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 ABCC6 Deficiency Manifesting as *Pseudoxanthoma elasticum* (PXE)

Protocol Number:	**INZ701-201**
Investigational Product:	INZ-701 (recombinant human ectonucleotide pyrophosphatase/phosphodiesterase 1 [ENPP1] fused to the Fc fragment of IgG1; rhENPP1-Fc)
Indication:	ATP-binding cassette sub-family C member 6 (ABCC6) Deficiency manifesting as *Pseudoxanthoma elasticum* (PXE)
Development Phase:	1/2
US IND Number:	156761
EudraCT Number:	2020-004000-33
ClinicalTrials.gov Identifier:	NCT05030831
Sponsor:	Inozyme Pharma, Inc. [redacted]
Sponsor's Responsible Signatory:	[redacted] Chief Medical Officer
Protocol Version:	8.0
Effective Date:	14 June 2023

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SPONSOR PROTOCOL APPROVAL PAGE

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 ABCC6 Deficiency Manifesting as *Pseudoxanthoma elasticum* (PXE)
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Sponsor:	Inozyme Pharma, Inc.

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.

[redacted] 6/14/2023

Date

Chief Medical Officer
Inozyme Pharma, Inc.

INVESTIGATOR SIGNATURE PAGE

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 ABCC6 Deficiency Manifesting as *Pseudoxanthoma elasticum* (PXE)
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Sponsor:	Inozyme Pharma, Inc.

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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2. 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 ABCC6 Deficiency Manifesting as *Pseudoxanthoma elasticum* (PXE)
Development Phase Phase 1/2
Planned Number of Study Sites Approximately 4 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 a cohort to evaluate an alternate dosing regimen and/or enroll up to 6 additional subjects to further evaluate and corroborate the PK and PD of INZ-701 at an existing dose level.
Indication ATP-binding cassette sub-family C member 6 (ABCC6) Deficiency
Rationale for Treatment with INZ-701 ABCC6 Deficiency is a rare, autosomal recessive genetic disease characterized by a progressive ectopic deposition of calcium phosphate crystals on various extracellular matrices which leads to fragmentation of elastic fibers affecting the elastin-rich tissues such as the skin, the retina, and the vascular wall. Clinically diagnosed as *Pseudoxanthoma elasticum* (PXE) in adults, ABCC6 Deficiency has a high morbidity and cardiovascular and ophthalmological manifestations. Ocular changes include angioid streaks reflecting mineralization of Bruch's membrane behind the pigmented retinal epithelium, which allows neovascularization of the retina, leading to loss of visual acuity, hemorrhage, and blindness. Cardiovascular manifestations include intermittent claudication, gastrointestinal (GI) hemorrhages associated with stenoses of GI arteries, and stroke. Ectopic mineralization has also been noted in kidneys, joints, and tendons in patients with ABCC6 Deficiency, demonstrating this is a systemic and heterogenous disease. Studies have shown that ABCC6 transports intracellular adenosine triphosphate (ATP) to the extracellular space of hepatocytes where ATP is hydrolyzed by the ENPP1 enzyme to generate inorganic pyrophosphate (PPi) and adenosine monophosphate (AMP). Loss of function mutations in the ABCC6 gene leads to approximately 50% decrease in systemic plasma PPi which, in turn, leads to ectopic mineralization of elastin rich tissues.

Abcc6$^{-/-}$ mice demonstrate a 50% to 70% reduction in plasma PPi and subsequently develop ectopic mineralization of connective tissues in several organs, including skin, eyes, arterial blood vessels, liver, and kidneys. Treatment of *Abcc6*$^{-/-}$ mice with PPi, either through injection or dietary supplementation, raised serum levels of PPi and prevented ectopic calcification. As seen with the *Abcc6*$^{-/-}$ mouse model, PXE patients show a 2- to 2.5-fold reduction of PPi levels which results in ectopic calcification. These findings demonstrate that a chronic state of low serum PPi, is the major cause of the pathologic mineralization of elastic fibers in affected tissues such as the blood vessels, skin, and eyes.

Plasma PPi is generated by the ENPP1 enzyme, a type II transmembrane glycoprotein which cleaves extracellular ATP to form AMP and PPi. Systemic overexpression of an ENPP1 transgene in *Abcc6*$^{-/-}$ mice using a cytomegalovirus (CMV) promoter leads to a normalization of serum PPi levels and a significant decrease in organ and tissue calcifications. Further, experiments indicate that subcutaneous (SC) injection of soluble INZ-701 (rhENPP1-Fc) normalizes serum PPi levels and prevents skin calcification in *Abcc6*$^{-/-}$ mice, suggesting that a soluble recombinant ENPP1, such as INZ-701, restores PPi to normal levels and potentially prevents calcification of Bruch's membrane and other tissues.

The Sponsor is developing the investigational product, INZ-701, for the treatment of ABCC6 Deficiency. INZ-701 is a recombinant fusion protein that contains the extracellular domains of human ENPP1 coupled with an Fc fragment from an IgG1 antibody (rhENPP1-Fc).

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

Objectives

Primary Objective:

- Assess the safety and tolerability of multiple ascending SC doses of INZ-701

Secondary Objectives:

- Assess the immunogenicity of multiple ascending SC doses of INZ-701
- Study the pharmacokinetics (PK) of multiple ascending SC doses of INZ-701
- Study the long-term safety and pharmacodynamic (PD) changes from baseline in PPi after administration of multiple SC doses of INZ-701

Exploratory Objectives:

- Assess changes in calcification of arteries and organs (including the eye)
- Assess changes in clinical measures associated with underlying ABCC6 Deficiency, including cardiac, vascular, ophthalmologic, and renal parameters
- Assess changes in physical function
- Assess changes in patient, clinician, and caregiver reported outcomes and quality of life

Study Design

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

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

Safety events will be characterized and graded using the National Cancer Institute-Common Terminology Criteria of Adverse Events 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 3 parts, a Screening Period of up to 60 days, a 32-day Dose Evaluation Period, and an Extension Period during which subjects may continue to receive INZ-701 until it is approved and available in the country where the subject resides or until an alternative study for subjects to continue receiving study drug is available.

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

The study design of the Dose Evaluation Period is a MAD 3 + 3 with 3 dose cohorts. 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, with a twice weekly dose regimen. The maximum exposure level, based on the no-observed-adverse-effect-level (NOAEL) values from chronic Good Laboratory Practice (GLP) toxicology studies, is set at [redacted] µg/mL and [redacted] hr*µg/mL for maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time zero to the time of last measurable concentration (AUC_{last}), respectively.

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.

In the Extension Period, INZ-701 administration will initially be at the dose and dose schedule assigned in the Dose Evaluation Period. The Sponsor may modify the assigned

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

Study visits will be in-clinic every 4 weeks until Week 48 of the Extension Period and then every 12 weeks (remote or in-clinic) 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.

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 as per the protocol 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 not exercising as required per protocol.

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. 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 doses, with a final dose on Day 29. 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 the 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 Day 29 assessments, 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 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.

Subjects who participate in the Extension Period will continue to receive INZ-701 at the prescribed dose regimen assigned in the Dose Evaluation Period. In the Extension Period post-Week 48, the INZ-701 dose and dose regimen may be changed and could be either weight-based or potentially non-weight based as determined by safety and PK/PD data. 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.

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 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 at minimum to follow-up on the administration procedure, compliance, and potential 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, which will not be less than 1 hour. 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, 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 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.

Safety Monitoring

Study INZ701-201will 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 throughout 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 that cohort and any prior cohort, which will not be less than 1 hour.

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 have a remote or 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 their last dose.

Dose Modifications (mg/kg)

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.

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

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 on or after Day 32 of the Dose Evaluation Period may re-enroll in the study in the Extension Period at the Investigator's discretion following approval from the Sponsor. Subjects will be required to re-consent in order to re-enroll; subject dose regimen is as described in the protocol.

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. 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 an independent DSMB.

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] µg/mL and AUC_{last} of [redacted] hr*µg/mL) will require regulatory authority approval via a substantial amendment before implementation.

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 therapeutic protein products 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 will occur on Day 32. Based on experience with other therapeutic protein products, this is considered a sufficient period of observation to detect any event associated with a DLT.

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) as follows:

- Stop enrollment at that dose level
- Declare maximum tolerated dose (MTD) at the next lower dose level
- Resume cohort enrollment. If no other DLTs are observed in the 3 subjects after completing the 32-day Dose Evaluation Period, the cohort will be expanded by 3 subjects

- De-escalate to an existing lower dose level and enroll up to 3 new subjects for a maximum of 6 subjects in the dose cohort
- Add a lower dose level, enroll, and dose 3 new subjects in that dose cohort
- De-escalate current subjects in this cohort to a lower dose

At the completion of an expanded cohort with only 1 DLT, the DSMB will convene to review data 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 recommendations as follows:

- 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 by the Sponsor in collaboration with the Investigators following DSMB recommendation.

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

Study Stopping Criteria

Dosing should 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 Principal Investigator 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 EOS 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 ABCC6 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 60 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 PXE supported by prior genetic identification of biallelic *ABCC6* mutations (ie, homozygous or compound heterozygous)
3. Male or female, 18 to <70 years of age at Screening
4. Plasma PPi <1300 nM at Screening
5. Subjects who are being treated with statins or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors must have been on treatment for at least 6 months prior to Screening and no new anti-lipid therapy can be introduced within 6 months of Screening
6. Women of child-bearing potential (WOCBP) as defined in Clinical Trials Facilitation and Coordination Group (CTFG 2020) must have a negative serum pregnancy test at Screening

7. WOCBP and partners of fertile males who are WOCBP must be using or agree to use one 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.
8. 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.
9. In the opinion of the Investigator, must be willing and able to complete the Dose Evaluation Period
10. 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 ABCC6 Deficiency) that precludes study participation or may confound interpretation of study results, including known uncontrolled thyroid, or unrelated connective tissue, bone, mineral, lipid, ophthalmologic, or muscle disease
2. Active retinal bleeding in both eyes during Screening
3. Clinically significant abnormal laboratory result at Screening in the opinion of the Investigator, including but not limited to, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 (Chronic Kidney Disease-Epidemiology Collaboration equation) or 25-hydroxyvitamin D levels <12 ng/mL
4. Known active fungal, bacterial, and/or viral infection including human immunodeficiency virus, hepatitis B virus, hepatitis C virus, or COVID-19 infection.
5. Malignancy within the last 5 years, except non-melanoma skin cancers or cervical carcinoma in situ
6. Known intolerance to INZ-701 or any of its excipients
7. Unable to or unwilling to discontinue the use of any prohibited medication as provided in the protocol. Discontinuation should be undertaken only if considered not detrimental and indicated by the subject's treating physician.
8. 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
9. Subjects who are pregnant, trying to become pregnant, or breastfeeding
10. 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
- Presence of neutralizing antibodies
- Incidence, frequency, and severity of AEs, treatment-related AEs, treatment-emergent AEs (TEAEs), TEAEs associated with hypersensitivity reactions, and SAEs
- Vital signs and weight
- Physical examinations
- Laboratory tests including chemistry with eGFR, hematology, and urinalysis, and additional biochemical parameters of interest
- Incidence of anti-drug antibodies
- Incidence of DLTs
- Concomitant medications
- Electrocardiogram (ECG)
- Holter Monitoring and/or Cardiac Telemetry (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 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}), terminal 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

- Change from baseline in PPi levels, phosphate, calcium, alkaline phosphatase, and intact parathyroid hormone
- Changes from baseline of blood and urine biomarkers as available

Exploratory Efficacy Endpoints

The following assessments are required:

- Echocardiogram

- Renal ultrasound
- Carotid ultrasound
- Ophthalmologic tests
  - Optical coherence tomography (OCT), color fundus photography, and autofluorescence photography
  - Best corrected visual acuity using Early Treatment Diabetic Retinopathy Study letter charts

The following assessments are not required. However, if the site has the ability (ie, resources, staff, etc.) to conduct them they are strongly recommended. For any nonrequired assessment not conducted by Day 1, the subject will not have the assessment conducted at any time during the study. Baseline $Na^{18}F$-PET/CT imaging may be performed within 2 months after the first dose of INZ-701; if not conducted within the first 2 months after the first dose, the subject will not have the imaging assessment conducted at any time during the study.

- $Na^{18}F$-PET/CT
- Pulse Wave Velocity
- Ankle-Brachial Pressure Index
- Global Impression Scales
- Patient Reported Outcomes Measurement Information System (PROMIS), Pain Interference, Fatigue, and Physical Function - Upper Extremity
- Vision Function Questionnaire
- Work Productivity and Activity Impairment Questionnaire
- Edinburgh Claudication Questionnaire

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.

Timing of Analysis

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

An interim analysis will be conducted when all subjects have completed the Week 48 visit. Additional interim analyses may be conducted in the Extension Period based on subject enrollment.

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

Efficacy Analyses

Changes in blood and urine PD biomarkers associated with ABCC6 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 set. The primary safety endpoint will be evaluated by examining incidence and type of TEAEs.

PK, PD, Immunogenicity, and 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	**-60 to -2**	**-1**	**1**	**2-7**	**8**	**11**	**15**	**18**	**22**	**25**	**29**	**30**	**31**	**32**
Visit Window			**± 1 day** [c]										**+1 day**	
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													
Medical History, ABCC6 Deficiency Specific History, Demographics [g]	X													
Safety Evaluations														
Vital Signs [h]	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 [k]	X		X											
Clinical Safety Laboratory Evaluations [l, m]	X	X [n]	X		X		X		X		X			X
24-hour Urine [o]			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	**-60 to -2**	**-1**	**1**	**2-7**	**8**	**11**	**15**	**18**	**22**	**25**	**29**	**30**	**31**	**32**
Visit Window			**± 1 day** [c]										**+1 day**	
Pregnancy test (WOCBP only) – serum at Screening and Day -1, urine at additional assessments [p]	X	X [q]	X											X
Immunogenicity [l, r]			X		X		X		X		X			X
Adverse Event Monitoring	Throughout study													
Prior and Concomitant Medications	Throughout study													
INZ-701 Administration														
INZ-701 Injection (SC) [s]			X		X	X	X	X	X	X	X			X [s]
Required Efficacy, Biomarker, PK/PD Evaluations														
Inorganic pyrophosphate (PPi) [l, t]	X		X	X	X	X	X	X	X	X	X	X	X	X
INZ-701 PK and ENPP1 specific activity [l, u]			X	X	X	X	X	X	X	X	X	X	X	X
25(OH)D [v]	X													
Exploratory Biomarkers (blood and urine) [l, o, v]			X [v]				X [v]				X [v]			
TmP/GFR (serum and urine phosphate and creatinine) [o]			X								X			
Echocardiogram	X													
Renal ultrasound [w]	X													
Carotid ultrasound	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	-60 to -2	-1	1	2-7	8	11	15	18	22	25	29	30	31	32
Visit Window			± 1 day [c]										+1 day	
Ophthalmologic exam [w, x]	X													
Not Required Exploratory Efficacy Evaluations [y]														
$Na^{18}F$-PET/CT [w, y]	X													
Ankle-Brachial Pressure Index and Pulse Wave Velocity [y]	X													
Global Impression Scales [y, z]	X													
PROMIS, WPAI [y]	X													
Vision Function Questionnaire [y]	X													
Edinburgh Claudication Questionnaire [y]	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 PXE supported by prior genetic identification of biallelic *ABCC6* mutations) before undergoing any physical 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 (for WOCBP only) must be repeated within 30 days of dosing (and can be done locally).

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 Subjects 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 their safety data assessment 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 will be done at Screening where required per institutional policy.

g Medical History includes date and method of ABCC6 Deficiency diagnosis. Each subject must have a documented 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 when INZ-701 is administered during visits on Days 1 to 15. After Day 15, record vital signs once, obtained prior to INZ-701 administration.

i Weight obtained at Day 1 will be used to calculate the dose of INZ-701 to be administered during the Dose Evaluation Period.

j Electrocardiogram: Standard 12-lead ECGs are to be obtained prior to dosing and read centrally. Additional ECGs may be collected if clinically indicated.

k Cardiac Telemetry and/or Holter monitoring should be obtained if required per site specific procedures and/or Investigator discretion. Cardiac telemetry, if performed, should be obtained at Day 1 beginning pre-dose and continuing through 24 hours post-dose.

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 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.

m Clinical Safety Laboratory Evaluations: Obtain prior to dosing (if applicable); includes blood chemistry panel with liver function tests, hematology panel including complete blood count with differential, and urinalysis (see Appendix A). On Days 1, 15, and 29, samples will also be collected 6 hours post-dose (±30 min), to include serum chemistry assessment of ionized calcium (collected locally), phosphate, and calcium. Additional safety laboratory evaluations may be collected during the Dose Evaluation Period to monitor safety at institutions where required or if clinically indicated. Care should be taken to not exceed the maximum allowed blood volume for any time period. Cholesterol and triglycerides will be assessed at Screening only. Routine urinalysis required only at Screening and on Days 1 and 32 and early termination.

n Day-1 Clinical Safety Laboratory Evaluations may be performed if it is an Investigator or site-specific requirement for determining subject eligibility.

o 24-hour Urine: Calcium, phosphate, and creatinine will be measured. Sample collection will be started on Days -1 and 28 and collected pre-dose at Days 1 and 29. At the Day 1 and 29 visits that include 24-hour urine collection and urine collection for 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 biomarker assessments, 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 ABCC6 Deficiency.

p Pregnancy Test: Serum pregnancy test should be performed at the Screening Visit in WOCBP; if the subject is not dosed within 30 days of Screening, the serum pregnancy test must be repeated. If the subject is dosed within 30 days of Screening, a urine pregnancy test will be performed at Day 1 before dosing. A serum test will be performed in the event of a positive or inconclusive urine test.

q Day -1 Pregnancy Test: A serum pregnancy test may be performed at Day -1 (in lieu of a urine pregnancy test at Day 1) if required by the study site.

r 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).

s INZ-701 Administration: 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 and tolerability data from the first subject and will decide if dosing of the second subject in the cohort/dose level is safe and can proceed. Information regarding fasting, administration of INZ-701, and safety monitoring are provided in Sections 9.1.2, 9.1.3, and 9.1.4. INZ-701 administration on Day 32 is the first dose of the Extension Period; after completion of Day 32

assessments, subjects who participate in the Extension Period will continue to receive INZ-701 and be monitored for safety either in the clinic or in their home by the subject, subject's caregiver(s), or a qualified healthcare provider (under the supervision of the Investigator) until the next study visit at Week 8 (Table 2).

t PPi Sampling: Pre-dose sample must be collected in the morning. Follow PK/PD collection schedule (Table 5).

u PK and ENPP1 Specific Activity samples will be obtained according to the PK/PD sampling schedule (Table 5).

v Exploratory Biomarkers include 1,25(OH)$_2$D, 25(OH)D, intact PTH, C-reactive protein, β2-microglobulin, osteopontin, CTX, P1NP, and bone specific alkaline phosphatase in serum; and FGF23 (intact and C-terminal) and adenosine triphosphate in plasma; (see Appendix A). 25(OH)D levels will be measured during Screening for eligibility and need not be collected at Day 1. Only intact PTH and intact FGF23 will be measured pre-dose and at 6 hours post-dose at Days 1, 15, and 29.

w $Na^{18}F$-PET/CT, renal ultrasound and ophthalmologic exam conducted within 6 months prior to Screening may be used as Baseline if they meet study requirements in the opinion of the Sponsor. Historical $Na^{18}F$-PET/CT that do not meet the specifications above may be considered for the study Baseline upon Investigator discretion in consultation with the Sponsor. Baseline $Na^{18}F$-PET/CT imaging may be performed within 2 months after the first dose of INZ-701; if not conducted within the first 2 months after the first dose, the subject will not have the imaging assessment conducted at any time during the study.

x Ophthalmologic Exam: See Section 10.3.2 for details.

y Not Required Exploratory Efficacy Assessments: 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 subject will not have the assessment conducted at any time during the study. The exception to this is $Na^{18}F$-PET/CT (see footnote w).

z Global Impression Scales: At Screening, Investigators will complete the Clinical Global Impression of Status/Severity and will administer the Patient Global Impression of Status/Severity and Caregiver Global Impression of Status/Severity, if applicable.

1,25(OH)$_2$D=1,25-dihydroxyvitamin D; 25(OH)D=25-hydroxyvitamin D; ABCC6=ATP-binding cassette sub-family C member 6; CT=computed tomography; CTX=carboxy terminal cross-linked telopeptide of type I collagen; ECG=electrocardiogram; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; FGF23=fibroblast growth factor 23; HIV=human immunodeficiency virus; P1NP=procollagen type 1 N-terminal propeptide; PD=pharmacodynamic(s); PET=positron emission tomography; PI=Principal Investigator; PK=pharmacokinetic(s); PPi=inorganic pyrophosphate; PROMIS=Patient Reported Outcomes Measurement Information System; PTH=parathyroid hormone; PXE=*Pseudoxanthoma elasticum*; SC=subcutaneous; TmP/GFR=tubular maximum reabsorption rate of phosphate adjusted for glomerular filtration rate; 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]	As per the prescribed dose regimen [b]										
Safety Evaluations											
Vital Signs [c]	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
Electrocardiogram [e]		X			X			X			X
Clinical Safety Laboratory Evaluations [f, g]	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 [h]
Immunogenicity [f, j]	X	X			X			X			X
Adverse Event Monitoring	Throughout the study [k]										
Concomitant Medications	Throughout the study [k]										
Required Efficacy, Biomarker, PK/PD Evaluations											
Inorganic pyrophosphate (PPi) [f, l]	X	X	X	X	X	X	X	X	X	X	X
INZ-701 concentration and serum ENPP1 specific activity [f, l]	X	X			X			X			X
Echocardiogram					X						X
Renal ultrasound											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**										
Carotid ultrasound					X						X
Ophthalmologic exam [m]											X
Exploratory Biomarkers (blood and urine) [f, h, n]		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 [o]											
$Na^{18}F$-PET/CT [o, p]											X
Ankle-Brachial Pressure index and Pulse Wave Velocity [o]					X						X
Global Impression Scales [o, q]		X			X			X			X
PROMIS, WPAI [o]		X			X			X			X
Vision Function Questionnaire [o]		X			X			X			X
Edinburgh Claudication Questionnaire [o]		X			X			X			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 to INZ-701 dosing 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 End of Study (Safety Follow-up) Visit (Table 4) 30 days after their last dose. 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 in consultation with the Sponsor will prescribe the required post-dose monitoring duration for each subject. Information regarding administration of INZ-701 and safety monitoring are provided in Sections 9.1.2, 9.1.3, and 9.1.4.

c Vital Signs will be recorded prior to INZ-701 administration at the in-clinic visits.

d Weight: If the subject's weight changes more than 5% of the Day 1 weight, the dose will be weight adjusted unless a flat dose is being used.

e Electrocardiogram: Standard 12-lead ECGs are to be 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 is to 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. 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.

g Clinical Safety Laboratory Evaluations: Obtain prior to dosing (if applicable); includes blood chemistry panel with liver function tests, hematology panel including complete blood count with differential, and urinalysis. Cholesterol and triglycerides will be assessed at the Week 48 Visit 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, a blood sample for serum creatinine and phosphate should be collected as part of the safety laboratory tests.

i Pregnancy Test: Urine tests 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 samples for antibody analysis must be collected pre-dose. Additional samples may be obtained if clinically indicated (eg, suspected hypersensitivity reaction).

k AEs and concomitant medications must be assessed minimally at each in clinic visit and during any communication with the subjects and may be more frequent based on Investigator discretion as per the subject's individual needs (eg, weekly).

l PPi, ENPP1 specific activity, and INZ-701 PK: See Table 4 for the sample collection schedule. PPi samples must be collected in the morning.

m Ophthalmologic Exam: See Section 10.3.2 for details. Ophthalmologic exam will be performed within 1 month of or concurrent with the Week 48 Visit. If conducted outside the context of this study, results that meet study requirements in the opinion of the Sponsor within the correct timeframe may be submitted for the Week 48 assessment.

n Exploratory Biomarkers include $1,25(OH)_2D$, 25(OH)D, intact parathyroid hormone, C-reactive protein, β2-microglobulin, osteopontin, CTX, P1NP and bone specific alkaline phosphatase in serum; and FGF23 (intact and C-terminal) in plasma (see Appendix A).

o Not Required Exploratory Efficacy Assessments: 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 subject will not have the assessment conducted at any time during the study. The exception to this is $Na^{18}F$-PET/CT (see footnote p).

p $Na^{18}F$-PET/CT will not be performed at Week 48 if the subject has had less than 24 weeks of study participation. Baseline $Na^{18}F$-PET/CT imaging may be performed within 2 months after the first dose of INZ-701; if not conducted within the first 2 months after the first dose, the subject will not have the imaging assessment conducted at any time during the study.

q Global Impression Scales: In the Extension Period, Investigators will complete the Clinical Global Impression of Improvement and will administer the Patient Global Impression of Improvement and Caregiver Global Impression of Improvement, if applicable.

$1,25(OH)_2D$=1,25-dihydroxyvitamin D; 25(OH)D=25-hydroxyvitamin D; CT=computed tomography; CTX=carboxy terminal cross-linked telopeptide of type I collagen; ECG=electrocardiogram; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; FGF23=fibroblast growth factor 23; P1NP=procollagen

type 1 N-terminal propeptide; PD=pharmacodynamic(s); PET=positron emission tomography; PK=pharmacokinetics(s); PPi=inorganic pyrophosphate; PROMIS=Patient Reported Outcomes Measurement Information System; 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

Study Visit	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**											
Safety Evaluations												
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
Height				X				X				X
Physical Exam/Vital Signs[b]		X		X		X		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

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

Study Visit	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 concentration and serum ENPP1 specific activity		X		X		X		X		X		X
Ophthalmologic Exam				X				X				X
Exploratory Biomarkers (blood) [c, i]		X		X		X		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 9.1.2, 9.1.3, and 9.1.4.

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. 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 and only during in-clinic visits.
i Exploratory Biomarkers include 25(OH)D, iPTH, and osteopontin in serum and FGF23 (intact and C-terminal) in plasma (See Appendix A).

25(OH)D=25-hydroxyvitamin D; CBC=complete blood count; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; FGF23=fibroblast growth factor 23; iPTH=intact parathyroid hormone; 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
Timing	**30 days after last dose of INZ-701**
Compliance Window	**+7 days**
Vital Signs	X
Height, Weight	X
Physical Exam	X
Electrocardiogram [a]	X
Safety Laboratory Evaluations [b, c]	X
Pregnancy test (WOCBP only) –urine	X
Adverse Events	X
Concomitant Medications	X
Inorganic pyrophosphate (PPi) [b]	X
INZ-701 concentration and ENPP1 specific activity [b]	X
Immunogenicity [b]	X
Global Impression Scales [d, e]	X
PROMIS and WPAI [e]	X
Exploratory Biomarkers (blood and urine) and Second Morning Urine (phosphate, calcium, creatinine) and serum phosphate and creatinine (as part of the safety labs) [b, f]	Complete if NOT performed within 24 weeks of EOS visit
Ankle-Brachial Pressure Index and Pulse Wave Velocity [e]	Complete if NOT performed within 24 weeks of EOS visit
Echocardiogram	Complete if NOT performed within 48 weeks of EOS visit
Renal ultrasound	Complete if NOT performed within 48 weeks of EOS visit
Carotid ultrasound	Complete if NOT performed within 48 weeks of EOS visit
Ophthalmologic exam	Complete if NOT performed within 48 weeks of EOS visit
$Na^{18}F$-PET/CT [e]	Complete if NOT performed within 48 weeks of EOS visit

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

a Electrocardiogram: Standard 12-lead ECGs will be read centrally.

b Blood Collection: INZ-701 is to 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 blood samples. If maximum allowed blood volume has been reached for any given time-period, prioritize 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 or when clinically indicated. Care should be taken to not exceed maximum blood volume for any time period.

d Global Impression Scales: Investigators will complete the Clinical Global Impression of Improvement and will administer the Patient Global Impression of Improvement and Caregiver Global Impression of Improvement, if applicable.

e Not Required Exploratory Efficacy Assessments: Global Impression Scales, Ankle-Brachial Pressure Index, Pulse Wave Velocity, PROMIS, WPAI, and $Na^{18}F$-PET/CT will be completed only if Baseline is available.

f Exploratory Biomarkers: See Appendix A. Second Morning Urine (phosphate, calcium, creatinine) and serum phosphate and creatinine as part of the safety evaluation.

CT=computed tomography; ECG=electrocardiogram; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; EOS=end of study; PET=positron emission tomography; PPi=inorganic pyrophosphate; PROMIS=Patient Reported Outcomes Measurement Information System; TmP/GFR=tubular maximum reabsorption rate of phosphate adjusted for glomerular filtration rate; 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) [a]	**PPi (plasma sample)** [a, b]
Screening (Day -30 to -1)	Not applicable	Single sample
1-7 **Note: Days 2-7 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), 144 hours (± 3 hours), and 168 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 Day 15: 6 hours (± 30 min) post-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 [a]	Single sample [a]
For Subjects Participating in the Extension Period		
Through Week 48	Single pre-dose sample at Weeks 8, 12, 24, 36 and 48	Single pre-dose sample every 4 weeks starting at Week 8 through Week 48
After Week 48	Single pre-dose sample every 24 weeks	Single pre-dose sample every 12 weeks (at in-clinic visits only)
Safety Follow-up Visit		
30 days after last dose	Single sample	Single sample

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.

a 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 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.

b Pre-dose PPi: Samples must be collected in the morning.

ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; PD=pharmacodynamic(s); PK=pharmacokinetic(s); PPi=inorganic pyrophosphate.

3. GLOSSARY OF TERMS

Term	Definition
$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
ABCC6	ATP-binding cassette sub-family C member 6
ABI	ankle-brachial pressure index
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AMP	adenosine monophosphate
ATP	adenosine triphosphate
AUC_{last}	area under the plasma concentration-time curve from time zero to the 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
BCVA	best corrected visual acuity
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
CNV	choroidal neovascularization
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
CTFG	Clinical Trials Facilitation and Coordination Group
DLT	dose limiting toxicity
DSMB	Data Safety Monitoring Board
EC	Ethics Committee

Term	Definition
ECG	electrocardiogram
eCRF	electronic case report form
ECQ	Edinburgh Claudication Questionnaire
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1
EOS	end of study
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	immunoglobulin
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
NOAEL	no-observed-adverse-effect level
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

Term	Definition
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PPi	inorganic pyrophosphate
PROMIS	Patient Reported Outcomes Measurement Information System
PTH	parathyroid hormone
PWV	pulse wave velocity
PXE	*Pseudoxanthoma elasticum*
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
SAS	safety analysis set
SC	subcutaneous
SMP	Safety Management Plan
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal 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
VEGF	vascular endothelial growth factor
V/F	apparent volume of distribution after extravascular administration of drug
WOCBP	women of child-bearing potential
WPAI	Work Productivity and Activity Impairment Questionnaire

4. INTRODUCTION

The Sponsor is developing the investigational product, INZ-701, as a treatment for adenosine triphosphate (ATP)-binding cassette sub-family C member 6 (ABCC6) Deficiency. INZ-701 is a recombinant human fusion protein that contains the extracellular domains of human ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) coupled with an Fc fragment from an immunoglobulin (Ig)G1 antibody (rhENPP1-Fc).

In 2021, the United States Food and Drug Administration (FDA) Office of Orphan Products Development granted Orphan Drug Designation to INZ-701 for the treatment of ABCC6 Deficiency.

INZ701-201 is a multiple ascending dose (MAD), dose-finding study in adult subjects (18 to <70 years of age) with ABCC6 Deficiency manifesting as *Pseudoxanthoma elasticum* (PXE) that seeks to identify a dose for further clinical development in ABCC6 Deficiency.

4.1. ABCC6 Deficiency

ABCC6 Deficiency is a rare, serious, systemic, and progressively debilitating genetic condition with high morbidity and mortality that affects patients throughout the life span. ABCC6 Deficiency has a spectrum of phenotypes affecting skin, the retina, the vascular wall, and the cardiovascular system. A key pathophysiological feature in ABCC6 Deficiency is the progressive ectopic deposition of calcium phosphate crystals on various extracellular matrices which leads to fragmentation of elastic fibers. Adult patients with ABCC6 Deficiency are diagnosed with PXE (Le Saux et al 2001; Bergen et al 2000; Ringpfeil et al 2000). ABCC6 Deficiency affects approximately 1 in 50,000 people worldwide, and PXE is diagnosed twice as frequently in females as in males (Uitto et al 2014).

Patients with PXE have low levels of inorganic pyrophosphate (PPi) (Kauffenstein et al 2018). Extracellular PPi is a potent endogenous inhibitor of abnormal or pathological mineralization (Fleisch&Bisaz 1962; Fleisch et al 1966; Orriss et al 2016). PPi modulates the crystallization of calcium and phosphate into hydroxyapatite in collagen 1 to form bone and teeth and antagonizes crystallization in other non-osseous tissues. Mechanistically, PPi intercalates with high affinity in growing calcium orthophosphate crystals and causes a disordered crystalline structure thereby preventing the growth of the calcium hydroxyapatite crystal (Kauffenstein et al 2018). Data from the literature suggest that ABCC6 regulates serum PPi levels by controlling the release of adenosine triphosphate (ATP) by hepatocytes into the extracellular space where it serves as a substrate for ENPP1 activity (Jansen et al 2013).

As a consequence, the chronic state of low serum PPi caused by ABCC6 Deficiency is the major cause of the pathologic mineralization of elastic fibers in affected tissues (Zhao et al 2017; Dabisch-Ruthe et al 2014). Treatment of *Abcc6*$^{-/-}$ mice with high doses of PPi, either through injection or dietary supplementation, raises serum levels of PPi and prevents ectopic calcification (Pomozi et al 2017; Dedinszki et al 2017).

The clinical manifestations of ABCC6 Deficiency span the entire age spectrum. Diagnosis can occur during infancy where patients with ABCC6 Deficiency present with an acute calcification phenotype called Generalized Arterial Calcification of Infancy type 2 (GACI-2). In all other patients, diagnosis occurs because of either early cutaneous, mucosal, or retinal

findings or development of ocular and cardiovascular complications. PXE is characterised primarily by calcifications in the elastic tissues of three major organ systems: skin, eyes, and cardiovascular system. Skin presentation allows for the earliest diagnostic opportunity. Skin manifestations anticipate a general systemic pathological soft tissue calcification process that will later involve the eye and cardiovascular system. The earliest ocular finding is typically *peau d'orange*, small dark spots within an area of a slightly whitish or opaque fundus reflex. A later, more serious ocular presentation is the development of angioid streaks, which are cracks in the elastic membrane behind the retina (Bruch's membrane) resulting from calcification of elastic fibers of the membrane. Subsequent choroidal neovascularization (CNV) usually results in association with angioid streaks, and fluid leaks or bleeding from these blood vessels typically lead to distortion or progressive loss of vision with accompanying impairment of quality of life (Finger et al 2011).

Rapid blindness can occur over a period of months. Although treatment with anti-vascular endothelial growth factor (VEGF) therapy can slow the progression of visual loss by addressing the CNV, the underlying calcification of Bruch's membrane can continue increasing the incidence of further CNV over time. As the disease progresses, cardiovascular manifestations usually occur and manifest as increased risk of ischemic stroke and early myocardial infarcts, as well as intermittent claudication and hypertension. One study found a relative risk of ischemic stroke of 3.6 versus the general population (van den Berg et al 2000), but a quantification of relative risk of myocardial infarction is unknown. These cardiovascular complications lead to arterial narrowing associated with calcification of the elastic lamina of medium-sized arteries, as well as calcification of other cardiovascular tissues (Gliem et al 2013; Li et al 2009; Uitto&Li 2018). In addition, gastrointestinal (GI) bleeding has been reported in 15% of PXE patients compared to 0.1% of the general population (Goral et al 2007; Hu et al 2003; Neldner 1988). The pathophysiologic mechanism of these hemorrhages is unclear but could be related to calcification of the vasculature supplying these organs.

4.2. Rationale for Treatment with INZ-701

ABCC6 Deficiency is a rare, autosomal recessive genetic disease caused by loss of function mutations in the ABCC6 gene. Clinically diagnosed as PXE in adults, ABCC6 Deficiency has a high morbidity and cardiovascular and ophthalmological manifestations.

Abcc6$^{-/-}$ mice demonstrate a 50% to 70% reduction in plasma PPi and subsequently develop ectopic mineralization of connective tissues in several organs, including skin, eyes, arterial blood vessels, liver, and kidneys. Treatment of *Abcc6*$^{-/-}$ mice with PPi, either through injection or dietary supplementation, raised serum levels of PPi and prevented ectopic calcification (Pomozi et al 2017; Dedinszki et al 2017). As seen with the *Abcc6*$^{-/-}$ mouse model, PXE patients show a 2- to 2.5-fold reduction of PPi levels which results in ectopic calcification (Jansen et al 2014). These findings demonstrate that a chronic state of low serum PPi, is the major cause of the pathologic mineralization of elastic fibers in affected tissues such as the blood vessels, skin, and eyes.

Plasma PPi is generated by the ENPP1 enzyme, a type II transmembrane glycoprotein which cleaves extracellular ATP to form AMP and PPi (Nitschke et al 2018). Systemic overexpression of an ENPP1 transgene in *Abcc6*$^{-/-}$ mice leads to a normalization of serum PPi

levels and a significant decrease in organ and tissue calcifications (Zhao et al 2017). Further, experiments indicate that subcutaneous (SC) injection of soluble INZ-701 (rhENPP1-Fc) normalizes serum PPi levels and prevents skin calcification in *Abcc6*$^{-/-}$ mice, suggesting that a soluble recombinant ENPP1, such as INZ-701, restores PPi to normal levels and potentially prevents calcification of Bruch's membrane and other tissues (Jacobs et al 2022).

The current treatments for patients with PXE do not prevent the progressive systemic pathological calcification affecting the eyes, arteries, or skin. Treatment involves coordinated care by a multidisciplinary team (dermatologist, primary care physician, ophthalmologist, cardiologist, vascular surgeon, plastic surgeon, genetics professional, gastroenterologist, neurologist, nutritionist) depending on clinical manifestations, intraocular injection of anti-angiogenic drugs for the treatment of macular degeneration, and surgical or radiologic intervention as indicated for GI bleeding or severe peripheral vascular disease. Experimental treatment with oral pyrophosphate and bisphosphonates has not shown efficacy in clinical studies, and these agents have not been approved anywhere in the world as treatment for ABCC6 Deficiency.

The Sponsor is developing the investigational product, INZ-701 (rhENPP1-Fc), as a treatment of ABCC6 Deficiency. [redacted]

Study INZ701-201 is a MAD, dose-finding study followed by a long-term open-label Extension Period in adult subjects (18 to <70 years of age) with ABCC6 Deficiency manifesting as PXE. Study INZ701-201 will evaluate general safety and immunological parameters to determine the risk-benefit profile of INZ-701 and will identify the INZ-701 dose for further clinical development in ABCC6 Deficiency.

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.

4.2.1. 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 INZ-701, 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 mouse 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 regimen, for 28 days (Table 1). 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 cohort 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. All subjects receiving 0.2 mg/kg, 0.6 mg/kg, and 1.8 mg/kg twice weekly will receive a total of 8 doses of INZ-701 in the Dose Evaluation Period, resulting in a total 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 (ie, on Day 32), subjects may continue receiving the same dose and dose schedule in the Extension Period until the selected dose regimen has been determined.

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] µg/mL and area under the plasma concentration-time curve from time zero to the time of last measurable concentration [AUC_{last}] of [redacted] hr*µg/mL) will require regulatory authority approval via a substantial amendment prior to implementation.

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

4.3. Overall Risks and Potential Benefits

4.3.1. 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 therapeutic protein products 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.

4.3.1.1. Hypersensitivity

Given the potential of hypersensitivity reactions with any therapeutic protein product, 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 9.1.2 and Section 9.1.4 for information on monitoring and management of suspected hypersensitivity reactions to INZ-701.

4.3.1.2. Immunogenicity

Anti-drug antibodies (ADA) to INZ-701 will be assessed by 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. Samples may be used to assess and further establish assays for specificity confirmation (ie, titer) and neutralizing antibodies. A blood sample will also be collected and stored until a validated assay is available to assess the presence of cross-reactive immunologic material (CRIM), such as endogenous ENPP1.

Please see Section 10.8 for additional information.

4.3.1.3. Phlebotomy and Subcutaneous Injection

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

4.3.1.4. 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.

4.3.1.5. Radiation

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 $Na^{18}F$-positron emission tomography (PET)/computed tomography (CT) scan is not a required procedure and should only be performed at the discretion of the Investigator following consultation with the subject. The estimated dose equivalent radiation is approximately 25 mSv for each full body $Na^{18}F$- PET)/CT scan.

The total estimated radiation dose shall not exceed radiation limits set by the local Independent Ethics Committee (IEC) or Institutional Review Board (IRB). The subject's total radiation dose equivalent will depend on the duration of their study participation and total number of $Na^{18}F$-PET/CT performed (see Section 10.3.1.1) and shall not exceed 75 mSv over the duration of the study.

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.

4.3.1.6. 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.

4.3.1.7. Discontinuation of Current Treatment Options

The eligibility criteria of Study INZ701-201 require the cessation of several unapproved therapies (see Section 9.3) which have been used experimentally in the treatment of ABCC6 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. 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 ABCC6 Deficiency. Current treatment includes use of VEGF inhibitor therapy (for ophthalmic manifestations), lifestyle, lipid-lowering and dietary measures (for reducing vascular risk factors), and vascular surgery (for severe cardiovascular manifestations) (Germain 2017). These and other non-disease specific therapies carry potential risks.

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 (Akhtar Ali et al 2018). 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).

4.3.1.8. COVID-19 Exposure and Infection

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.

4.3.2. Risk Mitigation

Based on evidence from nonclinical studies, the risk/benefit assessment of INZ-701 is favorable in adults with ABCC6 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 therapeutic protein products and with study procedures have also been included in the Study INZ701-201 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.

4.3.3. Benefits

The potential benefits for use of INZ-701 in humans are based upon results from the literature and the Sponsor's nonclinical program. Overexpression of human ENPP1 in *Abcc6*$^{-/-}$ mice normalized plasma PPi levels and reduced tissue calcification (Zhao et al 2017). It is hypothesized that INZ-701 enhances 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 pathological calcification in murine models of ABCC6 Deficiency.

Subjects taking part in Study INZ701-201 may or may not derive a clinical benefit from receiving INZ-701 for ABCC6 Deficiency. Study INZ701-201 will evaluate general and immunological safety parameters to determine the risk-benefit profile of INZ-701 and will identify the INZ-701 dose for further clinical development in ABCC6 Deficiency.

4.3.4. Risk: Benefit Overall Conclusions

Available data indicate that INZ-701 has the potential to show safety and efficacy in the treatment of ABCC6 Deficiency; nonclinical data identified no undue safety issues that would preclude use in patients with ABCC6 Deficiency and no DLT was identified at single doses as high as [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 ABCC6 Deficiency, the risk-benefit is considered to be favorable in Study INZ701-201 and clinical investigation of INZ-701 is warranted in ABCC6 Deficiency.

5. OBJECTIVES

5.1. Primary Objective

- Assess the safety and tolerability of multiple ascending SC doses of INZ-701

5.2. Secondary Objectives

- Assess the immunogenicity of multiple ascending SC doses of INZ-701
- Study the PK of INZ-701 administered as multiple SC doses

- Study the long-term safety and PD changes from baseline in PPi after administration of multiple SC doses of INZ-701

5.3. Exploratory Objectives

- Assess changes in calcification of arteries and organs (including the eye)
- Assess changes in clinical measures associated with underlying ABCC6 Deficiency, including cardiac, vascular, ophthalmologic, and renal parameters
- Assess changes in physical function
- Assess changes in patient, clinician, and caregiver reported outcomes and quality of life

6. 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.

6.1. 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
- Presence of neutralizing antibodies
- Incidence, frequency, and severity of AEs, treatment-related AEs, treatment-emergent AEs (TEAEs), 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 ADA
- Incidence of DLTs
- Concomitant medications
- Electrocardiogram (ECG)
- Holter Monitoring and/or Cardiac Telemetry (if required per site specific procedures and/or Investigator discretion)
- Pregnancy testing

In the Extension Period post-Week 48, safety assessments will be summarized. Safety variables include:

- Changes from baseline in the ENPP1 enzyme activity
- Presence of neutralizing antibodies
- 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 with eGFR, hematology, and urinalysis, and additional biochemical parameters of interest
- Concomitant medications
- Urine pregnancy testing
- Incidence of ADA

6.2. Pharmacokinetic Endpoints

The following PK endpoints will be assessed through the Dose Evaluation Period (Day 32):

- 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}), terminal 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.

Trough (pre-dose) serum concentrations of INZ-701 and ENPP1 specific activity will be measured in the Extension Period (through Week 48 and post-Week 48).

6.3. Pharmacodynamic Endpoints

The following PD endpoints will be assessed in the Extension Period (through Week 48 and post-Week 48):

- Change from baseline in PPi levels, phosphate, calcium, alkaline phosphatase, and intact parathyroid hormone (PTH)
- Changes from baseline of blood and urine biomarkers as available

6.4. Exploratory Efficacy Endpoints

$Na^{18}F$-PET/CT, renal ultrasound, and ophthalmologic evaluations that were conducted up to 6 months prior to Screening may be used for Baseline if no prohibited drugs as described in

Section 9.3 were used during this period prior to enrollment, and if conducted consistent with the protocol in the opinion of the Sponsor. Historical $Na^{18}F$-PET/CT that do not meet the specifications above may be considered for the study Baseline upon Investigator discretion in consultation with the Sponsor.

The following efficacy assessments are required through Extension Period Week 48:

- Echocardiogram
- Renal ultrasound
- Carotid ultrasound
- Ophthalmologic tests:
  - Optical coherence tomography (OCT), color fundus photography, and autofluorescence photography
  - Best corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study letter charts

The following 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 subject will not have the assessment conducted at any time during the study. Baseline $Na^{18}F$-PET/CT imaging may be performed within 2 months after the first dose of INZ-701; if not conducted within the first 2 months after the first dose, the subject will not have the imaging assessment conducted at any time during the study.

- $Na^{18}F$-PET/CT
- Pulse Wave Velocity (PWV)
- Ankle-Brachial Pressure Index (ABI)
- Global Impression Scales
- Patient Reported Outcomes Measurement Information System (PROMIS), Pain Interference, Fatigue, and Physical Function - Upper Extremity
- Vision Function Questionnaire
- Work Productivity and Activity Impairment Questionnaire (WPAI)
- Edinburgh Claudication Questionnaire

The following exploratory efficacy assessment will be measured in the Extension Period post-Week 48:

- Ophthalmologic tests (OCT and BCVA)

7. INVESTIGATIONAL PLAN

7.1. Study Design

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

Anticipated enrollment in the Phase 1 portion of 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 a cohort to evaluate an alternate dosing regimen and/or enroll up to 6 additional subjects to further evaluate and corroborate the PK and PD of INZ-701 at an existing dose level.

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

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 7.2.5.

The study design for the Dose Evaluation Period is presented in Figure 1. Dose escalation between cohorts during the Dose Evaluation Period is presented in Figure 2.

Subject participation consists of 3 parts, a Screening Period of up to 60 days, a 32-day Dose Evaluation Period, and an Extension Period during which subjects may continue to receive INZ-701 until it is approved and available in the country where the subject resides or until an alternative study for subjects to continue receiving study drug is available.

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

The study design during the Dose Evaluation Period is a MAD 3 + 3 with 3 dose cohorts. Based on nonclinical findings and nonclinical pharmacology modeling, the planned doses will be 0.2 mg/kg, 0.6 mg/kg, and 1.8 mg/kg SC, with a twice weekly dose regimen. The maximum exposure level, based on no-observed-adverse-effect level (NOAEL) values from chronic GLP toxicology studies, is set at [redacted] µg/mL and [redacted] hr*µg/mL for C_{max} and AUC_{last}, respectively.

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

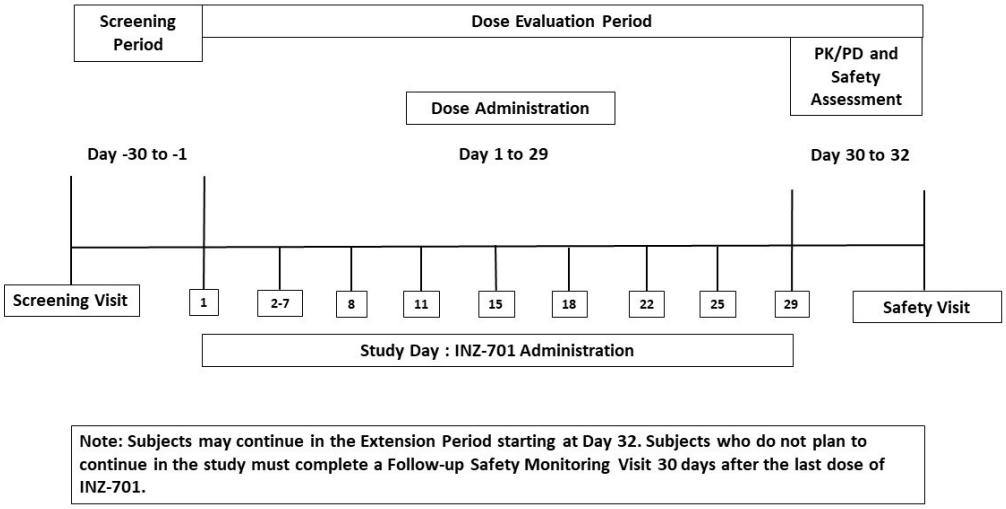
In the Extension Period, INZ-701 administration will initially be at the dose and dose schedule assigned in the Dose Evaluation Period. The Sponsor may modify the assigned dose and/or dosing regimen in the Extension Period post-Week 48 based on cumulative review of safety and PK/PD data, including population PK. This may include a flat dose (non-weight based) regimen or a once weekly flat or weight-based dose regimen that will not exceed the highest dose determined to be safe by the Sponsor and DSMB. This change may be applied on an individual cohort basis at the discretion of the Sponsor once all subjects in the given cohort complete Week 48.

Study visits will be in-clinic every 4 weeks until Week 48 of the Extension Period and then every 12 weeks (remote or in-clinic) 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.

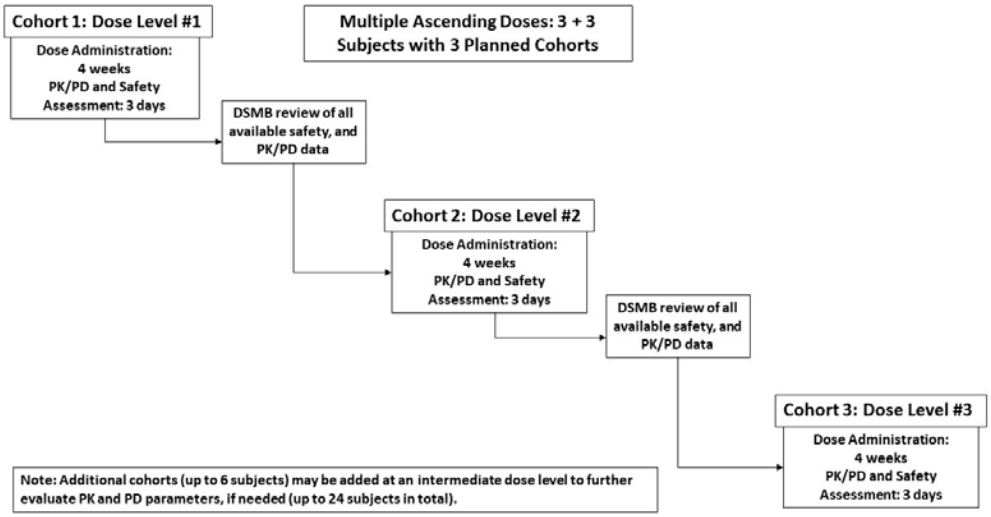
Assessments during the Screening and Dose Evaluation Periods will be performed at each visit as indicated in Table 1 and during the Extension Period as indicated in Table 2 and Table 3 and at the EOS as indicated in Table 4.

Figure 1: INZ701-201 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 2: INZ701-201 Study Design – Cohort Plan



DSMB=Data Safety Monitoring Board; PD=pharmacodynamic; PK=pharmacokinetic.

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 as per Section 10.1.3.1 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 blood 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 not exercising as required per Sections 10.2.2 and 10.6.

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. As noted in Section 9.1.2, 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 observed 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 for sample collection at any given time-period, blood collection 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 9.1.3). 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, with a final dose on Day 29. 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 of the second subject 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 after the Day 29 dose of INZ-701 on Days 30 to 32.

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 (eg, off-site administration) and be monitored for safety in the long-term 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.

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 to INZ-701 dosing will be allowed if the transition takes <2 weeks, unless determined otherwise by the Investigator in consultation with the Sponsor.

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.

Subjects who participate in the Extension Period will continue to receive INZ-701 at the prescribed dose regimen assigned in the Dose Evaluation Period. In the Extension Period post-Week 48, the INZ-701 dose and dose regimen may be changed and could be either weight-based or potentially non-weight based as determined by the safety and PK/PD data. 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 as described in Table 5.

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 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 at minimum to -follow-up on the administration procedure, compliance, and potential 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, which will not be less than 1 hour. 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, 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. 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.

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

The 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. 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.

7.2. Safety Monitoring

Study INZ701-201 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 8.4), and protocol-specified dose escalation and study stopping criteria (see Sections 7.2.5 and 7.2.6).

Collection of safety data will be ongoing and reviewed at frequent intervals throughout the study. Immunogenicity will be monitored throughout 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 that cohort and any prior cohort, which will not be less than 1 hour.

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 have a remote or 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. Adverse events and concomitant medications must be assessed minimally at each in-clinic visit and during any communication with the subjects and may be more frequent based on Investigator discretion as per the subject's individual needs (eg, weekly). All subjects will complete a safety follow-up visit approximately 30 days after their last dose.

7.2.1. 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 one biostatistical expert.

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 safety and available 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.

7.2.2. Dose 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 Section 7.2.5.

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

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

7.2.3. 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. At minimum, all AE data, chemistry, and hematology will be evaluated, and ADAs in the event of a suspected immunologically relevant AE.

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 an independent 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 escalate 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 Good Laboratory Practice (GLP) toxicology studies (maximum plasma concentration [C_{max}] of [redacted] µg/mL and area under the plasma concentration-time curve from time zero to the time of last measurable concentration [AUC_{last}] of [redacted] hr*µg/mL) will require regulatory authority approval via a substantial amendment prior to implementation.

7.2.4. 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 scheduled for Days 30 to 32.

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.

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.

Subjects who withdraw from the study for reasons other than safety on or after Day 32 of the Dose Evaluation Period may re-enroll in the study in the Extension Period as described in Section 8.5.1.

Criteria for early discontinuation of subjects from treatment and study are provided in Section 8.4 and Section 8.5, respectively.

7.2.5. Cohort Stopping Criteria

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 Sponsor's 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 enzyme replacement therapies (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) as follows:

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

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

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

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

7.2.6. Study Stopping Criteria

Dosing should 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 7.2.5. 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 EOS visit will be planned according to Table 4 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.

7.3. Number of Sites and Subjects

INZ701-201 is a multicenter study, with approximately 4 sites globally expected to participate. Anticipated enrollment in the Phase 1 portion of 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. Once all subjects in Cohort 3 complete Day 32, the Sponsor may choose to enroll up to 6 additional subjects at any dose and dose schedule deemed safe, not to exceed 3.6 mg/kg weekly; subjects may be added to an additional cohort to evaluate an alternate dosing regimen and/or to further evaluate and corroborate the PK and PD of INZ-701 at an existing dose level.

7.4. 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.

7.5. 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.

7.6. 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.

7.6.1. Termination of the 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 7.2.6)

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.

8. POPULATION

8.1. 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, following International Conference on Harmonisation (ICH) Good Clinical Practice (GCP)
2. Clinical diagnosis of PXE supported by prior genetic identification of biallelic *ABCC6* mutations (ie, homozygous or compound heterozygous)
3. Male or female, ages 18 to <70 years of age at Screening
4. PPi <1300 nM at Screening
5. Subjects who are being treated with statins or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors must have been on treatment for at least 6 months prior to Screening and no new anti-lipid therapy can be introduced within 6 months of Screening

6. Women of child-bearing potential (WOCBP) as defined in Clinical Trials Facilitation and Coordination Group (CTFG 2020) must have a negative serum pregnancy test at Screening
7. WOCBP and partners of fertile males who are WOCBP must be using or agree to use one 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.
8. 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.
9. In the opinion of the Investigator, must be willing and able to complete all aspects of the study
10. Agree to provide access to relevant medical records

8.2. 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 ABCC6 Deficiency) that precludes study participation or may confound interpretation of study results, including known uncontrolled thyroid, or unrelated connective tissue, bone, mineral, lipid, ophthalmologic, or muscle disease
2. Active retinal bleeding in both eyes during Screening
3. Clinically significant abnormal laboratory result at Screening, including but not limited to, eGFR <60 mL/min/1.73m^2 (Chronic Kidney Disease-Epidemiology Collaboration equation) or 25-hydroxyvitamin D levels <12 ng/mL
4. Known active fungal, bacterial, and/or viral infection including human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, or COVID-19 virus
5. Malignancy within the last 5 years, except non-melanoma skin cancers or cervical carcinoma in situ
6. Known intolerance to INZ-701 or any of its excipients
7. Unable or unwilling to discontinue the use of any prohibited medication as provided in Section 9.3. Discontinuation should be undertaken only if considered not detrimental and indicated by the subject's treating physician.
8. 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

9. Subjects who are pregnant, trying to become pregnant, or breastfeeding
10. Subjects who are trying to father a child

8.3. Estimated Duration of Subject Participation

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

8.4. 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 scheduled for Days 30 to 32. All subjects who discontinue treatment will be asked to complete the EOS (Safety Follow-up) Visit 30 days after their 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 dysfunction, or unacceptable toxicity which necessitates removal from study treatment
- Subject experiences worsening ABCC6 Deficiency clinical condition or disease progression requiring initiation of current treatment options prohibited in Section 9.3, 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.

8.5. 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 scheduled for Days 30 to 32.

All subjects who discontinue from the study will be asked to complete the EOS (Safety Follow-up) Visit 30 days after their 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
- 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.

8.5.1. Subject Re-enrollment

Subjects who withdraw from the study for reasons other than safety on or after Day 32 of the Dose Evaluation Period may re-enroll in the study in 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; subjects who re-enroll will initially receive the same dose that they were taking before withdrawing from the study for a period of 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.

8.6. 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.

9. TREATMENT OF SUBJECTS

During the Dose Evaluation period, all subjects will receive open-label INZ-701 as a single agent as specified in Table 6.

Table 6: INZ-701 Weekly Dose Levels for 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

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, eligible subjects will be administered INZ-701 at the dose and dose schedule assigned in the Dose Evaluation Period. The Sponsor may modify the assigned dose and/or dosing regimen in the Extension Period post-Week 48 based on cumulative review of safety and PK/PD data, including population PK. This may include a flat dose (non-weight based) regimen or a once weekly flat or weight-based dose regimen that will not exceed the highest dose determined to be safe by the Sponsor and DSMB. This change may be applied on an individual cohort basis at the discretion of the Sponsor once all subjects in the given cohort complete Week 48.

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).

9.1. Investigational Product: INZ-701

INZ-701 is an investigational product being studied in patients with ABCC6 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 regulations. Additional information on physical and chemical properties of INZ-701 is provided in the IB.

9.1.1. 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 Sponsor's designee unless other instructions have been provided for final disposition of INZ-701.

For off-site administration of INZ-701 by the subject, 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 the subject to support dosing until the next in-clinic visit. The subject, 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.

9.1.2. Post-dose Safety Monitoring

Subjects will be monitored in the clinic 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 after discharge from the clinic.

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 for 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 the assigned doses twice weekly and remain in the clinic for at least 6 hours 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 sampling 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 cohort and any prior cohort, which will not be less than 1 hour. The Investigator, following consultation with the Sponsor, will prescribe the required post-dose monitoring duration for each subject in the Extension Period. 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, 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.

9.1.3. 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 (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 post-dose 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 the 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 healthcare provider 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 an SC injection at the assigned dose and schedule during the Extension Period (Table 2 and Table 3). For off-site administration, subjects will be provided with a recurring 4-week supply of INZ-701 up to Week 48 and a recurring 12-week supply of INZ-701 after Week 48 of the study. 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.

9.1.4. Monitoring and Management of Suspected Hypersensitivity

Given the potential of hypersensitivity reactions with any therapeutic protein product, 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 injection-site 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 9.1.2. 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.

9.1.5. Missed Doses

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 8.4 for early treatment discontinuation, Section 8.5 for early study discontinuation, and Section 8.6 for replacement of subjects.

In the Extension Period, for any single period of interruption in dosing lasting <2 weeks, the subject may resume dosing at the Investigator's discretion. For any repeat multiple-interruptions or an interruption ≥2 weeks, the Investigator must consult with the Sponsor prior to resuming dosing.

9.2. 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 will be recorded.

For dose administration outside of the study site, the subject, their caregiver(s), or delegated healthcare provider will complete a dose diary to record each dose administered.

9.3. Prior, Concomitant, and Prohibited Medications

Definitions of prior and concomitant medications are provided in Section 10.5.

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.

The medications listed below may not be taken prior to dosing or initiated during the study as described. If the washout periods below are not met or the Investigator determines that the subject requires any of the prohibited medications below, then the Investigator may consult with the Sponsor to discuss study participation.

- Systemic oral or transdermal estrogen (use for contraception and treating symptoms of menopause is allowed), selective estrogen receptor modulators, hormone ablation therapy, tibolone
  - No more than 1 month of cumulative use within 6 months prior to first dose of INZ-701
- Calcimimetics
  - Cannot start treatment while on study after the first dose of INZ-701; however, these medications are allowed if the subject was already on treatment at the time of Screening
- Systemic corticosteroids (≥5 mg prednisone equivalent per day)
  - Cannot start treatment while on study after the first dose of INZ-701; however, these medications are allowed if the subject was already on treatment at the time of Screening

- Biologic bone modulators (eg, denosumab)
  - Cannot start treatment while on study after the first dose of INZ-701; however, these medications are allowed if the subject was already on treatment at the time of Screening
- Oral bisphosphonates
  - No use within 1 year prior to the first dose of INZ-701
- Intravenous 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
  - No more than 3 years of cumulative use, unless last dose received ≥5 years prior to the first dose of INZ-701
- Pyrophosphate containing medications
  - No use within 14 days prior to the first dose of INZ-701

Other than the medications specifically prohibited in this protocol, 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.

10. 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, drug concentration, and other laboratory evaluations are described briefly in the following sections. Consult the study manuals for additional information and guidance on procedures.

10.1. 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. The Investigator will confirm that the subject meets Inclusion Criterion No. 2 (clinical diagnosis of PXE supported by prior genetic identification of biallelic *ABCC6* mutations) before undergoing any physical 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.

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.

10.1.1. 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 obtained (Section 14.4).

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

10.1.2. Eligibility

Potential subjects for entry into the study are evaluated according to protocol-defined inclusion and exclusion criteria (Sections 8.1 and 8.2). 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.

10.1.3. Repeat Screening Assessments and Rescreening

10.1.3.1. Repeat Screening Assessments

The screening window is 60 days during which repeat testing for transient clinical safety laboratory abnormalities that do not meet eligibility criteria is permitted with written approval from the Sponsor.

Repeat Testing of PPi

If a subject's PPi level is ≥1300 nM, the test may be repeated within the 60-day screening window.

- If the repeat PPi result is ≥1300 nM the subject is deemed a screened failure and may not participate in the study.
- If the repeat PPi result is <1300 nM the test must be repeated a second time to confirm the result and subject eligibility.
    - if the second PPi result is <1300 nM, the subject may participate in the study.
    - if the second PPi is ≥1300 nM, the subject is deemed a screened failure and may not participate in the study.

A serum pregnancy test (for WOCBP only) must be completed within 30 days prior to dosing and will be repeated, as needed, when Screening is >30 days of the planned dosing date.

10.1.3.2. Rescreening

If a subject does not meet eligibility criteria, the subject may be rescreened up to 2 times after consultation with the Sponsor if the Investigator believes there has been a change in eligibility status.

The Investigator will consult with the Sponsor to determine which of the screening procedures must be repeated to determine the subject's eligibility. All subjects who are rescreened will, at minimum, have their PPi repeated irrespective of their prior screening value, and the repeat value must meet the eligibility criteria of <1300 nM to participate in the study.

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.

10.1.4. Medical History, ABCC6 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 ABCC6 related history to include PXE-like manifestations).

The specific diagnosis 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 *ABCC6* mutations performed by a CAP/CLIA certified laboratory using a CE-marked test.

Treatment history, including the use of pain medications to treat symptoms associated with PXE, physical/occupational therapy, and use of assistive devices will be recorded (start date, stop date, dose, dose regimen).

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

10.2. Pharmacodynamic Evaluations and Clinical Intermediates

ABCC6 Deficiency is a rare genetic disorder characterized by low levels of plasma PPi which can result in calcifications in 3 major organ systems: skin, eyes, and cardiovascular system. Therefore, the goal of treatment with an ENPP1 therapeutic protein product is to mitigate clinical and developmental complications associated with ABCC6 Deficiency and subsequent low serum PPi manifesting as PXE. 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, Table 4 and Table 5). Efficacy variables, clinical intermediates, and associated analyses are described in Section 12.4.

Note: If needed, blood samples will be collected as indicated in Table 1, Table 2, Table 3, Table 4 and Table 5 and stored for analysis when assays are available.

10.2.1. Plasma Inorganic Pyrophosphate

Low plasma PPi levels are a characteristic of ABCC6 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 treatment with an ENPP1 therapeutic protein product is to bring extracellular PPi levels to therapeutically effective levels and correct clinical abnormalities associated with ABCC6 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 and Table 5 and the Laboratory Manual.

10.2.2. Biomarkers Associated with Bone Health

PPi affects bone mineralization and turnover and is known to be low in ABCC6 Deficiency. Therefore, other biochemical markers associated with bone health will be measured, such as, serum and urine phosphate and calcium, 25(OH)D, $1,25(OH)_2D$, bone specific alkaline phosphatase, FGF23, and intact PTH.

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 Table 5 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 pre-dose blood samples. 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. 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 tubular maximum reabsorption rate of phosphate adjusted for glomerular filtration rate (TmP/GFR) assessment at Days 1 and 29 of the Dose Evaluation Period, the last 2 hours of the 24-hour urine collection will be collected separately, an aliquot from the 2-hour urine collection will be removed for TmP/GFR assessment and the remainder of the urine will be combined with the rest of the 24-hour urine collection. An aliquot of each 24-hour urine sample will be stored frozen for future urine biomarkers associated with ABCC6 Deficiency. A second morning urine sample will be collected in the Extension Period at Weeks 12, 24, 36, 48, 72, 96, 120, 144, 168 and 192 for urine calcium, phosphate, and creatinine

assessment. At the same time, a blood sample for serum creatinine and phosphate will be collected as part of the safety laboratory tests.

10.3. Efficacy Evaluations

Efficacy evaluations will be performed as indicated in Table 1, Table 2, Table 3, and Table 4.

10.3.1. Imaging

Imaging assessments will be performed at Baseline and at scheduled timepoints during the Extension Period, if applicable. Historical tests performed within 6 months prior to Screening could be used as Baseline upon Investigator discretion in consultation with the Sponsor. Baseline $Na^{18}F$-PET/CT imaging may be performed within 2 months after the first dose of INZ-701; if not conducted within the first 2 months after the first dose, the subject will not have the imaging assessment conducted at any time during the study.

$Na^{18}F$-PET/CT is a recommended assessment and echocardiogram, renal ultrasound, and carotid ultrasound are required assessments. These 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.

10.3.1.1. Positron Emission Tomography – Computed Tomography

$Na^{18}F$-PET/CT will be a full body scan with radioactive tracer that measures neointimal proliferation and calcification in arteries as well as organ calcifications. Subjects will complete up to 3 PET/CTs during the study: at Baseline, Week 48, and EOS, if a PET/CT was not performed within 48 weeks of the EOS Visit.

10.3.1.2. Echocardiogram

An echocardiogram should be performed at Baseline and at scheduled time points during the Extension Period, if applicable. The echocardiogram will be used to measure heart function (left ventricular ejection volume, blood flow) calcification of heart and valves, arterial stiffness, and to identify any other abnormalities.

10.3.1.3. Renal Ultrasound

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

10.3.1.4. Carotid Ultrasound

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

10.3.2. Ophthalmologic Assessments

The primary ocular alteration in PXE is due to calcification in Bruch's membrane, which is characterized by a mottled aspect of the temporal retinal midperiphery, called *peau d'orange*, and angioid streaks, which represent ruptures in Bruch's membrane. The latter may lead to subretinal choroidal neovascularization with a risk for spontaneous hemorrhage and scar formation with subsequent loss of vision (Gliem et al 2013).

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

10.3.2.1. Optical Coherence Tomography

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

10.3.2.2. Color Fundus Photography

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

10.3.2.3. Autofluorescence Photography

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

10.3.2.4. Best Corrected Visual Acuity

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

10.3.3. Cardiovascular and Peripheral Vascular Reactivity Assessments

PXE patients are at high risk of vascular disease, especially peripheral artery disease and cerebrovascular disease, which is thought to be the result of a proposed unique type of arterial wall disease. Baseline assessments of vascular disease will include the following: arterial stiffness as measured by carotid-femoral PWV, carotid ultrasound for intimal media thickness, lower limb intermittent claudication using ABI, and the Edinburgh Claudication Questionnaire (ECQ).

10.3.3.1. 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.

10.3.3.2. 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.

10.3.4. Patient, Clinician, and Caregiver Reported Outcomes

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

10.3.4.1. Global Impression Scales

10.3.4.1.1. 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 will be completed by the Investigator at the Baseline Visit.

During the Extension Period, the Investigator will complete the CGI of Improvement at scheduled time points.

10.3.4.1.2. Patient Global Impression Scales

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

During the Extension Period, the PGI of Improvement will be completed at scheduled time points.

10.3.4.1.3. Caregiver Global Impression Scales

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

If applicable during the Extension Period, the CaGI of Improvement will be completed at scheduled time points.

10.3.4.2. 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 (https://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 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, Fatigue, and Physical Function – Upper Extremity will be performed at scheduled time points.

- 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 Custom-9 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 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.

10.3.4.3. Vision Function Questionnaire

The Vision Function Questionnaire SA (self-administered) (VFQ-25), is a patient reported outcome developed by the National Eye Institute that measures the influence of visual impairment on generic health domains as well as task-oriented domains related to visual functioning (National Eye Institute 2000). It was developed to measure condition-specific symptoms for glaucoma, macular degeneration, cataracts, diabetic retinopathy, and cytomegalovirus retinitis. Over its many years of use, it has been used in many other diagnoses, including stroke, intracranial hypertension, multiple sclerosis, and at least one clinical study for PXE.

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

10.3.4.4. Work Productivity and Activity Impairment Questionnaire

The WPAI will be administered to assess the impact of ABCC6 Deficiency on a subject's employment status and ability to work.

10.3.4.5. Edinburgh Claudication Questionnaire

Patient assessment of the symptoms of lower limb intermittent claudication are detected using the ECQ administered by the Investigators and scored as "asymptomatic" or "symptomatic." The ECQ is a 6-question patient administered questionnaire to measure the symptoms for intermittent claudication. It was found to have excellent reliability when repeated at 6 months.

10.4. Safety Measurements

Assessments to derive safety variables are described below and will be conducted according to the time points indicated in Table 1, Table 2, Table 3, and Table 4. Safety endpoints and associated analyses are described in Section 12.5.

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

10.4.1. 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
- GI system
- Nervous system

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

10.4.1.1. 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.

Obtain vital signs at scheduled timepoints. Additional measurements should be obtained as clinically indicated.

10.4.1.2. Height and Weight

Height (centimeters) and weight (kilograms) will be obtained at each indicated visit (prior to dosing, if applicable). The weight obtained at Day 1 will be used to calculate the dose of INZ-701 to be administered on a mg/kg basis for the duration of the Dose Evaluation Period. If the subject's weight changes by more than 10% from Baseline, the Investigator may re-calculate their dose using the weight at the study visit.

10.4.2. Electrocardiogram

Standard 12-lead ECGs will be collected at scheduled time points and will be read centrally. Additional ECGs may be performed per site specific safety monitoring procedures, if clinically indicated.

10.4.3. Holter Monitoring and/or Cardiac Telemetry

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

10.5. Prior and Concomitant Medications

Use of concomitant medications as described in Section 9.3 will be assessed throughout the study.

Prior 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 INZ701. 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.

10.6. 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 biomarkers throughout the study at scheduled time points. 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, PK, 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 ABCC6 Deficiency or related deficiencies and development of drugs to treat these disorders. Samples will be retained at minimum until marketing authorization is granted.

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-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. 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 at the designated visits for 24-hour urine collection in the Dose Evaluation Period. An aliquot of each 24-hour urine sample will be stored frozen for future urine biomarkers associated with ABCC6 Deficiency.

10.6.1. Clinical Laboratory Evaluations for Safety

Routine blood chemistry panels including liver function tests, a hematology panel including complete blood count 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 9.3). See Appendix A for protocol-specified analytes.

10.6.2. 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, WOCPB and partners of fertile males who are WOCBP must agree to use 1 highly effective form of 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; if the subject is not dosed within 30 days of Screening, the serum pregnancy test must be repeated. If the subject is dosed within 30 days of Screening, a urine pregnancy test will be performed at Day 1 before dosing. 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 11.3.6).

10.7. 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.

10.8. Immunogenicity

Anti-drug antibodies to INZ-701 will be assessed by 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. 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 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).

10.9. Biomarkers

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

11. ADVERSE EVENTS

11.1. Definitions

11.1.1. 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 AEs 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.

11.1.2. 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)

11.2. Adverse Event Reporting

All AEs (which includes SAEs and adverse events of special interest [AESIs] as defined in Section 11.2.6), 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 study treatment 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.

11.2.1. 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
Treatment-emergent AEs / SAEs / AESIs	Date of first dose of INZ-701 through 30 days following last dose of INZ-701	Not applicable

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

11.2.2. Expedited Reporting Requirements

It is the responsibility of the Investigator to report SAEs (and AESIs as defined in Section 11.2.6) that occur during the reporting period whether or not considered related to INZ-701. Events must be reported to the Sponsor or Sponsor's designee immediately and no later than 24 hours of awareness of the event or safety information, whether initial or follow-up, by electronic mail:

- **For SAEs Email [redacted] Safety Inbox: [redacted]**
- Required AESI Email Inozyme PV Inbox: [redacted]

Note: If an AESI is deemed serious, send it 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 email, 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). [redacted] will serve as the 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 11.2.6) 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.

11.2.3. Eliciting Adverse Events

Care will be taken not to introduce bias when obtaining AE (including SAEs and AESIs as defined in Section 11.2.6) 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.

11.2.4. 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 as defined in Section 11.2.6) until the events are resolved or have stabilized, the subject is lost to follow-up, or it has been determined that the 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. All AEs will be assessed in accordance with the safety management plan.

11.2.5. 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.

11.2.6. 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 11.2.2. 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.

11.2.7. 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

Grad	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 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.

ADL=activities of daily living; AE=adverse event; CTCAE=Common Terminology Criteria of Adverse Events; NCI=National Cancer Institute; SAE=serious adverse event.

Source: CTCAE v5 (NCI 2017).

11.2.8. 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	• Exposure to INZ-701 has not occurred OR • Administration of INZ-701 and the occurrence of the AE are not reasonably related in time OR • 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	• Administration of INZ-701 and the occurrence of the AE are reasonably related in time AND • 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.

11.3. Adverse Events – Special Circumstances

11.3.1. 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. The end date for the first entry will be the start date for the new entry.

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.

11.3.2. 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).

11.3.3. 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.

11.3.4. 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.

11.3.5. 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.

11.3.6. 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.

11.3.7. 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".

11.4. Urgent Safety Measures

The Sponsor is required to follow global regulations including European Union regulations which state that the appropriate regulatory bodies, including IRBs and IECs, 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

12. 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.

12.1. Study Conduct Analysis

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

12.2. Population Characteristics

Subject demographics, disease, and baseline characteristics will be listed and summarized using appropriate descriptive statistics for all subjects.

12.3. Study Populations

The following populations will be analyzed:

- The safety analysis set (SAS) includes all enrolled subjects with ABCC6 Deficiency receiving at least one dose of INZ-701.
- The pharmacokinetic analysis set (PKAS) is a subset of the SAS including subjects with evaluable pharmacokinetics data.

12.4. Efficacy Analyses

Radiography and imaging, ophthalmologic assessments, cardiovascular and peripheral vascular reactivity assessments, and patient, clinician and caregiver reported outcomes will be summarized by dose and visit with descriptive statistics. Specific methods of analyses for all exploratory efficacy endpoints will be detailed in the SAP.

12.5. Safety Analyses

Safety evaluations will include AE and SAE reporting, DLTs, ECGs, vital signs (temperature, respiratory rate, blood pressure, and heart rate), physical examination, body weight and height, clinical laboratory parameters (hematology, biochemistry, and urinalysis), serum and urine pregnancy tests, concomitant medication reporting and immunogenicity.

All subjects who were enrolled and received at least one dose of INZ-701 will be included in the SAS. Safety data will be listed and summarized by dose and visit with descriptive statistics.

The primary safety endpoint will be evaluated by examining incidence and type of TEAEs; including clinically significant changes from Baseline through the EOS (Safety Follow-up) Visit in clinical laboratory parameters, 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.

12.6. Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

Pharmacokinetic analysis will be performed on the PKAS, 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.

Changes in blood and urine PD biomarkers associated with ABCC6 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.

12.7. Extent of Exposure

The extent of study treatment will be assessed, and summary statistics will be presented for the safety population.

12.8. Timing of Analysis

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

An interim analysis will be conducted when all subjects have completed all assessments at Week 48. 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 the study defined in Section 7.6).

12.9. 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.

13. DATA RECORDING, RETENTION, AND MONITORING

13.1. 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.

13.2. 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.

13.3. 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.

13.4. 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 hepatitis 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 ABCC6 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.

14. ETHICAL AND LEGAL ASPECTS

14.1. 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.

14.2. 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.

14.3. 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.

14.4. 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.

14.5. 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.

14.6. 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 7.6.1).
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.

14.7. 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.

14.8. 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.

15. REFERENCES

Akhtar Ali S, Ng C, Votava-Smith JK, Randolph LM, Pitukcheewanont P. Bisphosphonate therapy in an infant with generalized arterial calcification with an ABCC6 mutation. Osteoporos Int. 2018 Nov;29(11):2575-9.

Bergen AA, Plomp AS, Schuurman EJ, Terry S, Breuning M, Dauwerse H, et al. Mutations in ABCC6 cause pseudoxanthoma elasticum. Nat Genet. 2000 Jun;25(2):228-31.

Boyce AM, Gafni RI, Ferreira CR. Generalized Arterial Calcification of Infancy: New Insights, Controversies, and Approach to Management. Curr Osteoporos Rep. 2020 Jun;18(3):232-41.

CTFG. Recommendations related to contraception and pregnancy testing in clinical trials. 2020 [21 Sep 2020]; Available from: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1.pdf.

Dabisch-Ruthe M, Kuzaj P, Gotting C, Knabbe C, Hendig D. Pyrophosphates as a major inhibitor of matrix calcification in Pseudoxanthoma elasticum. J Dermatol Sci. 2014 Aug;75(2):109-20.

Dedinszki D, Szeri F, Kozak E, Pomozi V, Tokesi N, Mezei TR, et al. Oral administration of pyrophosphate inhibits connective tissue calcification. EMBO Mol Med. 2017 Nov;9(11):1463-70.

FDA Safety Communication: The FDA Warns that Biotin May Interfere with Lab Tests (28 Nov 2017). 2017; Available from: https://www.fda.gov/medical-devices/safety-communications/fda-warns-biotin-may-interfere-lab-tests-fda-safety-communication.

Finger RP, Fenwick E, Marella M, Charbel Issa P, Scholl HPN, Holz FG, et al. The relative impact of vision impairment and cardiovascular disease on quality of life: the example of pseudoxanthoma elasticum. Health Qual Life Outcomes. 2011;9:113.

Fleisch H, Bisaz S. Isolation from urine of pyrophosphate, a calcification inhibitor. Am J Physiol. 1962 Oct;203:671-5.

Fleisch H, Russell RG, Straumann F. Effect of pyrophosphate on hydroxyapatite and its implications in calcium homeostasis. Nature. 1966 Nov 26;212(5065):901-3.

Germain DP. Pseudoxanthoma elasticum. Orphanet J Rare Dis. 2017 May 10;12(1):85.

Gliem M, Zaeytijd JD, Finger RP, Holz FG, Leroy BP, Charbel Issa P. An update on the ocular phenotype in patients with pseudoxanthoma elasticum. Front Genet. 2013;4:14.

Goral V, Demir D, Tuzun Y, Keklikci U, Buyukbayram H, Bayan K, et al. Pseudoxantoma elasticum, as a repetitive upper gastrointestinal hemorrhage cause in a pregnant woman. World J Gastroenterol. 2007 Jul 28;13(28):3897-9.

Guy W. The Clinical Global Impression Scale. A. John Rush Jr MBF, and D Blacker, editor. Washington, DC, USA: American Psychiatric Publishing, Inc.; 1976.

Hu X, Plomp A, Wijnholds J, Ten Brink J, van Soest S, van den Born LI, et al. ABCC6/MRP6 mutations: further insight into the molecular pathology of pseudoxanthoma elasticum. Eur J Hum Genet. 2003 Mar;11(3):215-24.

Jacobs IJ, Cheng Z, Ralph D, O'Brien K, Flaman L, Howe J, et al. INZ-701, a recombinant ENPP1 enzyme, prevents ectopic calcification in an *Abcc6*$^{-/-}$ mouse model of pseudoxanthoma elasticum. Exp Dermatol. 2022;31:1095–101.

Jansen RS, Küçükosmanoglu A, de Haas M, Sapthu S, Otero JA, Hegman IEM, et al. ABCC6 prevents ectopic mineralization seen in pseudoxanthoma elasticum by inducing cellular nucleotide release. Proceedings of the National Academy of Sciences of the United States of America. 2013;110(50):20206-11.

Jansen RS, Duijst S, Mahakena S, Sommer D, Szeri F, Varadi A, et al. ABCC6-mediated ATP secretion by the liver is the main source of the mineralization inhibitor inorganic pyrophosphate in the systemic circulation-brief report. Arterioscler Thromb Vasc Biol. 2014 Sep;34(9):1985-9.

Kauffenstein G, Yegutkin GG, Khiati S, Pomozi V, Le Saux O, Leftheriotis G, et al. Alteration of Extracellular Nucleotide Metabolism in Pseudoxanthoma Elasticum. J Invest Dermatol. 2018 Aug;138(8):1862-70.

Le Saux O, Beck K, Sachsinger C, Silvestri C, Treiber C, Goring HH, et al. A spectrum of ABCC6 mutations is responsible for pseudoxanthoma elasticum. Am J Hum Genet. 2001 Oct;69(4):749-64.

Li Q, Jiang Q, Pfendner E, Varadi A, Uitto J. Pseudoxanthoma elasticum: clinical phenotypes, molecular genetics and putative pathomechanisms. Exp Dermatol. 2009 Jan;18(1):1-11.

Miyai K, Ariyasu D, Numakura C, Yoneda K, Nakazato H, Hasegawa Y. Hypophosphatemic rickets developed after treatment with etidronate disodium in a patient with generalized arterial calcification in infancy. Bone Rep. 2015 Dec;3:57-60.

National Eye Institute. 25-Item Visual Functioin Questionnaire (VFQ-25). 2000.

NCI. Common Terminology Criteria for Adverse Events V5.0 (CTCAE). Published: November 27, 2017. 2017; Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf.

Neldner KH. Pseudoxanthoma elasticum. Clin Dermatol. 1988 Jan-Mar;6(1):1-159.

Nitschke Y, Yan Y, Buers I, Kintziger K, Askew K, Rutsch F. ENPP1-Fc prevents neointima formation in generalized arterial calcification of infancy through the generation of AMP. Exp Mol Med. 2018 Oct 29;50(10):139.

Orriss IR, Arnett TR, Russell RG. Pyrophosphate: a key inhibitor of mineralisation. Curr Opin Pharmacol. 2016 Jun;28:57-68.

Otero JE, Gottesman GS, McAlister WH, Mumm S, Madson KL, Kiffer-Moreira T, et al. Severe skeletal toxicity from protracted etidronate therapy for generalized arterial calcification of infancy. J Bone Miner Res. 2013 Feb;28(2):419-30.

Pomozi V, Brampton C, van de Wetering K, Zoll J, Calio B, Pham K, et al. Pyrophosphate Supplementation Prevents Chronic and Acute Calcification in ABCC6-Deficient Mice. Am J Pathol. 2017 Jun;187(6):1258-72.

Ringpfeil F, Lebwohl MG, Christiano AM, Uitto J. Pseudoxanthoma elasticum: Mutations in the MRP6 gene encoding a transmembrane ATP-binding cassette (ABC) transporter. Proceedings of the National Academy of Sciences. 2000;97(11):6001-6.

Uitto J, Jiang Q, Váradi A, Bercovitch LG, Terry SF. PSEUDOXANTHOMA ELASTICUM: DIAGNOSTIC FEATURES, CLASSIFICATION, AND TREATMENT OPTIONS. Expert Opin Orphan Drugs. 2014;2(6):567-77.

Uitto J, Li Q. Vascular Mineralization in Pseudoxanthoma Elasticum: Etidronate to the Rescue? J Am Coll Cardiol. 2018 Mar 13;71(10):1127-9.

van den Berg JS, Hennekam RC, Cruysberg JR, Steijlen PM, Swart J, Tijmes N, et al. Prevalence of symptomatic intracranial aneurysm and ischaemic stroke in pseudoxanthoma elasticum. Cerebrovasc Dis. 2000 Jul-Aug;10(4):315-9.

Zhao J, Kingman J, Sundberg JP, Uitto J, Li Q. Plasma PPi Deficiency Is the Major, but Not the Exclusive, Cause of Ectopic Mineralization in an Abcc6(-/-) Mouse Model of PXE. J Invest Dermatol. 2017 Nov;137(11):2336-43.

APPENDIX A. CLINICAL LABORATORY ANALYTES

Screening, Dose Evaluation Period, and Extension Period Through Week 48

<table>
<tr>
<td rowspan="3">Serum Chemistry [a]:
• Alkaline phosphatase
• Alanine aminotransferase
• Aspartate aminotransferase
• Bilirubin - total and direct
• Gamma glutamyl transferase
• Blood urea nitrogen
• Lactate dehydrogenase
• Creatinine with eGFR reporting
• Glucose
• Cholesterol
• Triglycerides
• Amylase
• Lipase
• Calcium [b]
• Ionized calcium
• Phosphate [b]
• Protein - total
• Albumin
• Sodium
• Potassium
• Chloride
• Bicarbonate
• Creatine kinase
• Uric acid</td>
<td>Hematology [a]:
• Hemoglobin
• Hematocrit
• Erythrocytes
• White blood cells
• Neutrophils (absolute, %)
• Lymphocytes (absolute, %)
• Monocytes (absolute, %)
• Eosinophils (absolute, %)
• Basophils (absolute, %)
• Platelet count</td>
</tr>
<tr>
<td>Urinalysis [a]:
• Routine dipstick</td>
</tr>
<tr>
<td>Pregnancy Testing:
• WOCBP only (serum at Screening and urine at all other visits; serum if positive or inconclusive urine test)</td>
</tr>
<tr>
<td>PK/PD/Immunogenicity:
• Plasma inorganic pyrophosphate (PPi)
• Serum ENPP1 specific activity
• Serum anti-drug antibodies and neutralizing antibodies
• Serum INZ-701 activity and concentration</td>
<td>Exploratory Biomarkers:
• Serum 1,25(OH)$_2$D and 25(OH)D [d]
• Serum intact parathyroid hormone
• Serum C-reactive protein
• Plasma FGF23 (intact and C-terminal)
• Serum β2-microglobulin
• Serum osteopontin
• Serum CTX
• Serum P1NP
• Serum bone specific alkaline phosphatase
• Plasma adenosine triphosphate</td>
</tr>
</table>

Screening, Dose Evaluation Period, and Extension Period Through Week 48

Hypersensitivity Samples, if applicable • IgE • IgG • Serum tryptase • Serum histamine • complement activation (C3, C4) • Acute phase reactants (to include, at minimum C-reactive protein)	**Second Morning Urine to Derive TMP/GFR [b]:** • Calcium • Phosphate • Creatinine

Note: Consult Laboratory Manual for time points, collection, processing, and shipping instructions. If maximum allowed blood volume (as per local guidance) may be reached for any given time-period, prioritize blood collection as follows: clinical safety laboratory evaluations, immunogenicity, PPi, ENPP1 specific activity, and other biomarkers.

a Screening safety laboratory evaluations may be performed at a local laboratory.

b Calcium phosphate product will also be calculated and reported.

c At the Day 1 and 29 visits 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 analysis to help with understanding ABCC6 Deficiency.

d 25(OH)D assessment will be performed with serum chemistry at Screening for evaluation of Exclusion Criterion No. 3.

$1,25(OH)_2D$=1,25-dihydroxy vitamin D; 25(OH)D=25-hydroxyvitamn D; CTX= carboxy terminal cross-linked telopeptide of type I collagen; eGFR=estimated glomerular filtration rate; FGF23=fibroblast growth factor 23; Ig=immunoglobulin; P1NP= procollagen type 1 N-terminal propeptide; TmP/GFR=tubular maximum reabsorption rate of phosphate adjusted for glomerular filtration rate; WOCBP=women of childbearing potential.

Extension Period Post-Week 48

<table>
<tr>
<td rowspan="3">Serum Chemistry:
• Alkaline phosphatase
• Alanine aminotransferase
• Aspartate aminotransferase
• Bilirubin - total and direct
• Gamma glutamyl transferase
• Blood urea nitrogen
• Creatinine with eGFR reporting
• Glucose
• Calcium [a]
• Phosphate [a]
• Protein - total
• Albumin
• Sodium
• Potassium
• Chloride
• Bicarbonate</td>
<td>Hematology:
• Hemoglobin
• Hematocrit
• Erythrocytes
• White blood cells
• Neutrophils (absolute, %)
• Lymphocytes (absolute, %)
• Monocytes (absolute, %)
• Eosinophils (absolute, %)
• Basophils (absolute, %)
• Platelet count</td>
</tr>
<tr>
<td>Urinalysis:
• Routine dipstick (local)</td>
</tr>
<tr>
<td>Pregnancy Testing:
• WOCBP only (urine at all visits; serum if positive or inconclusive urine test)</td>
</tr>
<tr>
<td>PK/PD/Immunogenicity:
• Plasma inorganic pyrophosphate (PPi)
• Serum ENPP1 specific activity
• Serum INZ-701 concentration
• Serum anti-drug antibodies</td>
<td>Exploratory Biomarkers:
• Serum 25(OH)D
• Serum intact parathyroid hormone
• Plasma FGF23 (intact and C-terminal)
• Serum osteopontin</td>
</tr>
<tr>
<td>Hypersensitivity Samples, if applicable:
• IgE
• IgG
• Serum tryptase
• Serum histamine
• complement activation (C3, C4)
• Acute phase reactants (to include, at minimum C-reactive protein)</td>
<td>Second Morning Urine to Derive TMP/GFR [a]:
• Calcium
• Phosphate
• Creatinine</td>
</tr>
</table>

Note: Consult Laboratory Manual for time points, collection, processing, and shipping instructions. If maximum allowed blood volume has been reached for any given time-period, prioritize as follows: clinical safety laboratory evaluations, immunogenicity, PPi, ENPP1 specific activity, and other biomarkers.

a Calcium phosphate product will also be calculated and reported.

25(OH)D=25-hydroxyvitamn D; FGF23=fibroblast growth factor 23; Ig=immunoglobulin; TMP/GFR=tubular maximum reabsorption rate of phosphate adjusted for glomerular filtration rate; WOCBP=women of child-bearing 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[1]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable [1]
- Intrauterine device [1]
- Intrauterine hormone-releasing system [1]
- Bilateral tubal occlusion [1]
- Vasectomized partner [1,2]
- Sexual abstinence[3]

Definitions:

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

A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the post-menopausal 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 in the context of this guidance are considered to have low user dependency.
[2] Vasectomized partner is a highly effective birth control method provided that the 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 the study treatments. 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