40	44	48 ^a	
Compliance Window	±1 week											
INZ-701 SC Dose Administration ^b	Dose administration at the prescribed dose and dose schedule ^b											
Safety Evaluations												
Vital Signs ^c	X	X	X	X	X	X	X	X	X	X	X	X
Weight ^d		X			X			X				X
Height												X
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X			X			X				X
Clinical Safety Laboratory Evaluations ^{f, g}	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test (WOCBP) ⁱ	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity ^{fj}		X			X			X				X
Adverse Event Monitoring	Throughout Study											
Prior and Concomitant Medication/Therapy	Throughout Study											
Efficacy, Biomarker, PK-PD Evaluations												
Inorganic pyrophosphate (PPi) ^{f, k}	X	X			X			X				X
FGF23 ^f	X	X			X			X				X
INZ-701 Concentration and serum ENPP1 specific activity ^{f, k}	X	X			X			X				X
Na ¹⁸ F-PET/CT or Low Dose CT ^l (Note: not performed in Germany)												X
Echocardiogram					X							X

Table 2: Schedule of Events – Extension Period Through Week 48

Study Period	Extension Period											
Week of Assessment	8	12	16	20	24	28	32	36	40	44	48 ^a	
Compliance Window	±1 week											
Renal ultrasound											X	
Exploratory Biomarkers (blood) ^{f, m}		X			X			X			X	
Second Morning Urine (phosphate, calcium, creatinine) and serum phosphate and creatinine _h		X			X			X			X	
Not Required Exploratory Efficacy Evaluations ⁿ												
X-ray ^{m, n} (Note: not performed in Germany)					X						X	
DEXA ^{k, m} (Note: not performed in Germany)					X						X	
2MWT/6MWT ^{m, o}		X			X			X			X	
Hand-held dynamometry, Grip strength, and Range of motion ^m		X			X			X			X	
PROMIS, WPAI ^m		X			X			X			X	
Global Impression Scales ^{m, p}		X			X			X			X	
Ankle-Brachial Pressure Index and Pulse Wave Velocity ^m					X						X	
Carotid ultrasound ^m					X						X	
Spirometry ^m					X						X	
Labelling prior to Transiliac Crest Bone Biopsy (if biopsy will be performed) ^{m, q}											X	
Transiliac Crest Bone Biopsy (Optional) ^{m, q}											X	

Note: During the Extension Period, subjects who desire to transfer to another investigative site may be accommodated with discussion between the Investigator and the Sponsor to determine which of the assessments will need to be obtained at both sites to establish new Baselines. Any interruption this may cause will be allowed if the transition takes <2 weeks, unless determined otherwise by the Investigator in consultation with the Sponsor.

- a All subjects who do not wish to continue in the Extension Period beyond 48 weeks will be asked to complete the EOS (Safety Follow-up) Visit (Table 4) 30 days after their last dose in the study. For early INZ-701 and study discontinuations, subjects should complete the Week 48 assessments if possible and return for the Safety Follow-up Visit.
- b INZ-701 will be administered at the assigned dose level and schedule by SC injection starting on Day 32 of the Dose Evaluation Period after completion of PK/PD and safety assessments. The Investigator, following consultation with the Sponsor, will prescribe the required post-dose monitoring duration for each subject. The appropriate duration of monitoring for each subject will be based on available and emerging clinical safety data. Information regarding administration of INZ-701 and safety monitoring are provided in Sections 8.1.2, 8.1.3, and 8.1.4.
- c Vital Signs will be recorded prior to INZ-701 administration.
- d Weight: If the subject's weight changes more than 10% of the Day 1 weight, the dose will be weight adjusted unless a flat dose is being used.
- e Electrocardiogram: Standard 12-lead ECGs obtained prior to dosing (if applicable) and will be read centrally.
- f Blood Collection: All blood draws will be collected, processed, and shipped (if applicable) as outlined in the Laboratory Manual. INZ-701 should be administered within 10 minutes of the pre-dose blood collection (may be extended up to 1 hour in case of challenges with the PPi sample processing). Subjects should fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before the collection of the PPi blood samples. If maximum allowed blood volume (per local guidance) may be reached for any given time-period, samples will be prioritized as follows: clinical safety laboratory evaluations, immunogenicity, PPi, ENPP1 specific activity, other biomarkers. Additional blood samples may be drawn if the INZ-701 dose is changed.
- g Clinical Safety Laboratory Evaluations: Obtain prior to dosing (if applicable); includes serum chemistry panel with liver function tests, and hematology panel including CBC with differential. Cholesterol and triglycerides will be assessed at the Week 48 Visit only. Magnesium will be assessed at Week 24 and 48 only. Additional safety laboratory evaluations may be collected during the extension period to monitor safety at institutions where required or when clinically indicated. Care should be taken to not exceed the maximum allowed blood volume for any time period.
- h Second Morning Urine sample will be collected for urine calcium, phosphate and creatinine. At the same time blood sample for serum creatinine and phosphate will be collected as part of the safety laboratory tests.
- i Pregnancy Test: A urine test will be performed at all visits. A serum test will be performed in the event of a positive or inconclusive urine test.
- j Immunogenicity: All blood samples for antibody analysis must be drawn pre-dose. Additional samples may be obtained if clinically indicated (eg, suspected hypersensitivity reaction).
- k PPi, ENPP1 Specific Activity, and INZ-701 PK: Follow Table 5 for the sample collection schedule. PPi samples must be collected in the morning.
- l Na¹⁸F-PET/CT, Low Dose CT, X-rays, and DEXA not performed in Germany. Na¹⁸F-PET/CT, Low Dose CT, X-rays, and DEXA need not be performed at Week 48 if the subject has had less than 24 weeks of study participation. Na¹⁸F-PET/CT (or low dose CT) scan will only be performed at the Week 48 Visit.
- m Exploratory Biomarkers: include 25(OH)₂D, intact PTH, C-reactive protein, β 2-microglobulin, P1NP, CTX, and BALP in serum and osteopontin, FGF23 (C-terminal), and ATP in plasma (Appendix A).
- n Exploratory Efficacy Assessments are not required. However, if the site has the ability (ie, resources, staff, etc.) to conduct them they are strongly recommended. For any non-required assessment not conducted by Day 1, the PI 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 (except for the Walk Tests; see footnote p).
- o X-ray (standing long legs and upper extremities, including hand and wrist): Images will be read by a central imaging vendor.
- p Walk Tests: The subject should attempt the walk test at the Week 48 Visit, even if the subject was unable to complete the 2MWT at Screening. If the subject is unable to complete the 6MWT, they should attempt the 2MWT.
- q Global Impression Scales: In the Extension Period, Investigators will complete the CGI-I and will administer the PGI-I and CaGI-I, if applicable.

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- r If a transiliac crest bone biopsy and Na¹⁸F-PET/CT or low dose CT are performed, Na¹⁸F-PET/CT or low dose CT must be performed first. Tetracycline loading prior to bone biopsy is required: two courses of tetracycline (3 days each) separated by a 12-day (±1 day) interim period ending 4 days (±1 day) prior to biopsy. The post study-treatment bone biopsy will be performed at the Week 48 Visit and will not be required if INZ-701 is discontinued prior to Week 48. If tetracycline was used for the first bone biopsy demeclocycline should be used for the second biopsy, if available. If demeclocycline is not available tetracycline may be used for both biopsies.

2MWT=2-minute walk test; 6MWT=6-minute walk test; 25(OH)D=25-hydroxyvitamin D; ATP=adenosine triphosphate; BALP=bone specific alkaline phosphatase; CaGI-3=Caregiver Global Impression of Status/Severity; CaGI-I=Caregiver Global Impression of Improvement; CBC=complete blood count; CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Status/Severity; CT= computed tomography; CTX=carboxy terminal cross-linked telopeptide of type I collagen; DEXA=dual-energy X-ray absorptiometry; ECG=electrocardiogram; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; EOS=end of study; FGF23=fibroblast growth factor 23; Na¹⁸F-PET/CT=sodium fluoride positron emission tomography/computed tomography; P1NP=procollagen type 1 N-terminal propeptide; PD=pharmacodynamic; PGI-I=Patient Global Impression of Improvement; PGI-S=Patient Global Impression of Status/Severity; PET/CT=positron emission tomography/computed tomography; PI=principal investigator; PK=pharmacokinetic; PPi=inorganic pyrophosphate; PROMIS=Patient Reported Outcomes Measurement Information System; PTH=parathyroid hormone; SC=subcutaneous; WOCBP=women of child-bearing potential, WPAI=Work Productivity and Activity and Impairment Questionnaire.

Table 3: Schedule of Events – Extension Period Post Week 48

	Remote or In- clinic **	In- clinic	Remote or In-clinic **	In- clinic	Remote or In- clinic **	In- clinic	Remote or In- clinic **	In- clinic	Remote or In- clinic **	In- clinic	Remote or In- clinic **	In- clinic
Week	60	72	84	96	108	120	132	144	156	168	180	192
Compliance Window	±4 weeks											
INZ-701 SC Dose Administration ^a	As per the prescribed dose regimen											
Phone Calls	Site to contact subjects minimally every 4 weeks (±2 weeks) *											
Weight		X		X		X		X		X		X
Height				X				X				X
Vital Signs ^b	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam		X		X		X		X		X		X
ECG				X				X				X
Clinical Safety Laboratory Evaluations ^{c, d}		X		X		X		X		X		X
Second Morning Urine Sample ^e		X		X		X		X		X		X
Urine Pregnancy Test (WOCBP) ^f	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity ^{c, g}		X		X		X		X		X		X
Adverse Event Monitoring	Throughout the study											
Concomitant Medications	Throughout the study											
Required Efficacy, Biomarker, PK/PD Evaluations												
Inorganic pyrophosphate (PPi) ^{c, h}	X	X	X	X	X	X	X	X	X	X	X	X

Exploratory Biomarkers (blood) ^{c, i}		X		X		X		X		X		X
Not Required Exploratory Efficacy Evaluations												
DEXA ^{j, k}				X				X				X
6MWT ^{j, l}				X				X				X

* The study site will contact subjects minimally every 4 weeks to monitor for safety and compliance.

** Remote visits every 12 weeks completed by the Investigator can be performed in-clinic at the discretion of the PI.

Note: All subjects will be asked to complete the EOS (Safety -Follow-up) Visit (Table 4) 30 days after their last dose in the study.

For subjects who continue in the study beyond 48 weeks, contact will be made via telephone for safety follow-up every 4 weeks.

- a INZ-701 will be administered at the assigned dose level and schedule by SC injection. The Investigator, following consultation with the Sponsor, will prescribe the required post-dose monitoring duration for each subject based on review of individual and cumulative safety data. The post-dose monitoring duration may be reassessed based on available and emerging clinical safety data. Information regarding administration of INZ-701 and safety monitoring are provided in Sections 8.1.2, 8.1.3, and 8.1.4.
- b Vital Signs will be taken only at in-clinic visits.
- c Blood Collection: All blood draws should be collected, processed, and shipped (if applicable) as outlined in the Laboratory Manual. INZ-701 should be administered within 10 minutes of the pre-dose PPi blood collection (may be extended up to 1 hour in case of challenges with the PPi sample processing). Subjects should fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before the collection of the PPi blood samples. If maximum allowed blood volume (per local guidance) may be reached for any given time-period, samples will be prioritized as follows: clinical safety laboratory evaluations, immunogenicity, PPi, other biomarkers. Additional blood samples may be drawn if the INZ-701 dose is changed.
- d Clinical Safety Laboratory Evaluations: Obtain prior to dosing (if applicable); includes blood chemistry panel with liver function tests, hematology panel including CBC with differential, and urinalysis. Magnesium will be assessed every 48 weeks. Additional safety laboratory evaluations may be collected during the Extension Period to monitor safety at institutions where required or when clinically indicated. Care should be taken to not exceed the maximum allowed blood volume for any time-period.
- e Second Morning Urine (phosphate, calcium, creatinine) and serum phosphate and creatinine as part of the safety evaluation.
- f Pregnancy Test: A urine test will be performed at all visits. A serum test will be performed in the event of a positive or inconclusive urine test. For WOCBP, monthly pregnancy tests should be performed at home in between study visits with results reported to the study site.
- g Immunogenicity: All blood samples for antibody analysis must be drawn pre-dose. Additional samples may be obtained if clinically indicated (eg, suspected hypersensitivity reaction).
- h PPi must be collected in the morning. PPi only done during in-clinic visits.
- i Exploratory Biomarkers: include FGF23, P1NP, CTX, and BALP in serum and osteopontin (See Appendix A).
- j Exploratory Efficacy Assessments are not required. However, if the site has the ability (ie, resources, staff, etc.) to conduct them they are strongly recommended. For any non-required assessment not conducted by Day 1, the PI 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 (except for the Walk Tests; see footnote l).

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- k DEXA not performed in Germany. DEXA only performed every 48 weeks. If end of study visit is within 24 weeks of previous imaging procedures, they need not be repeated.
- l Walk Tests: The subject should attempt the walk test at the post Week 48 Visits, even if the subject was unable to complete the 6MWT at Screening or at Week 48.

6MWT=6-minute walk test; BALP=bone specific alkaline phosphatase; CBC=complete blood count; CTX=carboxy terminal cross-linked telopeptide of type I collagen; DEXA=dual-energy X-ray absorptiometry; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; P1NP=procollagen type 1 N-terminal propeptide; PD=pharmacodynamic; PI=Principal Investigator; PK=pharmacokinetic; PPi=inorganic pyrophosphate; SC=subcutaneous; WOCBP=women of child-bearing potential

Table 4: Schedule of Events – End of Study Visit (Safety Follow-up Visit)

	EOS (Safety Follow-up) Visit
Days After Treatment	30 days after last dose of INZ-701
Compliance Window	+ 7 days
Vital Signs	X
Height, Weight	X
Physical Exam	X
Electrocardiogram ^a	X
Clinical Safety Laboratory Evaluations ^{b, c}	X
Pregnancy test (WOCBP only) –urine	X
Adverse Events	X
Prior and Concomitant Medication/Therapy	X
Inorganic pyrophosphate (PPi), FGF23 ^b	X
INZ-701 PK and ENPP1 specific activity ^b	X
Immunogenicity ^b	X
Exploratory Biomarkers (blood), Second Morning Urine (phosphate, calcium, creatinine) and Serum phosphate and creatinine for TmP/GFR ^{b, d}	X
2MWT/6MWT ^e	X
PROMIS, WPAI	X
Global Impression Scales ^f	X

Note: The EOS (Safety Follow-up) Visit will be conducted for all subjects 30 days after the last dose of INZ-701.

- a Electrocardiogram: Standard 12-lead ECGs will be read centrally.
- b Blood Collection: All blood draws should be collected, processed, and shipped (if applicable) as outlined in the Laboratory Manual. Subjects should fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before blood sample collection. If maximum allowed blood volume (per local guidance) may be reached for any given time-period, samples will be prioritized as follows: clinical safety laboratory evaluations, immunogenicity, PPi, ENPP1 specific activity, other biomarkers.
- c Clinical Safety Laboratory Evaluations: Additional safety laboratory evaluations may be collected to monitor safety at institutions where required. Care should be taken to not exceed the maximum allowed blood volume for any time-period. Additional assessments may be performed if clinically indicated.
- d Exploratory Biomarkers: See [Appendix A](#), Second Morning Urine for TmP/GFR and Calcium: A urine sample (from the second morning void) and a blood sample (within 1 hour of the urine sample) will be collected to assess phosphate and creatinine levels to calculate TmP/GFR, if feasible. In addition, the urine sample will be tested for calcium levels.
- e 2MWT/6MWT: Subjects should attempt the walk test at their last visit in the study, even if they were unable to complete the 2MWT at Screening or Week 48 Visit.
- f Global Impression Scales: Investigators will complete the CGI-I and will administer the PGI-I and CaGI-I, if applicable.

2MWT=2-minute walk test; 6MWT=6-minute walk test; CaGI-3=Caregiver Global Impression of Status/Severity; CaGI-I=Caregiver Global Impression of Improvement; CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Status/Severity; CT= computed tomography; DEXA=dual-energy X-ray absorptiometry; ECG=electrocardiogram; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; FGF23=fibroblast growth factor 23; PGI-I=Patient Global Impression of Improvement; PK=Pharmacokinetic; PPi=inorganic pyrophosphate; PROMIS=Patient

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Reported Outcomes Measurement Information System; WOCBP=women of child-bearing potential;
WPAI=Work Productivity and Activity and Impairment Questionnaire

Table 5: PK/PD Sampling Schedule

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)

Note: If not possible to obtain the samples at scheduled time, PK/PD samples should be collected as close to the scheduled time as possible. Actual collection time will be noted in the eCRF.

- a Pre-dose PPi samples must be collected in the morning.
- b **Blood Collection:** All blood draws should be collected, processed, and shipped (if applicable) as outlined in the Laboratory Manual. INZ-101 should be administered within 10 minutes of the pre-dose blood collection (may be extended up to 1 hour in case of challenges with the PPi sample processing). Subjects must fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before the collection of pre-dose study samples. Subjects should also refrain from eating, drinking, and exercising during the 2 hours prior to the 6 hours post-dose blood sample collection. If maximum allowed blood volume (per local guidance) may be reached for any given time period, prioritize as follows: clinical safety laboratory evaluations, immunogenicity, PPi, ENPP1 specific activity, other biomarkers. Additional blood samples may be drawn if the INZ-701 dose is changed in the Extension Period.

eCRF= electronic case report form; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1;
PD=pharmacodynamic; PK=pharmacokinetic; PPi=inorganic pyrophosphate.

2. GLOSSARY OF TERMS

Term	Definition
1,25(OH) ₂ D	1,25-dihydroxyvitamin D
2MWT	2-minute walk test
6MWT	6-minute walk test
25(OH)D	25-hydroxyvitamin D
ABI	ankle-brachial pressure index
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AMP	adenosine monophosphate
ARHR2	autosomal recessive hypophosphatemic rickets type 2
ATP	adenosine triphosphate
ATS	American Thoracic Society
AUC _{last}	area under the plasma concentration-time curve from time zero to time of last measurable concentration
AUC _{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC _{tau}	area under the concentration-time curve over the dosing interval
CaGI	Caregiver Global Impression
CAP/CLIA	College of American Pathologists/Clinical Laboratory Improvement Amendments
CE	Conformité Européene (European Conformity)
CGI	Clinical Global Impression
CL/F	clearance after extravascular administration of drug
C _{max}	maximum plasma concentration
C _{min}	minimum plasma concentration
CRIM	cross-reactive immunologic material
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria of Adverse Events
DEXA	dual-energy X-ray absorptiometry
DLT	dose limiting toxicity
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture

Term	Definition
eGFR	estimated glomerular filtration rate
ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1
EudraCT	European Union Drug Regulating Authorities Clinical Trials
ERT	enzyme replacement therapy
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
FIH	first-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
Ig	immunoglobulin
IND	Investigational New Drug (application)
INZ-701	recombinant human ectonucleotide pyrophosphatase/phosphodiesterase 1 fused to the Fc fragment of IgG1
IRB	Institutional Review Board
MAD	multiple ascending dose
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHLI	Natural History Lead-In
NIH	National Institutes of Health
OCT	optical coherence tomography
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PET	positron emission tomography
PGI	Patient Global Impression
PI	Principal Investigator
PK	pharmacokinetic(s)
PPi	inorganic pyrophosphate
PROMIS	Patient Reported Outcomes Measurement Information System
PTH	parathyroid hormone

Term	Definition
PWV	pulse wave velocity
QOD	every other day
rhENPP1-Fc	recombinant human ectonucleotide pyrophosphatase/phosphodiesterase 1 fused to the Fc fragment of IgG1
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SERM	selective estrogen receptor modulator
SMP	Safety Management Plan
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration
TmP/GFR	tubular maximum reabsorption rate of phosphate adjusted for glomerular filtration rate
V/F	apparent volume of distribution after extravascular administration of drug
VFA	vertebral fracture assessment
WOCBP	women of child-bearing potential
WPAI	Work Productivity and Activity Impairment Questionnaire

3. INTRODUCTION

The Sponsor is developing the investigational product, INZ-701, as an enzyme replacement therapy (ERT) for the treatment of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) Deficiency. INZ-701 is a recombinant fusion protein that contains the extracellular domains of human ENPP1 coupled with an Fc fragment from an immunoglobulin (Ig)G1 antibody.

In 2018, both the United States Food and Drug Administration (FDA) Office of Orphan Products Development and the European Medicines Agency Committee for Orphan Medical Products granted Orphan Drug Designation to INZ-701 for the treatment of ENPP1 Deficiency.

INZ701-101 is a first-in-human (FIH), multiple ascending dose (MAD) dose-finding study in adult subjects (18 to <65 years of age) with ENPP1 Deficiency that seeks to identify a dose for further clinical development in ENPP1 Deficiency.

3.1. ENPP1 Deficiency

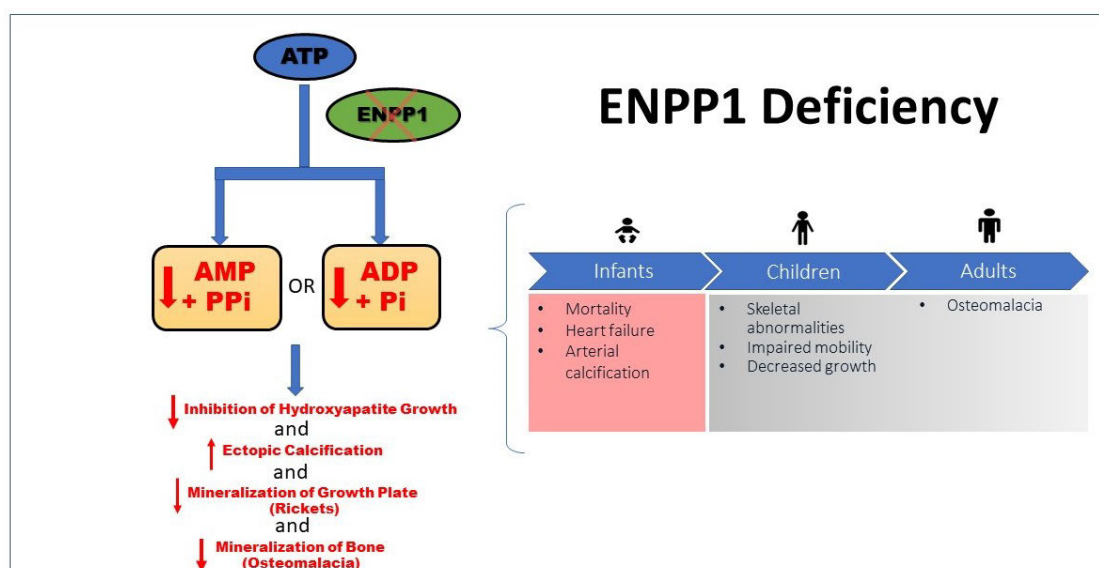
ENPP1 Deficiency is an ultra-rare, genetic disorder with an incidence of 1 in 64,000 pregnancies (Chunn, et al. 2022) caused by inactivating mutations in the ENPP1 gene that encodes the ENPP1 enzyme. The ENPP1 enzyme hydrolyzes adenosine triphosphate (ATP) to generate either inorganic pyrophosphate (PPi) plus adenosine monophosphate (AMP) or inorganic phosphate (Pi) plus adenosine diphosphate (ADP). As a consequence, a deficiency in the ENPP1 enzyme results in a decrease in PPi. PPi is an inhibitor of hydroxyapatite crystal deposition ie, mineralization, and therefore a reduction in PPi leads to mineralization in tissues that would normally not occur (since there is a loss of inhibition), resulting in a number of physiological changes and ultimately, clinical manifestations and pathological consequences which are shown in [Figure 1](#).

These pathological consequences can be devastating. In infants who suffer from ENPP1 Deficiency, an acutely life-threatening phenotypic presentation can result, in which there is generalized arterial calcification and ultimately a high rate of mortality. Among infants between ages 0 and 6 months, the risk of mortality ranges from 55% to 85% in the published medical literature ([Ferreira et al 2021](#); [Rutsch et al 2008](#)).

The ENPP1 enzyme is not only critical in regulating soft tissue calcification, but in the regulation of normal bone growth as well. ENPP1 Deficiency is associated with changes in bone microarchitecture ([Hajjawi et al 2014](#)). These microarchitectural changes can result from a compensatory increase in fibroblast growth factor 23 (FGF23) production (Edmonston and Wolf 2021). Elevated FGF23 levels may lead to hypophosphatemic rickets (Beck-Nielsen et al 2019; White et al 2001). As a result, almost 80% of patients with ENPP1 Deficiency will also present later in childhood, with an abnormality in the growth of long bones. More specifically there is an under-mineralization of the growing bones including the growth plate. The under-mineralization is due to low levels of Pi and the accompanying radiographic changes have been consistent with those of rickets (Hoppner et al 2021).

To date, there are no approved therapies for ENPP1 Deficiency and therefore there is a high unmet medical need for a treatment.

Figure 1: Overview of ENPP1 Deficiency



AMP/ATP=adenosine mono-/tri- phosphate; ARHR2=autosomal recessive hypophosphatemic rickets type 2; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; FGF23=fibroblast growth factor 23; GACI=Generalized Arterial Calcification of Infancy; PPi=inorganic pyrophosphate
References: [Orriss et al 2016](#), [Meyer 1984](#), [Hajjawi et al 2014](#), [Hori et al 2011](#), [Saito et al 2011](#)

3.2. Rationale for Treatment with INZ-701

The Sponsor is developing the investigational product, INZ-701, as an ERT for the treatment of ENPP1 Deficiency. Like endogenous ENPP1, the primary substrate for INZ-701 is ATP, which is cleaved to AMP and PPi, thereby increasing plasma PPi levels. Since ENPP1 Deficiency is caused by lack of sufficient or active ENPP1 enzyme, replacing the endogenous human enzyme with INZ-701 ERT should increase plasma PPi, and in turn, address the clinical manifestations of this disease (as described in Section 3.1 and shown in Figure 1).

There is strong preclinical evidence to support the above concept that replacing the missing ENPP1 enzyme (ie, ERT) can restore circulating PPi levels and in turn, treat the tissue and organ abnormalities in this disease. The proof of concept for this therapeutic approach has been demonstrated in preclinical animal models of ENPP1 Deficiency. Treatment with recombinant ENPP1-Fc fusion proteins restored circulating PPi levels, reduced tissue/organ calcification, and significantly improved relevant clinical symptoms and signs (Albright et al 2015; Khan et al 2018). Inozyme has also evaluated INZ-701 in a mouse model of ENPP1 Deficiency. Administration of INZ-701 led to a significant increase in plasma PPi translating into prevention of soft tissue calcification and skeletal abnormalities (Cheng et al 2021). Further details regarding the nonclinical program, which elaborate on the proof of concept for the efficacy of INZ-701 as a treatment for ENPP1 Deficiency can be found in the INZ-701 Investigator's Brochure (IB).

INZ-701 is a recombinant human ENPP1 fused to the Fc fragment of IgG1 (rhENPP1-Fc).

[REDACTED] Comprehensive information on physical characteristics and available nonclinical and clinical data are provided in the INZ-701 Investigator's Brochure (IB), which should be reviewed prior to initiating the study.

Given the above, Study INZ701-101 is a FIH, MAD, dose-finding study followed by a long-term open-label Extension Period in adult subjects (18 to <65 years of age) with ENPP1 Deficiency. Study INZ701-101 will evaluate general safety and immunological parameters to determine the risk-benefit profile of INZ701 in ENPP1 Deficiency and will identify the INZ-701 dose for further clinical development in ENPP1 Deficiency.

3.2.1. Rationale for Starting Dose Selection and Dosing Schedule

Data from nonclinical studies in mice and nonhuman primates have been used to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of INZ701, including change in PPI and the PK-PD coupling for attaining therapeutically effective PPI levels.

Cynomolgus monkeys received multiple administrations of up to 30 mg/kg subcutaneous (SC) doses in 2 studies. The data were described using a 1 compartment model with first order absorption and were used to characterize the PK of INZ-701. The PK model was validated by assessing goodness of fit plots, parameter precision, and a visual predictive check.

Data from 4 studies in juvenile and adult asj/asj mice were combined into a separate single database and used to characterize the PK and PD (defined as change in PPI) of INZ-701. One study used a single administration and 3 studies used multiple administrations of INZ-701, with doses ranging from 0.2 to 5 mg/kg SC every other day (QOD). The mouse PK model was validated using the same assessments as for the primate PK model. The PK parameters were then fixed, and the PD data were fit to an indirect effect turnover model, which permitted a lag in time between the measured concentrations and a measurable effect (PPI).

Once validated, the monkey PK model was scaled up to humans using a standard allometric function, and the mouse PD model was used without modification because no scaling metrics were available.

Based upon results from nonclinical studies, the initial administered doses of INZ-701 will be 0.2 mg/kg, 0.6 mg/kg, and 1.8 mg/kg SC, on a twice weekly dosing regimen, for 28 days (Table 1 and Table 6). These doses bracket the efficacious dose extrapolated from a murine model of disease using an allometric conversion to human-equivalent doses; normalization of data was conducted with one half logarithm based on clinical pharmacology modeling of PPI and all nonclinical data.

The first dose of INZ-701 will be administered on Day 1. From Days 8 to 29, subjects will receive their assigned doses. After the dose on Day 29, all subjects will have PK/PD assessments to determine what changes, if any, occurred in the PK/PD profile of INZ-701. In total, all subjects will receive 8 doses of INZ-701 in the Dose Evaluation Period, resulting in

an exposure of 1.6 mg/kg, 4.8 mg/kg, and 14.4 mg/kg per respective dose cohort. The Data Safety Monitoring Board (DSMB) will review all available safety and PK/PD data for subjects in each cohort. After the 72-hour post-dose PK/PD sample is collected on Day 32, subjects may continue receiving the same dose at the same dosing interval in the Extension Period until the selected dose has been determined.

At that time, the next dose may be titrated upward should the data warrant such a decision. Any change to increase the proposed maximum dose (3.6 mg/kg weekly) or maximum exposure level established by chronic Good Laboratory Practice (GLP) toxicology studies (maximum plasma concentration [$C_{\max}$] of [REDACTED] and area under the plasma concentration-time curve from time zero to time of last measurable concentration [AUC_{last}] of [REDACTED]) will require regulatory authority approval via a substantial amendment prior to implementation.

Additional information on the rationale for starting dose and dose schedule is provided in the IB.

3.3. Overall Risks and Potential Benefits

3.3.1. Risks

Since limited clinical data is available with INZ-701 in humans, identification and mitigation of risks are based upon results from the Sponsor's nonclinical studies, known risks associated with ERT in humans, and known risks from study procedures. Reproductive toxicities are unknown. Other unexpected toxicities may also occur (eg, adverse central nervous system symptoms).

Please refer to the IB for nonclinical pharmacology, safety, and toxicology study results.

3.3.1.1. Hypersensitivity

Given the potential of hypersensitivity reactions with any ERT, subjects will be monitored for such signs or symptoms, including shortness of breath, laryngeal edema, urticaria, pruritic rash, malaise, nausea, or vomiting. Please see Section 8.1.2 and Section 8.1.4 for information on monitoring and management of suspected hypersensitivity reactions to INZ-701.

3.3.1.2. Immunogenicity

Anti-drug antibodies (ADA) to INZ-701 will be assessed by a laboratory using a validated method. Samples will be stored to enable future testing including determinations of whether the antibodies are directed against the Fc or ENPP1 enzyme portions of INZ-701, if feasible. Samples may be used to assess and further establish assays for specificity confirmation (ie, titer) and neutralizing antibodies. A blood samples will also be collected and stored until a validated assay is available in order to assess the presence of cross-reactive immunologic material (CRIM), such as endogenous ENPP1.

Please see Section 9.8 for additional information.

3.3.1.3. Phlebotomy and Subcutaneous Injection

The risks associated with drawing blood and subcutaneous injections include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

3.3.1.4. Injection Site Reaction

Injection site reactions are common with the use of a therapeutic protein product and typically resolve without issue. The Investigator may offer treatment which may include, but is not limited to, the use of an antihistamine, corticosteroid, or other intervention as medically indicated per the practice of the Investigator and the policies of the site.

3.3.1.5. Radiation

Note: Radiation is not a risk for those subjects in whom they are not performed (eg, Germany).

Radiographic imaging procedures are critical to determine the level and effect of calcification and effect on vascular and organ function and bone health in subjects enrolled in this study. The estimated dose equivalent radiation is approximately 25 mSv for each full body Na¹⁸F-positron emission tomography (PET)/computed tomography (CT) scan or 3 mSv to 4 mSv for each full body low dose CT without contrast, 0.1 mSv for each X-ray, and 0.001 mSv for each dual-energy X-ray absorptiometry (DEXA). The total radiation dose equivalent for each subject opting for the full body Na¹⁸F-PET/CT scans during participation in the study is approximately 50 mSv. The total radiation dose equivalent for each subject opting for the full body low dose CT without contrast scans during participation in the study is approximately 6 to 8 mSv. These doses are estimated for adults and should fall below the annual radiation limits set by the local Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

All procedures involving exposure to radiation should not be conducted in subjects for whom there is a medical reason to avoid radiation as determined by the Investigator.

3.3.1.6. Transiliac Crest Bone Biopsy (optional)

As with any surgical procedure, transiliac crest bone biopsies have associated risks. Some possible complications include bruising and discomfort at the biopsy site, bone fracture, prolonged bleeding from the biopsy site, and infection near the biopsy site or in the bone.

The study will label bone with 2 courses of demeclocycline or tetracycline (3 days each) separated by a 12-day (± 1 day) interim period ending 4 days (± 1 day) prior to biopsy. If demeclocycline is not available at the time of the first bone biopsy, tetracycline may be used. If tetracycline was used for the first bone biopsy demeclocycline should be used for the second biopsy, if available. If demeclocycline is not available tetracycline may be used for both biopsies.

3.3.1.7. Discrimination

To the fullest extent possible, the Investigators will not disclose to third parties (insurance companies, etc.) any information about the participants without their expressed consent.

3.3.1.8. Discontinuation of Current Treatment Options

The eligibility criteria of Study INZ701-101 require the cessation of several unapproved therapies for ENPP1 Deficiency, and cessation of these unapproved therapies may have potential risks. However, review of the current literature suggests that the potential benefits of treatment with INZ-701 outweigh these risks. Discontinuation of oral phosphate or bisphosphonates should be undertaken only if considered not detrimental and indicated by the subject's treating physician. Any taper of calcitriol and phosphate must be done under the guidance of the prescribing physician and only if deemed not detrimental to subject's health. Treatment must not be withdrawn to fulfill study eligibility if it is considered necessary for clinical management of the patient.

Currently, there is no established standard treatment for ENPP1 Deficiency. The current treatment of osteomalacia due to ENPP1 Deficiency is based on the treatment regime of FGF23-mediated hypophosphatemic rickets and consists of the use of calcitriol (or analogues) and phosphate supplementation. This conventional therapy does not normalize serum phosphate and bone mineralization. These and other non-disease-specific therapies carry potential risks.

These medications (calcitriol [or analogs] and phosphate) should be stopped in accordance with [Appendix C](#).

One report in the literature suggests that etidronate, a bisphosphonate and PPI analogue, may have a therapeutic effect in the acute infantile form of the disease ([Rutsch et al 2008](#)). However, patients treated with etidronate are subject to selection and ascertainment bias because only living patients are treated and patients who have died are ignored ([Boyce et al 2020](#)). Furthermore, bisphosphonates suppress bone turnover and may lead to adynamic bone disease ([Otero et al 2013](#), [Miyai et al 2015](#)). In addition, bisphosphonates are not used in adult patients with ENPP1 Deficiency, the patient population for this study. As in the cases of other forms of hypophosphatemic rickets, treatment with oral phosphate and calcitriol leads to incomplete healing of rickets and/or side effects and is cumbersome, often resulting in poor compliance. Burosumab is a monoclonal antibody against FGF23 that increases renal reabsorption of phosphate. Burosumab is indicated for the treatment of X-linked hypophosphatemia (Crysvita [US package insert] Revised March 2023). Use of oral phosphate, calcitriol, or burosumab might increase the risk of ectopic calcification in ENPP1 Deficiency, and treatment with burosumab would not be expected to alleviate ectopic calcification, possibly increasing the mineralization of the already entombed osteocytes.

3.3.1.9. COVID-19 Exposure and Infection

There is a potential risk for exposure to and infection with COVID-19 for subjects when visiting and staying at the study site. The risk of COVID-19 infection in subjects can occur at any time during the study while the global pandemic continues. As specified in the study entry criteria for Germany and France, subjects infected with COVID-19 and/or still suffering symptoms from a prior COVID-19 infection would not be eligible but could potentially rescreen (see Section [9.1.3.2](#)), possibly leading to increases in the number of subjects screened and the total study time.

Additionally, constraints at a clinical site due to COVID-19 may cause a temporary halt to enrollment at a clinical site, which would increase the total study time.

Due to the evolving COVID-19 pandemic and affiliated guidelines on safety and minimizing risk of exposure, subject visits and assessments will be conducted in accordance with the site's COVID-19 policies and procedures. The Investigator may choose to conduct certain study visits and/or assessments that do not require in person evaluation via telemedicine or equivalent method, provided by the site. Similarly, the Investigator may choose to reschedule a study visit or assessment to ensure the safety of the subject and study staff. Visits and assessments not conducted in accordance with the protocol due to COVID-19 will be documented as such in the subject's source records and clinical database.

Recent studies have shown that visiting the hospital does not appear to impose a risk of contracting COVID-19. In a recently published retrospective case-control study from 39 US emergency departments, it was reported that colocation with COVID-19 patients was not associated with acquisition of COVID-19 ([Ridgway & Robicsek, 2020](#)). These results showed that patients who visit the hospital are not likely to be at increased risk of contracting COVID-19. A similar concern is of acquiring COVID-19 from healthcare workers, especially in their pre-symptomatic phase. This risk was also shown to be low; in a recent study, less than 1% of patients exposed to an infected healthcare worker developed COVID-19 ([Baker et al., 2020](#)).

3.3.2. Risk Mitigation

Based on evidence from nonclinical studies, the risk/benefit assessment of INZ-701 is expected to be favorable in adults with ENPP1 Deficiency. Since limited clinical data is available with INZ-701 in humans, unexpected toxicities may occur. Compliance with the eligibility criteria and study procedures, diligent safety monitoring, and applying dose limiting toxicity (DLT) criteria where appropriate may mitigate the risk to subjects in this study. Procedures to mitigate known risks with the use of ERTs and with study procedures have also been included in the Study INZ701-101 protocol.

The risk of COVID-19 exposure and infection at the study site should be minimal because clinical facilities will follow all their local governmental and institutional requirements for pandemic mitigation.

Investigators will ensure subjects are tested for COVID-19 in accordance with their local governmental and institutional requirements prior to being enrolled in the study. If stricter local requirements are in place at the study site than specified in this protocol, then they must be followed. In Germany and France only, COVID-19 testing within 5 days prior to first dose (Day 1) will serve to mitigate the risk of misreporting adverse events (AEs)/serious adverse events (SAEs) attributed to viral infection.

3.3.3. Benefits

The potential benefits for use of INZ-701 in humans are based upon results from the literature and the Sponsor's nonclinical program. It is hypothesized that INZ-701 will restore ENPP1 activity, which in turn may allow the circulating levels of PPI, an important regulator of calcification, to reach therapeutically effective levels. The results from the Sponsor's pharmacology studies clearly demonstrated the therapeutic effects of INZ-701 in prevention

of both pathological calcification and intimal proliferation in murine models of ENPP1 Deficiency.

Subjects taking part in Study INZ701-101 may or may not derive a clinical benefit from receiving INZ-701 for ENPP1 Deficiency. Study INZ701-101 will evaluate general and immunological parameters to determine the risk-benefit profile of INZ-701 and will identify the INZ-701 dose for further clinical development in ENPP1 Deficiency.

3.3.4. Risk: Benefit Overall Conclusions

Available data indicate that INZ-701 has the potential to show safety and efficacy in the treatment of ENPP1 Deficiency; nonclinical data identified no undue safety issues that would preclude use in patients with ENPP1 Deficiency and no DLT was identified at single doses as high as [REDACTED].

[REDACTED]. The hypothesized mechanism of action reinforced by nonclinical data therefore supports clinical investigation of INZ-701 in the proposed indication. The risk of COVID-19 exposure and infection during the conduct of the study has been minimized by study procedures and requirements and does not impact the overall risk:benefit analysis for this study.

Given the unmet medical need for therapies to treat ENPP1 Deficiency, the risk-benefit is considered to be favorable in Study INZ701-101 and clinical investigation of INZ-701 is warranted in ENPP1 Deficiency.

4. OBJECTIVES

4.1. Primary Objectives

- Assess the safety and tolerability of multiple ascending SC doses of INZ-701
- Assess the immunogenicity of multiple ascending SC doses of INZ-701
- Study the PK of multiple ascending SC doses of INZ-701
- Study the long-term safety and PD changes from baseline in PPi and associated biomarkers of ENPP1 Deficiency after administration of multiple SC doses of INZ-701

4.2. Exploratory Objectives

- 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

5. ENDPOINTS AND CRITERIA FOR EVALUATION

The study has been designed with an appropriate population, sufficient size, and duration to enable a preliminary assessment of safety and efficacy as related to the following criteria for evaluation.

5.1. Safety and Immunogenicity

Safety assessments will be summarized at Baseline and at each observed time point through Week 48. Safety variables include:

- Changes from baseline in the ENPP1 enzyme activity and neutralizing antibodies
- Incidence, frequency, and severity of AEs, treatment-related AEs, treatment-emergent AEs (TEAEs) associated with hypersensitivity reactions and SAEs
- Vital signs, height and weight
- Physical examinations
- Laboratory tests including chemistry with estimated glomerular filtration rate (eGFR), hematology, and urinalysis, and additional biochemical parameters of interest
- Incidence of any ADA
- Incidence of DLTs
- Concomitant medications
- Electrocardiogram (ECG)

After Extension Period Post Week 48, safety assessments will be summarized. Safety variables include:

- Incidence, frequency, and severity of AEs, treatment-related AEs, TEAEs associated with hypersensitivity reactions and SAEs
- Vital signs, height and weight
- Physical examinations
- Laboratory tests including chemistry, hematology, and second morning urine (urinalysis),
- Additional biochemical parameters of interest and pre-dose PPI
- Concomitant medications
- Urine pregnancy testing
- ECG
- Incidence of any ADA

5.2. Pharmacokinetic Endpoints

The following PK Endpoints will be assessed until Extension Period Week 48:

- INZ-701 plasma concentration-time profiles and determination of noncompartmental PK parameters including time to maximum plasma concentration (T_{max}), C_{max} , AUC_{last} , area under the 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 after extravascular administration of drug (CL/F), and apparent volume of distribution after extravascular administration of drug (V/F)
- Assess linearity between ascending INZ-701 SC doses and PK parameters

There will be no PK Endpoints measured in the Extension Period post Week 48.

5.3. Pharmacodynamic Endpoints

The following PD Endpoints will be assessed until Extension Period Week 48:

- Changes from baseline in 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

The following PD Endpoints will be assessed in the Extension Period post Week 48:

- PPI

5.4. Exploratory Efficacy Endpoints

Na¹⁸F-PET/CT or low dose CT, X-rays, DEXA, renal ultrasound, and bone biopsies that were conducted within up to 6 months prior to Screening can be used for Baseline if no prohibited drugs as described in the study entry criteria were used during this period prior to enrollment and if conducted consistent with the protocol in the opinion of the Sponsor. Historical Na¹⁸F-PET/CT, low dose CT, and/or X-rays that do not meet the specifications above may be considered for the study Baseline upon Investigator discretion in consultation with the Sponsor. The following Exploratory Efficacy Endpoints will be assessed until Extension Period Week 48:

- Skeletal assessment
 - DEXA and X-ray
- Arterial and organ calcification
 - Either Na¹⁸F-PET/CT or low dose CT (full body) without contrast
 - Echocardiogram
 - Renal ultrasound
- Cardiovascular and peripheral vascular reactivity function

– Echocardiogram

The following assessments are not required. However, if the site has the ability (ie, resources, staff, etc.) to conduct them they are strongly recommended. For any non-required assessment not conducted by Day 1, the Principal Investigator (PI) may arrange to have it conducted within 2 months following the first dose; 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, even if they were unable to complete the 2-minute walk test (2MWT) at Screening.

- 2MWT, 6-minute walk test (6MWT)
- 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 of standing long legs and upper extremities, including hand and wrist
- Ankle-Brachial Pressure Index (ABI)
- Pulse Wave Velocity (PWV)
- Carotid ultrasound
- Spirometry
- Bone histomorphometry using transiliac crest bone biopsy (optional)

Exploratory Efficacy Endpoints measured in the Extension Period post Week 48 will be 6MWT and DEXA.

6. INVESTIGATIONAL PLAN

6.1. Study Design

Study INZ701-101 is a Phase ½, multicenter, open-label, FIH, 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 ENPP1 Deficiency for further clinical development. No placebo will be used in the study.

Anticipated enrollment in the study is 9 subjects, assuming 3 cohorts are enrolled with no cohort expansion. The maximum number of subjects that could 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 DSMB in collaboration with the Sponsor. In addition, once all subjects in Cohort 3 complete Day 32, the Sponsor may choose to add additional cohorts to evaluate an intermediate dose level and/or alternative dosing regimen of an existing dose level, and/or enroll up to 6 additional subjects in one or more existing cohorts to further evaluate and corroborate the PK and PD of INZ-701 at an existing dose level. The dose and schedule that may be evaluated in an additional cohort will not exceed the cumulative twice weekly dose of 1.8 mg/kg (ie, 3.6 mg/kg weekly). The Sponsor will inform the Investigator in writing of the dose and schedule to be administered, and the Investigator will inform the subject accordingly and document the discussion in the subject source records.

Subjects will be 18 to <65 years of age, with a confirmed genetic diagnosis of ENPP1 Deficiency and biochemical evidence of hypopyrophosphatemia (ie, PPI <1300 nM).

Safety events will be characterized and graded using the National Cancer Institute (NCI)-Common Terminology Criteria of Adverse Events (CTCAE) version 5.0 grading scale. Safety assessments, including assessments for DLTs, will be performed throughout the study. Dose limiting toxicity will be evaluated and managed per the pre-defined DLT criteria and rules specified in Section 6.2.5.

The study design for the Dose Evaluation Period is presented in [Figure 2](#) and the dose escalation plan is presented in [Figure 3](#).

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. Subjects may participate in the Dose Evaluation Period only. Participation in the Extension Period is not a requirement. To participate in the Extension Period, the Investigator must assess the subject's safety data through Day 29 of the Dose Evaluation Period to confirm that dosing may continue; the subject must be willing and able to comply with the study and Investigator's requirements for dosing and must provide written informed consent to continue in the study. During the Extension Period, visits will be every 4 weeks until Week 48 and then every 12 weeks until the subject leaves the study. Subjects will complete an End of Study (EOS) Visit (Safety Follow-up Visit) 30 days after their last dose of INZ-701.

Assessments during the Screening and Dose Evaluation Periods will be performed at each visit as indicated in [Table 1](#) and during the Extension Period as indicated in [Table 2](#) and [Table 3](#).

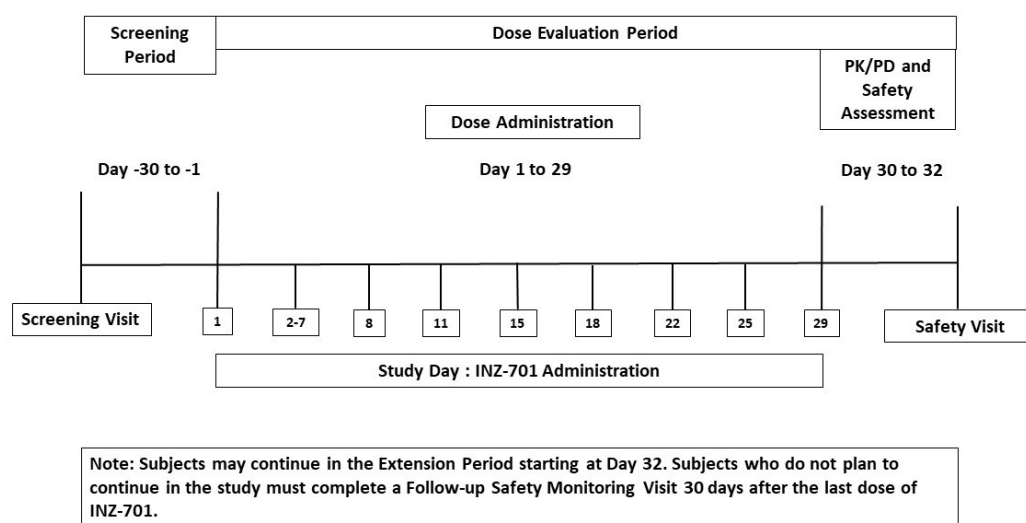
The study design of the Dose Evaluation Period is a MAD 3 + 3 with 3 dose cohorts. Additional cohorts may be added to evaluate an intermediate dose and/or an alternative dosing regimen of an existing dose level. Based on nonclinical findings and nonclinical pharmacology modeling, the initial planned doses will be 0.2 mg/kg, 0.6 mg/kg, and 1.8 mg/kg all twice weekly, not to exceed 3.6 mg/kg 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 cohort through Day 32 and recommendation from an independent DSMB. The decision to escalate to the next dose cohort will be made by the Sponsor in collaboration with the Investigators based upon the recommendation of the DSMB. The recommendation from the DSMB will be communicated by the Sponsor in writing to the Investigators, who will have 48 hours to communicate agreement or any concerns. Escalation to the next dose level will occur after resolution of any concerns, if needed. Enrollment in the next cohort will not begin until the decision to dose has been sent to each participating site in writing.

After the last subject in each cohort completes the Dose Evaluation Period, the Sponsor will conduct an ongoing review of cumulative safety and PK/PD data, including population PK, to determine if an alternative dosing regimen may be selected for the Extension Period. This may include a flat dose (non-weight based) dosing regimen or a once weekly weight-based dosing regimen that will not exceed the maximum exposure level established by chronic GLP toxicology studies determined as safe by the Sponsor and DSMB. The selected dosing regimen can be applied on an individual cohort basis at the discretion of the Sponsor once all subjects in the specific cohort complete Week 48.

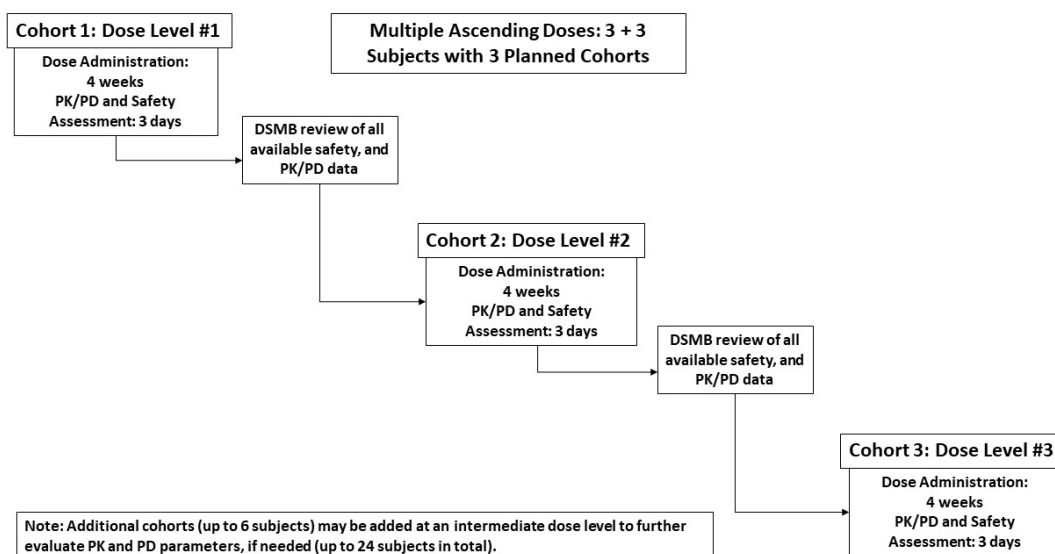
The first administration of the selected dose will be at the clinical site under medical supervision. The Investigator will determine how long the subject will receive the selected dose in the clinic and when they may return to off-site administration. The change to the selected dose may coincide with the subject's next in-clinic visit, and PK and PPi samples will be collected.

Figure 2: INZ701-101 Study Design – Dose Evaluation Period



Visits from Day 1 to 29 have a ± 1 day window. Visits from Day 30 to 32 have a ± 1 day window.

Figure 3: INZ701-101 Study Design – Cohort Plan



DSMB=Data Safety Monitoring Board

Screening Period

During the Screening Period, assessments will be performed to determine eligibility. Screening procedures may be conducted over several days as necessary and assessments should be conducted in a manner and order to minimize subject burden. A subject will be enrolled into the study if they meet all eligibility criteria. For subjects who do not meet eligibility criteria, certain assessments may be retested and/or the subject may be rescreened after consultation with the Sponsor (see Section 9.1.3.2).

Dose Evaluation Period

Subjects may be admitted to the clinical study site for all or a portion(s) of the 32-day Dose Evaluation Period, at the discretion of the Investigator. Subjects must fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before the collection of pre-dose study samples. Subjects should also refrain from eating, drinking, and exercising during the 2 hours prior to the 6 hours post-dose blood sample collection. There are no additional restrictions on eating, drinking, or exercise for post-dose study sample collections. The Investigator will document the subject's compliance with fasting and no-exercise requirement as required per protocol (see Section 9.2.2).

Blood and urine samples will be collected. INZ-101 should be administered within 10 minutes of the pre-dose blood collection. In case of challenges with the PPI sample processing, the subject should not be dosed until site staff have ensured the laboratory samples have been processed and meet the quality requirements (ie, that the samples have not hemolyzed and that the filtered PPI sample [at applicable time points] is clear and colorless). This may take up to approximately 1 hour after the blood draw. If there is a problem with the PPI processing, the sample should be redrawn. As noted in Section 8.1.2, subjects will be

observed for at least 36 hours following the first administration of INZ-701 and for 6 hours after each subsequent dose for safety monitoring. Subjects will be monitored for 24 hours after the dose on Day 29 to monitor safety and collect study samples.

If maximum allowed blood volume (per local guidance) may be reached during sample collection for any given time-period, samples will be prioritized as follows: clinical safety laboratory evaluations, immunogenicity, PPI, ENPP1 specific activity, other biomarkers.

The Investigator or an appropriately qualified delegate will administer INZ-701 at the prescribed dose and dosing interval for each given cohort (see Section 8.1.3). For each subject, the first dose of INZ-701 will be administered on Day 1. On Days 8 to 29, subjects will receive the cohort-assigned doses. Dosing in each cohort between the first and second subject must be staggered by at least 8 days; the second subject in each cohort cannot receive INZ-701 until after the first subject has received their second dose of INZ-701 and completed the required 6-hour safety monitoring for that dose. The Investigator will assess the safety and tolerability data from the first subject to determine if dosing of the second subject may proceed and will inform the Sponsor accordingly. The third subject in each cohort cannot receive INZ-701 until after the second subject has received their first dose of INZ-701 and completed 6 hours of safety monitoring for that dose. The Investigator will assess the safety and tolerability data from the second subject to determine if dosing of the third subject may proceed and will inform the Sponsor accordingly.

The Dose Evaluation Period includes PK/PD sample collection and safety assessments on Days 30 to 32 following the Day 29 dose of INZ-701.

Extension Period

Participation in the Extension Period is not a requirement. 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 subject must be willing and able to comply with the study and Investigator's requirements for dosing and must provide written informed consent to continue in the Extension Period.

The Investigator and subject will discuss available options to enable the subject to continue to receive INZ-701 and be monitored for safety in the long-term Extension Period (ie, off-site administration [dose administration and safety monitoring at the subject's home or a designated location other than the clinical site]). In the event the subject provides consent to participate in the Extension Period prior to their safety data assessment through Day 29, the Investigator will reconfirm and document the subject's affirmation of consent to continue in the study.

Subjects should receive their first dose in the Extension Period after collection of PK/PD samples and the safety assessments on Day 32.

During the Extension Period, subjects who desire to transfer to another investigative site may be accommodated with discussion between the Investigator and the Sponsor. Any interruption this may cause will be allowed if the transition takes <2 weeks, unless determined otherwise by the Investigator in consultation with the Sponsor.

Subjects who participate in the Extension Period will receive INZ-701 at the dose and dose schedule assigned in the Dose Evaluation Period.

During the Extension Period, INZ-701 will be administered in the clinic by qualified site personnel until the Investigator determines that dosing may occur off-site (eg, at the subject's home) by the subject, the subject's caregiver(s), and/or delegated healthcare provider. The Investigator will ensure the subject, the subject's caregiver(s), and/or delegated healthcare provider(s) successfully complete dose administration training, including monitoring and management of signs and symptoms of hypersensitivity reactions, before the subject is transitioned to off-site dose administration. Off-site dose administration may be stopped or reinitiated at any time during the study as needed.

The Investigator, following consultation with the Sponsor, will prescribe the required post-dose monitoring duration for each subject. For doses administered at the study site, the subject will be monitored by site staff. For doses administered away from the study site (eg, the subject's home) the subject will be monitored, as prescribed by the Investigator following consultation with the Sponsor, by the subject, the subject's caregiver(s), or by a qualified home healthcare professional (under the supervision of the Investigator) for a minimum of 1-hour post-dose. Subjects will be monitored for injection-site and hypersensitivity reactions.

For those subjects who transition to self-administration or administration by a caregiver in the Extension Period, site staff will contact the subject at least weekly for the first 4 weeks to evaluate safety and compliance and address any questions the subject may have. The Investigator may choose to extend the duration of these communications as needed.

The administered dose for a subject may change once the selected dosing regimen has been determined. The first administration of the selected dose will be at the clinical site under medical supervision. The Investigator will determine how long the subject will receive the selected dose in the clinic and when they may return to off-site administration. The change to the selected dose may coincide with the subject's next in-clinic visit.

Subjects should fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before the collection of the PPi blood samples. Blood and urine samples will be collected. INZ-101 should be administered within 10 minutes of the pre-dose blood collection (may be extended up to 1 hour in case of challenges with the PPi sample processing). If maximum allowed blood volume (per local guidance) may be reached for any given time-period, samples will be prioritized as follows: clinical safety laboratory evaluations, immunogenicity, PPi, ENPP1 specific activity, other biomarkers. Additional study samples may be collected if the INZ-701 dose is changed.

Extension Period - After Week 48

Participation in the Extension Period is not a requirement.

During the Extension Period, subjects who desire to transfer to another investigative site may be accommodated with discussion between the Investigator and the Sponsor. Any interruption this may cause will be allowed if the transition takes <2 weeks, unless determined otherwise by the Investigator in consultation with the Sponsor.

Subjects who participate in the Extension Period will receive INZ-701 at the dose and dose schedule assigned in the Dose Evaluation Period.

Subjects should fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before the collection of the PPi blood samples. Blood

and urine samples will be collected. INZ-101 should be administered within 10 minutes of the pre-dose blood collection (may be extended up to 1 hour in case of challenges with the PPI sample processing). If maximum allowed blood volume (per local guidance) may be reached for any given time-period, samples will be prioritized as follows: clinical safety laboratory evaluations, immunogenicity, PPI, ENPP1 specific activity, other biomarkers. Additional study samples may be collected if the INZ-701 dose is changed.

End of Study Visit (Safety Follow-up Visit) – All Subjects

The EOS (Safety Follow-up Safety) Visit will be conducted 30 days after the last dose of INZ-701 (greater than 5 half-lives of INZ-701) for all subjects. This will include a urine pregnancy test for subjects who are women of child-bearing potential (WOCBP). Pregnancies for female partners of male subjects will also be reported.

6.2. Safety Monitoring

Study INZ701-101 will be supervised by qualified personnel, study monitors, and the Sponsor. Specific safety measures include formation of an independent, charter-defined DSMB, staggered dosing of subjects in the Dose Evaluation Period, gated enrollment, individual subject early treatment discontinuation criteria (Section 6.2.4), and protocol-specified dose escalation, cohort stopping, and study stopping criteria (Sections 6.2.3, 6.2.5 and 6.2.6).

Collection of safety data will be ongoing and reviewed at frequent intervals throughout the study. Immunogenicity will be monitored continuously during the study.

After all subjects in a cohort complete the Dose Evaluation Period, a DSMB will review all available safety and PK/PD data and recommend appropriateness of dose escalation. The Sponsor in collaboration with the Investigator will determine the minimum duration of post-dose monitoring for the Extension Period for that cohort and any prior cohort.

Subjects will be monitored after each dose for injection-site and hypersensitivity reactions. Subjects will be given instructions to contact the site and/or go to the nearest emergency room if they experience AEs. Subjects will be trained to recognize the signs and symptoms of hypersensitivity reactions, including anaphylaxis, and will be provided with an adrenaline (epinephrine) auto-injector and be trained in its use.

Through Week 48 of the Extension Period, subjects will return to the clinic every 4 weeks for evaluation. After Week 48, subjects will return to the clinic for an in-clinic visit every 24 weeks until the subject leaves the study. In addition, the study site will contact subjects minimally every 4 weeks to monitor for safety and compliance. All subjects will complete a safety follow-up visit approximately 30 days after the last dose.

6.2.1. Data Safety Monitoring Board

An independent DSMB is described in the DSMB Charter. The DSMB will be comprised of members with expertise in the treatment of rare metabolic disorders and an immunologist.

The DSMB will review all available safety data at regular intervals. After all subjects in a cohort complete a given dose level during the Dose Evaluation Period, the DSMB will review all available safety and PK/PD data and recommend if dose escalation is appropriate.

During the Extension Period, the DSMB will monitor safety in accordance with the DSMB charter.

6.2.2. Dose (mg/kg) Modifications

During the Dose Evaluation Period, no dose modifications are allowed for an individual subject. A cohort may be de-escalated to a lower dose based upon DSMB recommendation as per protocol.

During the Extension Period, the prescribed dose for a subject may change once the selected dosing regimen (ie, dose and dose schedule) has been determined. This determination will be made based upon review of all safety and PK/PD data after all subjects have completed the Dose Evaluation Period. When the selected dosing regimen has been determined, all subjects in the Extension Period will be prescribed the selected dosing regimen.

6.2.3. Dose Escalation Criteria for the Dose Evaluation Period

Escalation to the next dose cohort will proceed after review of all available safety and PK/PD data from all subjects in the current cohort and recommendation from an independent DSMB. At minimum, all AE data, chemistry, and hematology will be evaluated, and ADAs in the event of a suspected immunologically relevant AE. The last dose of the Dose Evaluation Period for each subject will be administered on Day 29 and the last PK/PD blood collection of the Dose Evaluation Period will occur on Day 32.

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. The recommendation from the DSMB will be communicated by the Sponsor in writing to the Investigators, who will have 48 hours to communicate agreement or any concerns. Escalation to the next dose level will occur after resolution of any concerns, if needed. Enrollment in the next cohort will not begin until the decision to dose has been sent to each participating site in writing.

Any change to increase the proposed maximum dose (3.6 mg/kg weekly) or maximum exposure level established by chronic GLP toxicology studies (C_{max} of [REDACTED] and AUC_{last} of [REDACTED]) will require regulatory authority approval via a substantial amendment prior to implementation.

6.2.4. Early Treatment and Study Discontinuation

Subjects may choose to terminate their participation in the study at any time for any reason or may be withdrawn by the Investigator. The Sponsor or its designee should be notified within 24 hours of the Investigator awareness of all early treatment discontinuations. Any subject who discontinues the study prior to completion of the Dose Evaluation Period will be asked to complete the PK/PD and safety assessments on Days 30 to 32.

Subjects who withdraw may be re-enrolled following approval from the Sponsor and re-consent.

Subjects who discontinue INZ-701 will be offered the opportunity to remain in the study for follow-up and assessment of their disposition. Such subjects will complete applicable study questionnaires for their duration on study.

All subjects who discontinue treatment or the study will be asked to complete the EOS (Safety Follow-up) Visit 30 days after their last dose of INZ-701.

6.2.5. Cohort Stopping Criteria

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

The DLT period for dose evaluation assessment for each cohort will occur from Day 1 for the first subject in the cohort until the last subject in the cohort has completed Day 32. The rationale for this DLT period relies on the ability to observe and capture acute AEs leading to a DLT. In addition to traditional DLTs associated with biochemical and hematological SAEs, DLT events in ERTs are associated with acute hypersensitivity reactions. Based upon experience with other ERTs, this should be a sufficient period of observation to detect any event associated with a DLT.

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

- Stop enrollment at that dose level
- Declare 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 to make dosing and dose level recommendations.

For each dose level, if 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) with consideration to the following :

- Stop enrollment at that dose level
- Declare MTD at the next lower dose level
- 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.

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

6.2.6. Study Stopping Criteria

Dosing can be stopped for all subjects if suspected adverse drug reactions and/or changes in safety data (including but not limited to vital signs, ECG, cardiac telemetry, or clinical laboratory results) are observed and these changes pose a significant health risk.

Additionally, dosing will also be stopped for all subjects for any single serious Grade ≥ 3 event deemed by the PI as related to INZ-701 unless inextricably linked to disease progression or some alternate cause.

The Sponsor will consider DSMB recommendations throughout the course of the study in accordance with Section 6.2.5. If safety considerations warrant, the Sponsor may stop the study at any time. The decision to stop the study will be reached only after review of all available safety, tolerability, PK, PD, and efficacy data.

The study will be stopped if the positive evaluation or the approval of the regulatory authority is canceled. The Sponsor also reserves the right to discontinue the study at any time for non-safety related reasons.

The Sponsor will inform the Investigators, the DSMB, and the regulatory authorities of the decision to stop the study. All participating sites will be informed without delay on the decision to stop dosing or stop the study via formal correspondence within 1 business day directly by the Sponsor or by the designated contract research organization (CRO). Subjects will be followed according to protocol and the final study visit will be planned according to the schedule of events to monitor safety in these subjects.

If the study stopping criteria are met, a decision to restart dosing will require regulatory authority approval via a substantial amendment.

6.3. Number of Sites and Subjects

INZ701-101 is a multicenter study, with approximately 10 sites globally expected to participate. Anticipated enrollment in the study is 9 subjects, assuming 3 cohorts are enrolled with no cohort expansion. The maximum number of subjects that could 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 DSMB in collaboration with the Sponsor. In addition, once all subjects in Cohort 3 complete Day 32, the Sponsor may choose to add additional cohorts to evaluate an intermediate dose level and/or an alternative dosing regimen of an existing dose level, and/or enroll up to 6 additional subjects in one or more existing cohorts to further evaluate and corroborate the PK and PD of INZ-701.

6.4. Method of Assigning Subjects to Treatment Groups

All subjects will be sequentially assigned a unique identification number upon providing informed consent. All eligible subjects will receive INZ-701 at the assigned dose level in this single-arm study; dose cohorts will be enrolled sequentially.

6.5. Blinding

No subjects or study personnel will be blinded to treatment assignment. The study is designed as an open-label study; all subjects will receive INZ-701. Where possible, objective measures have been incorporated into the study design to minimize bias.

6.6. End of Study

The end of the study is defined as the date of the last protocol-specified visit/assessment for the last subject participating in the study.

6.6.1. Termination of the Clinical Study

If the Investigator, the Sponsor, or the Sponsor's designee becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, then the clinical study may be terminated.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study
- Failure to enroll subjects at the required rate
- A decision by the Sponsor to suspend the study, or to suspend or discontinue development of INZ-701, for any reason
- Events that trigger study stopping criteria (Section 6.2.6)

The study may also be terminated at the Sponsor's discretion in the absence of such a finding at any time and for any reason.

7. POPULATION

7.1. Inclusion Criteria

Individuals eligible to participate must meet all of the following inclusion criteria:

1. Must provide written or electronic consent after the nature of the study has been explained, and prior to any research-related procedures, per International Conference on Harmonisation (ICH) Good Clinical Practice (GCP)
2. Clinical diagnosis of ENPP1 Deficiency supported by prior genetic identification of biallelic ENPP1 mutations (ie, homozygous or compound heterozygous)
3. Male or female, ages 18 to <65 years of age at Screening

4. PPI <1300 nM screening
5. WOCBP (as defined in Clinical Trials Facilitation and Coordination Group [CTFG 2020]) must have a negative serum pregnancy test at Screening
6. WOCBP and partners of fertile males who are WOCBP must be using or agree to use 1 highly effective form of contraception (per CTFG 2020) and a barrier method from at least 1 month before the first dose of INZ-701 through 30 days after last dose of INZ-701 (greater than 5 half-lives of INZ-701). WOCBP and partners of fertile males who are WOCBP must also agree to not donate ova from the period following the first dose of INZ-701 through 30 days after last dose of INZ-701.
7. Males who are sexually active must agree to use condoms from the period following first dose of INZ-701 through 30 days after the last dose of INZ-701. Males must also agree to not donate sperm from the period following the first dose of INZ-701 through 30 days after last dose of INZ-701.
8. In the opinion of the Investigator, must be willing and able to complete the Dose Evaluation Period
9. Agree to provide access to relevant medical records

7.2. Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate:

1. In the opinion of the Investigator, presence of any clinically significant disease (outside of those considered associated with the diagnosis of ENPP1 Deficiency) that precludes study participation or may confound interpretation of study results, including known uncontrolled cardiovascular, thyroid, or unrelated connective tissue, bone, mineral, lipid, or muscle disease
2. Clinically significant abnormal laboratory result at Screening in the opinion of the Investigator, including but not limited to screening laboratory results demonstrating
 - a. eGFR (Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] equation) <60 mL/min/1.73m²,
 - b. 25-hydroxyvitamin D (25[OH]D) levels <12 ng/mL, or
 - c. Intact parathyroid hormone (iPTH) >40% above the upper limit of normal
3. Known active fungal, bacterial, and/or viral infection including human immunodeficiency virus, hepatitis B virus, hepatitis C virus, or COVID-19 infection. In Germany and France only, a negative COVID-19 test result is required within 5 days prior to the first dose of INZ-701.
4. Malignancy within the last 5 years, except non-melanoma skin cancers or cervical carcinoma in situ
5. Known intolerance to INZ-701 or any of its excipients
6. Unable or unwilling to discontinue the use of any prohibited medication (examples include 1,25-dihydroxyvitamin D, phosphate, anti-FGF23 [eg, burosumab],

calcimimetics, calcium-containing antacids, systemic corticosteroids, PTH suppressors). Discontinuation should be undertaken only if considered not detrimental and indicated by the subject's treating physician (see [Appendix C](#) for guidelines on recommended washout periods).

7. Concurrent participation in another non-Inozyme interventional clinical study and/or receipt of any other investigational new drug within 5 half-lives of the last dose of the other investigational drug or from 4 weeks prior to the first dose of INZ-701, whichever is longer, or use of an investigational device through completion of participation in the study
8. Subjects who are pregnant, trying to become pregnant, or breastfeeding
9. Subjects who are trying to father a child

7.3. Estimated Duration of Subject Participation

Subject participation consists of a Screening Period of up to 30 days, a 32-day Dose Evaluation Period, and, for subjects who consent to continue on study, 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. All subjects will complete an EOS (Safety Follow-up) Visit 30 days after their last dose of INZ-701.

7.4. Early INZ-701 Discontinuation Criteria

A subject may discontinue study treatment at any time. The Sponsor or its designee should be notified within 24 hours of the Investigator awareness of all early treatment discontinuations. Any subject who chooses to discontinue treatment prior to completion of the Dose Evaluation Period will be asked to complete the PK/PD and safety assessments on Days 30 to 32. All subjects who discontinue treatment at or prior to Week 48 will be asked to complete the Follow-up Safety Monitoring Visit 30 days after the last dose of INZ-701.

Reasons for early discontinuation from study treatment may include, but are not limited to:

- Subject experiences significant and disabling disease progression, organ disfunction, or unacceptable toxicity which necessitates removal from study treatment
- Subject experiences worsening ENPP1 Deficiency clinical condition or disease progression requiring initiation of current treatment options prohibited in [Section 7.2](#) and [Section 8.4](#), based on the subject's treating physician criteria and as per local guidelines
- Subject requests to withdraw from study treatment
- Occurrence of an AE or clinically significant laboratory abnormality that, in the opinion of the Investigator, warrants permanent discontinuation from study treatment.
- Subject becomes pregnant during the study.

The Sponsor should be notified as soon as possible of any discontinuation of INZ-701 due to an AE.

7.5. Early Study Discontinuation Criteria

Subjects may withdraw their consent to participate in the study at any time without prejudice. The Investigator must comply with any subject who requests to be withdrawn.

A subject may be discontinued from study participation at any time at the discretion of the Investigator in accordance with clinical judgment. The Sponsor or its designee should be notified within 24 hours of the Investigator awareness of all subject discontinuations.

Any subject who chooses to withdraw from the study prior to completion of the Dose Evaluation Period will be asked to complete the PK/PD and safety assessments on Days 30 to 32.

All subjects who discontinue from the study will be asked to complete the Follow-up Safety Monitoring Visit 30 days after the last dose of INZ-701.

Early termination from the study may occur if:

- In the opinion of the Investigator, the subject cannot safely participate in the procedures required by the protocol
- A subject withdraws consent to participate
- A subject requires or has taken medication prohibited by the protocol
- A subject is unwilling or unable to comply with study requirements
- A subject was erroneously enrolled into the study or does not meet the eligibility criteria
- A subject is lost to follow-up
- Active infection with COVID-19
- Non-compliance with dosing or assessment requirements

If a subject fails to return for a scheduled visit, a documented effort must be made to determine the reason. If the subject cannot be reached after 2 attempts, a certified letter should be sent to the subject requesting contact with the Investigator. Contacts should be recorded in the study records.

7.5.1. Subject Reenrollment

Subjects who withdraw from the study for reasons other than safety reasons on or after Day 32 of the Dose Evaluation Period may re-enroll in the study at the Extension Period at the Investigator's discretion and following approval from the Sponsor. Subjects will be required to re-consent in order to re-enroll, and subjects who re-enroll will initially receive the same dose that they were receiving before withdrawing from the study for 4 weeks. After 4 weeks, the subject's dose may be modified if the dose regimen for the cohort in which the subject was originally enrolled has changed or if a new dose and schedule has been selected for all subjects.

7.6. Replacement of Subjects

Subjects who are considered non-evaluable for the Dose Evaluation Period for whatever reason, or withdraw, or are removed from the study after receiving INZ-701 and prior to completion of the Dose Evaluation Period may be replaced on a case-by-case basis at the discretion of the Sponsor.

8. TREATMENT OF SUBJECTS

During the Dose Evaluation Period, subjects will receive open-label INZ-701 as a single agent as specified in [Table 6](#).

Table 6: INZ-701 Weekly Dosing Levels in the Dose Evaluation Period

Cohort Dose Level	INZ-701 Dose Cohorts (n=3 per cohort with an optional 3 subject expansion)
1	0.2 mg/kg twice weekly
2	0.6 mg/kg twice weekly
3	1.8 mg/kg twice weekly
Additional Cohorts	The Sponsor will determine the appropriate safe dose and dose schedule (not to exceed 3.6 mg/kg weekly).

Note: The Sponsor may decide to enroll up to 6 additional subjects into the Dose Evaluation Period at any dose and dose schedule deemed safe, not to exceed 1.8 mg/kg twice weekly or 3.6 mg/kg weekly.

During the Extension Period, subjects will be administered INZ-701 at the dose and dose schedule assigned in the Dose Evaluation Period. However, the administered dose and dose schedule for a subject may change once the selected dosing regimen has been determined upon completion of the Dose Evaluation Period, at which time all subjects will be assigned to the selected dosing regimen.

If the subject's dose schedule is twice weekly, each dose should be separated from the prior dose by 2 to 3 days. If a separation of only one day is necessary to ensure that a dose is not missed, the doses can be separated by a single day between doses, but doses should not be given on consecutive days.

If the subject's dose schedule is weekly, each dose should be separated from the prior dose by approximately 6 days (± 1 day).

8.1. Investigational Product: INZ-701

INZ-701 is an investigational product being studied in patients with ENPP1 Deficiency. INZ-701 is supplied as a lyophilized powder intended for reconstitution and injection by SC route. INZ-701 is supplied in a 2R vial, containing 25 mg INZ-701. INZ-701 should be stored at 2°C to 8°C prior to dilution and administration.

INZ-701 was manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) regulations. Additional information on physical and chemical properties of INZ-701 is provided in the IB.

8.1.1. INZ-701 Accountability

INZ-701 will be stored in a secure, limited access location at controlled temperatures as described in the IB and according to product packaging. The storage facility must be available for inspection by the study monitor at any time during the study. INZ-701 will be dispensed in accordance with the conditions specified in this protocol.

Pharmacy Staff or designee must maintain accountability records for all INZ-701 received, dispensed, returned, and/or lost during the study. This record must be kept current and made available to the study monitor for inspection. Following the close-out of the study, all unused INZ-701 must be returned to the Sponsor and/or its designee unless other instructions have been provided for final disposition of INZ-701.

For off-site administration of INZ-701 by the subject, the subject's caregiver(s), or delegated health care provider during the Extension Period, a sufficient supply of the investigational product and associated supplies will be dispensed to support dosing until the next in-clinic visit. The subject, the subject's caregiver(s), or healthcare provider will be required to document the date, time, injection volume, and injection site for each dose administered and return used vials to the study site for drug accountability.

8.1.2. Post-dose Safety Monitoring

During the Dose Evaluation Period, following administration of the first dose of INZ-701, subjects will be observed for at least 36 hours in the clinic to monitor safety and to collect PK/PD samples. During Days 3 to 7, all subjects will have PK/PD sampling and safety assessments. On Days 8 through 25, subjects will receive their assigned doses twice weekly and will remain in the clinic for at least 6 hours after each dose for safety monitoring and to collect PK/PD samples.

Subjects will receive their last dose of INZ-701 during the Dose Evaluation Period on Day 29 and will be observed for 24 hours for safety monitoring and to collect PK/PD samples. PK/PD samples will be collected on Day 30 (24-hour sample). On Days 31 and 32, all subjects will have PK/PD sample collection and safety assessments.

After all subjects in a cohort complete the Dose Evaluation Period, the Sponsor in collaboration with the Investigators will determine the minimum duration of post-dose monitoring for the Extension Period for that subject.

Subjects who participate in the Extension Period will receive INZ-701 twice weekly at the dose assigned in the Dose Evaluation Period. The Investigator, following consultation with the Sponsor, will prescribe the required post-dose monitoring duration for each subject based on review of individual and cumulative safety data. The recommended post-dose monitoring duration may be reassessed based on available and emerging clinical safety data.

For doses administered at the study site, the subject will be monitored by site staff. For doses administered away from the study site (eg, the subject's home) the subject will be monitored, as prescribed by the Investigator following consultation with the Sponsor, by the subject, the

subject's caregiver(s), or by a qualified home healthcare professional (under the supervision of the Investigator) for a minimum of 1-hour post-dose. Subjects will be monitored for injection-site and hypersensitivity reactions.

An EOS (Safety Follow-up) Visit will be conducted 30 days after the last dose of INZ-701 (greater than 5 half-lives of INZ-701) for all subjects.

8.1.3. INZ-701 Administration

During the Dose Evaluation Period, INZ-701 will be administered by qualified site personnel as a SC injection at the assigned dose and schedule (see [Table 1](#)). Dosing in each cohort between the first and second subject must be staggered by at least 8 days; the second subject in each cohort cannot receive INZ-701 until after the first subject has received their second dose of INZ-701 and completed the required 6-hour safety monitoring for that dose. The Investigator will assess the safety and tolerability data from the first subject to determine if dosing of the second subject may proceed and will inform the Sponsor accordingly. The third subject in each cohort cannot receive INZ-701 until after the second subject has received their first dose of INZ-701 and completed 6 hours of safety monitoring for that dose. The Investigator will assess the safety and tolerability data from the second subject to determine if dosing of the third subject may proceed and will inform the Sponsor accordingly.

For each subject, the first dose of INZ-701 will be administered on Day 1. On Days 8 to 29, subjects will receive the proposed doses twice weekly, with a final dose on Day 29. If possible, the dose should be administered at approximately the same time on each dosing day.

During the Extension Period, INZ-701 will be administered in the clinic by qualified site personnel until the Investigator determines that dosing may occur off-site (eg, at the subject's home) by the Subject or their caregiver(s) and/or delegated healthcare provider. The Investigator will ensure the subject, the subject's caregiver(s), and/or delegated healthcare provider(s) successfully complete dose administration training, including monitoring and management of signs and symptoms of hypersensitivity reactions, before the subject is transitioned to off-site dose administration. Off-site dose administration may be stopped or reinitiated at any time during the study as needed.

INZ-701 will be administered as a SC injection at the assigned dose and schedule during the Extension Period (see [Table 2](#) and [Table 3](#)). The Investigator should consult with the Sponsor if at any time during the Extension Period INZ-701 is not administered during a 2-week window or if more than one episode of missing multiple doses occurs.

8.1.4. Monitoring and Management of Suspected Hypersensitivity

Given the potential of hypersensitivity reactions with any ERT, subjects will be monitored for such signs or symptoms, including shortness of breath, laryngeal edema, urticaria, pruritic rash, malaise, nausea, or vomiting. Subjects will be monitored after each dose for site reactions and hypersensitivity reactions. Subjects will be provided instructions to contact the site and/or go to the nearest emergency room if they experience any AEs. Subjects will be trained to recognize the signs and symptoms of hypersensitivity reactions, including anaphylaxis, and will be provided with an adrenaline (epinephrine) auto-injector and be trained in its use.

Subjects will be monitored for symptoms following the guidelines in Section 8.1.2. Symptoms can be treated with epinephrine, antihistamine, and/or corticosteroid as medically indicated. The Investigator will prescribe rescue medications as part of the orders for off-site administration.

8.1.5. Dose Modifications (mg/kg) and Missed Doses

During the Dose Evaluation Period, no dose modifications are allowed for an individual subject. A cohort may be de-escalated to a lower dose based upon DSMB recommendation as per protocol.

Criteria for early treatment discontinuation are described in Section 7.4.

If a subject misses a scheduled dose in the Dose Evaluation Period, that dose can be given within 24 hours of the intended time of the missed dose without any further changes in subsequent dosing. If this does not occur, the subject will be terminated from treatment and followed per the early termination procedures. See Section 7.4 for early INZ-701 discontinuation, Section 7.5 for early study discontinuation, and Section 7.6 for replacement of subjects.

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

If a subject's prescribed dose (ie, mg/kg) is adjusted or if their weight changes by $\geq 10\%$ from Baseline, the Investigator may re-calculate their dose using the weight at the study visit (unless a flat dose is being used).

8.2. Dose Administration Compliance

Dose administration compliance will be documented in the source records and electronic case report form (eCRF) by recording the date and time of each dose administration. Reasons for any noncompliance should be recorded.

For dose administration outside of the clinical site, the subject, subject's caregiver(s), or the home healthcare provider will complete a dose diary to record each dose.

8.3. Prior and Concomitant Medication or Therapy

Definitions of prior and concomitant medications are provided in Section 9.5.

If a subject is receiving high-dose biotin supplements (found in multivitamins, biotin supplements, and supplements for hair, skin, and nail growth), advise the caregiver and the laboratory regarding potential interference in laboratory assessments (FDA 2017).

Subjects who are being treated with statins or PCSK9 inhibitors and are on stable doses in the opinion of the Investigator should be maintained on treatment.

Other than the medications specifically prohibited in this protocol (see Section 8.4), subjects may receive concomitant medications as required. Changes to concomitant medications or non-drug therapies (including changes in dose or frequency) should be recorded at each visit.

8.4. Prohibited Medication or Therapy

Use of medications that may confound the interpretation of study results is prohibited throughout the Dose Evaluation Period and Extension Period. Confounding medications include those discussed below and in [Appendix C](#).

If subject is receiving calcitriol and oral phosphate, after the calcitriol has been stopped, the phosphate may be tapered to avoid hypercalcemia/hypercalcuria per standard of care.

If clinically indicated, as determined by the PI in consultation with the Sponsor, calcium supplementation could be used during the Extension Period.

Recommended bisphosphonate washout periods are listed in [Appendix C](#); bisphosphonates cannot be used during the study.

Discontinuation of 1,25-(OH)₂D and phosphate should be undertaken only if considered not detrimental and indicated by the subject's treating physician. Treatment must not be withdrawn to fulfill study eligibility if it is considered necessary for clinical management of the patient.

Additional prohibited medications throughout the Dose Evaluation Period and Extension Period include:

- Calcimimetics or PTH suppressors and modulators
- Systemic corticosteroids (>5 mg prednisone equivalent per day, systemic oral or transdermal estrogen (use for contraception is allowed), selective estrogen receptor modulators (SERMs), hormone ablation therapy, tibolone
- Anti-FGF23 (eg, burosumab) or other biologic bone modulators

9. PROCEDURES AND ASSESSMENTS

Parameters to be assessed, along with the timing of assessments are provided in [Table 1](#), [Table 2](#), [Table 3](#), [Table 4](#) and [Table 5](#). Screening-specific assessments, along with measures of efficacy, safety, INZ-701 concentration, and other laboratory evaluations are described briefly in the following sections. Consult the study manuals for additional information and guidance on procedures.

9.1. Screening and Baseline Assessments

During the Screening Period, assessments will be performed to determine eligibility and/or provide a Baseline to determine changes due to administration of INZ-701 (other than those specifically required within a short time before the first dose).

The Investigator will confirm that the subject meets Inclusion Criterion No. 2 (clinical diagnosis of ENPP1 Deficiency supported by prior identification of biallelic ENPP1 mutations) before undergoing any physical or invasive Screening procedures.

Screening procedures may be conducted over several days as necessary and assessments should be conducted in a manner and order to minimize subject burden.

Screening/Baseline assessments must be done prior to administration of first dose of INZ-701 unless otherwise specified in this protocol.

In Germany and France only, a negative COVID-19 test must be obtained within 5 days of first dose for all subjects. Additional COVID-19 testing may be performed in accordance with the site's institutional policies and procedures.

All Screening biomarker assessments performed to determine eligibility will be performed by a College of American Pathologists/Clinical Laboratory Improvement Amendments (CAP/CLIA) certified laboratory using assays that meet Conformité Européene (CE)-marked requirements.

9.1.1. Informed Consent

Before any screening assessments or study procedures are conducted, an informed consent form (ICF) and an authorization for use and release of medical records must be signed (Section 13.4).

Before any Extension Period assessments of study procedures are conducted the subject must consent to the Extension Period.

9.1.2. Eligibility

Potential subjects for entry into the study are evaluated according to protocol-defined inclusion and exclusion criteria (Sections 7.1 and 7.2). Individuals deemed ineligible do not need to complete all Screening procedures; however, the reason for screen failure and results of all completed assessments must be documented in the eCRF.

9.1.3. Repeat Screening Assessments and Rescreening

9.1.3.1. Repeat Screening Assessments

Subjects who are within 60 days of the start of Screening Period can undergo repeat assessment for transient abnormalities with approval from the Sponsor.

For those subjects who have completed all Screening assessments and are deemed eligible but are unable to be dosed within 30 days from the start of Screening (day of consent), the serum pregnancy test (WOCBP only) and COVID-19 test (in Germany and France only) will be repeated within the protocol specified window prior to dosing.

9.1.3.2. Rescreening

If a subject does not meet the eligibility criteria, they may be rescreened up to two times after consultation with the Sponsor if the Investigator believes there has been a change in eligibility status (eg, after resolution of an infection or vitamin D insufficiency). The Investigator will consult with the Sponsor to determine which of the Screening procedures must be repeated to determine eligibility and/or establish the study baseline.

Subjects must sign a new ICF prior to rescreening and will be assigned a new study identification number.

No exceptions to eligibility criteria (ie, protocol waivers) will be granted.

9.1.4. Medical History, ENPP1 Deficiency History, and Demographics

A complete medical history will be collected at Screening by the Investigator or qualified designee. Medical history should include all active conditions and any past condition considered to be clinically significant by the Investigator. Subjects must be willing to provide access to prior medical records for the collection of biochemical and radiographic data, as well as disease history. Historical reports, images, tissue samples, photos, videos, etc., may be collected. Disease history will be collected (including ENPP1 related history to include *Pseudoxanthoma elasticum* [PXE]-like manifestations).

The specific diagnosis of ENPP1 Deficiency will be recorded, along with date of onset, clinical presentation, and date and method of diagnosis. Any available family history will be noted, including any available previous mutation analysis results from relevant family members with appropriate inheritance patterns.

Each subject must have documented historical genetic mutation analysis confirming *ENPP1* mutations performed by a CAP/CLIA certified laboratory using a CE-marked test.

The review will also include an assessment of symptoms and conditions associated with osteomalacia, one of the clinical manifestations of ENPP1 Deficiency. Osteomalacia treatment history, including the use of pain medications to treat symptoms associated with osteomalacia, physical/occupational therapy, and use of assistive devices will be recorded (start date, stop date, dose, dosing regimen).

Demographic information, including age, sex, ethnicity, and race, will be collected following local regulations.

9.2. Pharmacodynamic Evaluations and Clinical Intermediates

ENPP1 Deficiency is an ultra-rare genetic disorder characterized by early-onset osteoporosis and low levels of plasma PPI and serum phosphate, which can result in rickets/osteomalacia, skeletal deformities, and impaired growth and development ([Ferreira et al 2014](#), [Moran 1975](#), [Rutsch et al 2008](#)).

Therefore, the goal of ENPP1 ERT is to mitigate clinical and developmental complications associated with ENPP1 Deficiency. Assessments to derive efficacy and clinical intermediate variables are described below and will be conducted according to the Schedule of Events ([Table 1](#), [Table 2](#), [Table 3](#), and [Table 4](#)). Efficacy variables, clinical intermediates, and associated analyses are described in [Section 11.3](#).

Note: If needed, blood samples will be collected according to the Schedule of Events ([Table 1](#), [Table 2](#), [Table 3](#), and [Table 4](#)) and stored for analysis when assays become available.

9.2.1. Plasma Inorganic Pyrophosphate

Low plasma PPi levels are a characteristic of ENPP1 Deficiency. Change from Baseline in PPi levels is the primary endpoint and biomarker of clinical relevance in this study. INZ-701 specifically cleaves ATP to generate AMP and PPi. The therapeutic goal of ENPP1 ERT is to bring extracellular PPi levels to therapeutically effective levels and correct clinical abnormalities associated with ENPP1 Deficiency.

PPi will be measured via a series of samples obtained throughout the study. PPi data may be used to adjust INZ-701 dose levels. PPi levels will also serve as the primary PD marker for PK/PD analysis in this study.

Samples will be collected, processed, and shipped as indicated in [Table 1](#), [Table 2](#), [Table 3](#), [Table 4](#), [Table 5](#) and the Laboratory Manual.

9.2.2. Biomarkers Associated with Bone Health

In addition to low plasma PPi, ENPP1 deficient patients are characterized biochemically by low serum phosphate, high urine phosphate, low renal TmP/GFR, normal calcium (Ca), low-normal urine Ca, normal 25(OH)D, low-normal 1,25(OH)₂D, high bone-specific alkaline phosphatase (BALP), high FGF23, and normal PTH ([IOF 2019](#)).

Biomarkers examined as primary and secondary clinical intermediates and additional exploratory biomarkers are summarized in [Appendix A](#). Samples will be collected, processed, and shipped as indicated in [Table 1](#), [Table 2](#), [Table 3](#), [Table 4](#), and the Laboratory Manual. If possible, samples should be collected at approximately the same time of day throughout the study to minimize intrasubject variability due to diurnal variation.

Subjects should fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before the collection of the pre-dose blood sample. INZ-101 should be administered within 10 minutes of the pre-dose blood collection (may be extended up to 1 hour in case of challenges with the PPi sample processing). Subjects should also refrain from eating, drinking, and exercising during the 2 hours prior to the 6 hours post-dose blood sample collection. There are no additional restrictions on eating, drinking, or exercise for post-dose study sample collections.

For TmP/GFR assessment at Day 1 of the Dose Evaluation Period and at Week 48 of the Extension Period a second morning urine collection will be obtained prior to blood sample collection and will be submitted for biomarker assessment. An aliquot of each 24-hour urine sample will be stored frozen for future urine biomarkers associated with ENPP1 Deficiency.

9.3. Efficacy Evaluations

Evaluations will be performed according to the schedules in [Table 1](#), [Table 2](#), [Table 3](#), and [Table 4](#).

9.3.1. Radiography and Imaging

Note: Na¹⁸F-PET/CT or low dose CT, X-rays, and DEXA will not be performed in Germany.

Radiographic and imaging assessments will be performed. Historical tests performed within 6 months prior to Screening could be used as Baseline upon Investigator discretion in

consultation with the Sponsor. X-rays, Na¹⁸F-PET/CT or low dose CT, DEXA, echocardiogram, renal ultrasound, and carotid ultrasound will be collected and read centrally.

All procedures involving exposure to radiation should not be conducted in subjects for whom there is a medical reason to avoid radiation as determined by the Investigator.

9.3.1.1. X-Rays

Standard X-rays will be obtained to detect skeletal deformities. Obtain X-rays of the standing long legs and upper extremities, including hand and wrist. Images will be read by a central imaging vendor.

9.3.1.2. DEXA

DEXA will be used to evaluate changes in bone mineral density and changes in surrounding mineralization. Bone mineral density will include measurements of whole body, lumbar spine, proximal femur, and forearm. DEXA of the lumbar spine will include a vertebral fracture assessment (VFA). Lateral thoracic and lumbar spine measurements will be obtained if there is no VFA for DEXA. A separate procedure manual will give specific instructions for acquisition of scans as well as performance of Instrument Quality Control.

9.3.1.3. Computed Tomography

Subjects will receive a Na¹⁸F-PET/CT or a low dose CT (full body) without contrast as determined by the Investigator in consultation with the Sponsor.

9.3.1.3.1. Low Dose – Computed Tomography

Low dose CT (full body) without contrast will be performed in those not receiving Na¹⁸F-PET/CT and will identify soft tissue/organs and arteries.

9.3.1.3.2. Positron Emission Tomography – Computed Tomography

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 as well as microcalcifications and newly developing calcium deposits.

9.3.1.4. Renal Ultrasound

Bilateral renal ultrasounds will be performed to assess for nephrocalcinosis, nephrolithiasis, or other abnormalities.

9.3.1.5. Carotid Ultrasound

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

9.3.1.6. Echocardiogram

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.

9.3.2. Other Instrumental Assessments

9.3.2.1. Ankle-Brachial Pressure Index

The ABI 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. ABI will be assessed locally.

9.3.2.2. Pulse Wave Velocity

Pulse wave velocity 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. PWV will be assessed locally.

9.3.2.3. Bone Histomorphology and Transiliac Crest Bone Biopsy (optional)

Bone biopsies are optional. Bone biopsies will be performed on any subject consenting to the procedure. Bone biopsies are performed at Baseline and the Week 48 Visit of the Extension Period and will not be repeated if INZ-701 is discontinued prior to Week 48. Labeling with demeclocycline prior to the first transiliac crest bone biopsy and with tetracycline prior to the second transiliac crest bone biopsy is required: 2 courses of label (3 days each) separated by a 12-day (± 1 day) interim period with the bone biopsy occurring 4 days (± 1 day) later. If demeclocycline is not available at the time of the first bone biopsy, tetracycline may be used. If tetracycline was used for the first bone biopsy demeclocycline should be used for the second biopsy, if available. If demeclocycline is not available tetracycline may be used for both biopsies.

9.3.3. Functional Outcomes

For all performance outcomes, testing will be completed by a trained assessor. Subject positioning for testing and assessor instructions will be provided.

9.3.3.1. Walking Ability

Walk tests are a submaximal exercise measurement used to measure functional capacity in ambulatory patients combining cardiopulmonary, neuromuscular, and musculoskeletal functions. The 6MWT was originally developed by the American Thoracic Society ([ATS 2002](#)) for use with adults, and is now commonly used in both adult and pediatric populations ([Mylius et al 2016](#)), and with children with neuromuscular diseases such as spinal muscular atrophy ([Montes et al 2018](#)), Duchenne muscular dystrophy ([McDonald et al 2013](#)), and infantile-onset Pompe disease ([van der Meijden et al 2018](#)).

The 2MWT is included in the National Institutes of Health (NIH) Toolbox and is increasingly being used to measure the same properties.

If a subject is unable to complete at least the 2MWT at baseline, additional assessments during the Dose Evaluation Period may be left to Investigator discretion. However, the

subject should attempt the walk test at the annual visits, final visit and the Follow-up Safety Monitoring Visit.

Obtain the resting heart rate prior to the test and the post-test heart rate. If the subject is unable to complete the 6MWT, they should attempt the 2MWT. This approach ensures information about gait will be captured for all subjects, even those not able to complete the full 6-minute duration. The distances walked in 2 minutes and 6 minutes will be compared to age-matched normative data (percent predicted values).

Testing equipment and instructions will be provided. Assistive devices such as walkers and canes will be permissible if deemed necessary by the subject or Investigator to safely walk the required distance. The use of, or any changes in, assistive devices will be recorded on the eCRF.

If local regulations permit and with subject consent, sites may record the administration of the assessment on video. Videos will be sent to a representative of the Sponsor for removal of subject identifiers. The Sponsor will only receive videos with subject identifiers removed. The videos will be labeled with the subject identification (ID) and date.

9.3.3.2. Hand-held Dynamometry

Hand-held dynamometry is a direct measurement of strength commonly used in clinical research involving both children and adults. Testing will be completed by a trained assessor. Subject positioning for testing, assessor instructions, and equipment will be provided. The make technique will be used which requires the examiner to hold the dynamometer stationary as the subject exerts a maximal force against the stationary dynamometer, resulting in a measurement of isometric force.

The following muscle groups will be assessed: shoulder abduction, shoulder flexion, elbow flexion, elbow extension, hip abduction, hip flexion, hip extension, knee flexion, and knee extension. Each muscle group will be measured 2 times bilaterally. Results will be compared to age- and sex-matched normative data (when available).

9.3.3.3. Grip Strength

Grip strength will be measured using a grip strength dynamometer. Equipment and assessor instructions will be provided. Grip will be assessed bilaterally with 1 practice and 1 maximal force measures taken for each hand and results will be compared to age and gender matched normative data (when available).

9.3.3.4. Range of Motion

Range of motion will be assessed using a goniometer. The stationary arm of the goniometer is aligned with the specified bony landmark on the stationary body segment, and the moving arm of the goniometer is aligned with the specified bony landmark of the limb that is moving. The fulcrum of the goniometer is specified for each motion measured using axis of motion and bony landmarks.

Range of motion will be assessed for the following: shoulder abduction, shoulder flexion, cervical rotation, cervical flexion, cervical lateral flexion, cervical extension, elbow flexion, elbow extension, hip abduction, hip flexion, hip extension, knee flexion, and knee extension.

9.3.4. Patient, Clinician, and Caregiver Reported Outcomes

9.3.4.1. Global Impression Scales

9.3.4.1.1. Clinical Global Impression Scales

The Clinical Global Impression (CGI) scales were developed for use in National Institute of Mental Health-sponsored clinical studies to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication (Guy 1976). The CGI provides an overall clinician-determined summary measure that considers all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.

The CGI of Status/Severity (CGI-S) will be completed by the Investigator at the Baseline Visit.

During the Extension Period, the Investigator will complete the CGI of Improvement (CGI-I).

9.3.4.1.2. Patient Global Impression Scales

The Patient Global Impression of Status/Severity (PGI-S) will be completed by the subject by the Investigator at the Baseline Visit.

During the Extension Period, the PGI of Improvement (PGI-I) will be completed at scheduled time points (see Table 1, Table 2, Table 3, and Table 4)

9.3.4.1.3. Caregiver Global Impression Scales

The Caregiver Global Impression of Status/Severity (CaGI-S) will be completed by the subject's caregiver at the Baseline Visit, if applicable.

If Applicable, during the Extension Period, the CaGI of Improvement (CaGI-I) will be completed.

9.3.4.2. Patient Reported Outcomes Measurement Information Systems

The PROMIS consists of a variety of questionnaires developed by the NIH to evaluate physical, mental, and social well-being from the patient perspective (<http://www.healthmeasures.net>). These questionnaires have been used in clinical studies in people with chronic health conditions such as X-linked hypophosphatemia, arthritis, multiple sclerosis, and neurofibromatosis.

Each questionnaire contains up to 10 items which are rated by the participant on a 5-point Likert scale ranging from 1 (never) to 5 (always). Scores are summed for each questionnaire, with high scores indicating more of the domain being measured (eg, more fatigue, more physical function). Raw scores are converted to T-Scores based on a mean of 50 and a standard deviation of 10, allowing comparison of the study sample to the general population.

PROMIS Scales will include the Pain Interference, Pain Intensity, Physical Function – Upper Extremity, Physical Function – Mobility, Fatigue, and Cognitive Function and will be done. These assessments will be completed by the subject without assistance.

- The **PROMIS Pain Interference (short form 8a)** describes the functional impact of pain in a person's life, and the extent to which pain hinders the ability to work and to engage with social, cognitive physical and recreational activities.
- The **PROMIS Pain Intensity (scale 3a)** asks the patient to rate the intensity of their pain on a scale of 1 to 5 with a question each for pain at its worst, pain on average, and pain right now.
- The **PROMIS Custom 9-Item Upper Extremity Form** is used to evaluate a person's ability to perform activities of daily living requiring upper extremity strength and dexterity, such as managing clothing fasteners, cutting food, and lifting heavy objects.
- The **PROMIS Physical Function – Mobility (Short Form – Physical Function for Samples with Mobility Aid Users 11a)** asks about a person's ability to perform daily activities such as walking short distances, walking up steps, and getting on and off the toilet.
- The **PROMIS Fatigue Scale (short form 13a FACIT-Fatigue)** explores the impact of fatigue on a person's life with questions about both the symptoms of fatigue, such as feeling tired or listless as well as ability to perform typical daily activities.
- The **PROMIS Cognitive Function (short form 8a)** assesses patient-perceived functional abilities with regards to cognitive tasks, including the perception that one's cognitive ability with regards to the domain of inquiry (eg, concentration and memory) has not changed.

9.3.4.3. Work Productivity and Activity Impairment Questionnaire

The WPAI will be administered to assess the impact of ENPP1 Deficiency on a subject's employment status and ability to work.

9.4. Safety Measurements

Assessments to derive safety variables are described below and will be conducted according to [Table 1](#), [Table 2](#), [Table 3](#), and [Table 4](#). Safety endpoints and associated analyses are described in [Section 11.4](#).

Any unfavorable changes in vital signs, weight, and physical examination findings considered clinically significant by the Investigator will be reported as an AE.

9.4.1. Physical Examination

A complete physical examination includes an assessment of systemic organ involvement and inspection of:

- General appearance

- Head, ears, eyes, nose, and throat
- Neck
- Skin
- Cardiovascular system
- Respiratory system
- Gastrointestinal system
- Nervous system

Pregnancy will be recorded with physical examination findings on the CRF. Physical examination will also include vital signs, height, and weight measurements, neurological exam, spirometry, and otoscopy.

Physical examinations must be performed by the Investigator or a medically qualified delegate.

Any clinically significant abnormality found with the physical examination conducted during the screening visit should be recorded as a pre-existing condition (ie, part of the medical history).

9.4.1.1. Vital Signs

Vital signs assessed in this study include systolic blood pressure and diastolic blood pressure (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), and temperature (°C). Vital signs should be measured after the subject has been at rest ≥ 5 minutes.

Blood pressure (systolic and diastolic) measurements should be taken from the same arm throughout the study via an automated monitor that uses an oscillometric method while subjects are seated.

Respiratory rate will be measured over at least 15 seconds and adjusted per minute.

Body temperature can be measured using either oral or tympanic methods, but the method should be consistent throughout the study for a given subject.

Additional measurements should be obtained as clinically indicated.

9.4.1.2. Height and Weight

Height (centimeters) and weight (kilograms) will be obtained. Measurements will be made prior to dosing, if applicable. The measurement obtained at the Day 1 visit will be used to calculate the appropriate dose of INZ-701 to be administered on a mg/kg basis throughout the duration of the study. If a subject's weight changes by $\geq 10\%$ from Baseline, the Investigator may re-calculate their dose using the weight at the study visit (unless a flat dose is being used).

9.4.1.3. Spirometry

Spirometry will be performed using standard equipment and read locally. The test will measure vital capacity (VC), forced vital capacity (FVC), forced expiratory volume at 1.0

second (FEV1), forced expiratory flow 25 to 75% (FEF 25–75), and maximal voluntary ventilation (MVV).

9.4.2. Electrocardiogram

Standard 12-lead ECGs will be collected and will be read centrally. Additional ECGs may be performed per site specific safety monitoring procedures and/or if clinically indicated.

9.4.3. 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. If collected, they will be interpreted locally. Cardiac telemetry will be collected on Day 1, beginning pre-dose and continuing through 24-hours post-dose.

9.5. Prior and Concomitant Medications and Therapies

Use of concomitant medications and therapies as described in Section 8.3 will be assessed throughout the study.

Prior and concomitant medications include any drug (investigational, prescription, or over-the-counter), biological product (such as vaccines, blood, or blood components), herbal remedies or preparations, and supplements received in the 4 weeks prior to first dose of INZ-701. For excluded medications, any historical use should be reported.

Concomitant medications include any drug (prescription or over-the-counter), biological product (such as vaccines, blood, or blood components), herbal remedies or preparations, and supplements received after administration of the first dose of INZ-701 and throughout the study. All concomitant medications taken during the study will be recorded with indication, dose information, and dates of administration. Any changes to concomitant medication will also be documented.

Investigators should consult with the Sponsor regarding the timing of any planned vaccinations in relation to INZ-701 administration.

9.6. Clinical Laboratory Evaluations

Clinical laboratory assessments on blood and urine samples will be used to characterize the population, assess safety and efficacy, and characterize PK/PD and exploratory biomarkers throughout the study. If maximum allowed blood volume (per local guidance) may be reached for any given time-period, samples will be prioritized as follows: clinical safety laboratory evaluations, immunogenicity, PPI, ENPP1 specific activity, other biomarkers.

All clinical laboratory evaluations for safety, PPI, clinical intermediates, PK, immunogenicity, and biomarker blood draws should be collected, processed, and shipped as outlined in the Laboratory Manual. Additional blood draws for safety may be obtained if clinically indicated.

As allowed by local regulation and with the subject's consent, any unused blood or other biological samples remaining after the completion of all study testing may be stored and used

by the Sponsor outside of the context of this study for future research on ENPP1 Deficiency or related deficiencies and development of drugs to treat these deficiencies.

During the Dose Evaluation Period, subjects may be admitted to the clinical study site for all, or a portion(s) of the 32 days, at the discretion of the Investigator. Subjects must fast (refrain from eating or drinking other than water), and refrain from exercising for a minimum of 10 hours before the collection of pre-dose study samples. INZ-101 should be administered within 10 minutes of the pre-dose blood collection (may be extended up to 1 hour in case of challenges with the PPI sample processing). Subjects should also refrain from eating, drinking, and exercising during the 2 hours prior to the 6 hours post-dose blood sample collection. There are no additional restrictions on eating, drinking, or exercise for post-dose study sample collections.

During the Extension Period, subjects should fast and refrain from exercising as described. Additional blood samples may be drawn if the INZ-701 dose is changed.

Urine samples will be collected for a 24-hour period prior to dosing on Day 1 and Day 29. Additional urine samples (second morning urine) will be collected at visits when serum phosphate and creatinine are determined to calculate TmP/GFR values. Additionally, calcium will be measured in urine. An aliquot of each 24-hour urine sample will be stored frozen for future urine biomarkers associated with ENPP1 Deficiency.

9.6.1. Clinical Laboratory Evaluations for Safety

Routine blood chemistry panels including liver function tests, a hematology panel including complete blood count (CBC) with differential, and routine urinalysis screen will be conducted to assess eligibility and as a measure of safety throughout the study.

All clinical laboratory evaluations should be collected, processed, and shipped as outlined in the Laboratory Manual. Additional assessments may be performed if clinically indicated.

Additional safety laboratory evaluations may be collected to monitor safety at institutions where required. Care should be taken to not exceed the maximum allowed blood volume for any time-period. Additional clinical laboratory assessments may be performed if considered medically necessary by the Investigator. Fasting is not required for these additional assessments.

The site should advise the clinically laboratory if the subject is receiving biotin supplements as high-dose biotin may interfere with certain laboratory assessments (Section 8.3). See [Appendix A](#) for protocol-specified analytes.

9.6.2. Pregnancy Testing

The effects of INZ-701 on a fetus *in utero* or on the composition of sperm are unknown. Therefore, WOCBP must consent to pregnancy testing. Additionally, WOCBP and partners of fertile males who are WOCBP must agree to use 1 highly effective contraceptive method and fertile males must agree to use condoms per study eligibility requirements ([Appendix B](#)).

Women of child-bearing potential must have a negative serum pregnancy test at Screening. Urine pregnancy tests throughout the study will be conducted and analyzed at the local laboratory. If a urine pregnancy test is positive, the results will be confirmed with a serum

test, following the procedures of the clinical site. Pregnancy of a subject or partner of a subject must be reported and should be followed (see Section 10.3.6).

9.7. Drug Concentration Measurements

Blood samples will be obtained from all subjects for measurement of INZ-701 concentration in plasma and subsequent determination of PK parameters following the first dose (ie, single dose) and after multiple doses (ie, steady-state).

Samples will be obtained on indicated days and time points outlined in the PK/PD sampling schedule (Table 5). Based on emergent data, the Sponsor may change the frequency or timing of PK/PD sampling times but will not exceed the total number of samples currently specified in the protocol.

9.8. Immunogenicity

Anti-drug antibodies to INZ-701 will be assessed by a laboratory using a validated method. Samples will be stored to enable future testing including determinations of whether the antibodies are directed against the Fc or ENPP1 enzyme portions of INZ-701, if feasible. Samples may be used to assess and further establish assays for specificity confirmation (ie, titer) and neutralizing antibodies. Blood samples will also be collected and stored until a validated assay is available in order to assess the presence of CRIM, such as endogenous ENPP1. In the event of severe hypersensitivity reactions, including anaphylaxis, every effort should be made, if possible, to collect blood samples for the assessment of IgE and IgG antibodies and levels of acute phase reactants, serum tryptase, plasma histamine, and complement activation (C3, C4). Samples will be analyzed centrally, if feasible, or else at the local laboratory. Additional samples may be obtained if clinically indicated (eg, in cases of suspected hypersensitivity reaction).

9.9. Biomarkers

Blood and urine samples will be collected to evaluate relevant biomarkers (Appendix A).

10. ADVERSE EVENTS

10.1. Definitions

10.1.1. Adverse Event

An AE is any untoward medical occurrence (eg, sign, symptom, illness, disease, injury) in a subject administered any amount of INZ-701 or other protocol-imposed intervention regardless of attribution. Treatment-emergent adverse events are defined as any AE that newly appears, increases in frequency, or worsens in severity following initiation of INZ-701.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms/terms relating to a diagnosis.

10.1.2. Serious Adverse Event

An SAE is an event that results in any of the following:

- Death
- A life-threatening AE; Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Inpatient hospitalization or prolongation of existing hospitalization. Examples of visits to a hospital facility that do not meet the seriousness criteria for hospitalization include:
 - Outpatient surgery
 - Preplanned or elective procedures
 - Protocol procedures
- A congenital anomaly or birth defect (in a child or fetus of a subject exposed to INZ-701 prior to conception or during pregnancy)
- An important medical event that, based on appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (eg, anaphylaxis)

10.2. Adverse Event Reporting

All AEs (which includes SAEs and adverse events of special interest [AESI] as defined in Section 10.2.5), whether or not related to INZ-701, must be fully and completely documented. The Investigator may be asked to provide additional follow-up information.

If a subject is withdrawn from dosing with INZ-701 and/or the study because of an AE, it must be recorded. The subject should be followed and treated by the Investigator until the AE has resolved, stabilized, or a new chronic baseline has been established.

10.2.1. Adverse Event Reporting Periods

Safety reporting periods for this study are defined in Table 7.

Table 7: Safety Reporting Periods

Event Type	Reporting Period	Additional Requirements
Screening Period AEs / SAEs	Date of informed consent and prior to first dose of INZ-701	Report as AE/SAE only if related to study procedures during Screening/Baseline assessments

Event Type	Reporting Period	Additional Requirements
Treatment-emergent AEs / SAEs / AESIs	Date of first dose of INZ-701 through 30 days following last dose of INZ-701	

AE=adverse event; AESI=adverse event of special interest; SAE=serious adverse event

10.2.2. Expedited Reporting Requirements

It is the responsibility of the Investigator to report SAEs (and AESI as defined in Section 10.2.5) that occur during the reporting period Table 5 whether or not considered related to INZ-701. Events must be reported to the Sponsor or its designee immediately and no later than 24 hours of awareness of the event or safety information using the study specific form and associated documents, whether initial or follow-up, to the Sponsor's designee by electronic mail:

- **For SAEs, Email:** [REDACTED]
- Required AESI, Email Inozyme PV Inbox: [REDACTED]

NOTE: If an AESI is deemed serious, send to both [REDACTED] Safety Inbox and to Inozyme PV Inbox.

Investigators should not delay in the reporting of a suspected SAE to obtain additional information. Any additional information, if collected, can be reported to the Sponsor or its designee as a follow-up to the initial report.

The Sponsor may be required to report certain fatal or life-threatening SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that Investigators submit any information requested by the Sponsor as soon as it becomes available. The Investigator is encouraged to discuss any AEs with the Sponsor or Sponsor's designee if the issue of seriousness is unclear or questioned.

As per ICH Topic E 2 A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), the Sponsor will notify Regulatory agencies (eg, by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the Sponsor that an adverse drug reaction qualifies, followed by as complete a report as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

This study is to be conducted in accordance with the ICH Note for Guidance on GCP (ICH, Topic E6, 1996). The Sponsor may designate a primary liaison between the study site and the Sponsor and will be responsible for communication to the Sponsor and the study sites regarding study recruitment, study conduct, and any other significant clinical activities which occur during the course of the study.

The Sponsor's designee will notify all sites of suspected unexpected serious adverse reactions (SUSARs) and other safety concerns as outlined in the Safety Management Plan (SMP).

Investigators will be informed in writing of any new or emerging safety information as it becomes available. This will include and is not limited to AEs that are SUSARs. Notification

of safety information to Investigators will be performed in accordance with the SMP. In addition, Investigators will be instructed to notify subjects as soon as possible and at minimum prior to their next scheduled dose. SAEs reported to the Investigator outside of the reporting period will be reported to the Sponsor or its designee only if, in the judgment of the Investigator, the SAE may have been related to prior use of INZ-701 or protocol-imposed intervention.

At the last scheduled visit, the Investigator should instruct each subject to report, to the Investigator and/or to Sponsor directly, any subsequent SAEs that the subject's personal physician(s) believes may be related to previous use of INZ-701 or protocol-imposed intervention.

All SAEs (and AESIs as defined in Section 10.2.5) will continue to be followed until such events have resolved or the Investigator, in conjunction with the Sponsor or its designee, deems them to be chronic or stable, or the subject is lost to follow-up, or withdraws consent from the study. For some SAEs, the Sponsor may follow-up via telephone, fax, electronic mail, and/or monitoring to obtain additional case details (eg, hospital discharge summary, consultation report, autopsy report) deemed necessary to appropriately evaluate the SAE report.

10.2.3. Eliciting Adverse Events

Care will be taken not to introduce bias when obtaining AE (including SAEs) information. The Investigator will seek information on all AEs. At each visit the Investigator will ask the subject/caregiver an open-ended and non-leading verbal question (eg, "Have you noticed anything different since your last visit?") to assess whether any AEs have been experienced since the last report or visit and, as appropriate, by examination.

10.2.4. Recording and Assessment of Adverse Events

The Investigator or qualified designee responsible for the care of the subject will assess AEs for severity, relationship to INZ-701, and seriousness. These assessments should be made by a clinician with the training and authority to make a diagnosis (eg, MD/DO, physician's assistant, nurse practitioner, DDS).

Investigators should use precise medical terminology when recording AEs or SAEs. Record only 1 diagnosis, sign, or symptom per AE (eg, nausea and vomiting should not be recorded in the same entry but as 2 separate entries).

Whenever possible, a diagnosis should be recorded as the AE term rather than a series of symptoms/terms relating to a diagnosis. However, if the diagnosis is unknown, record sign(s) and/or symptom(s). If a diagnosis subsequently becomes available, the diagnosis should be recorded, replacing the original entry(s) where appropriate.

In general, AEs occurring secondary to other events (eg, cascade events) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE. However, medically important events that may be linked and/or separated in time should be recorded as independent events. For example, if severe hemorrhage leads to renal failure, both events should be recorded separately.

The Investigator should follow all unresolved AEs (which include SAEs and AESIs) until the events are resolved or have stabilized, the subject is lost to follow-up, or it has been determined that INZ-701 is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented in the subject's medical records to facilitate source data verification. Note that any new concomitant medication during the course of a study may indicate the occurrence of an AE.

10.2.5. Injection Site Reactions

Signs and symptoms of injection site reactions (ISRs) include local swelling, erythema, induration, pruritus, pain, and other relevant signs and symptoms adjacent to the site of injection. An ISR comprised of multiple signs and symptoms will be reported as a single event; the signs and symptoms comprising the ISR will be recorded in the clinical database and the ISR will be graded according to the most severe sign or symptom. If an ISR is identified by the Investigator as a component of a systemic hypersensitivity reaction, the signs and symptoms of the ISR will be recorded in the database as components of the systemic hypersensitivity reaction.

10.2.6. Adverse Events of Special Interest

The following AESIs will be evaluated:

- systemic hypersensitivity reactions, including anaphylaxis
- seizures

A systemic hypersensitivity reaction comprised of multiple signs and symptoms will be reported as a single event; the signs and symptoms comprising the systemic hypersensitivity reaction will be recorded in the clinical database and the reaction will be graded according to the most severe sign or symptom.

All AESIs will be reported to the Sponsor or Sponsor's designee as specified in Section 10.2.2. The list of events of special interest will be updated based on emerging data and will be reviewed for addition to the reference safety information (RSI). Any change to the RSI will be communicated to the sites by the Sponsor or their designee.

10.2.7. Severity Assessment

Severity (eg, NCI-CTCAE Grade 1, 2, 3, etc.) is not equivalent to seriousness, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

The Investigator will determine the severity of each AE/ SAE using NCI-CTCAE version 5.0 (NCI 2017). Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE version 5.0 as stated in Table 8.

Table 8: Adverse Event Severity Grading Scale

Grade	Description	
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	
2	Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) ^a	
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL ^b	
4	Life-threatening consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be reported as SAEs
5	Death related to AE	

a Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Source: CTCAE v5 (NCI 2017).

10.2.8. Causality Assessment

The Investigator will determine the causality/relationship (Table 9) of each AE and will record it on the source documents and AE eCRF.

Table 9: Adverse Event Causality Attribution Guidance

Relationship	Description
Not Related	<ul style="list-style-type: none"> Exposure to INZ-701 has not occurred <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> Administration of INZ-701 and the occurrence of the AE are not reasonably related in time <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> The AE is considered likely to be related to an etiology other than the use of IMP; that is, there are no facts, evidence, or arguments to suggest a causal relationship to the IMP
Related	<ul style="list-style-type: none"> Administration of INZ-701 and the occurrence of the AE are reasonably related in time <p style="text-align: center;">AND</p> <ul style="list-style-type: none"> The AE is more likely explained by exposure to INZ-701 than by other factors or causes

AE=adverse event; IMP= investigational medicinal product

Factors suggestive of a causal relationship could include, but are not limited to:

- Plausible temporal relationship
- Absence of alternative explanations
- Abatement of AE with discontinuation of INZ-701, and/or recurrence of AE with reintroduction of INZ-701 (ie, effect of dechallenge and/or rechallenge)
- Similarity to adverse reactions seen with related drug products. Known relationship to underlying mechanism of INZ-701 action
- Consistency with INZ-701 pharmacology
- Rarity of event in a given subject or disease state

- Absence of event prior to INZ-701 exposure

The Investigator's assessment of causality for individual AE reports is part of the documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities.

10.3. Adverse Events – Special Circumstances

10.3.1. Persistent or Recurrent Adverse Events

A persistent AE is one that continues, without resolution, between subject evaluation time points. Such an event should be recorded only once, and the highest grade of severity should be reported. Events that resolve but recur, should be recorded as separate AEs, each with their own start and stop dates and each graded according to the highest grade of severity noted.

10.3.2. Pre-existing Conditions

A pre-existing condition is one that is present at the time the ICF is signed; such conditions should be recorded as medical history.

A pre-existing condition should be recorded as an AE/SAE during the study only if the frequency, intensity, or character of the condition worsens during the study period. It is important to convey the concept that a pre-existing condition has changed by including applicable language in the verbatim description of the event (eg, more frequent headaches).

10.3.3. Physical Examination Findings

Prior to the first dose of INZ-701, any clinically significant abnormality should be recorded as a pre-existing condition (ie, part of the medical history). After the first dose of INZ-701 administration, any new clinically significant findings and/or abnormalities discovered on physical examination that meet the definition of an AE/SAE must be recorded as such.

10.3.4. Abnormal Laboratory Results

A clinical laboratory abnormality should be reported as an AE if deemed to be clinically significant by the Investigator. Examples that suggest clinical significance include:

- Accompanied by clinical symptoms
- Leading to a change in INZ-701 (eg, dose modification, interruption, permanent discontinuation)
- Requiring a change in concomitant therapy (eg, addition of, interruption of, discontinuation of, any other change in a concomitant medication, therapy, or treatment)
- The abnormality suggests a disease and/or organ toxicity

- The abnormality is of a degree that requires active management (eg, discontinuation of INZ-701, more frequent follow-up assessments, further diagnostic investigation)

This applies to any protocol or non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of INZ-701 that falls outside the laboratory reference range and meets the clinical significance criteria. This does not apply to any abnormal laboratory result that falls outside the laboratory reference range but that does not meet the clinical significance criteria (these will be analyzed and reported as laboratory abnormalities), those that are considered AEs of the type explicitly exempted by the protocol, or those which are a result of an AE that has already been reported.

Any laboratory result abnormality fulfilling the criteria for an SAE should also be reported.

10.3.5. Elective Procedures and Surgeries

For the purposes of this protocol, the following conventions will apply for AE or SAE reporting of elective procedures and surgeries:

A prescheduled elective procedure or a routinely scheduled treatment is not to be considered an SAE, even if the subject is hospitalized, provided:

- The condition requiring the prescheduled elective procedure or routinely scheduled treatment was present before and did not worsen or progress between the subject's consent to participate in the study and the time of the procedure or treatment
- The prescheduled elective procedure or routinely scheduled treatment is the sole reason for admission and intervention

An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or an SAE. Any concurrent medications should also be recorded as concomitant medications.

10.3.6. Pregnancy

Any subject who becomes pregnant during the study must be withdrawn from INZ-701 and will be followed to term.

A pregnancy is not an AE, but could qualify as an SAE, if a complication relating to the pregnancy occurs; regardless, all pregnancies occurring in female subjects and/or female partners of male subjects during this study are to be reported within 24 hours of the site's awareness of the pregnancy using the Pregnancy Report Form.

Pregnancy-associated SAEs will be processed and submitted, as necessary, as per the SUSAR reporting process. Abortion, whether therapeutic or spontaneous, should always be classified as an SAE (as the Sponsor considers these to be medically significant), and expeditiously reported to the Sponsor.

The Investigator must make every reasonable effort to follow the subject through resolution of the pregnancy (delivery or termination). In the event of pregnancy in the partner of a

subject, the Investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information.

Pregnancies, should they occur, will be captured from the date of the first dose of INZ-701 up to 30 days after the subject's last dose of study drug.

10.3.7. Death

All deaths that occur during the AE reporting period regardless of attribution will be recorded and expeditiously reported to the Sponsor. If the Investigator becomes aware of a death after the AE reporting period and considers it related to study drug, it will be reported as an SAE.

Death should be reported as a clinical outcome of a specific SAE and not as an SAE term. The event or condition that caused or contributed to the fatal outcome should be recorded as a single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Unexplained death" or "Death of unknown cause".

10.4. Urgent Safety Measures

The Sponsor is required to follow global regulations including European Union regulations which state that the appropriate regulatory bodies, including IRBs/IECs/research ethics boards, be notified according to their respective regulations of any new event resulting in the Sponsor and Investigator taking urgent safety measures to protect subjects against any immediate hazards.

Investigators are required to report any events which may require the implementation of urgent safety measures to Sponsor immediately and no later than 24 hours. Examples of situations that may require urgent safety measures include:

- Immediate need to revise the INZ-701 administration (eg, modified dose amount or frequency not defined in protocol)
- Change in the design which has a significant impact on the scientific value of the clinical study
- Detrimental study conduct or management
- Discovery that the quality or safety of the INZ-701 does not meet established safety requirements

11. STATISTICAL METHODS

A Statistical Analysis Plan (SAP), providing details about specific planned analyses, will be prepared and approved by the Sponsor prior to database lock. The final analysis will be based on all subject data collected through the end of the study. Data analyses will be provided for all subjects combined wherever appropriate. Descriptive statistics including means, medians, standard deviations, and ranges will be calculated for continuous variables, and categorical data will be summarized using frequency counts and percentages.

11.1. Study Conduct Analysis

Enrollment, significant protocol deviations, and subject disposition (eg, discontinuations from INZ-701 and from study and reported reasons) will be listed and summarized for all subjects. INZ-701 administration data will be listed and summarized.

11.2. Population Characteristics

Subject demographics (sex, age, race, ethnicity) and baseline characteristics will be listed and summarized using appropriate descriptive statistics for all subjects.

11.3. Efficacy and Biomarker Analyses

Changes in blood and urine PD markers associated with ENPP1 Deficiency will be described as changes from baseline and in a time-dependent manner during each phase of the study and will be summarized by dose and time with descriptive statistics.

Specific methods of analyses for all exploratory efficacy endpoints will be detailed in the SAP.

11.4. Safety Analyses

All subjects who were enrolled and received at least one dose of INZ-701 will be included in the safety analysis. Safety data will be listed and summarized.

The primary safety endpoint will be evaluated by examining incidence and type of TEAEs; including clinically significant changes from baseline through the Follow-up Safety Monitoring Visit in clinical laboratory test values, physical examination results, vital signs measurements, and ECG parameters that result in TEAEs.

Treatment-emergent AEs are defined as any AE occurring from the first dose of INZ-701 through 30 days after the last dose of INZ-701. TEAEs will be summarized using frequency counts and percentages. Treatment-emergent AEs will also be summarized by NCI-CTCAE grade and relationship to INZ-701. In addition, all DLTs, SAEs, deaths, and AEs leading to INZ-701 discontinuation will be summarized and listed separately.

11.5. Pharmacokinetic, Pharmacodynamic, and Exploratory Biomarker Analyses

Pharmacokinetic analysis will be performed on the PK population analysis set, and PK parameters of INZ-701 will be summarized by dose with descriptive statistics. Dose linearity of PK and PD parameters will also be assessed.

11.6. Timing of Analysis

Available data will be evaluated throughout the study for safety and observed changes from baseline in plasma PPi and other clinical intermediates.

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

The final analysis will be conducted when the last subject leaves the study (refer to end of study defined in Section 6.6).

11.7. Determination of Sample Size

The minimum sample size of 9 subjects was determined empirically to evaluate dose escalation of INZ-701 and characterize initial safety, PK, and PD in the Dose Evaluation Period. The maximum number of patients that could be enrolled in the study is 24. This assumes cohort expansion from 3 subjects to 6 subjects at each dose level due to the occurrence of DLTs (18 subjects). The Sponsor may decide to enroll up to 6 additional subjects into the Dose Evaluation Period at any dose and dose schedule deemed safe, not to exceed 3.6 mg weekly.

12. DATA RECORDING, RETENTION, AND MONITORING

12.1. Case Report Form

Participating study sites are required to submit data for each enrolled subject via an EDC system, using an eCRF. The EDC system is designed with a fully compliant audit trail per ICH E6 (R2) GCP. Site personnel will be trained on the EDC system before receiving access to the system. The Sponsor or its designee is responsible for maintaining a record of all system users. Study participants will not be identified by name on any study documents to be collected by the Sponsor.

All information requested in this protocol will be recorded on the eCRFs provided by the Sponsor or its designee (or via other data collection methods, eg, electronic laboratory data transfer). The Investigator is responsible for reviewing all eCRFs periodically, verifying for accuracy, and approving via electronic signature. Copies of completed eCRFs, saved to disk in .pdf format, will be sent to the Investigator's site at the completion of the study.

12.2. Availability and Retention of Records

Upon request, the Investigator must make study data accessible to the study monitor, other authorized representatives of the Sponsor, and Regulatory Agency inspectors. Monitoring will be performed either on site or electronically following clinical site and CRO Standard Operating Procedures (SOPs). A file for each subject must be maintained at the study site, which includes the signed ICF and the Investigator's copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

Investigators are required to maintain all study documentation, including documents created or modified in electronic format, for at least 15 years following the completion of the study. ICFs and adequate records for the receipt and disposition of all INZ-701 must be retained for a period of 2 years following the last date a marketing application (in an ICH region) is approved for the drug for the indication for which it is being investigated, or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is formally discontinued and FDA and other applicable Regulatory Authorities are notified, unless a longer period is required by applicable law or regulation.

The Investigator must not discard any records unless given written authorization by the Sponsor.

Subject identity information will be maintained in accordance with applicable national or country law or regulations.

12.3. Quality Control and Quality Assurance

Sponsor representatives and Regulatory Agency inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting various study records (eg, eCRFs and other pertinent data), provided subject confidentiality is respected. Monitoring may also be performed electronically following clinical site and CRO SOPs.

The Study Monitor is responsible for inspecting the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. The Investigator must agree to cooperate with the Monitor to ensure any problems detected in the course of these monitoring visits are resolved.

In accordance with ICH E6 (R2) GCP and the Sponsor's (or its designee's) audit plans, this study may be selected for an audit. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records may occur in order to evaluate the study conduct and compliance with the protocol, ICH E6 (R2) GCP, and applicable regulatory requirements.

12.4. Subject Confidentiality

The Sponsor and the site will collect and process personal data of study subjects strictly in accordance with applicable regional, federal, state, and local data protection laws and the conditions sets forth in the ICF signed by the subject. The Sponsor and site also will comply with applicable laws regarding special categories of data, including, as applicable, health data (including, but not limited to, results of HIV, Hepatitis B and C testing, and genetic data), and data regarding ethnicity.

Data collected during this study may be used to support the development, registration, or marketing of medicinal products. To the extent applicable, the Sponsor shall be deemed the controller of subject study data arising from the trial and the site shall be deemed a joint controller or a processor, depending on local law. To the extent that the site processes personal data on behalf of the Sponsor, in relation to such data the site shall only act in accordance with the terms of the study protocol and the Sponsor's reasonable written instructions and the site shall take appropriate technical and organizational measures against the unauthorized or unlawful processing of such personal data.

Once the subject signs and dates the ICF, the subject will be assigned a unique study code. The "key" to the code will be accessible only to a very small number of site employees. Case report forms, source documents, and specimens will be labelled only with the subject's code and not any direct identifiers such as the subject's name, medical record number, and home address. However, the subject's date of birth will also be collected by the site and used to

assist the Sponsor to verify the accuracy of the data, for example, that the results of study assessments are assigned to the correct subject. To comply with applicable law and verify compliance with this Protocol, the Sponsor's (or its designee's) monitors or independent auditors who validate the data on behalf of the Sponsor, representatives from applicable national or local regulatory authorities (eg, FDA, Health Canada, Italian Medicines Agency, Medicines and Healthcare products Regulatory Agency), and the cognizant ethical review board may be required to review the subject's original medical records. Monitoring and data verification may be performed remotely (on paper, at a different physical site, or electronically, on a computer, as necessary) if permitted by applicable law, provided that before remote review, the site will remove subject's direct identifiers (including the subject's name). If records are reviewed remotely, the monitor will securely destroy all copies of such medical records it has created after the review is completed. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place.

The results of this study containing the unique number, date of birth, and relevant medical information including ethnicity may be recorded and transferred to and used in other countries throughout the world. If personal data is transferred outside of the country where they originated, the site and Sponsor will ensure applicable data transfer mechanisms are in place to ensure the data receives essentially equivalent protection as are applicable in the originating country. The purpose of any such transfer would be to support regulatory submissions made by the Sponsor in such countries. All direct identifiers (including any nominative information such as the name, the address and all other personally identifiable information associated with a subject's name) in the subject's medical records will be kept strictly confidential. Sponsor access to subject's data shall be performed in such a way that no subject could be identified by such data.

The ICF obtained from the subject will include consent (or, if applicable, provides notice of other applicable legal basis) for (1) the processing of personal data for purposes of this study (including, but not limited to, reporting its results); (2) sharing of original medical records with Sponsor's representatives, regulatory authorities, and ethical review boards for study-related monitoring, auditing, ethical board review, and regulatory purposes; (3) sharing of coded personal data with the Sponsor and its representatives; and (4) remote monitoring and data verification. The subject's ICF also provides notice of data protection rights in the event of onward transfer and/or further disclosure of data. Additionally, as allowed by applicable law and the subject's ICF (to the extent such consent is required), the subject's coded personal data may be used outside of the context of this study for future research on ENPP1 Deficiency or related deficiencies and development of drugs to treat these deficiencies.

If there are any contradictions in terms of confidentiality requirements, the requirements of applicable data protection law will prevail. To the extent that the site processes personal data on behalf of the Sponsor, the terms shall also apply.

13. ETHICAL AND LEGAL ASPECTS

13.1. Ethical Conduct of the Study

The study will be conducted in compliance with the protocol, current ICH E6 (R2) GCP, the ethical principles of the Declaration of Helsinki, current FDA GCP guidelines, and any additional national or IRB/IEC or Regulatory Agency-required procedures, whichever represents the greater protection for the individual.

13.2. Regulatory Approval

The Sponsor or its designee will make the appropriate applications to the Regulatory Agency in each participating country for regulatory approval of the study and, if necessary, approval to import INZ-701. Subjects will not be screened until the required regulatory approvals have been obtained in the appropriate jurisdiction.

13.3. Ethics Committee Approval

The Investigator at the site is responsible for obtaining IRB/IEC approval for the final protocol, the Sponsor-approved ICF, and any materials used to recruit subjects. Written approval of these documents must be obtained from the IRB/IEC before any subject is enrolled at a site.

The Investigator is also responsible for:

- Obtaining IRB/IEC approval for any protocol amendments and ICF revisions before implementing the changes
- Providing the IRB/IEC with any required information before or during the study
- Submitting progress reports to the IRB/IEC, as required, during the conduct of the study; requesting re-review and approval of the study, as needed; providing copies of all IRB/IEC re-approvals and relevant communication to the Sponsor or its designee
- Reporting SAEs to the IRB/IEC in compliance with the standard operating procedures and policies of the IRB/IEC and with applicable regulatory requirements. Adequate documentation must be obtained by the Sponsor showing that the IRB/IEC was properly and promptly notified as required. Thus, the Investigator will retain adequate documentation of all SAEs submitted to the IRB/IEC and will notify the Sponsor if the IRB/IEC provides any feedback based on reviews of these reports.

13.4. Informed Consent

The Sponsor or its designee must review and approve the sample ICF and any amended ICFs, and any written information to be provided to subjects that is prepared by the Investigator prior to submission to the IRB/IEC for approval. An IRB/IEC-approved copy of the ICF and all amendments will be forwarded to the Sponsor.

The ICF documents the study-specific information the Investigator provides to the subject and the subject's agreement to participate. Among other things, the Investigator will fully explain in layman's terms the nature of the study, along with the aims, methods, potential risks, and any discomfort participation in the study may entail. The subject must personally sign and date the ICF before any study-related procedures are performed. The original and any amended, signed, and dated ICF(s) must be retained in the subject's file at the study site and a copy of the signed ICF must be given to the subject.

13.5. Compensation for Adverse Effects on Health

The Sponsor or its designee will adhere to local regulations regarding clinical study compensation guidelines to subjects whose health is adversely affected by taking part in the study.

13.6. Protocol Amendments and Study Termination

Protocol amendments and amendments to the ICF must be made only with the prior approval of the Sponsor and/or its designee. The IRB/IEC and Regulatory Agencies must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the study. The Investigator must send a copy of the approval letter from the IRB/IEC to the Sponsor and/or designee.

The Sponsor reserves the right to suspend or terminate the study (Section 6.6.1). The Investigator should notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to the Sponsor and/or designee.

13.7. Finance, Insurance, and Indemnity

A study site will not initiate participation until a fully executed Clinical Study Agreement is in place between the site and the Sponsor. The Clinical Study Agreement delineates all details associated with finance, insurance, and indemnity.

13.8. Publication Policy

Any publication or presentation by the Investigator and/or the Institution based on data or results from this study shall only be done in strict accordance with the Clinical Study Agreement executed between the Sponsor and the Institution and/or the Investigator, and in accordance with the requirements of the International Committee of Medical Journal Editors (ICMJE) and internal Sponsor policy.

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APPENDIX A. CLINICAL LABORATORY ANALYTES: SCREENING/DOSE EVALUATION PERIOD AND EXTENSION PERIOD

Screening, Dose Evaluation Period and Extension Period Up to Week 48	
Serum Chemistry: Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bilirubin - total and direct Gamma glutamyl transferase Blood urea nitrogen Lactate dehydrogenase Creatinine Glucose Calcium ^b Phosphate ^b Protein - total Albumin Sodium Potassium Chloride Bicarbonate Creatine kinase Uric acid Estimated glomerular filtration rate Cholesterol Triglycerides Amylase Lipase Magnesium	Hematology: Hemoglobin Hematocrit Erythrocytes White blood cells Neutrophils (absolute, %) Lymphocytes (absolute, %) Monocytes (absolute, %) Eosinophils (absolute, %) Basophils (absolute, %) Platelet count
	COVID-19 Test: (in Germany and France Only) COVID-19
	Urinalysis: Routine dipstick
	Pregnancy Testing: WOCBP only (urine at all visits; serum if positive or inconclusive urine test)

Screening, Dose Evaluation Period and Extension Period Up to Week 48	
PK/PD Variables/Biomarkers: Plasma PPi Serum ENPP1 specific activity Serum ADA and neutralizing Ab Serum INZ-701 activity and concentration	Exploratory Biomarkers: Serum 25(OH)D Serum intact PTH Plasma osteopontin Serum C-reactive protein Plasma FGF23 (C-terminal) Plasma intact FGF23 Serum β 2-microglobulin Serum PINP Serum CTX Serum BALP Plasma ATP
Hypersensitivity Samples, if applicable IgE IgG Serum tryptase Plasma histamine complement activation (C3, C4) Acute phase reactants (to include, at minimum C-Reactive Protein)	Second Morning Urine to Derive TmP/GFR Calcium Phosphate Creatinine

Note: Consult Laboratory Manual for collection, processing, and shipping instructions.

- a. At the Day 1 visit that includes 24-hour urine collection and urine collection for biomarkers (TmP/GFR), the last 2 hours of the urine collection will be collected separately, an aliquot from the 2-hour urine collection will be removed for the biomarker assessment, and the remainder of the urine will be combined with the rest of the 24-hour urine collection. An aliquot of the 24-hour urine sample will be stored frozen for future urine biomarkers associated with ENPP1 Deficiency.
- b. Calcium phosphate product will also be calculated and reported

Ab=antibody; ADA=anti-drug antibody; ATP=adenosine triphosphate; BALP=bone specific alkaline phosphatase; CTX=carboxy terminal cross-linked telopeptide of type I collagen; FGF23=fibroblast growth factor 23; Ig=immunoglobulin; PINP=procollagen type 1 N-terminal propeptide; PPi=inorganic pyrophosphate; PTH=parathyroid hormone; TmP/GFR=tubular maximum reabsorption rate of phosphate adjusted for glomerular filtration rate; WOCBP=women of childbearing potential.

Extension Post Week 48 Period	
Serum Chemistry: Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bilirubin - total and direct Gamma glutamyl transferase Blood urea nitrogen Creatinine Glucose Calcium ^b Phosphate ^b Protein - total Albumin Sodium Potassium Chloride Bicarbonate Creatine kinase Estimated glomerular filtration rate	Hematology: Hemoglobin Hematocrit Erythrocytes White blood cells Neutrophils (absolute, %) Lymphocytes (absolute, %) Monocytes (absolute, %) Eosinophils (absolute, %) Basophils (absolute, %) Platelet count
	Urinalysis: Routine dipstick
	Pregnancy Testing: WOCBP only (urine at all visits; serum if positive or inconclusive urine test)
Efficacy Variables/Biomarkers: Plasma PPI Serum INZ-701 concentration Serum ENPP1 specific activity Serum ADA	Exploratory Biomarkers: Serum 25(OH)D Plasma osteopontin Plasma FGF23 (C-terminal) Plasma FGF23 (Intact) Serum P1NP Serum CTX Serum BALP
Hypersensitivity Samples, if applicable: IgE IgG Serum tryptase Plasma histamine complement activation (C3, C4) Acute phase reactants (to include, at minimum C-Reactive Protein)	Second Morning Urine to Derive TmP/GFR Calcium Phosphate Creatinine

Note: Consult Laboratory Manual for collection, processing, and shipping instructions.

- a. At the visits that include urine collection for the biomarkers (TmP/GFR) but not the 24-hour urine collection (Weeks 12, 24, and 36), a second morning urine collection will be obtained prior to blood sample collection and will be submitted for biomarker assessment. Another aliquot of the 24-hour urine sample will be stored frozen for future urine biomarkers associated with ENPP1 Deficiency.
- b. Calcium phosphate product will also be calculated and reported

ADA=anti-drug antibody; ATP=adenosine triphosphate; BALP=bone specific alkaline phosphatase;
CTX=carboxy terminal cross-linked telopeptide of type I collagen; FGF23=fibroblast growth factor 23;
Ig=immunoglobulin; P1NP=procollagen type 1 N-terminal propeptide; PPi=inorganic pyrophosphate;
PTH=parathyroid hormone; TmP/GFR=tubular maximum reabsorption rate of phosphate adjusted for glomerular filtration rate; WOCBP=women of childbearing potential.

APPENDIX B. CONTRACEPTION AND FERTILITY DEFINITIONS

Contraception methods that can achieve a failure rate of <1% per year when used consistently and correctly are considered to be highly effective. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
 - Oral
 - Intravaginal
 - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
 - Oral
 - Injectable
 - Implantable¹
- Intrauterine device (IUD)¹
- Intrauterine hormone-releasing system (IUS)¹
- Bilateral tubal occlusion¹
- Vasectomized partner^{1,2}
- Sexual abstinence³

Definitions:

Females: For the purpose of this document, a woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Fertile Males: For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

¹ Contraception methods that are considered to have low user dependency.

² Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.

³ Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with INZ-701. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: [CTFG 2020](#)

APPENDIX C. GUIDELINE REGARDING MEDICATION WASHOUT PERIODS AND CONCOMITANT MEDICATIONS

The following suggestions should be considered for the washout periods for the listed medications/medication types.

If the washout periods noted below are not met, then the Investigator may consult with the Sponsor to discuss study participation.

If clinically indicated, as determined by the PI in consultation with the Sponsor, calcium supplementation could be used during the Extension Period. In addition, should the Investigator determine that the subject requires any of the prohibited medications below then the Investigator will consult with the Sponsor to determine continued subject participation.

Any taper of Calcitriol and Phosphate must be done under the guidance of the prescribing physician and only if deemed not detrimental to subject's health. Discontinuation of 1,25-(OH)₂D and phosphate should be undertaken only if considered not detrimental and indicated by the subject's treating physician. Treatment must not be withdrawn to fulfill study eligibility if it is considered necessary for clinical management of the subject.

- Calcimimetics or PTH suppressors and modulators
 - No use within 3 months prior to the first dose of INZ-701
- Systemic corticosteroids (>5 mg prednisone equivalent per day)
 - No use for more than 14 days within 3 months prior to the first dose of INZ-701
- Systemic oral or transdermal estrogen (use for contraception and treating symptoms of menopause is allowed), SERMs, hormone ablation therapy, tibolone
 - No more than 1 month of cumulative use within 6 months prior to the first dose of INZ-701
- Activated Vitamin D3 (1,25[OH]₂D/calcitriol [or analogs])
 - No use within 1 week of the first dose of INZ-701
- Phosphate or calcium supplements (including antacids containing calcium).
 - No use within 36 hours of the first dose of INZ-701
- Anti-fibroblast growth factor 23 (FGF23) (eg, burosumab) or other biologic bone modulators
 - No use within 18 months prior to the first dose of INZ-701
- Oral bisphosphonates
 - No use within the past year prior to the first dose of INZ-701
- Intravenous (IV) bisphosphonates
 - Zoledronic acid
 - No use within 3 years prior to the first dose of INZ-701

- No more than 1 dose received within 3 to 5 years prior to the first dose of INZ-701
- Ibandronate or pamidronate
 - No use within 12 months prior to the first dose of INZ-701
 - No more than 1 month of cumulative use within 3 years prior to the first dose of INZ-701