CLINICAL STUDY PROTOCOL

The ADAPT Study: An Open-label, Long-term Safety Study of INZ-701 in Patients with ENPP1 Deficiency and ABCC6 Deficiency

Protocol Number:	**INZ701-304**
Investigational Product:	INZ-701 (recombinant human ectonucleotide pyrophosphatase/phosphodiesterase 1 [ENPP1] fused to the Fc fragment of IgG1; rhENPP1-Fc)
Indication:	ENPP1 Deficiency; ABCC6 Deficiency
Development Phase:	2
US IND Number(s):	142398; 156761
EU CT Number:	2024-512715-42-00
ClinicalTrials.gov Identifier:	NCT06462547
Sponsor:	Inozyme Pharma, Inc. 321 Summer Street, Suite 400 Boston, MA 02210 USA +1 857.330.4340
Sponsor's Responsible Signatory:	[redacted]
Protocol Version:	2.0 (Ex-US)
Effective Date:	10 January 2025

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SPONSOR PROTOCOL APPROVAL PAGE

Title:	The ADAPT Study: An Open-label, Long-term Safety Study of INZ-701 in Patients with ENPP1 Deficiency and ABCC6 Deficiency
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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 Practice 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.



1/10/2025

Date

Inozyme Pharma, Inc.

INVESTIGATOR SIGNATURE PAGE

Title:	The ADAPT Study: An Open-label, Long-term Safety Study of INZ-701 in Patients with ENPP1 Deficiency and ABCC6 Deficiency
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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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1. SYNOPSIS

Title: The ADAPT Study: An Open-label, Long-term Safety Study of INZ-701 in Patients with ENPP1 Deficiency and ABCC6 Deficiency

Development Phase

Phase 2

Planned Number of Study Sites

Approximately 10 to 20 sites globally

Planned Number of Study Participants

Up to 200 study participants

Indication

Ectonucleotide Pyrophosphatase/Phosphodiesterase 1 (ENPP1) Deficiency and ATP-binding cassette sub-family C member 6 (ABCC6) Deficiency

Rationale for Treatment with INZ-701

ENPP1 Deficiency is a rare genetic disorder in which inactivating mutations in the ENPP1 gene lead to a deficiency in the ENPP1 enzyme. The ENPP1 enzyme hydrolyzes adenosine triphosphate (ATP) to generate inorganic pyrophosphate (PPi) plus adenosine monophosphate (AMP). A deficiency in this enzyme results in a decrease in PPi and AMP.

Infants with ENPP1 Deficiency frequently suffer from Generalized Arterial Calcification of Infancy (GACI), which has a high mortality rate due to ectopic calcification and vascular stenosis, due to low levels of PPi and AMP, respectively. The ENPP1 enzyme plays an important role in the regulation of normal bone growth. As a result, ENPP1 Deficiency can present clinically during childhood as an abnormality in the growth of long bones. More specifically, there is an undermineralization of the growing bones including the growth plate. The undermineralization is due to low levels of Pi and the accompanying radiographic skeletal changes are consistent with those of rickets. Adults with ENPP1 Deficiency suffer from osteomalacia, ectopic calcification, hearing loss, and other morbidities.
To date, there are no approved therapies for ENPP1 Deficiency and therefore, there is a high unmet medical need for a treatment.

ABCC6 modulates the transport of intracellular ATP to the extracellular space of hepatocytes where ATP is hydrolyzed by the ENPP1 enzyme to generate PPi and AMP. Loss-of-function mutations in the ABCC6 gene lead to approximately 50% decrease in systemic plasma PPi which, in turn, leads to ectopic mineralization of elastin-rich tissues.

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. Infants with ABCC6 Deficiency may present with symptoms nearly identical to infants with ENPP1 Deficiency, and this syndrome is referred to as GACI Type 2 (GACI-2). Older pediatric patients with ABCC6 Deficiency may develop or present with ischemic stroke secondary to cerebrovascular stenosis and insufficiency, as well as other signs and symptoms observed in adult patients.

There are limited effective treatment options for patients with ABCC6 Deficiency, which are focused on treatment of skin lesions and choroidal neovascularization. None of the current treatments address the root cause (ie, low levels of PPi), and the efficacy of current therapies is low.

INZ-701 is in development as a therapeutic protein for the treatment of ENPP1 Deficiency and ABCC6 Deficiency. Structurally it is a recombinant human ENPP1 fused to the Fc fragment of IgG1 (rhENPP1-Fc).

Inozyme has completed a Phase 1/2 study in adults with ENPP1 Deficiency (Study INZ701-101) and completed a Phase 1/2 study in adults with ABCC6 Deficiency (Study INZ701-201). Preliminary data from these studies indicate that INZ-701 therapy is safe and capable of increasing PPi to within normal levels. The pharmacokinetic (PK) properties of INZ-701 have been reproducible and predictable, with a half-life of approximately [redacted], supporting once-weekly dosing. Furthermore, data from patient reported outcome (PRO) measures support clinical activity in both diseases, as well as functional performance (six-minute walk test) and biomarker data support clinical activity in ENPP1-deficient patients.

In addition, Inozyme is conducting a Phase 1b clinical study to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of INZ-701 in infants (<1 year) with ENPP1 Deficiency (Study INZ701-104 [ENERGY]). Thus far, preliminary data indicate INZ-701 therapy is safe. More study participants are needed to assess PK and PD in this patient population. A Phase 3 study in the pediatric population has been initiated to assess the safety and efficacy of INZ-701 in study participants 1 to 12 years old (Study INZ701-106 [ENERGY 3]). Available data to date are presented in the INZ-701 Investigator's Brochure.

The purpose of this study (Study INZ701-304 [ADAPT]) is to assess the long-term safety of INZ-701 in patients with ENPP1 Deficiency or ABCC6 Deficiency who have received INZ-701 in a previous clinical study and choose to continue dosing for the potential treatment of their condition.

Objectives and Endpoints

Primary Objective	**Primary Endpoints**
• To assess the long-term safety of INZ-701	• Incidence, frequency, and severity of adverse events (AEs), treatment-emergent adverse event (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) • Changes in clinical laboratory tests including chemistry, hematology, and urinalysis resulting in an AE

	• Concomitant medications • Titers of anti-drug antibodies (ADA)
Secondary Objectives	**Secondary Endpoints**
• To confirm drug levels of INZ-701 with long-term use	• INZ-701 plasma PK parameters measured by immunoassay and enzymatic activity
• To assess the effect of long-term INZ-701 treatment on plasma PPi concentrations	• Plasma PPi concentrations based on a validated assay

Study Design

The ADAPT Study (INZ701-304) is an open-label study to assess the long-term safety of INZ-701 in patients with ENPP1 Deficiency or ABCC6 Deficiency who have received INZ-701 in a previous clinical study and choose to continue dosing for the potential treatment of their condition. Participants are eligible if they have completed the protocol-required safety and PK/PD and/or efficacy period(s) of a previous study with INZ-701 (as confirmed by the Sponsor).

The study will consist of a 30-day Screening Period, followed by an open-label Treatment Period during which all participants will receive once-weekly subcutaneous (SC) doses of INZ-701 and continue with treatment until INZ-701 is commercially available in the country/region of the participant's residence or until Inozyme chooses to discontinue development of INZ-701. Participants will complete an End of Study (EOS) safety follow-up visit approximately 30 days after their last designated study visit assigned by the Investigator and/or Sponsor.

Study participants will receive once-weekly doses of INZ-701; the dose will be determined by the participant's age and weight.

All study participants will receive their first dose of INZ-701 in-clinic (on Day 1) under medical supervision. Participants may be administered their second, third, and fourth doses (on Days 8, 15, and 22, respectively) offsite (eg, in the home setting) by a qualified home healthcare professional with explicit approval of the Investigator. All participants will return to the clinic for the Day 29 visit and dosing.

After the fifth dose (on Day 29), participants may transition to self-administration of INZ-701 or offsite administration by a caregiver/delegated healthcare provider as determined by the Investigator. The Investigator will ensure successful completion of dose preparation and administration training, including monitoring and management of signs and symptoms of hypersensitivity reactions, before the study participant is transitioned to offsite administration. Offsite administration may be stopped or reinitiated at any time during the study by the Investigator and/or Sponsor.

All study participants will be monitored for at least 2 hours following administration of each of their first 3 doses of INZ-701. For all subsequent doses, participants will be monitored for a minimum of 1-hour post-dose. For doses administered at the study site, the study participants will be monitored by site staff. If any doses prior to Day 29 are administered offsite, post-dose monitoring will be performed by a qualified home healthcare professional (under the supervision of the Investigator). After Day 29, for doses administered offsite, study

participants can transition to self-monitoring only if no systemic hypersensitivity reactions of any grade have occurred following previous INZ-701 injections. For all participants who transition to offsite administration in this study, the site staff will contact the study participant and/or their caregiver(s)/delegated healthcare provider(s) weekly for the first 4 weeks to assess safety and dosing compliance. The Investigator may choose to extend the duration and/or increase the frequency of these communications as needed.

Study participants will be monitored for safety throughout the study. Safety monitoring will include in-clinic assessments from Day 1 through Day 29 (safety assessments will be conducted by a qualified home healthcare professional for participants who receive any doses offsite prior to Day 29), and every 6 months thereafter, remote safety assessments every 12 weeks between in-clinic visits, and continual evaluation and follow-up of reported AEs. The Investigator will determine if any additional safety monitoring is required based upon the overall wellbeing and compliance of the study participant, their clinical judgment, and institutional policy and guidelines. In addition, following the completion of a remote assessment, the Investigator will determine whether an in-clinic assessment is required.

During in-clinic visits, when PPi sampling is performed, study participants may not be dosed until it is confirmed that their pre-dose PPi and immunogenicity samples (if applicable) have been successfully collected and processed; fasting requirements for participants are provided in the protocol. The PPi measurements taken pre-dose on Day 1 will be used for determination of Baseline PPi.

INZ-701 Dose and Route

INZ-701 will be administered by SC injection on a once-weekly basis as follows:

- Study participants from 1 year to <18 years of age will receive a dose of 2.4 mg/kg
- Study participants ≥18 years will either receive a 1.8 mg/kg dose or a 150 mg flat dose of INZ-701, as described in the Pharmacy Manual

Placebo/Active Control

None

Estimated Duration of Study Participation

Study participants will begin dosing with INZ-701 on Study Day 1 and may remain on INZ-701 therapy until it is commercially available in the country/region of the participant's residence or until Inozyme chooses to discontinue development of INZ-701.

Population

Inclusion Criteria

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

1. Provide written or electronic informed consent after the nature of the study has been explained, and prior to any research-related procedures, per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP)
2. Provide assent in accordance with local regulations, if <18 years of age
3. Male or female, greater than 1 year of age

4. Must have completed the protocol-required safety and PK/PD and/or efficacy period(s) of the INZ701-101, INZ701-201, INZ701-104, or INZ701-106 clinical studies in ENPP1 or ABCC6 Deficiency, as confirmed by the Sponsor
5. Women of childbearing potential (WOCBP, as defined in Clinical Trials Coordination Group [CTCG 2024]) must have a negative serum pregnancy test at Screening and must not be breastfeeding
6. 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
7. WOCBP and partners of fertile males who are WOCBP must be using or agree to use a highly effective form of contraception (as per CTCG 2024) 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)
8. In the opinion of the Investigator, able to complete all aspects of the study

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 or laboratory abnormality not associated with ENPP1 Deficiency or ABCC6 Deficiency, that will preclude study participation and/or may confound interpretation of study results
2. Known intolerance to INZ-701 or any of its excipients
3. Concurrent participation in another interventional clinical study and/or has received an investigational drug other than INZ-701 within 5 half-lives or within 4 weeks prior to the first dose of INZ-701 in this study, whichever is longer, or use of an investigational device
4. Pregnant, trying to become pregnant, or breastfeeding
5. Male participants trying to father a child

Prohibited Concomitant Medications

The following medications are prohibited for all participants for the duration of this study:

- Calcitriol or other active forms of vitamin D3 (or analogs)
- Oral phosphate supplements
- Anti-fibroblast growth factor 23 (FGF23) (eg, burosumab)

Pharmacokinetic Assessments:

INZ-701 drug concentrations will be measured at timepoints indicated in the Schedule of Events and trough serum concentration (C_{trough}) will be estimated. Other PK parameters may be calculated if feasible.

Statistical Considerations

Descriptive statistics will be employed for analysis of the safety data. The PK and PPi data will be evaluated by standard methods. There will be no hypothesis testing.

Determination of Sample Size

Sample size will be determined by the number of study participants who choose to continue receiving INZ-701 after completing the protocol-required safety and PK/PD and/or efficacy period(s) of a previous INZ-701 clinical study.
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SCHEDULE OF EVENTS

Table 1: Schedule of Events

Study Period	**Screening**[a]						**Quarterly Visits; Repeat Yearly After Month 12**[b]				**EOS Visit**
Day of Study	**-30 to -1**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**30 days post last designated visit**
In Clinic/Remote		in clinic	in clinic or offsite			in clinic	in clinic or remote*	in clinic	in clinic or remote*	in clinic	in clinic
Visit Window (Days)		None	±1	±1	±1	±1	±14	±14	±14	±14	±7
Informed Consent/Assent	X										
Inclusion/Exclusion Criteria	X										
Medical History, Disease History, Demographics, and Prior Medications	X[a]										
Phone Calls							Site to contact participants minimally once a month (±14 days)**				
Physical Examination	X[a]	X				X		X		X	X
Weight[c] and Height	X[a]	X						X		X	
Vital Signs	X[a]	X[d]	X[d]	X[d]	X[d]	X		X		X	
Clinical Safety Laboratory Parameters [d, f]	X[a]	X	X			X		X		X	X
Pregnancy Test[g]	X[a]	X				X	X	X	X	X	X
PPi Concentration [f, h, i]	X[a]	X				X		X		X	X
Immunogenicity (ADA) [f, h]		X				X		X		X	X
PK (INZ-701 Concentration and ENPP1 Specific Activity) [f, h]		X				X		X		X	X
CRIM [f]	X[i]										
INZ-701 Administration		Once weekly via SC injection [j, k]									
Adverse Event Collection	Ongoing										
Concomitant Procedures and Medications	Ongoing										

* Remote or in-clinic visits at Month 3 and Month 9 are to be completed by the Investigator and/or Sub-investigator; at these visits conducted in-clinic or remotely, the Investigator and/or Sub-investigator will evaluate safety, including medical history, AEs, concomitant medications/procedures, and general wellbeing. These visits are to be repeated yearly from Day 1.

** The study site will contact participants once a month at minimum to monitor for safety and compliance.

a. **Screening Assessments**: performed within 30 days of Day 1 as part of an existing Inozyme clinical study in which the participant is currently receiving INZ-701 may be used for Screening and do not need to be repeated. Screening may occur on the participant's last visit of the previous INZ-701 study. Screening and Day 1 assessments may occur on the same day (Day 1) if all screening assessments are completed, and all eligibility criteria are confirmed prior to dosing. For participants who have Screening and Day 1 assessments on the same day, clinical safety laboratory parameters, physical examination, weight and height, and vital signs do not need to be repeated. Separate samples for Screening and Day 1 should be collected for pregnancy test (if applicable) and PPi concentration.

b. **Quarterly Visits:** The assessments at Months 3, 6, 9, and 12 should be repeated at the given interval each year after Month 12 (ie, Months 15, 18, 21, and 24).

c. **Weight Measurement**s: The study participant's weight (in kilograms) will be obtained at each indicated visit and will be measured using a calibrated scale. The weight obtained at Day 1 will be used to calculate the initial dose of INZ-701 (in mg) to be administered on a mg/kg or flat-dose basis (as described in Section 3.3.1.1), and the weight measured at any subsequent in-clinic visit will be used to calculate the dose to be administered until the next weight measurement is obtained.

d. **Vital Sign**s: will be collected pre-dose (within 1 hour of dosing) and at 1 hour and 2 hours post-dose (±15 mins) for the first 3 doses. On Days 15, 22, and 29, vital signs will be collected prior to INZ-701 administration. Thereafter, vital signs will be collected pre-dose at the in-clinic visits that occur every 6 months. For the Day 8, 15, and 22 visits conducted offsite (eg, in the home setting), vital signs will be collected by a qualified home healthcare professional.

e. **Clinical Safety Laboratory Evaluation**s: will be obtained prior to dosing (if applicable); includes blood chemistry panel with liver function tests, hematology panel including CBC with differential, and urinalysis (see Appendix A). Clinical safety laboratory tests will be analyzed at a central laboratory, if feasible, or otherwise at the local laboratory.

f. **Blood Collectio**n: All blood samples will be collected, processed, and shipped (if applicable) as outlined in the Laboratory Manual. INZ-701 will be administered as soon as possible after the pre-dose study samples have been processed and are confirmed to be acceptable. Adult participants (≥18 years) must fast (refrain from eating or drinking other than water) and refrain from exercising for a minimum of 6 hours before the collection of pre-dose study samples. Pediatric participants must fast and refrain from exercise, only if feasible. If maximum allowed blood volume (per local guidance) is reached for any given time-period, sampling will be prioritized as follows: clinical safety laboratory evaluations, immunogenicity, PPi, ENPP1 specific activity.

g. **Pregnancy Tes**t: will be performed for women of child-bearing potential only; serum at Screening and urine at all other indicated visits. If a urine test is positive or inconclusive, a serum test will be performed at a central laboratory, if feasible, or otherwise at the local laboratory. Urine pregnancy tests will be conducted monthly and discussed at the monthly site phone call.

h. **PPi, PK, ENPP1 Specific Activity, and ADA**: will be assessed pre-dose at all indicated time points.

i. **CRIM:** A single blood sample for CRIM will be collected any time prior to dosing on Day 1 from participants with ENPP1 Deficiency who have not had a blood sample for CRIM collected during a previous study with INZ-701. All participants rolling over from Study INZ701-101 should have a blood sample for CRIM collected. If Day 1 has already occurred prior to the approval of this amendment, CRIM will be collected as soon as possible at the next study visit.

j. **INZ-701 Administration**: Study participants will receive once-weekly SC doses of INZ-701. Dosing must occur on the same day each week ± 2 days (eg, dose every Monday ± 2 days). The dose will be determined by the age and weight of the participant as described in Section 3.3.1.1. All study participants will receive their first dose in the clinic on Day 1. Participants may be administered their second, third, and fourth doses (on Days 8, 15, and 22) offsite (eg, in the home setting) by a qualified home healthcare professional with explicit approval of the Investigator. All participants will return to the clinic for the Day 29 visit and dosing. After the fifth dose (on Day 29), participants may transition to self-administration of INZ-701 or offsite administration by a

caregiver/delegated healthcare provider as determined by the Investigator. At in-clinic visits when PPi sampling is performed, study participants may not be dosed until it is confirmed that their pre-dose PPi and immunogenicity (if applicable) samples have been successfully collected and processed.

k. **Post-dose Monitoring**: For the first 3 doses (Days 1, 8, and 15), all study participants will be monitored for a minimum of 2 hours after each dose. For all subsequent doses, participants will be monitored for a minimum of 1-hour post-dose. For doses administered at the study site, the participants will be monitored by site staff. If any doses prior to Day 29 are administered offsite, post-dose monitoring will be performed by a qualified home healthcare professional (under the supervision of the Investigator). After Day 29, for doses administered offsite, study participants can transition to self-monitoring only if no systemic hypersensitivity reactions of any grade have occurred following previous INZ-701 injections, as described in Section 5.2.1.

ADA=anti-drug antibodies; AE=adverse event; CBC=complete blood count; CRIM=cross-reactive immunologic material; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; EOS=end of study; PK=pharmacokinetic(s); PPi=inorganic pyrophosphate; SC=subcutaneous.

2. GLOSSARY OF TERMS

Term	Definition
ABCC6	ATP-binding cassette subfamily C member 6
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AMP	adenosine monophosphate
ANOVA	analysis of variance
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{last}	area under the concentration-time curve from time zero to time of last measurable concentration
CL	clearance
CAP/CLIA	College of American Pathologists/Clinical Laboratory Improvement Amendments
C_{max}	maximum serum concentration
C_{trough}	trough serum concentration
CRIM	cross-reactive immunologic material
CTCAE	Common Terminology Criteria of Adverse Events
CTCG	Clinical Trials Coordination Group
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
eCTD	Electronic Common Technical Document
EDC	electronic data capture
ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1
EOS	End of Study
ERT	enzyme replacement therapy
EU	European Union
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
GACI	Generalized Arterial Calcification of Infancy
GCP	Good Clinical Practice
GI	gastrointestinal

Term	Definition
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
Ig	immunoglobulin
INZ-701	recombinant human ectonucleotide pyrophosphatase/phosphodiesterase 1 fused to the Fc fragment of IgG1 (also known as rhENPP1-Fc)
ISR	injection site reaction
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NOAEL	no-observed-adverse-effect-level
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
Pi	inorganic phosphate
PK	pharmacokinetic(s)
PKAS	Pharmacokinetic analysis set
PPi	inorganic pyrophosphate
PRO	patient reported outcome
PTH	parathyroid hormone
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
SC	subcutaneous(ly)
SERM	selective estrogen receptor modulator
SMP	Safety Management Plan
SOP	standard operating procedure
ss	steady state

Term	Definition
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
US	United States
WOCBP	women of childbearing potential

3. INTRODUCTION

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

In 2018, both the United States (US) Food and Drug Administration (FDA) and the European Commission granted orphan designation to INZ-701 for the treatment of ENPP1 Deficiency. In 2020, the FDA also granted fast track designation and rare pediatric disease designation to INZ-701 for the treatment of ENPP Deficiency. In 2021, both the FDA and the European Commission granted orphan designation to INZ-701 for the treatment of ABCC6 Deficiency.

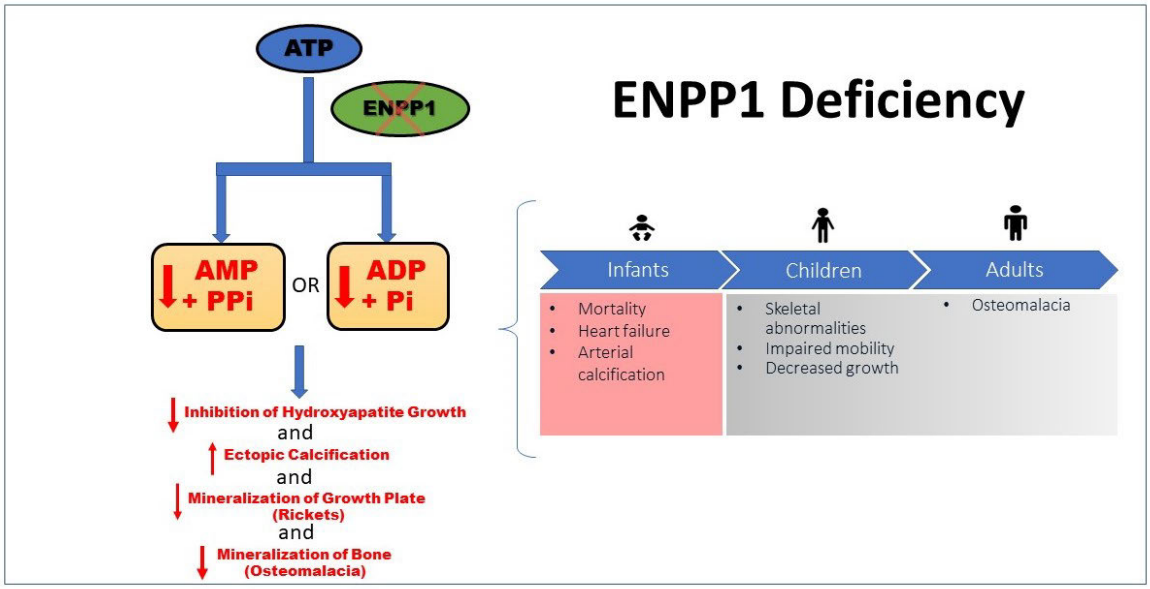
Two studies to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of INZ-701 in patients with ENPP1 Deficiency are ongoing: the ENERGY Study (INZ701-104) in infants <1 year old and the ENERGY 3 Study (INZ701-106) in children aged 1 year to <13 years. One study to evaluate the safety and efficacy of INZ-701 in patients with ENPP1 Deficiency is ongoing: the ENERGY 2 Study (INZ701-105) in infants from birth to <1 year of age. One study is complete in patients with ENPP1 Deficiency: INZ701-101 in adults ≥18 to 65 years old, and 1 study is complete in patients with ABCC6 Deficiency: INZ701-201 in adults ≥18 to <70 years old.

3.1. ENPP1 Deficiency

ENPP1 Deficiency is an ultra-rare genetic disorder with an incidence of 1 in 64,000 pregnancies (Chunn et al 2022), caused by inactivating mutations in the ENPP1 gene that encodes the ENPP1 enzyme.

The ENPP1 enzyme is an integral transmembrane protein whose extracellular domains carry pyrophosphatase and phosphodiesterase activities. ENPP1 hydrolyzes ATP to generate inorganic pyrophosphate (PPi) plus adenosine monophosphate (AMP) (Mackenzie et al 2012a). As a result, deficiency in this enzyme results in a decrease in PPi and AMP. Refer to Figure 1 for an overview of ENPP1 Deficiency.

Figure 1: Overview of ENPP1 Deficiency



ADP/AMP/ATP=adenosine di-/mono-/tri- phosphate; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; PPi=inorganic pyrophosphate
References: Mackenzie et al 2012a; Chanchlani et al 2020; Hoppner et al 2021; Scheinman and Carpenter 2022

ENPP1 Deficiency often presents as pathologic calcification of vascular tissue during infancy. During childhood, however, ENPP1 Deficiency may present as under-mineralization of bones and growth plates resulting clinically as an abnormality in the growth of long bones. The under-mineralization is due to low levels of Pi and has been characterized by radiographic skeletal changes consistent with those of rickets. Consistent with these radiographic changes, the skeletal abnormalities that may manifest in children with ENPP1 Deficiency are the typical clinical features of rickets, such as skeletal deformities (eg, bowed extremities), short stature, and bone pain. Adults with ENPP1 Deficiency suffer from osteomalacia, ectopic calcification, hearing loss, and other morbidities. To date, there are no approved therapies for ENPP1 Deficiency, and therefore, there is a high unmet medical need for a treatment.

3.2. ABCC6 Deficiency

ABCC6 Deficiency is a rare, autosomal recessive genetic disease, with high morbidity that affects patients throughout their lifespan. A rare acute infantile form resembles the acute infantile form of ENPP1 Deficiency and has thus been called Generalized Arterial Calcification of Infancy Type 2 (GACI-2), while the most common form diagnosed in adulthood is called Pseudoxanthoma elasticum (PXE). ABCC6 Deficiency is a rare disease that affects approximately 1 in 50,000 people worldwide. PXE is diagnosed twice as frequently in females as in males (Uitto et al 2014).

ABCC6 modulates the transport of intracellular ATP to the extracellular space of hepatocytes where ATP is hydrolyzed by the ENPP1 enzyme to generate PPi and AMP. Loss-of-function mutations in the ABCC6 gene lead to approximately 50% decrease in systemic plasma PPi which, in turn, leads to ectopic mineralization of elastin-rich tissues.

The progressive ectopic mineralization (ie, deposition of calcium phosphate crystals) leads to fragmentation of the elastic fibers in the elastin-rich tissues of the skin, the retina, and the vascular wall. The fragmentation ultimately results in organ system dysfunction, manifesting as clinically significant abnormalities of the cerebrovascular, cardiovascular, peripheral vascular systems, as well as profound ophthalmological/visual deficits.

As mentioned, infants with ABCC6 Deficiency may present with generalized arterial calcification resulting in cardiovascular symptoms nearly identical to infants with ENPP1 Deficiency. Patients with ABCC6 Deficiency may also develop neurological signs and symptoms (such as those of stroke) secondary to calcium deposition and stenosis of the cerebral arterial circulation. Peripheral vascular disease can also occur and may result in intermittent claudication. Ophthalmological changes include angioid streaks, reflecting mineralization of Bruch's membrane behind the pigmented retinal epithelium. When this occurs, neovascularization of the retina can occur, leading to loss of visual acuity, hemorrhage, and ultimately, blindness. Additionally, abnormalities in the vascular supply of central organs, for example, gastrointestinal (GI) hemorrhages and stenoses of GI arteries and stroke, have been known to occur. Ectopic mineralization has also been noted in kidneys, joints, and tendons in patients with ABCC6 Deficiency, demonstrating this is a systemic and heterogenous disease. Older pediatric patients with ABCC6 Deficiency may develop or present with ischemic stroke secondary to cerebrovascular stenosis and insufficiency, as well as other signs and symptoms observed in adult patients.

3.3. Rationale for Treatment with INZ-701

ENPP1 Deficiency: As described above, ENPP1 Deficiency is a rare genetic disorder in which inactivating mutations in the ENPP1 gene lead to a deficiency in the ENPP1 enzyme and in turn, results in a decrease in PPi that ultimately manifests clinically with the clinical situations described in the preceding section.

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

INZ-701 is in development as an enzyme replacement therapy (ERT) for the treatment of ENPP1 Deficiency. Structurally it is a recombinant human ENPP1 fused to the Fc fragment of IgG1 (rhENPP1-Fc).

ABCC6 Deficiency: As described above, ABCC6 Deficiency is a rare, autosomal recessive genetic disease with 2 phenotypic presentations of GACI Type 2 and PXE.

There are also limited effective treatment options for patients with ABCC6 Deficiency, which are focused on treatment of skin lesions and choroidal neovascularization. None of the current treatments address the root cause (ie, low levels of PPi), and the efficacy of current therapies is low.

In addition to development as an ERT for the treatment of ENPP1 Deficiency, INZ-701 is in development as a treatment for ABCC6 Deficiency since INZ-701 can increase PPi levels.

Phase 1/2 clinical studies: Inozyme has completed a Phase 1/2 clinical study in adults with ENPP1 Deficiency (Study INZ701-101) and completed a Phase 1/2 clinical study in adults with ABCC6 Deficiency (Study INZ701-201). Preliminary data from these studies indicate that

INZ-701 therapy is safe and is capable of increasing PPi to within normal levels. The PK properties of INZ-701 have been reproducible and predictable, with a half-life of approximately [redacted], supporting once-weekly dosing. Furthermore, data from patient reported outcome (PRO) measures support clinical activity in both diseases, as well as functional performance (six-minute walk test) and biomarker data support clinical activity in ENPP1-deficient patients.

In addition, Inozyme is conducting a Phase 1b clinical study to evaluate the safety, tolerability, PK, and PD of INZ-701 in infants (<1 year) with ENPP1 Deficiency (Study INZ701-104 [ENERGY]). Thus far, preliminary data indicate INZ-701 therapy is safe. More study participants are needed to assess PK and PD in this patient population. A Phase 3 study in the pediatric population has been initiated to assess the safety and efficacy of INZ-701 in study participants 1 to 12 years old (Study INZ701-106 [ENERGY 3]).

The purpose of this study (INZ701-304 [ADAPT]) is to assess the long-term safety of INZ-701 in patients with ENPP1 Deficiency or ABCC6 Deficiency who have received INZ-701 in a previous clinical study and choose to continue dosing for the potential treatment of their condition.

Additional information on the physical characteristics of the diseases and available nonclinical and clinical data are provided in the INZ-701 Investigator's Brochure (IB).

3.3.1. Rationale for Dose Selection and Dosing Schedule

Dosing for Adults with ENPP1 Deficiency and ABCC6 Deficiency:

INZ-701 has exhibited a favorable safety profile at all dose levels tested (0.2, 0.6 and 1.8 mg/kg twice weekly) in Studies INZ701-101 and INZ701-201, conducted in adult participants with ENPP1 Deficiency and ABCC6 Deficiency, respectively. In both studies there was an observed increase in PPi levels comparable to those observed in a study of healthy adult study participants.

The 1.8 mg/kg dose level (or the 150 mg fixed dose equivalent in adults) was selected for the ADAPT Study (INZ701-304), because uniform response and consistent, predictable PPi levels in the normal range will be important to ensure a rapid and durable response to therapy. The 3 doses tested (0.2, 0.6, and 1.8 mg/kg given subcutaneously [SC] twice weekly) were effective in restoring mean PPi levels in adult participants in the INZ701-101 study. However, there was a heterogeneous PPi response among the INZ-701 doses, with less variability at the highest dose of 1.8 mg/kg twice weekly in the INZ701-101 study. Furthermore, there was an apparent dose response effect on the biomarker fibroblast growth factor 23 (FGF23), which is important in the pathogenesis of hypophosphatemia in ENPP1 Deficiency; there appeared to be a greater reduction in plasma FGF23 at higher INZ-701 dose levels. In the INZ701-201 clinical study, there was a superior PPi response at the 1.8 mg/kg dose twice weekly. Therefore, Inozyme has chosen the 1.8 mg/kg dose (or a fixed dose equivalent).

Weekly Dosing:

Instead of twice-weekly dosing, which was the dosing regimen of the above studies, weekly dosing has been selected for this study, INZ701-304, because data from the aforementioned studies demonstrated a relatively long half-life of INZ-701. Pharmacokinetic analysis in adults with ENPP1 Deficiency showed that the mean half-life of INZ-701 was approximately [redacted]. Pharmacokinetic analysis in adults with ABCC6 Deficiency was consistent with that finding.

In addition, Inozyme conducted a PK modeling study to evaluate optimal dose frequency using PK data from adults with ENPP1 Deficiency (Study INZ701-101) and ABCC6 Deficiency (Study INZ701-201). This study showed that in adults with ENPP1 Deficiency, all dose levels with once-weekly dosing resulted in relatively consistent serum concentrations of INZ-701, and that INZ-701 concentrations in excess of 3000 ng/mL could be obtained with once-weekly 1.8 mg/kg dosing in all patients. At this serum concentration, substantial elevations of PPi into the normal range have been observed in the Phase 1/2 studies in adults. Therefore, these results support once-weekly dosing in clinical studies. Furthermore, once-weekly dosing will reduce injection frequency, minimize injection site reaction risk, and increase compliance.

Fixed Dosing:

The fixed dose of 150 mg in adults is supported by population PK modeling studies in which dosing in [redacted] simulated participants was compared in both ABCC6- and ENPP1-deficient patients, evaluating once-weekly dosing. In this simulation the 1.8 mg/kg weekly dose was compared to a fixed dose of [redacted] mg in adult patients weighing between 50 to 100 kg. Both simulated exposures and PD (PPi) results were nearly identical using either dosing method, indicating that INZ-701 could be administered as a fixed dose in adults without compromising exposure or PD properties. The 150 mg dose was selected for this protocol instead of [redacted] mg, because this dose can be easily prepared for injection by reconstituting 6 full vials of INZ-701 (25 mg/vial), which minimizes drug wastage, and simplifies the reconstitution and injection process. The excess drug administered over that used for the simulation ([redacted] mg) is minimal and amounts to a dose of [redacted] mg/kg in a 75 kg adult given weekly. This is well below the maximum dose already administered to adult patients at 1.8 mg/kg twice weekly.

Dosing for Children with ENPP1 Deficiency and ABCC6 Deficiency:

Inozyme is conducting a PK modeling study using PK data from adults (Study INZ701-101) and pediatrics (Study INZ701-104 [ENERGY]; INZ701-EAP-01) with ENPP1 Deficiency and from adults with ABCC6 Deficiency (Study INZ701-201).

In the initial modeling approach, the steady-state (ss) exposure metrics of interest were area under the concentration-time curve ($AUC_{,ss}$), maximum INZ-701 concentration over the dosing interval ($C_{max,ss}$), and INZ-701 concentration at the end of the dosing interval ($C_{trough,ss}$). All exposure metrics were calculated for the 1-week dosing interval at ss. One thousand (1000) participants were simulated in each age group. Pediatric weights were resampled from the appropriate age group in the National Health and Nutrition Examination Survey (NHANES) database; adult weights were simulated from a uniform distribution ranging from 50 to 100 kg. INZ-701 systemic clearance (CL) was scaled using body weight with age-dependent exponents to account for maturation of CL mechanisms in younger individuals, as detailed in Mahmood 2020. The volume of distribution was scaled allometrically with an exponent of 1. No other adjustments to the PK parameters were made for extrapolation into the pediatric subgroups. Adult exposures were simulated following once weekly administration of INZ-701 reference doses including 0.2, 0.6, 1.8, and 2.4 mg/kg; exposure targets were set using the median $AUC_{,ss}$ for each reference dose in the adult population.

Pediatric exposures were simulated under the following 2 dosing assumptions:

- First, an “optimized” dose was simulated that attempted to match the median $AUC_{,ss}$ in each pediatric subgroup to the median $AUC_{,ss}$ in the adult group for a particular

adult reference dose; this optimized dose was determined using only $AUC_{,ss}$ (not $C_{max,ss}$ or $C_{trough,ss}$)

- Second, the same adult dose was administered on mg per kg basis to all pediatric participants; this is referred to as "common" dosing, where all participants get the same dose on a mg per kg basis

To project pediatric doses, age-dependent exponents were added to the body weight covariate effect on CL to account for maturation effects on INZ-701 CL.

Following analysis of these studies, Inozyme concluded that candidate pediatric and infant doses in ENPP1-deficient patients could be chosen to match the median adult AUC of 1.8 or 2.4 mg/kg over a once-weekly dosing interval at ss and based on the PD response observed. The results of the analysis are shown in Table 2.

Table 2: Infant and Pediatric Doses to Match Adult Steady State INZ-701 AUC ($AUC_{,ss}$) at 1.8 and 2.4 mg/kg Administered Once Weekly

Age Group	Compared with Adult 1.8 mg/kg	
	Dose (mg/kg)	**Median $AUC_{,ss}$ (ng*week/mL)**
0 to <6 months	[redacted]	4095
6 to <12 months	[redacted]	4155
1 to <2 years	[redacted]	4185
2 to <6 years	[redacted]	4018
6 to ≤13 years	[redacted]	4066
Adults	[redacted]	4131
	Compared with Adult 2.4 mg/kg	
0 to <6 months	[redacted]	5714
6 to <12 months	[redacted]	5589
1 to <2 years	[redacted]	5566
1 to <2 years	[redacted]	5506
6 to ≤13 years	[redacted]	5560
Adults	[redacted]	5690

AUC=area under the curve.

3.3.1.1. Dose Rationale Conclusions

INZ-701 will be administered by SC injection on a once-weekly basis as follows:

- Study participants from 1 year to <18 years of age will receive a dose of 2.4 mg/kg
- Study participants ≥18 years will either receive a 1.8 mg/kg dose or a 150 mg flat dose of INZ-701, as described in the Pharmacy Manual

3.4. Overall Risks and Potential Benefits

3.4.1. Risks

Identification and mitigation of risks are based on results of nonclinical studies, preliminary data from the Phase 1/2 clinical study in adults with ENPP1 Deficiency and ABCC6 Deficiency, known risks associated with therapeutic protein products in humans, and known risks from study procedures.

Please refer to the IB for nonclinical pharmacology, safety, and toxicology study results and preliminary clinical data from the ongoing Studies INZ701-101 and INZ701-201 in adults, and Study INZ701-104 (ENERGY study) in infants.

3.4.1.1. Systemic Hypersensitivity

Given the potential for hypersensitivity reactions with any therapeutic protein product, study participants will be monitored for such signs and symptoms of systemic hypersensitivity, including shortness of breath, laryngeal edema, urticaria, pruritic rash, malaise, nausea, or vomiting. Please see Section 5.2.2 for information on monitoring and management of suspected hypersensitivity reactions to INZ-701.

3.4.1.2. Immunogenicity

Immunogenicity is a potential risk associated with any therapeutic protein product. In study participants who develop neutralizing (inhibitory) anti-drug antibodies (ADA), the effect of INZ-701 may be attenuated or lost, and these participants could develop hypersensitivity reactions; therefore, a comprehensive assessment of immunogenicity is planned. Anti-drug antibodies to INZ-701 will be assessed by a validated method.

Please see Section 8.6.6 for information on the sample collection and assay.

3.4.1.3. Phlebotomy and Subcutaneous Injection

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

3.4.1.4. Injection Site Reaction

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

3.4.1.5. Neurotoxicity

In mouse studies, there were sporadic clinical signs associated with central nervous system symptoms, and one mouse had a potential seizure. In human studies, no seizures have been reported. In clinical studies, nervous system disorder adverse events (AEs) have all been less than Grade 3 to date, and have included dizziness, headache, hypoaesthesia, migraine, presyncope, sinus headache, and syncope. Patients should be monitored for neurotoxicity.

3.4.1.6. Reproductive Toxicity

A pivotal juvenile mouse repeat-dose toxicology study demonstrated decreased reproductive performance at the highest dose of INZ-701 tested. This represents a 3.9-fold higher exposure level than the 1.8 mg/kg dose to be tested in this clinical study. Therefore, decreased fertility may result during adulthood. A pivotal reproductive toxicology study in mice will be conducted. The risks of INZ-701 to an unborn baby in individuals who take INZ-701 are unknown. Additional information is provided in the IB.

3.4.1.7. Hyperphosphatemia

In adults with ABCC6 Deficiency (Study INZ701-201), transient elevations in serum phosphate were observed in some study participants after INZ-701 administration, but none were considered clinically significant. In adults with ENPP1 Deficiency (Study INZ701-101), small increases in serum phosphate were observed after receiving INZ-701, but all were below the upper limit of the reference range. The risk of hyperphosphatemia is lower in ENPP1 Deficiency patients, given these patients suffer from phosphate wasting and are hypophosphatemic. Investigators should consult with the Sponsor if hyperphosphatemia occurs. Examples of actions which could be considered are dietary phosphate restriction, or if a study participant is receiving oral phosphate supplements, reducing or eliminating oral phosphate supplementation.

3.4.1.8. COVID-19 Exposure and Infection

COVID-19 testing will be conducted in accordance with local and/or institutional requirements as part of eligibility criteria, where required.

In addition, study 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 study participant and study staff. Visits and assessments not conducted in accordance with the protocol due to COVID-19 will be documented as such in the study participant's source records and clinical database.

3.4.2. Risk: Benefit Overall Conclusions

Clinical and nonclinical data have identified no undue safety concerns that would preclude long-term treatment of patients with ENPP1 and ABCC6 Deficiencies; no dose-limiting toxicities were identified in clinical studies up to the highest tested dose of 1.8 mg/kg twice weekly (Studies INZ701-101 and INZ701-201) and in nonclinical studies at single doses as high as [redacted] mg/kg and multiple doses for 3 months at [redacted] mg/kg every other day (QOD) in mice and [redacted] mg/kg QOD in nonhuman primates. Refer to the IB for further details.

However, it is recognized that, as with any investigational product, unexpected toxicities may occur. For this reason, compliance with the eligibility criteria and study procedures, diligent safety monitoring, including regular review of safety data are required to mitigate any potential risk to study participants in this study.

From a benefit perspective, data from the Sponsor's clinical and nonclinical program has thus far indicated that INZ-701 has the potential to be efficacious in this study population as discussed in

Section 3.3 with additional details in the IB. Given the above information and the context of the unmet medical need for therapies to treat ENPP1 Deficiency and ABCC6 Deficiency, the risk-benefit profile of INZ-701 and continued dosing of INZ-701 in this study population is considered favorable and supports the conduct of this study.

4. OBJECTIVES AND ENDPOINTS

The objectives of Study INZ701-304 and corresponding endpoints are listed in Table 3.

Table 3: Objectives and Endpoints of Study INZ701-304

Primary Objective	**Primary Endpoints**
• To assess the long-term safety of INZ-701	• Incidence, frequency, and severity of AEs, TEAEs, AESIs, and SAEs • Changes in clinical laboratory tests including chemistry, hematology, and urinalysis resulting in an AE • Concomitant medications • Titers of ADA
Secondary Objectives	**Secondary Endpoints**
• To confirm drug levels of INZ-701 with long-term use	• INZ-701 plasma PK parameters measured by immunoassay and enzymatic activity
• To assess the effect of long-term INZ-701 treatment on plasma PPi concentrations	• Plasma PPi concentrations based on a validated assay

ADA= anti-drug antibodies; AE=adverse event; AESI= adverse event of special interest; PPi=inorganic pyrophosphate; PK=pharmacokinetic; SAE= serious adverse event; TEAE= treatment-emergent adverse event.

5. INVESTIGATIONAL PLAN

5.1. Study Design

The ADAPT Study (INZ701-304) is an open-label study to assess the long-term safety of INZ-701 in patients with ENPP1 Deficiency or ABCC6 Deficiency who have received INZ-701 in a previous clinical study and choose to continue dosing for the potential treatment of their condition. Participants are eligible if they have completed the protocol-required safety and PK/PD and/or efficacy period(s) of a previous study with INZ-701 (as confirmed by the Sponsor). Up to 200 study participants are planned to be enrolled in this study.

The study will consist of a 30-day Screening Period, followed by an open-label Treatment Period during which all participants will receive once-weekly SC doses of INZ-701 and continue with treatment until INZ-701 is commercially available in the country/region of the participant's residence or until Inozyme chooses to discontinue development of INZ-701. Participants will complete an End of Study (EOS) safety follow-up visit approximately 30 days after their last designated study visit assigned by the Investigator and/or Sponsor.

Study participants will be monitored for safety throughout the study as described in Section 5.2.

Screening Period

The Screening Period will last up to 30 days during which assessments will be performed to determine eligibility and/or establish Baseline. Assessments conducted as part of an existing INZ-701 clinical study may be used for Screening if they have been completed within the 30-day Screening window. Screening may occur on the participant's last visit of the previous INZ-701 study. Screening procedures may be conducted over several days as necessary and shall be conducted in a manner and order to minimize participant burden. Screening and Day 1 assessments may occur on the same day (Day 1) if all screening assessments are completed, and all eligibility criteria are confirmed prior to dosing. For participants who have Screening and Day 1 assessments on the same day, clinical safety laboratory parameters, physical examination, weight and height, and vital signs do not need to be repeated. Separate samples for Screening and Day 1 should be collected for pregnancy test (if applicable) and PPi concentration. A study participant will be enrolled into the study if they meet all eligibility criteria.

Treatment Period

Study participants will begin dosing with INZ-701 on Study Day 1 and may remain on INZ-701 therapy until it is commercially available in the country/region of the participant's residence or until Inozyme chooses to discontinue development of INZ-701. INZ-701 will be administered as a once-weekly dose via SC injection; the dose will be determined by the participant's age and weight as outlined in Section 3.3.1.1.

All study participants will receive their first dose of INZ-701 in-clinic (on Day 1) under medical supervision. Participants may be administered their second, third, and fourth doses (on Days 8, 15, and 22, respectively) offsite (eg, in the home setting) by a qualified home healthcare professional with explicit approval of the Investigator. All participants will return to the clinic for the Day 29 visit and dosing.

After the fifth dose (on Day 29), participants may transition to self-administration of INZ-701 or offsite administration by a caregiver/delegated healthcare provider as determined by the Investigator; the details of post-dose monitoring requirements are provided in Section 5.2.1. The Investigator will ensure successful completion of dose administration training, including monitoring and management of signs and symptoms of hypersensitivity reactions, before the study participant is transitioned to offsite administration. Offsite administration may be stopped or reinitiated at any time during the study by the Investigator and/or Sponsor.

For all participants who transition to offsite administration in this study, the site staff will contact the study participant and/or their caregiver(s)/delegated healthcare provider(s) weekly for the first 4 weeks to assess safety and dosing compliance. The Investigator may choose to extend the duration and/or increase the frequency of these communications as needed.

During in-clinic visits when PPi sampling is performed, study participants may not be dosed until it is confirmed that their pre-dose PPi and immunogenicity samples (if applicable) have

been successfully collected and processed; fasting requirements are provided in Section 8.4. The PPi measurements taken pre-dose on Day 1 will be used for determination of Baseline PPi.

Study participants will return to the study site 30 days after their last designated study visit to complete an EOS safety follow-up visit.

5.2. Safety Monitoring

A Data Safety Monitoring Board (DSMB) will monitor safety as described in Section 5.2.3.

Study participants will be monitored for safety throughout the study. Safety monitoring will include in-clinic assessments from Day 1 through Day 29 (safety assessments will be conducted offsite by a qualified home healthcare professional for participants who receive any doses offsite prior to Day 29) and every 6 months thereafter, remote safety assessments every 3 months between in-clinic visits, and continual evaluation and follow-up of reported AEs.

For all participants who transition to offsite administration in this study, the site staff will contact the study participant and/or their caregiver(s)/delegated healthcare provider(s) weekly for the first 4 weeks to assess safety and dosing compliance. In addition, the study site will contact all participants in the study once a month at minimum after Day 29 to monitor for safety and compliance. The Investigator will determine if any additional safety monitoring is required based upon the overall wellbeing and compliance of the study participant, their clinical judgment, and institutional policy and guidelines. Following the completion of a remote assessment, the Investigator will determine whether an in-clinic assessment is required.

Participants will complete an EOS safety follow-up visit approximately 30 days after their last designated study visit assigned by the Investigator and/or Sponsor.

Clinical laboratory tests, physical examination, vital signs, AEs, and immunogenicity will be assessed throughout the study.

Study participants will be monitored for injection site and systemic hypersensitivity reactions and immunogenicity throughout the study.

Adverse events will be characterized and graded as per Investigator judgment for seriousness, relatedness, and severity of each AE/serious adverse event (SAE). Grading criteria in National Cancer Institute-Common Terminology Criteria of Adverse Events (NCI-CTCAE) version 5.0 (NCI 2017) will be used by the Investigator as applicable.

5.2.1. Post-dose Monitoring

All study participants will be monitored for at least 2 hours following administration of each of their first 3 doses of INZ-701. For all subsequent doses, the Investigator will prescribe the required post-dose monitoring duration for each study participant, which will not be less than 1 hour.

For doses administered at the study site, the study participants will be monitored by site staff. If any doses prior to Day 29 are administered offsite, post-dose monitoring will be performed by a qualified home healthcare professional (under the supervision of the Investigator). After Day 29, study participants can transition to self-monitoring only if no systemic hypersensitivity reactions of any grade have occurred following previous INZ-701 injections. Instructions will be provided

to the study participants or caregiver(s)/healthcare provider(s) for monitoring and management of symptoms of hypersensitivity as per Section 5.2.2.

5.2.2. Monitoring and Management of Suspected Hypersensitivity

Given the potential of hypersensitivity reactions with any therapeutic protein product, study participants will be monitored for the signs and symptoms of systemic hypersensitivity reactions, including shortness of breath, laryngeal edema, urticaria, pruritic rash, malaise, nausea, or vomiting. The Investigator will treat suspected and confirmed signs and symptoms of hypersensitivity reactions as medically indicated.

Study participants will be monitored for injection site and systemic hypersensitivity reactions for 2 hours following each of their first 3 doses of INZ-701. For all subsequent doses, the Investigator will prescribe the required post-dose monitoring duration for each study participant, which will not be less than 1 hour. Study participants can transition to self-monitoring only if no systemic hypersensitivity reactions of any grade have occurred following previous INZ-701 injections.

Study participants and/or their caregiver(s)/healthcare provider(s) will be both trained and provided with written instructions on how to monitor and manage the signs and symptoms of systemic hypersensitivity reactions, including anaphylaxis. The Investigator will prescribe rescue medication for offsite administration by the participant and/or their caregiver(s)/healthcare provider(s) in accordance with clinical practice and institutional guidelines and provide necessary training for use.

5.2.3. Data Safety Monitoring Board

An independent DSMB will provide safety oversight. The DSMB will review safety data at regular intervals in accordance with the DSMB charter. The composition, duties, and responsibilities of the DSMB are described in the DSMB charter. The DSMB will be comprised of members with expertise in the treatment of rare metabolic disorders and at least one biostatistical expert. All DSMB members will be independent from and not affiliated with the study or Sponsor. The DSMB may perform ad hoc reviews for safety events, including but not limited to, reported suspected unexpected serious adverse reactions (SUSARs). Decisions regarding study continuation and/or modification will be made by the Sponsor based upon DSMB recommendations.

5.3. End of Study

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

5.3.1. Termination of the Study

The study may be terminated at any time during the open-label Treatment Period if the Investigator and/or Sponsor become aware of a condition or event that suggests a possible risk to study participants if the study were to continue. If safety considerations warrant, the Sponsor may stop the study at any time. Conditions that may warrant termination of the clinical study include but are not limited to:

- Safety reasons as determined by the Sponsor
- The discovery of an unexpected, relevant, or unacceptable risk to the study participants
- Failure to enroll study participants at the required rate
- A decision by the Sponsor to terminate the study, or to suspend or discontinue development of INZ-701, for any reason

The Sponsor will inform the Investigators, DSMB, and regulatory authorities of the decision to stop the study. The Sponsor will inform participating sites via formal correspondence within 1 business day of a decision to stop dosing or stop the study. Study participants will be instructed to return to the clinic for an EOS safety follow-up visit 30 days after their last designated study visit assigned by the Investigator and/or Sponsor.

6. POPULATION

6.1. Inclusion Criteria

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

1. Provide written or electronic informed consent after the nature of the study has been explained, and prior to any research-related procedures, per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP)
2. Provide assent in accordance with local regulations, if <18 years of age
3. Male or female, greater than 1 year of age
4. Must have completed the protocol-required safety and PK/PD and/or efficacy period(s) of the INZ701-101, INZ701-201, INZ701-104, or INZ701-106 clinical studies in ENPP1 or ABCC6 Deficiency, as confirmed by the Sponsor
5. Women of childbearing potential (WOCBP, as defined in Clinical Trials Coordination Group [CTCG 2024]) must have a negative serum pregnancy test at Screening and must not be breastfeeding
6. 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
7. WOCBP and partners of fertile males who are WOCBP must be using or agree to use a highly effective form of contraception (as per CTCG 2024) 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)
8. In the opinion of the Investigator, able to complete all aspects of the study

6.2. 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 or laboratory abnormality not associated with ENPP1 Deficiency or ABCC6 Deficiency, that will preclude study participation and/or may confound interpretation of study results

2. Known intolerance to INZ-701 or any of its excipients
3. Concurrent participation in another interventional clinical study and/or has received an investigational drug other than INZ-701 within 5 half-lives or within 4 weeks prior to the first dose of INZ-701 in this study, whichever is longer, or use of an investigational device
4. Pregnant, trying to become pregnant, or breastfeeding
5. Male participants trying to father a child

6.3. Estimated Duration of Study Participation

Study participants will begin dosing with INZ-701 on Study Day 1 and may remain on INZ-701 therapy until it is commercially available in the country/region of the participant's residence or until Inozyme chooses to discontinue development of INZ-701.

6.4. Early Treatment Discontinuation

Study participants who discontinue INZ-701 treatment will complete the EOS safety follow-up visit 30 days after their last designated study visit assigned by the Investigator and/or Sponsor.

Reasons for discontinuation of INZ-701 may include, but are not limited to:

- Study participant experiences significant and disabling disease progression, organ dysfunction, or unacceptable toxicity
- Study participant or caregiver withdraws consent for administration of INZ-701
- Occurrence of an AE or clinically significant laboratory abnormality, that, in the opinion of the Investigator, warrants permanent discontinuation of INZ-701
- Study participant becomes pregnant or is planning pregnancy
- A change in the study participant(s) risk/benefit profile
- Study participants for whom care has been withdrawn or who transition to end of life care or hospice during the study

The Investigator will notify the Sponsor within 24 hours of becoming aware of a study participant's discontinuation from the study.

6.5. Early Study Discontinuation

For participants who discontinue from the study, every effort will be made to complete the EOS safety follow-up visit 30 days after their last designated study visit.

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

- Withdrawal of consent: Study participants and/or caregivers may withdraw their consent to participate in the study at any time without prejudice. The Investigator must comply with all participant and caregiver requests to be withdrawn from the study.
- Lost to follow-up: Lost to follow-up is defined as failing to return for scheduled study visits. If a study participant fails to return for a scheduled visit the Investigator will

make all reasonable efforts to contact the caregiver(s) to determine status and the reason why. If the study participant is unresponsive, the Investigator will withdraw the participant from the study. All attempts to contact the study participant's caregiver(s) will be documented in the source records.

- Death

The Investigator will notify the Sponsor within 24 hours of becoming aware of a study participant's discontinuation from the study.

6.5.1. Re-enrollment of Participants

Participants who withdraw from the study for reasons other than safety may re-enroll after reconsenting and will receive the same dose that they were receiving prior to withdrawal. Upon re-enrollment, participants will be required to follow the schedule of events described in Table 1 starting with Day 1 (first dose).

6.6. Prohibited Medications

The following medications are prohibited for all participants for the duration of this study:

- Calcitriol or other active forms of vitamin D3 (or analogs)
- Oral phosphate supplements
- Anti-FGF23 (eg, burosumab)

Participants who need to taper or discontinue calcitriol or other active forms of vitamin D3 (or analogs) and phosphate supplements for the purposes of participating in this study must be do so under the guidance of the treating physician and only if deemed not detrimental to the study participant's health. Treatment must not be withdrawn to fulfill study eligibility if it is considered necessary for the clinical management of the study participant.

The Medical Monitor should be consulted if the Investigator determines that the study participant requires any of the prohibited medications due to participant safety concerns and to determine continued study participation.

6.7. Contraception Use and Pregnancy

The Investigator will counsel study participants who are or become of childbearing potential and who are or become sexually active during the study on the appropriate use of contraception in accordance with CTCG guidance (CTCG 2024; see Appendix B) and local guidelines. In addition, the Investigator will counsel these study participants not to donate sperm or ova throughout the study. Given that a study participant's childbearing status may change during the study, Tanner stage and sexual behavior should be monitored throughout the course of the study. Inclusion criteria are in place for sexually active male and female participants as described in Section 6.1.

Study participants who become pregnant during the study must stop INZ-701 administration, and the Investigator will make all reasonable efforts to follow the pregnancy through delivery or termination. All pregnancies occurring in female participants and in female partners of male participants are to be reported within 24 hours of the Investigator's awareness of the pregnancy

using the Pregnancy Report Form. Additional details on reporting of pregnancy are provided in Section 9.3.6.

7. STUDY TREATMENT

7.1. Investigational Product: INZ-701

The investigational product, INZ-701, is supplied as a lyophilized powder and is reconstituted prior to dosing. INZ-701 is manufactured, packaged, and labeled according to Good Manufacturing Practices regulations.

Investigator sites are required to store vials of INZ-701 at 2-8°C in a secure, limited-access location. Refer to the INZ-701 Pharmacy Manual for additional details on the storage, preparation, and administration of reconstituted INZ-701. Additional information on the physical and chemical properties, formulation, and stability of INZ-701 is provided in the IB.

7.1.1. Blinding

This is an open-label study. No study participants or study personnel will be blinded to treatment assignment.

7.1.2. INZ-701 Preparation and Administration

INZ-701 will be prepared and administered in accordance with the Pharmacy Manual. Reconstituted INZ-701 will be administered via SC injection into the abdomen (within approximately 5 cm of the navel), posterior or lateral aspect of upper arm, or anterior aspect of upper thigh or buttocks, at approximately the same time of day on each dosing day, when possible. The dose should be administered once weekly, on the same day each week ± 2 days.

The INZ-701 dose to be administered will be determined by the study participant's age and weight as outlined in Section 3.3.1.1.

All study participants will receive their first dose of INZ-701 in-clinic (on Day 1) under medical supervision. Participants may be administered their second, third, and fourth doses (on Days 8, 15, and 22, respectively) offsite (eg, in the home setting) by a qualified home healthcare professional with explicit approval of the Investigator. All participants will return to the clinic for the Day 29 visit and dosing.

After the fifth dose (on Day 29), participants may transition to self-administration of INZ-701 or offsite administration by a caregiver/delegated healthcare provider as determined by the Investigator; the details of post-dose monitoring are provided in Section 5.2.1. The Investigator will ensure the participants and/or their caregiver(s)/healthcare provider(s) have successfully completed training on dose preparation, administration, and post-dose monitoring. A sufficient supply of INZ-701 and associated supplies, including but not limited to needles, syringes and sharp containers will be dispensed to support dosing until the next in-clinic visit.

For all participants who transition to offsite administration in this study, the site staff will contact the participant and/or their caregiver(s)/delegated healthcare provider(s) weekly for the first 4 weeks to assess safety and dosing compliance. Thereafter, the Investigator will determine the

frequency of contact based on compliance, wellbeing of the study participant, clinical judgment, and in accordance with institutional and local guidelines.

Offsite administration of INZ-701 may be stopped and/or reinitiated at any time during the study as needed.

7.1.3. Missed Doses of INZ-701

If a dose of INZ-701 is not administered as planned, ie, once weekly, on the same day each week ±2 days, the study participant must receive their next dose of INZ-701 on the subsequent dosing day. For any single period of interruption in dosing lasting <2 weeks, the participant may resume dosing at the Investigator's discretion. For any repeat multiple-interruptions or interruption ≥2 weeks, the Investigator must consult with the Sponsor prior to resuming dosing.

7.1.4. INZ-701 Accountability

The Investigator or designee will maintain accountability records for all INZ-701 received, dispensed, returned, and/or lost/damaged during the study. This record must be kept current and made available to the Study Monitor. For doses administered in the clinic, the site staff will record the date, time, injection volume, and injection site for each dose administered.

For doses administered offsite, the study participant and/or their caregiver(s)/delegated healthcare provider(s) will be instructed to document the date, time, injection volume, and injection site for each dose administered. If a study participant discontinues INZ-701, the study participant and/or their caregiver(s)/delegated healthcare provider(s) will return unused vials to the site for a final compliance assessment and drug accountability.

7.1.5. Dose Administration Compliance

The Investigator, or designee, will assess study participant compliance with the prescribed dosing regimen throughout the study and document the findings in the study participant's source records. Reasons for any noncompliance will be documented. 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.

8. PROCEDURES AND ASSESSMENTS

A description of assessments to be performed at each visit is provided below. The timing of assessments to be performed at each visit is provided in Table 1.

8.1. Blood Collection Volumes

The total volume of blood to be collected will be determined by the participant's weight and/or age as specified in the Laboratory Manual. Ultimately, the Investigator will determine the maximum volume of blood that may be collected in accordance with the protocol, based on the allowable limits for the study participant's weight and/or age per institutional requirements and/or local guidelines.

If necessary, the Investigator may conduct blood sampling over multiple days for visits with an allowable ± window. For visits that do not have an allowable window, the Investigator will consult with the Sponsor to determine the sampling schedule.

Adult participants (≥18 years) must fast (refrain from eating or drinking other than water) and refrain from exercising for a minimum of 6 hours before the collection of pre-dose study samples. Pediatric participants must fast and refrain from exercise, only if feasible. If maximum allowed blood volume (per local guidance) is reached, the Investigator will prioritize blood sampling as follows: clinical safety samples (including ADA), PPi, PK, and ENPP1 activity. Samples not collected due to blood volume limitations will not be reported as protocol deviations.

8.2. Signing of Informed Consent

Before any Screening assessments or study procedures are conducted, the study participant or caregiver(s) must sign an Informed Consent Form (ICF) and provide written authorization for the release and use of medical records to verify eligibility (Section 12.4). Additionally, study participants who are minors (<18 years old) will provide their assent in accordance with local regulations. Study participants must be dosed within 30 days from the start of Screening (day of consent/assent).

8.3. Screening

Following written informed consent and applicable assent, study participants will undergo Screening assessments for evaluation for eligibility according to the inclusion and exclusion criteria (Sections 6.1 and 6.2, respectively) and to determine Baseline (pre-dose on Day 1) as indicated in the Schedule of Events (Table 1). The Screening Period will last up to 30 days. Screening assessments to determine eligibility may be completed over several days and should be conducted in a manner and order to minimize participant burden. Screening assessments must be completed after informed consent is obtained (Section 8.2).

Any assessments performed within 30 days of Day 1 as part of an existing Inozyme clinical study in which the participant is currently receiving INZ-701 may be used for Screening and do not need to be repeated. Screening may occur on the participant's last visit of the previous INZ-701 study. Screening and Day 1 assessments may occur on the same day (Day 1) if all screening assessments are completed, and all eligibility criteria are confirmed prior to dosing.

A unique identification (ID) number will be assigned to each study participant at the time of Screening.

If a study participant does not meet any of the eligibility criteria, Screening will stop and the reason for screen failure will be documented in the study participant's source records and in the clinical database.

The following assessments will be performed during Screening:

- Plasma PPi concentrations: Will be assessed to determine Baseline.
- COVID-19 test: A negative test is required within 5 days prior to Study Day 1 as a safety criterion in accordance with country-specific requirements and/or local institutional policy. Study participants who meet all other eligibility criteria and test

positive for COVID-19 may defer Study Day 1 until they test negative and must receive their first dose within the 30-day Screening Period.

- Pregnancy test: A negative serum pregnancy test result is required at Screening to determine eligibility of WOCBP; a urine test will also be performed pre-dose at Day 1. Study participants who test positive will be able to rescreen once they are no longer pregnant or breastfeeding.
- Medical history, disease history, demographics, and prior medications: Will be collected at Screening including disease history, clinical and genetic diagnosis, medications taken within the past 60 days, all active conditions and any past condition considered to be relevant to ENPP1 or ABCC6 Deficiency by the Investigator. Disease history will include previous history of GACI and PXE-like manifestations. Available family history will be noted, including any available previous mutation analysis results from relevant family members with appropriate inheritance patterns. Demographic information, including age, date of birth, sex, ethnicity, and race, will be collected as permitted by local regulations.
- Safety assessments: Will include weight and height measurements, physical examination, vital signs, clinical laboratory evaluations (serum chemistry and hematology), and urinalysis (if feasible). Monitoring of AEs and concomitant medications will start after the ICF is signed.

8.4. Plasma PPi Concentrations

Plasma PPi concentrations is a secondary endpoint. Details of the analysis of this endpoint are provided in Section 10.4.

Blood samples for PPi measurement will be collected pre-dose in the morning at the time points indicated in the Schedule of Events (Table 1). Refer to see Section 8.1 for blood collection volume limits and fasting requirements. Study participants may not begin dosing with INZ-701 or leave the clinic until it is confirmed that the PPi samples have been successfully processed. Samples will be collected, processed, and shipped as outlined in the Laboratory Manual and analyzed using a validated assay at a central laboratory in accordance with applicable policies and procedures.

8.5. Pharmacokinetic Evaluation

INZ-701 PK and ENPP1 activity will be assessed as secondary endpoints in this study. Blood samples will be collected according to the Schedule of Events (Table 1).

Samples for PK will be collected, processed, and shipped as outlined in the Laboratory Manual. PK samples will be taken pre-dose (see Section 8.1 for blood collection volume limits and fasting requirements). Samples will be analyzed for INZ-701 concentration and ENPP1 activity to generate concentration-time profiles; bioanalyses will be performed at a central laboratory using validated assays. Details of the estimation of PK parameters are described in Section 10.5.

8.6. Safety Evaluations

The long-term safety assessment of INZ-701 is the primary endpoint of this study. Adverse events are one of the outcome measures to assess safety and tolerability. Any changes in vital signs, weight, physical examination, and abnormal clinical laboratory parameters considered clinically significant by the Investigator will be reported as an AE.

Definitions of AEs and instructions for AE monitoring and reporting are provided in Section 9. The assessments to measure the remaining safety endpoints are described below and will be conducted according to the time points indicated in Table 1. All safety analyses are described in Section 10.6.

8.6.1. 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

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

Any clinically significant abnormality identified during the physical examination conducted at Screening will be recorded as a pre-existing condition (ie, part of medical history). Any changes in the physical examination that are considered clinically significant by the Investigator will be reported as an AE.

8.6.2. 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), oxygen saturation, and temperature (°C).

Vital signs will be measured after the study participant has been at rest ≥5 minutes. Respiratory rate will be measured over at least 15 seconds and adjusted per minute. Body temperature can be measured using the most appropriate method for the age of the study participant using calibrated equipment.

Vital signs will be collected pre-dose (within 1 hour of dosing) and at 1 hour and 2 hours post-dose (± 15 mins) for the first 3 doses. On Days 15, 22, and 29, vital signs will be collected prior to INZ-701 administration. Thereafter, vital signs will be collected pre-dose at the in-clinic

visits that occur every 6 months. For the Day 8, 15, and 22 visits conducted offsite (eg, in the home setting), vital signs will be collected by a qualified home healthcare professional.

8.6.3. Weight Measurements

The study participant's weight (in kilograms) will be obtained at each indicated visit and will be measured using a calibrated scale. The weight obtained at Day 1 will be used to calculate the initial dose of INZ-701 (in mg) to be administered on a mg/kg or flat-dose basis (as per Section 3.3.1.1) and the weight measured at any subsequent in-clinic visit as specified in Table 1 will be used to calculate the dose to be administered until the next weight measurement is obtained.

8.6.4. Clinical Safety Laboratory Evaluations

See Appendix A for details on specific routine serum chemistry, hematology, and urinalysis evaluations, as well as blood samples for hypersensitivity analysis as applicable. Safety laboratory tests will be performed at a central laboratory, if feasible, or otherwise at the local laboratory. All laboratories that provide safety data must be College of American Pathologists/Clinical Laboratory Improvement Amendments (CAP/CLIA) certified.

Routine blood chemistry panels including liver function tests, kidney function tests, a hematology panel including complete blood count with differential, and routine urinalysis, if feasible, will be conducted to assess safety throughout the study. Urine will be collected as clinically feasible for urinalysis dipstick, as well as phosphate, creatinine, and calcium assessment.

Additional laboratory analytes may be requested by the Sponsor, including any performed at the Investigator's discretion, if clinically indicated.

8.6.5. 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 WOCPB must agree to use 1 highly effective contraceptive method and fertile males must agree to use condoms per study eligibility requirements (Appendix B).

For WOCBP, pregnancy tests will be performed as indicated in Table 1. A serum test will be performed at Screening and urine at all other indicated visits. If a urine test is positive or inconclusive, a serum test will be performed. Urine pregnancy tests will be conducted monthly and discussed at the monthly site phone call.

8.6.6. 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, when an appropriate assay is available. Samples may be used to assess and further establish assays for specificity confirmation (ie, titer) and neutralizing antibodies.

For participants with ENPP1 Deficiency who have not had a blood sample for CRIM collected during a previous study with INZ-701, peripheral blood mononuclear cells (PBMCs) isolated

from a blood sample will be collected any time during the Screening Period or prior to dosing on Day 1 and stored until a validated assay is available to assess the presence of CRIM, such as endogenous ENPP1. All participants rolling over from Study INZ701-101 will have a blood sample for CRIM collected. If Day 1 has already occurred prior to the approval of this amendment, CRIM will be collected as soon as possible at the next study visit.

Immunogenicity will be assessed pre-dose at all indicated time points in Table 1. See Appendix A for immunogenicity evaluations. Immunogenicity and neutralizing antibodies samples will be collected, processed, and shipped as outlined in the Laboratory Manual; assessments will be performed at a central laboratory.

In the event of systemic hypersensitivity reactions, including anaphylaxis, per Investigator's discretion and/or upon Sponsor request, blood samples will be collected for the assessment of IgE and IgG antibodies and levels of acute phase reactants, serum tryptase, histamine, and complement activation (C3, C4). Additional samples may be obtained if clinically indicated per Investigator's discretion and/or upon Sponsor request (eg, in cases of suspected hypersensitivity reaction). See Appendix A for details on the hypersensitivity evaluations. Samples will be analyzed centrally, if feasible, or else at the local laboratory.

8.6.7. Prior and Concomitant Medications or Therapies

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 within 60 days prior to Study Day 1.

Use of concomitant medications will be assessed throughout the study and 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.

Non-drug therapies (eg, hearing aids, mobility aids) and medical/surgical procedures will be recorded.

8.7. Biological Sample Storage and Retention

As allowed by local regulation and with the study participant(s)'/caregiver(s)' consent, any unused biological samples (ie, serum, plasma, and urine) remaining after the completion of study assessments may be stored and used by the Sponsor outside of the context of this study for future research on ENPP1 Deficiency, ABCC6 Deficiency, or related deficiencies and development of therapies to treat these conditions. Samples will be retained at minimum until INZ-701 marketing authorization is granted, unless the study participant(s)/caregiver(s) withdraw consent to store the samples.

9. ADVERSE EVENTS

9.1. Definitions

9.1.1. Medical Dictionary for Regulatory Activities

Medical Dictionary for Regulatory Activities (MedDRA) provides a single standardized international medical terminology which can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use. As a result, MedDRA is designed for use in the registration, documentation and safety monitoring of medicinal products through all phases of the development cycle (ie, from clinical trials to post-marketing surveillance). Furthermore, MedDRA supports ICH electronic communication within the ICH's Electronic Common Technical Document (eCTD) and the E2B Individual Case Safety Report.

The adoption of a dedicated single standardized terminology offers a number of clear advantages for regulators, industry and other stakeholders including healthcare professionals, patients and research organizations:

- Removal of the need to convert data from one terminology to another preventing the loss and/or distortion of data and allowing savings in resources;
- Improvements in the ease, quality and timeliness of data available for effective analysis, exchange and decision making;
- Consistency of the terminology throughout the different stages of the development of a medicinal product allowing effective cross-references and analysis of data;
- Facilitation of the electronic exchange of data relating to medicinal products.

In the light of these advantages, ICH is continuously pursuing the development and maintenance of MedDRA for improving the effectiveness and transparency of medical product regulation which in turn contributes to the global protection of public health. MedDRA is periodically updated and the most up-to-date version will be used.

9.1.2. Adverse Event

An AE is any untoward medical occurrence (eg, sign, symptom, illness, disease, injury, including clinically significant abnormal laboratory findings) in a study participant administered any amount of INZ-701 or other protocol-imposed intervention regardless of attribution after signing of the informed consent. Treatment-emergent AEs (TEAEs) are defined as any AE that newly appears (if clinically significant) or a pre-existing condition that changes in nature, severity, or frequency, following initiation of INZ-701 in the ADAPT Study (INZ701-304) (ie, Study Day 1). Any ongoing AE from a previous INZ-701 study (that started before signing informed consent) will be recorded as part of medical history.

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.

The term "disease progression" should not be used to describe an AE, but rather a specific AE term should be used.

9.1.3. Serious Adverse Event

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

- Death
- Life-threatening
  Note: Life-threatening refers to an event that places the study participant 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
  - Emergency room visits that do not result in hospital admission
  - Preplanned or elective procedures
  - Protocol procedures
- An important medical event that, based on appropriate medical judgment, may jeopardize the study participant and may require medical or surgical intervention to prevent one of the outcomes listed above (eg, anaphylaxis)

9.2. Adverse Event Reporting

Safety reporting periods for this study are defined in Section 9.2.1.

All AEs, which include SAEs and adverse events of special interest (AESIs; as defined in Section 9.2.5), whether or not related to INZ-701, must be fully and completely documented. The Investigator may be asked to provide additional follow-up information.

If a study participant is withdrawn from study treatment and/or the study because of an AE, it must be recorded. The study participant should be followed and treated by the Investigator until the AE has resolved, stabilized, or a new chronic Baseline has been established.

9.2.1. Adverse Event Reporting Periods

Safety reporting periods for this study are defined in Table 4.

Table 4: Safety Reporting Periods

Event Type	Reporting Period [a]	Additional Requirements
Screening Period AEs / SAEs	From date of informed consent through the start of dosing (Study Day 1)	Report as AE/SAE only if related to study procedures during Screening/Baseline assessments
Treatment-emergent AEs / SAEs / AESIs	From date of first dose of INZ-701 through 30 days after last dose on study	Not applicable

AE=adverse event; AESI=adverse event of special interest; SAE=serious adverse event.
a All unresolved AEs (which include SAEs and AESIs) should be followed until the events are resolved or have stabilized, the study participant is lost to follow-up, or it has been determined that the INZ-701 is not the cause of the AE/SAE.

9.2.2. Expedited Reporting Requirements

It is the responsibility of the Investigator to report SAEs and AESIs (as defined in Section 9.2.5) that occur during the reporting period (Table 4) 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 using the study-specific form and associated documents, whether initial or follow-up, by electronic mail.

For all SAEs and AESIs Email: Inozyme Pharmacovigilance Inbox at [redacted]

Investigators should not delay the reporting of a suspected SAE or AESI 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 E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), the Sponsor will notify regulatory authorities (eg, by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the Sponsor that an adverse drug reaction qualifies, followed by as complete a report as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

The Sponsor or Sponsor's designee will notify all sites of suspected unexpected serious adverse reactions (SUSARs) and other safety concerns as required by regulatory agencies, Investigators, and ethics committees in compliance with all reporting requirements as per local regulations and 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 study participants 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 will instruct each study participant to report to the Investigator and/or to Sponsor directly, any subsequent SAEs that the study participant's personal physician(s) believes may be related to previous use of INZ-701 or protocol-imposed intervention.

All SAEs and AESIs 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 study participant 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.

9.2.3. Eliciting Adverse Events

Care will be taken not to introduce bias when obtaining AEs (including SAEs and AESIs) information. The Investigator will seek information on all AEs. At each visit the Investigator will ask the study participants/caregiver(s) 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.

9.2.4. Recording and Assessment of Adverse Events

The Investigator or qualified designee responsible for the care of the study participant 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, Doctor of Medicine, Doctor of Osteopathic Medicine, physician's assistant, nurse practitioner, Doctor of Dental Surgery).

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 AESI) until the events are resolved or have stabilized, the study participant is lost to follow-up, or it has been

determined that the INZ-701 is not the cause of the AE/SAE/AESI. Resolution of AEs, SAEs and AESIs (with dates) should be documented in the study participant'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 SMP.

9.2.4.1. Injection Site Reactions

Signs and symptoms of injection site reactions (ISRs) include swelling, erythema, induration, pruritus, pain, and other relevant signs and symptoms adjacent to the site of injection. If an ISR is identified by the Investigator as a component of a hypersensitivity reaction, the signs and symptoms of the ISR will be recorded in the database as components of the hypersensitivity reaction (Section 9.2.5).

9.2.5. 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 9.2.2. The list of AESIs will be updated based on emerging data and will be reviewed for addition to the reference safety information. Any change to the reference safety information will be communicated to the sites by the Sponsor or their designee.

9.2.6. 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 Investigators will use their judgment to determine the severity of each particular AE/SAE by following the grading criteria specified in CTCAE version 5.0 (NCI 2017) as applicable for that specific AE/SAE and as applicable for the patient population in this clinical study (eg, pediatrics). If the specific AE/SAE is not found in the CTCAE version 5.0 document, or if the CTCAE reference ranges are not appropriate for the pediatric population based on clinical significance and level of intervention needed, the Investigator will follow the general guidelines (principles) for AE/SAE severity grading, as stated in the introductory section of the CTCAE version 5.0 document and excerpted from that document below in Table 5.

Table 5: Adverse Event Severity Grading Scale

Grade	Description	
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	
2	Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental 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 will always be reported as SAEs**
5	Death related to AE	

a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b Self-care ADL refers 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 for Adverse Events; SAE=serious adverse event.
Source: CTCAE v5 (NCI 2017)

9.2.7. Causality Assessment

The Investigator will determine the causality/relationship of each AE as described in Table 6 and will record it on the source documents and AE electronic case report form (eCRF).

Table 6: 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 INZ-701, ie, there are no facts, evidence, or arguments to suggest a causal relationship to INZ-701
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.

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 study participant 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.

9.3. Adverse Events – Special Circumstances

9.3.1. Persistent or Recurrent Adverse Events

A persistent AE is one that continues, without resolution, between study participant 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.

9.3.2. 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).

9.3.3. Physical Examination Findings

Prior to Study Day 1, any clinically significant abnormality should be recorded as a pre-existing condition (ie, part of medical history). After Study Day 1, 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.

9.3.4. Abnormal Laboratory Results

A clinical laboratory abnormality will 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 laboratory result from tests performed after Study Day 1 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.

9.3.5. 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 study participant 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 study participant'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.

9.3.6. Pregnancy

Study participants who become pregnant during the study must be withdrawn from INZ-701 treatment 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 participants and/or female partners of male participants 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, is considered by the Sponsor as medically significant and will be classified as an SAE. Refer to Section 9.2.2 for SAE reporting guidelines.

The Investigator must make every reasonable effort to follow the participant through resolution of the pregnancy (delivery or termination). In the event of pregnancy in the partner of a participant, the Investigator should make every reasonable attempt to obtain the partner's consent

for release of protected health information and to follow the pregnancy to term, in accordance with local guidelines.

Pregnancies, should they occur, will be captured from the date of the first dose of INZ-701 (ie, Study Day 1) up to 30 days after the last dose (ie, EOS visit).

9.3.7. 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".

9.4. Urgent Safety Measures

The Sponsor is required to follow global regulations, including European Union (EU) regulations, which state that the appropriate regulatory bodies, including ethics committees, be notified according to their respective regulations of any new event resulting in the Sponsor and Investigator taking urgent safety measures to protect study participants 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

10. STATISTICAL METHODS

A Statistical Analysis Plan (SAP), providing details about specific planned analyses, will be prepared and approved by the Sponsor. The final analysis will be based on all study participant data collected through the end of the study. Data analyses will be provided for all study participants combined wherever appropriate.

Descriptive statistics including means, medians, standard deviations, and interquartile ranges will be calculated for continuous variables, and categorical data will be summarized using frequency counts and percentages. Descriptive statistics will be employed for analysis of the safety data. The PK and PPi data will be evaluated by standard methods. There will be no hypothesis testing.

10.1. Study Conduct Analysis

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

10.2. Population Characteristics

Study participant demographics, disease, and Baseline characteristics will be listed and summarized using appropriate descriptive statistics for all participants.

10.3. Study Populations

The following populations will be analyzed:

- Safety analysis set: includes all enrolled study participants receiving at least a partial dose of INZ-701.
- Pharmacokinetic analysis set (PKAS): is a subset of the safety analysis set including study participants with evaluable INZ-701 PK data.

10.4. Efficacy Analyses

Efficacy analysis is a secondary endpoint and will be performed on the mean change from Baseline in plasma PPi concentrations over time. Measurements of plasma PPi concentration will be analyzed using one-way repeated measures analysis of variance (ANOVA) to evaluate the overall treatment effect across all time points. Mauchly's test will be used to test the underlying assumption of sphericity (5 occasions, viz., Weeks 8, 13, 26, 39, and 52), treatment-by-time interaction, and within-participant errors. The specific model will have fixed effects for [redacted] An [redacted] will be used to model the within-participant correlation structure. The primary result will be the treatment effect estimated at 12 months.

10.4.1. Missing Data

10.4.1.1. Missing Outcome Data

Repeatedly measured data, defined as outcome data, will be addressed using likelihood-based statistical models that allow inclusion of all enrolled participants having at least one post-baseline measure in the analysis of the secondary outcome.

Sensitivity analyses to assess the robustness of the primary analysis result to missing data, will be conducted on the secondary endpoint. These analyses may include but are not limited to:

- Last Observation Carried Forward (LOCF): The last non-missing post-baseline observation will be carried forward in the corresponding endpoint for evaluation. If no post-baseline observation is available, the Baseline observation will be used for evaluation. If no Baseline is available, the LOCF approach will not be performed.
- Multiple Imputation: Multiple imputation using a Markov Chain Monte Carlo approach by 100 times.

10.5. Pharmacokinetic Analyses

Pharmacokinetic analysis will be performed on the PKAS, and PK parameters of INZ-701 will be summarized by dose with descriptive statistics.

INZ-701 concentration data will be used to provide rough PK parameter estimates for each individual if feasible. Trough serum concentration (C_{trough}) will be estimated by noncompartmental analysis. Other PK parameters may be calculated if feasible.

10.6. Safety Analyses

Safety evaluations will include AE and SAE reporting (including AESI), vital signs (temperature, respiratory rate, oxygen saturation, blood pressure, and heart rate), physical examination, body weight and height/length, clinical laboratory parameters (hematology, serum chemistry, and urinalysis), concomitant medication reporting, and immunogenicity. Safety data will be listed and summarized by dose and visit with descriptive statistics.

The safety endpoint will be evaluated by examining incidence and type of TEAEs, including clinically significant changes from Baseline through the EOS visit in clinical laboratory parameters, physical examination results, and vital signs measurements that result in TEAEs.

Treatment-emergent AEs as defined in Section 9.1.2 will be summarized using frequency counts and percentages. Treatment-emergent AEs will also be summarized by NCI-CTCAE version 5 grade and relationship to INZ-701. In addition, all SAEs, deaths, and AEs leading to INZ-701 discontinuation will be summarized and listed separately.

10.7. Extent of Exposure

The extent of study treatment will be assessed, including duration on treatment and treatment compliance, and summary statistics will be presented for the Safety analysis set.

10.8. Timing of Analysis

Available safety data will be evaluated throughout the study.

The Sponsor may conduct one or more interim analyses. A final analysis will be conducted when INZ-701 becomes commercially available or the Sponsor discontinues development of INZ-701.

10.9. Determination of Sample Size

Sample size will be determined by the number of study participants who choose to continue receiving INZ-701 after completing the protocol-required safety and PK/PD and/or efficacy period(s) of a previous INZ-701 clinical study. Up to 200 participants are planned to be enrolled in this study.

11. DATA RECORDING, RETENTION, AND MONITORING

11.1. Source and Records

Source documents are the originals of any document, image, or video used by the Investigator that support verification of the existence of the study participant(s) and substantiates the integrity of the data collected during the study. The Investigator will permit representatives of the Sponsor, its designees and regulatory bodies to have direct access to the source documents to verify the data reported in the eCRFs and to collect and analyze the data.

11.2. Case Report Form

The Investigator, or designee, is responsible for entering study data into an electronic data capture (EDC) system provided by the Sponsor. 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. The Investigator is responsible for the accuracy of the data entered into the eCRFs and approving the data and completed eCRF via electronic signature. A copy of the completed eCRFs, saved to disk in .pdf format, will be sent to the Investigator at the completion of the study. Data not recorded on the eCRFs will be provided via other methods such as electronic laboratory and imaging data transfer.

11.3. 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. A file for each study participant must be maintained at the study site which includes the signed ICF and the source documentation related to that study participant. 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 25 years or as per local requirements. The 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.

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

11.4. Monitoring

Monitoring will be conducted in accordance with ICH E6 (R2) GCP, the monitoring plan and applicable standard operating procedures (SOPs). Monitoring will be performed on site or virtually in accordance with applicable SOPs. The frequency and method of monitoring will be

determined by factors such as the study design, enrollment rate at the site, and frequency of study participant(s) visits.

The Study Monitor is responsible for reviewing the source records and eCRFs 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 Study Monitor must have access to study participant medical records and other study-related records needed to verify the entries on the eCRFs. The Investigator must agree to cooperate with the Study Monitor to ensure any problems detected in the course of these monitoring visits are resolved.

11.5. Quality Assurance

In accordance with ICH E6 (R2) GCP, the Sponsor's (or its designee's), regulatory agencies or ethics committees may conduct quality assurance audits at any time during or following completion of the study to evaluate the study conduct and compliance with the protocol, ICH E6 (R2) GCP, and applicable regulatory requirements. The Investigator must agree to allow auditors/inspectors direct access to all study-related documents and facilities where the study was conducted and to allocate time to discuss observations and findings.

11.6. Study Participant Confidentiality

The Sponsor and the site will collect and process personal data of study participants strictly in accordance with applicable regional, federal, state, and local data protection laws and the conditions set forth in the ICF signed. 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 genetic data), and data regarding ethnicity. Study participants will not be identified by name on any study documents collected by the Sponsor.

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 study participant data arising from the study 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 ICF is signed and dated, the study participant 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 labeled only with the study participant's code and not any direct identifiers such as the study participant's name, medical record number, and home address. However, the study participant'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 study participant. 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 study participant'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 study participant's direct identifiers (including the participant'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 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 study participant's name) in the study participant's medical records will be kept strictly confidential. Sponsor access to study participant's data shall be performed in such a way that no participant could be identified by such data.

The ICF obtained from the study participant 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 study participant'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 study participant's ICF (to the extent such consent is required), the study participant's coded personal data may be used outside of the context of this study for future research on ENPP1 Deficiency, 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.

12. ETHICAL AND LEGAL ASPECTS

12.1. 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 ethics committee or regulatory agency-required procedures, whichever represents the greater protection for the individual.

12.2. 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. Study participants will not be screened until the required regulatory approvals have been obtained in the appropriate jurisdiction.

12.3. Ethics Committee Approval

The Investigator at the site is responsible for obtaining local or central ethics committee approval for the final protocol, the Sponsor-approved ICF, and any materials used to recruit study participants. Written approval of these documents must be obtained from the ethics committee before any study participant is enrolled at a site.

The Investigator is also responsible for:

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

12.4. Informed Consent

The Sponsor or its designee will review the ICF, and any amended ICFs, and any written information to be provided to study participants and/or their caregiver(s) that is prepared by the Investigator prior to submission to the ethics committee for approval. A copy of the ethics committee approved ICF, its amendments, and affiliated approvals will be forwarded to the Sponsor.

The ICF documents the study-specific information the Investigator provides to the study participant's caregiver(s) and their 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 study participant's caregiver(s) must personally sign and date the ICF before any study-related procedures are performed. In addition, the study participant's assent will be obtained in accordance with local regulations. The original and any amended, signed and dated ICF(s) and assent forms, if

applicable, must be retained in the study participant's file at the study site and copies given to the study participant's caregiver(s).

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

12.5. Compensation for Adverse Effects on Health

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

12.6. 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 ethics committees and regulatory agencies must be informed of all amendments and give approval for any amendments likely to affect the safety of the study participants or the conduct of the study. The Investigator must send a copy of the approval letter from the ethics committee to the Sponsor and/or designee.

The Sponsor reserves the right to suspend or terminate the study (Section 5.3.1). The Investigator will notify the ethics committee in writing of the study's completion or early termination and send a copy of the notification to the Sponsor and/or designee.

12.7. 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.

12.8. Publication Policy

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

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APPENDIX A. CLINICAL LABORATORY ANALYTES

<table>
<tr>
<td rowspan="3">Serum Chemistry:
• Alkaline phosphatase
• Alanine aminotransferase
• Aspartate aminotransferase
• Bilirubin – total and direct
• Gamma glutamyl transferase
• Blood urea nitrogen
• Lactate dehydrogenase
• Creatinine
• Glucose
• Amylase
• Lipase
• Calcium
• Phosphate
• Protein – total
• Albumin
• Sodium
• Potassium
• Chloride
• Bicarbonate or available alternate method (CO_2 or alkaline reserve)
• Creatine kinase</td>
<td>Hematology:
• Hemoglobin
• Hematocrit
• Erythrocytes
• Erythrocyte indices (MCV, MCH, MCHC, RDW)
• White blood cells
• Neutrophils (absolute, %)
• Lymphocytes (absolute, %)
• Monocytes (absolute, %)
• Eosinophils (absolute, %)
• Basophils (absolute, %)
• Platelet count</td>
</tr>
<tr>
<td>Urinalysis [a]:
• Urinalysis, routine dipstick
• Urine phosphate, creatinine, and calcium</td>
</tr>
<tr>
<td>Pregnancy Test [b]:
Serum or urine</td>
</tr>
<tr>
<td rowspan="2">Safety:
• Serum intact parathyroid hormone</td>
</tr>
<tr>
<td>PK/PD/Immunogenicity:
• Plasma PPi
• Serum ENPP1 specific activity
• Serum anti-drug antibodies and neutralizing antibodies, and CRIM
• Serum INZ-701 concentration</td>
<td>Hypersensitivity Samples (if applicable) [c]:
• IgE
• IgG
• Serum tryptase
• Histamine
• Complement activation (C3, C4)
• Acute inflammatory markers: C-reactive protein</td>
</tr>
</table>

Note: Consult the Laboratory Manual for sample collection, processing, and shipping instructions, as applicable. The Investigator will determine the maximum volume of blood that may be collected in accordance with the protocol and the allowable limits for the study participant's weight and/or age per institutional requirements and/or guidelines. If necessary, the Investigator may conduct blood sampling over multiple days for visits with an allowable ± window. For visits that do not have an allowable window, the Investigator will consult with the Sponsor to determine the sampling schedule.

a. Urine will be collected if clinically feasible.
b. Serum or urine pregnancy test will be performed for all female participants of childbearing potential.
c. Tests for hypersensitivity reaction, including anaphylaxis, will be performed per Investigator's discretion and/or upon Sponsor request.

CRIM=cross-reactive immunologic material; ENPP1=ectonucleotide pyrophosphatase/phosphodiesterase 1; Ig=immunoglobulin; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PPi=inorganic pyrophosphate; RDW=red cell distribution width.

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[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2,3]
- Sexual abstinence[4]

Definitions:

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

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

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

[1] Hormonal contraception may be susceptible to interaction with investigational medicinal product, which may reduce the efficacy of the contraception method.

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] 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.

[4] 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 participant.

Source: CTCG 2024