PROPEL: Prospective Observational Registry for ENPP1 Deficiency and Early-Onset ABCC6 Deficiency

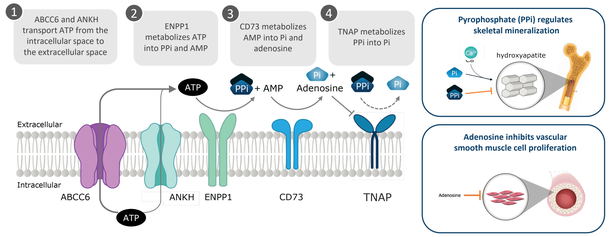
Lothar Seefried[1], David Weber[2], Liz Molloy[3], Christine O'Brien[3], Ruth du Moulin[4], Kurt Gunter[4], M. Zulf Mughal[5]

1. University Hospital at the Julius-Maximilians University, Würzburg, Germany, 2. Children's Hospital of Philadelphia, Philadelphia, USA, 3. GACI Global, Argyle, USA, 4. Inozyme Pharma, Boston, USA, 5. Al Jalila Children's Specialty Hospital, Dubai, UAE

INTRODUCTION

INORGANIC PYROPHOSPHATE (PPi)-ADENOSINE PATHWAY

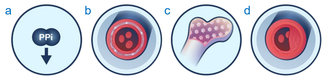
- PPi is a critical regulator of skeletal mineralization and thus overall bone health.
- Physiologic bone mineralization requires a balance of inorganic phosphate (Pi) and PPi.
- PPi directly antagonizes formation / propagation of calcium-phosphate (hydroxyapatite) crystals.
- AMP and adenosine are important regulators of vascular smooth muscle cell proliferation.



- There are several key proteins involved in the metabolic pathway that produces PPi and adenosine.
- Defects in these enzymes and transporters can lead to abnormal bone mineralization and/or pathologic calcification.

ENPP1 DEFICIENCY

- ENPP1 Deficiency is a rare genetic disorder caused by inactivating mutations in the *ENPP1* (ectonucleotide pyrophosphatase/phosphodiesterase 1) gene (biallelic prevalence 1:64,000).
- ENPP1 Deficiency is associated with low levels of plasma PPi (a) and AMP leading to ectopic (especially vascular) calcification (b) (Generalized Arterial Calcification of Infancy [GACI] Type 1, pathologic skeletal mineralization (c) (Autosomal Recessive Hypophosphatemic Rickets Type 2 [ARHR2]) and occlusive neo-intimal proliferation (d).



- **Infants with ENPP1 Deficiency have 50% mortality in the first 6 months of life.**
- Survivors typically develop cardiovascular complications (e), hearing loss (f), hypophosphatemic rickets with bone deformities (g), joint and ligament calcifications (h), impaired growth (i), pain and immobility leading to poor quality of life and function.

ABCC6 DEFICIENCY (EARLY-ONSET)

- Similarly, ABCC6 Deficiency, caused by biallelic mutations in the *ABCC6* (ATP-binding cassette transporter protein subfamily C member 6) gene, is a disorder of pathological mineralization and intimal proliferation manifesting in a spectrum of phenotypes, likely resulting from low PPi (a) and adenosine due to reduced ATP, the substrate for ENPP1 (prevalence 1:25,000 to 1:50,000).
- The early-onset form (GACI Type 2) resembles ENPP1 Deficiency. Infants (10% mortality by 6 months) present with widespread arterial calcification (b), severe cardiovascular (c) and/or neurovascular complications (d), which can also present in children along with retinal disease (e).

- **In both cases, early genetic testing is key for appropriate treatment decision-making**

STUDY RATIONALE AND OBJECTIVES

- Much of the current knowledge of ENPP1 and ABCC6 Deficiency is based on case reports or small retrospective studies.
- No targeted therapy exists for these diseases.
- This global, multicenter, prospective observational registry (PROPEL, NCT06302439), co-sponsored with GACI Global, is designed to systematically collect clinical information to inform a comprehensive understanding of the burden of illness and progressive nature of these diseases.

KEY OBJECTIVES:

- Collect retrospective data on medical and disease history.
- Collect prospective data from standard of care visits, at least annually.
- Capture impact to patients through annual patient-reported outcome (PRO) questionnaires.
- Offer and collect optional blood draw for PPi analysis.

KEY ELIGIBILITY CRITERIA

KEY INCLUSION CRITERIA:

A confirmed prenatal or postnatal molecular genetic diagnosis* of ENPP1 Deficiency with biallelic mutations (ie, homozygous or compound heterozygous).

OR

Monoallelic ENPP1 mutation* in combination with one of the specific clinical symptoms associated with disease (please refer to protocol for the complete list).

OR

A confirmed prenatal or postnatal molecular genetic diagnosis* of early-onset** ABCC6 Deficiency with biallelic mutations.

*All genetic diagnoses must be performed by a College of American Pathologists/Clinical Laboratory Improvement Amendments (CAP/CLIA) certified laboratory or regional equivalent.
**Early-onset ABCC6 Deficiency defined as diagnosis of GACI-2 before 18 years of age for participants of any enrollment age.

KEY EXCLUSION CRITERIA:

- Patients who are currently participating in an INZ-701 interventional clinical study, apart from expanded access programs and long-term safety follow-up studies.
  - Note: Participants in interventional studies can be included in the registry once their involvement in the treatment period of the clinical study has been completed.

STUDY DURATION AND GOVERNANCE

STUDY DURATION:

- Minimum of 10 years, and for as long as participants consent.

STUDY GOVERNANCE AND DATA OUTPUTS:

- The main objective of the study is to improve the understanding of ENPP1 Deficiency and ABCC6 Deficiency among the medical, scientific and patient community.
- To that end, data will be available to all researchers with scientifically impactful questions once the **Steering Committee** determines the database has enough data for meaningful analyses.
- The Steering Committee will form a **Data Transparency Committee** whose main objective will be to evaluate data requests and provide tables/listings to researchers whose requests are approved.
- All approved requests carry the obligation of publishing the findings in a peer-reviewed setting.

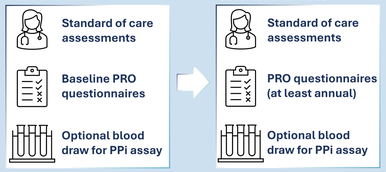
Steering Committee	Data Transparency Committee	Data Outputs
• Main governing body • Responsible for study oversight • Representation from the sponsor (Inozyme), patient advocacy group (GACI Global) and investigators	• Responsible for review of data access requests • Ensures that the provided tables / listings are used appropriately • Ensures data privacy	• Specific tables / listings pertinent to the scientific questions being asked • Patient health information will never be shared, and individual patient data will not be provided

PROCEDURES AND ASSESSMENTS

RETROSPECTIVE DATA COLLECTION:

- Data collected from existing sources:
  - Medical charts
  - Electronic medical records
  - Notes
- → **Minimal burden on the participant**

PROSPECTIVE DATA COLLECTION:



- Observational visits conducted at the standard of care frequency
- Data entry conducted at least:
  - Twice a year for ages 0-1
  - Annually for ages >1

ASSESSING BURDEN OF DISEASE – PATIENT-REPORTED OUTCOMES (PROs):

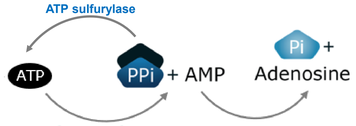
- The PRO scales were chosen based on the current understanding of the functional impact of ENPP1 or ABCC6 Deficiency on patients and use direct patient (or parent/caregiver proxy as applicable) input.
- The participant (or parent/caregiver proxy) can complete PROs at the time of scheduled assessments.

Assessment	Adults	Children 5 to <18*
PROMIS	Cognitive Function, Fatigue, Pain Intensity, Pain Interference, Physical Function	Cognitive Function, Fatigue, Pain Intensity, Pain Interference, Mobility
QoL	• Short Form (SF)-36 • Patient Global Impression of Status/Severity (PGI-S)	• Short Form (SF)-10 • Caregiver Global Impression of Status/Severity (CaGI-S)

*Parent Proxy questionnaires will be used for ages 5 to <18; PROMIS, Patient Reported Outcomes Measurement Information Systems.

OPTIONAL BLOOD DRAW FOR PPi ASSAY:

- Both ENPP1 Deficiency and ABCC6 Deficiency are characterized by **low PPi levels.**
- The use of PPi as a diagnostic/prognostic marker in mineralization disorders depends on our ability to reliably measure and monitor changes in PPi levels.
  - Study in healthy volunteers demonstrated that measuring PPi after an overnight fast provides a consistent and reproducible measure.
- PROPEL study will utilize CLIA/COLA* validated method that has sensitivity across a wide range of PPi levels, **with particular focus on ability to measure low PPi levels**, characteristic of hypermineralization disorders.
- The assay utilizes ATP sulfurylase to convert filtered plasma PPi to ATP, which is detected utilizing luciferase/luciferin luminescence to produce light from newly formed ATP.

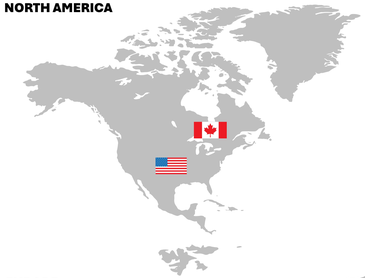


*CLIA, Clinical Laboratory Improvement Amendment; COLA, Commission on Office Laboratory Accreditation

CURRENT STATUS

The PROPEL study is active and open for enrollment.

NORTH AMERICA



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Clinicaltrials.gov NCT06302439

REFERENCES

- Zhou X, et al. Int J Biol Sci. 2012;8:778–790.
- Collins MT, et al. Nat Rev Endocrinol. 2022;19:473–491.
- Bourne LE, et al. J Endocrinol. 2021;248:R51–R65.
- Ralph D, et al. Am J Pathol. 2022;192:762–770.
- Szeri F, et al. J Bone Miner Res. 2022;37(5):1024–1031
- Dubey RK, et al. Hypertension. 2020;75:109–118
- Khursigara G, et al. Bone. 2023; 171:116750

AUTHOR DISCLOSURES

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