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# RARE PATIENTS
# RARE SOLUTIONS

Corporate Presentation

November 2024

**Ella**
Living with ENPP1 Deficiency

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The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements. For a discussion of risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the “Risk Factors” section in our most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission, as well as discussions of potential risks, uncertainties and other important factors, in the Company’s most recent filings with the Securities and Exchange Commission.

In addition, the forward-looking statements included in this presentation represent our views as of the date of this presentation. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements in the future, we specifically disclaim any obligation to do so. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.

# Inozyme is at the forefront of developing novel therapies for rare diseases that affect bone health and blood vessel function

**ENPP1 Deficiency, ABCC6 Deficiency and calciphylaxis are serious diseases affecting bone health and blood vessel function linked to dysregulation of the PPi-Adenosine Pathway with no approved therapies**

**Lead product candidate, INZ-701, demonstrated a rapid, significant, and sustained increase in PPi levels, preliminary evidence of efficacy, and a favorable safety profile across multiple clinical trials**

**Currently in pivotal trial for ENPP1 Deficiency; Completed Phase 2 trial for ABCC6 Deficiency and treatment period in Phase 1b trial in calciphylaxis program**

**Experienced team with a track record of success in rare disease**

**In a position of financial strength, with several expected upcoming milestones and a pipeline designed for long-term value creation**

- $131.6M expected to fund operations into Q4 2025 as of 9/30/24
- 64.24M common shares outstanding as of 10/29/24

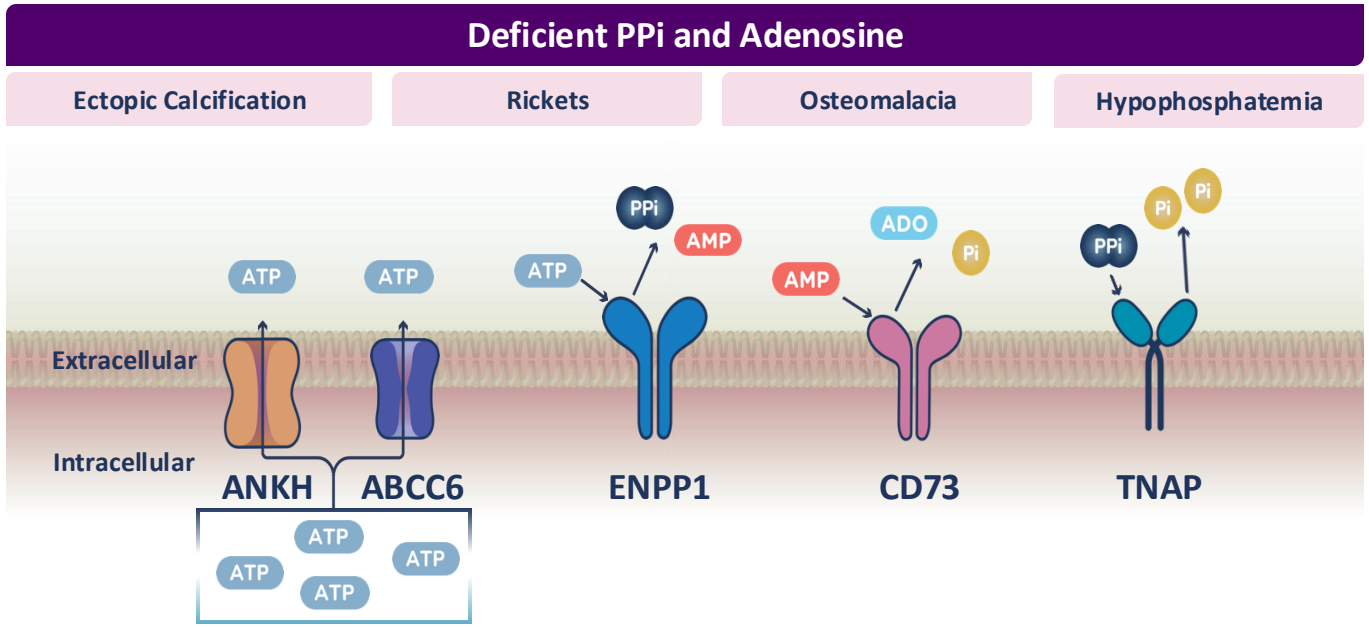
# INZ-701 is an ENPP1 ERT in development for ENPP1 Deficiency, ABCC6 Deficiency, and calciphylaxis

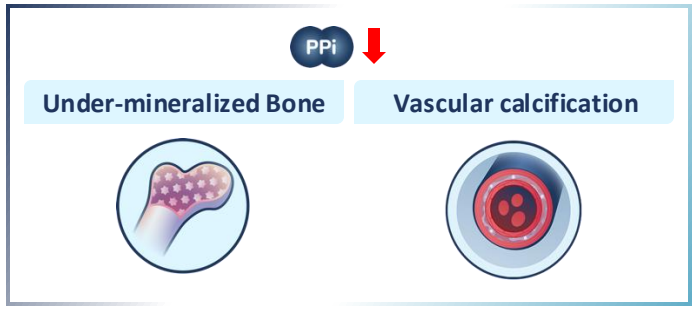
## INDICATIONS

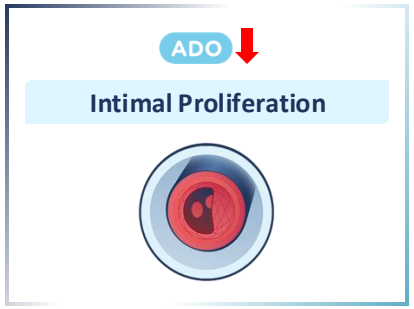
- ***ENPP1 Deficiency:*** *ENPP1 mutations reduce levels of PPi and adenosine*
- ***ABCC6 Deficiency:*** *ABCC6 mutations result in low levels of extracellular ATP, PPi and adenosine*
- ***Calciphylaxis:*** *Severe complication of end-stage renal disease marked by low levels of PPi*

## MOA

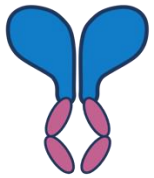
- ***INZ-701*** *is a Fc fusion protein containing the extracellular domain of ENPP1*
- ***ENPP1*** *catalyzes hydrolysis of ATP to AMP and PPi*
  - *PPi inhibits ectopic Ca-Pi crystal formation in blood vessels and soft tissue*
  - *PPi deficiency leads to hypophosphatemia, rickets, & osteomalacia*
  - *Adenosine deficiency leads to intimal proliferation and obstruction of blood vessels*



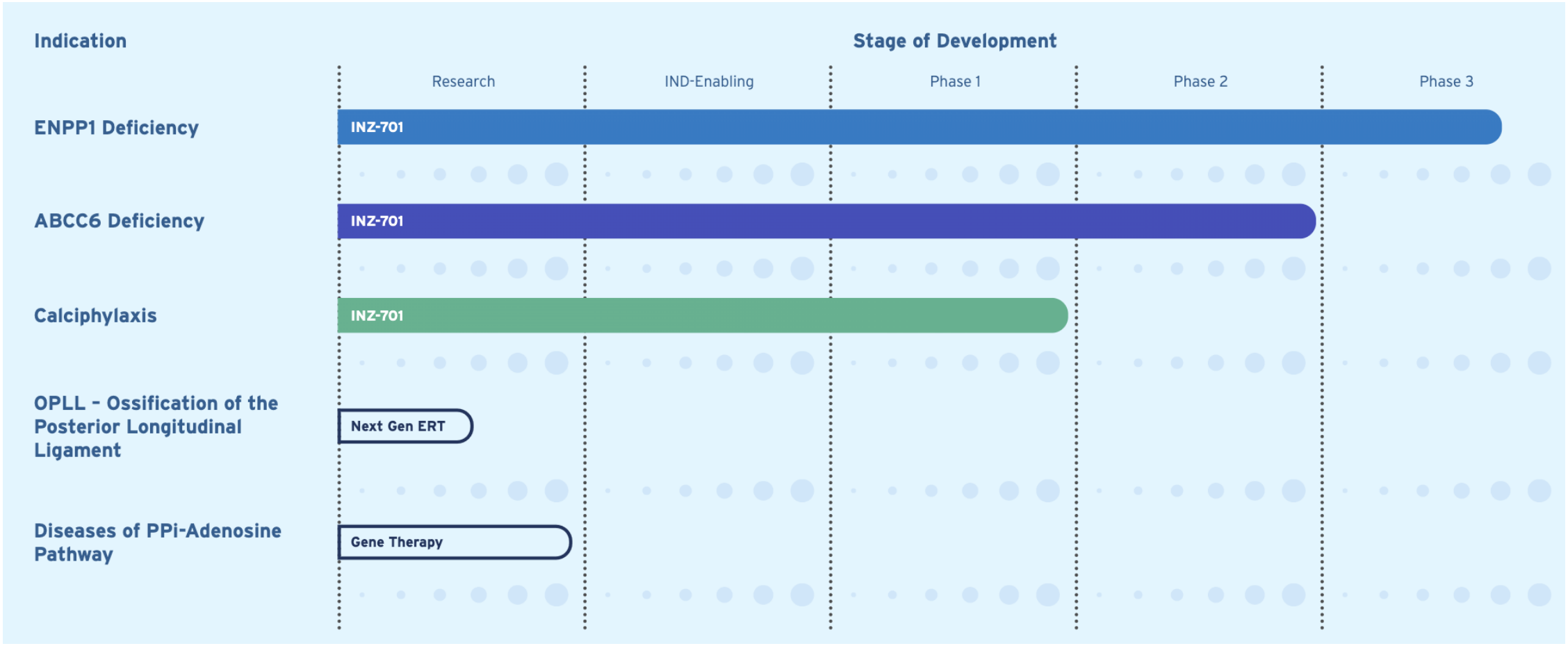




ENPP1
+
Fc fragment



INZ-701

# INZ-701 has the potential to be an impactful first-to-market therapy in multiple diseases




Inozyme retains worldwide, exclusive development and commercial rights to INZ-701

# Diseases linked to PPi-Adenosine Pathway present significant opportunities across major markets

**North America: ~20,900 Pts**

| | |
|---|---|
| ENPP1 | 2,800 |
| ABCC6 | 7,600 |
| Calciphylaxis | 10,500 |

**Brazil: ~8,500 Pts**

| | |
|---|---|
| ENPP1 | 1,600 |
| ABCC6 | 4,200 |
| Calciphylaxis | 2,700 |

**EU: ~21,000 Pts**

| | |
|---|---|
| ENPP1 | 4,100 |
| ABCC6 | 10,600 |
| Calciphylaxis | 6,300 |

**Japan: ~9,900 Pts**

| | |
|---|---|
| ENPP1 | 900 |
| ABCC6 | 2,500 |
| Calciphylaxis | 6,500 |

**Major Markets ~60,300 pts**

| | |
|---|---|
| ENPP1 | 9,400 |
| ABCC6 | 24,900 |
| Calciphylaxis | 26,000 |

**Note: Patients with monoallelic *ENPP1* mutations and OPLL patients with pathogenic *ENPP1* variants represent additional market opportunities**

Sources: Company estimates. Ferreira et al. Genet Med, 2021. Ferreira et al. Orphanet Journal of Rare Diseases, 2022. Nigwekar SU, et al. J Gen Intern Med. 2014; Nigwekar SU, et al. J Am Soc Nephrol. 2016. Chinnadurai, R., Huckle, A., Hegarty, J. et al. Calciphylaxis in end-stage kidney disease: outcome data from the United Kingdom Calciphylaxis Study. J Nephrol 34, 1537–1545 (2021). https://doi.org/10.1007/s40620-020-00908-9 USRDS Annual Data Report 2021. https://adr.usrds.org/2021/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities. Supplemented ERA-EDTA Registry data evaluated the frequency of dialysis, kidney transplantation, and comprehensive conservative management for patients with kidney failure in Europe - Kidney International (kidney-international.org) Prevalence of calciphylaxis estimated to be 2% of hemodialysis patients.

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# ENPP1 Deficiency

**Ella**
Living with ENPP1 Deficiency

# ENPP1 Deficiency is a lifelong, multisystem, rare genetic disease with high mortality and morbidity

**GACI/IIAC**
**0-1 Years (~1-2%)***

***50% mortality within 6 months of birth***

- Severe cardiovascular complications

**ARHR2 (Rickets)**
**1 to <13 years (~25-30%)***

***Impaired growth Orthopedic surgery***

- Skeletal defects: Rickets
- Cardiovascular complications
- Hearing loss

**ARHR2 (Osteomalacia)**
**13+ Years (~65-70%)***

***Bone & joint pathology***

- Skeletal defects: Osteomalacia
- Joint, tendon, and ligament complications
- Hearing loss

**Biallelic Genetic Prevalence[1]: 1:64,000**

| | | | |
|---|---|---|---|
| PATIENTS IN US/CANADA | ~ 2,800 | PATIENTS IN JAPAN | ~ 900 |
| PATIENTS IN EUROPE | ~ 4,100 | PATIENTS IN BRAZIL | ~ 1,600 |

Note: Estimates do not include symptomatic patients with monoallelic mutations

*Estimated percent of total prevalence., 1. Ferreira et al. Orphanet Journal of Rare Diseases, 2022. GACI: Generalized Arterial Calcification of Infancy, IIAC : Idiopathic Infantile Arterial Calcification, ARHR2: Autosomal Recessive Hypophosphatemic Rickets Type 2

# Completed Phase 1/2 trial of INZ-701 in adults with ENPP1 Deficiency successfully met all study objectives

## Safety

- **Favorable safety profile** was maintained
- Low/moderate, sometimes transient, ADA titers

## PK/PD

- **PK data** from cohort 4 **support once-weekly dosing**
- **PPi remained elevated** with long-term treatment

## Clinical

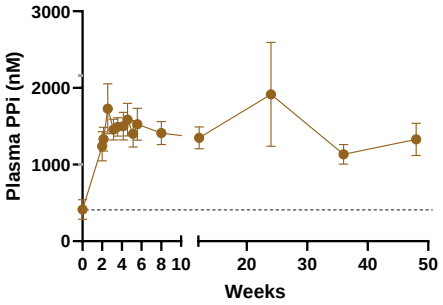
- Favorable response on **clinical outcomes** (PROs and 6MWT) was **maintained**
- Bone biomarker response consistent with restoring proper bone mineralization

# Significant increase in PPi levels were associated with improvement in phosphate and FGF-23 and supports MOA

## Pooled Cohorts 1-3: Baseline vs mean Week 2-48 PPi, FGF-23, and Pi levels (±SEM)

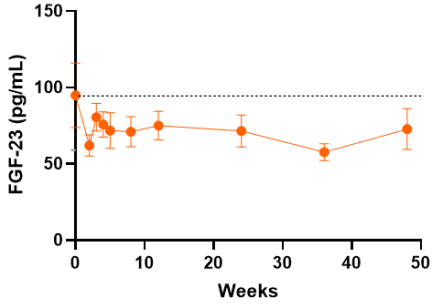
**Plasma PPi**

Ref range : 1002-2169nM



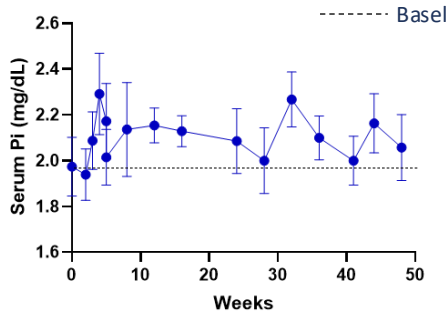

**Serum FGF-23**

Ref range : <59pg/mL



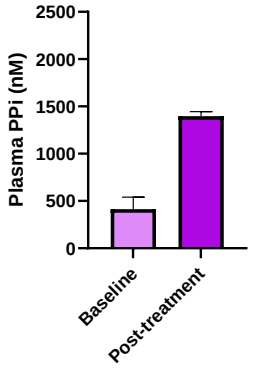

**Serum Pi**

Ref range : 2.5-4.5mg/dL

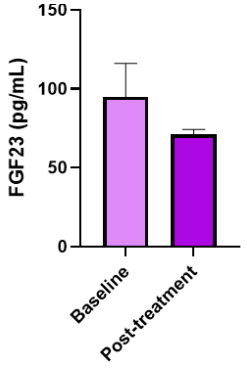



## Pooled Cohorts 1-3: Mean PPi, FGF-23 and Pi levels (±SEM)

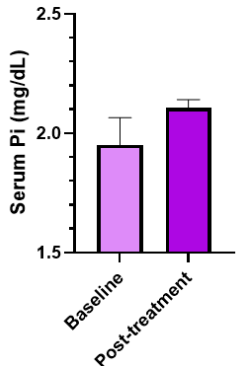
**Plasma PPi**




**Serum FGF-23**




**Serum Pi**




Note: Serum Pi increases observed in absence of phosphate and active vitamin D supplementation

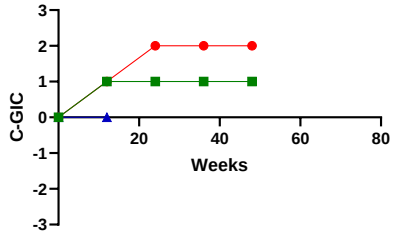
Data cut Jan 25 2024 ; Data presented as mean ± SEM

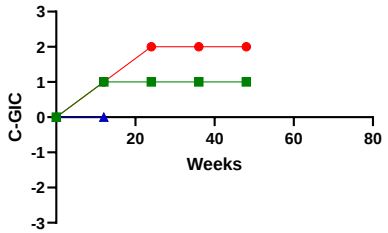
# Global Impression of Change Scale: Concordant improvement in C-GIC and P-GIC in all three dose cohorts

**Clinician's Global Impression**

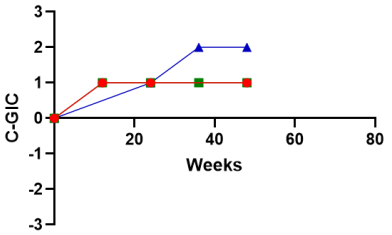
**Patient's Global Impression**

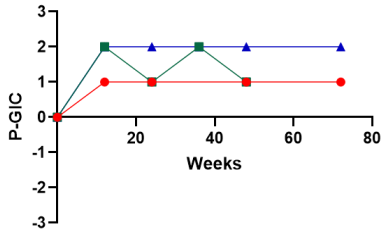
## Cohort 1 (0.2mg/kg) (n=3)



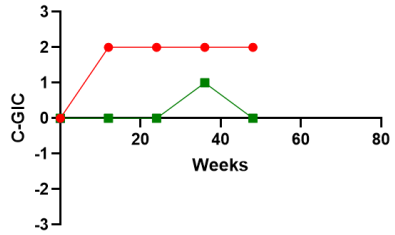



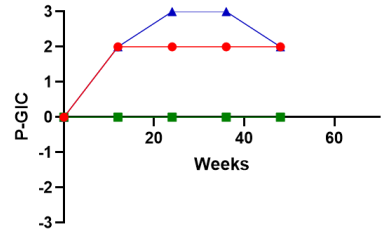

## Cohort 2 (0.6mg/kg) (n=3)




## Cohort 3 (1.8mg/kg) (n=3)*




| -3 | -2 | -1 | 0 | 1 | 2 | 3 |
|---|---|---|---|---|---|---|
| Very much worse | Much worse | Minimally worse | No Change | Minimally improved | Much improved | Very Much improved |

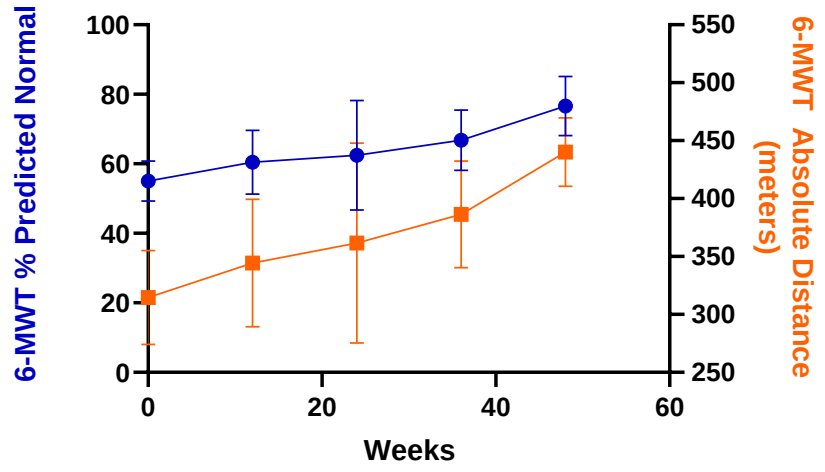
* n=2 for C-GIC

Data cut 25 Jan 24

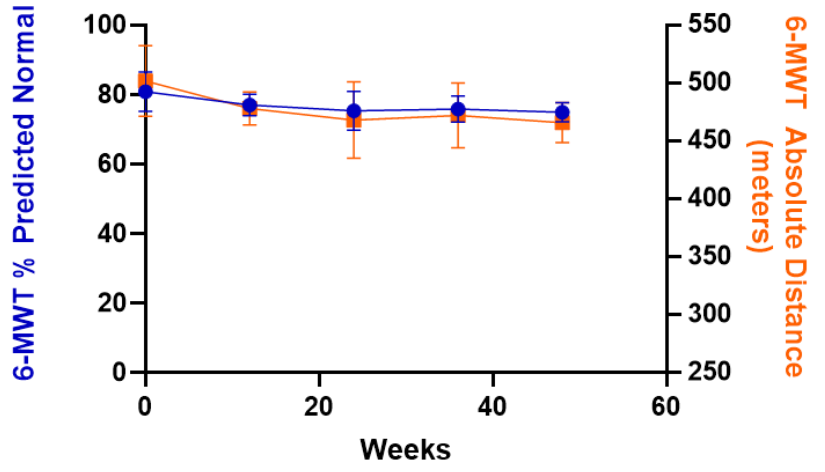
Colors represent individual patients in respective cohorts

# INZ-701 showed trend for improvement in 6-minute walk test (6-MWT)

**Patients with <70% predicted of healthy 6-MWT at baseline (n=5)**




**Patients with >70% predicted of healthy 6-MWT at baseline (n=4)**




- Greater improvement observed in patients with poor baseline 6-MWT
- Stable 6-MWT scores observed in patients with higher baseline values

Data cut Jan 25, 2024; Data presented as ± SEM

# ENPP1 Deficiency: Planned Path to Global Approval

Pediatric Trial in Pediatric ENPP1 Deficiency Ongoing

# ENERGY 3: Pivotal trial in pediatric patients with ENPP1 Deficiency (ARHR2)

## Patient recruitment underway – Topline data expected early 2026

**Population: Pediatric**

- Confirmed genetic diagnosis
- Radiographic evidence of skeletal abnormalities
- ≥1 year and <13 years
- Low plasma PPi

**Design: Randomized (2:1), Open Label**

| | Randomized Treatment Period | Open Label Extension Period |
|---|---|---|
| n = up to 33 | Randomization: INZ-701 Arm – 2.4 mg/kg weekly; Control Arm – Conventional Therapy; 52 weeks | All patients to receive INZ-701 beyond 52 weeks |

Multicenter, Multinational

**Endpoints**

**US**

- **Primary**: Change in plasma PPi from baseline over time
- **Secondary**: Trends in RGI-C score, RSS, Growth Z-score; PK

**EU**

- **Co-Primary**:
  - Change in plasma PPi from baseline over time
  - RGI-C score (with p<0.2)
- **Secondary**: RSS, Growth Z-score; PK

RGI-C: Radiographic Global Impression of Change, RSS: Rickets Severity Score, PK: Pharmacokinetic, ARHR2: Autosomal Recessive Hypophosphatemic Rickets Type 2, ClinicalTrials.gov: NCT06046820

# Planned path to global approval of INZ-701 in ENPP1 Deficiency

| | Endpoints |
|---|---|
| **ENERGY 1: Infant** (0-12 mos.)<br>Phase 1b<br>Single arm (n=8) | ***Safety*** *and* ***tolerability*** *as primary;* ***PPi*** *and* ***survival*** *as secondary* |
| **ENERGY 2: Infant** (0-12 mos.)<br>Pivotal<br>Single arm per agreed PIP**<br>(n=12) | ***PPi + survival*** *as co-primary* |
| **ENERGY 3: Pediatric**<br>**(**≥1-<13 yrs.)<br>Pivotal<br>Randomized – 2:1 (n=33) | ***PPi*** *as sole primary* (US) and co-primary with* ***RGI-C*** *(EU)* |

## Basis for Planned Marketing Applications

### 1st BLA/MAA

- Adult Phase 1/2 full data
- ENERGY-3 full data
- ENERGY-1 available data
- ENERGY-2 available data
  - Natural history control group; patients matched on covariates associated with mortality

### Additional filings

- Japan, Brazil, Middle East

RGI-C: Radiographic Global Impression of Change, BMC/BMD: Bone mineral content/density, BLA: Biologics license application, MAA: Marketing authorisation application

*Supported by trends in appropriate secondary endpoints
**Plan to conduct this trial ex-U.S.. Discussions are ongoing with FDA regarding design of this trial in the U.S.
***Subject to regulatory discussions and appropriate financial resources

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# ABCC6 Deficiency

**Sienna**
Living with ABCC6 Deficiency

# ABCC6 Deficiency is a multisystem, rare genetic disease: High morbidity and a continuum of effects across age groups

**GACI-2**
**0-1 Years**

***~10% mortality within 12 months of birth*** [1]

- Severe cardiovascular complications and pulmonary hypertension

**Pediatric**
**1 to <18 years**

***Multisystem vasculopathy and strokes*** [2]

- Progressive cardiovascular calcification/stenosis of major arteries
- Cerebrovascular calcification - including stroke
- Initial retinal calcification

**PXE**
**18+ Years**

***Blindness, cardiovascular disease and mobility impairment*** [3-7]

- Progressive arterial calcification
- Increased incidence of stroke and dementia
- Retinal calcification – Angioid streaks, atrophy
- Progressive calcification and fragmentation of elastic fibers

**Genetic Prevalence: 1:25,000 - 1:50,000** [8-9]

Sources: 1. Ferreira et al. JBMR 2021; 2. Grossi et al, Eur J Med Genet, 63 2020; 3. Shimada et al. Int.J.Mol.Sci. 2021; 4.Risseeuw et al. Retina, 2019; 5. Leftheriotis et al. J Vasc Surg, 2011; 6. Vanakker et al. Hum Mutat. 2008; 7. Van den Berg et al. Cerebrovasc Dis, 2000; 8. Internal, Unpublished Data; 9. Ferreira et al. Genet Med, 2021

# Completed Phase 1/2 trial of INZ-701 in adults with ABCC6 Deficiency successfully met all study objectives

## Safety

- INZ-701 demonstrated a **favorable safety profile**
- No serious or severe adverse events
- Low/moderate, sometimes transient, ADA titers

## PK/PD

- **Rapid** and **sustained increase in PPi** observed in highest dose cohort (1.8 mg/kg)

## Clinical

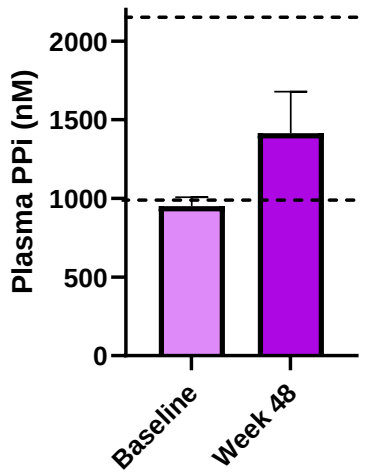
- **Positive changes** in multiple affected organ systems (cerebrovasculature and choroidal layer of eye) support **improvements in vascular health**
- Improvement in visual function (VFQ-25) and multiple PROs observed

VFQ-25: Visual Function Questionnaire; PRO: Patient Reported Outcomes; ADA: Anti-drug antibodies

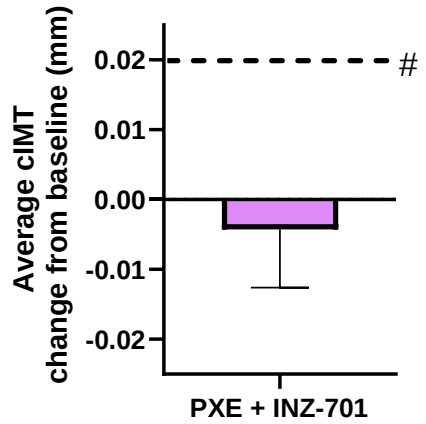
# INZ-701 showed benefit across multiple domains relevant for future pivotal trial

**Combined cohort 1-3 data comparing baseline to week 48**

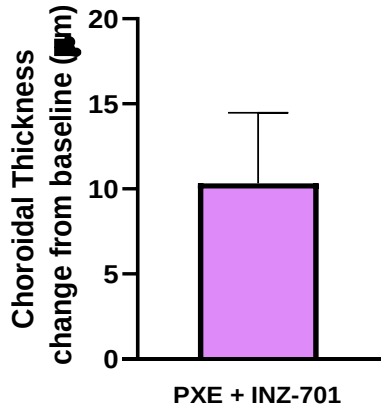
## PPi increased




## Carotid artery intima-media thickness decreased (cIMT)




## Choroidal thickness increased




Normal range

Mean annual cIMT change in TEMP study1

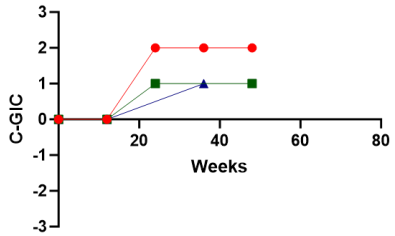
Data cut – 10 Jan 2024; Data presented as mean ± SEM Source: 1. Kranenburg et al, JACC, 2018

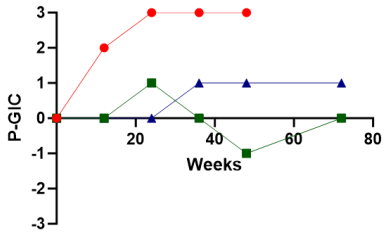
# Global Impression of Change Scale: Concordant improvement in C-GIC and P-GIC in all three dose cohorts

Clinician's Global Impression

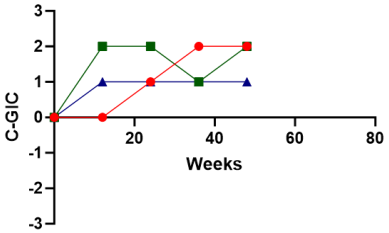
Patient's Global Impression

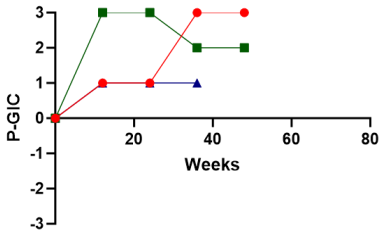
## Cohort 1 (0.2mg/kg) (n=3)



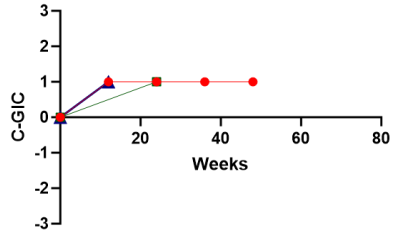



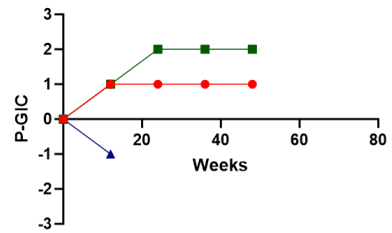

## Cohort 2 (0.6mg/kg) (n=3)




## Cohort 3 (1.8mg/kg) (n=3)




| -3 | -2 | -1 | 0 | 1 | 2 | 3 |
|---|---|---|---|---|---|---|
| Very much worse | Much worse | Minimally worse | No Change | Minimally improved | Much improved | Very Much improved |

Data cut – 10 Jan 2024

Colors represent individual patients in respective cohorts

# ABCC6 Deficiency: Planned Path to Global Approval

# Focused on pediatric population with ABCC6 Deficiency

## Unmet Need

- Retrospective natural history study (early-onset) and interventional study (adults) identified **risk of stroke** and **retinal disease** as consistent presentation in ABCC6 Deficiency

## Market

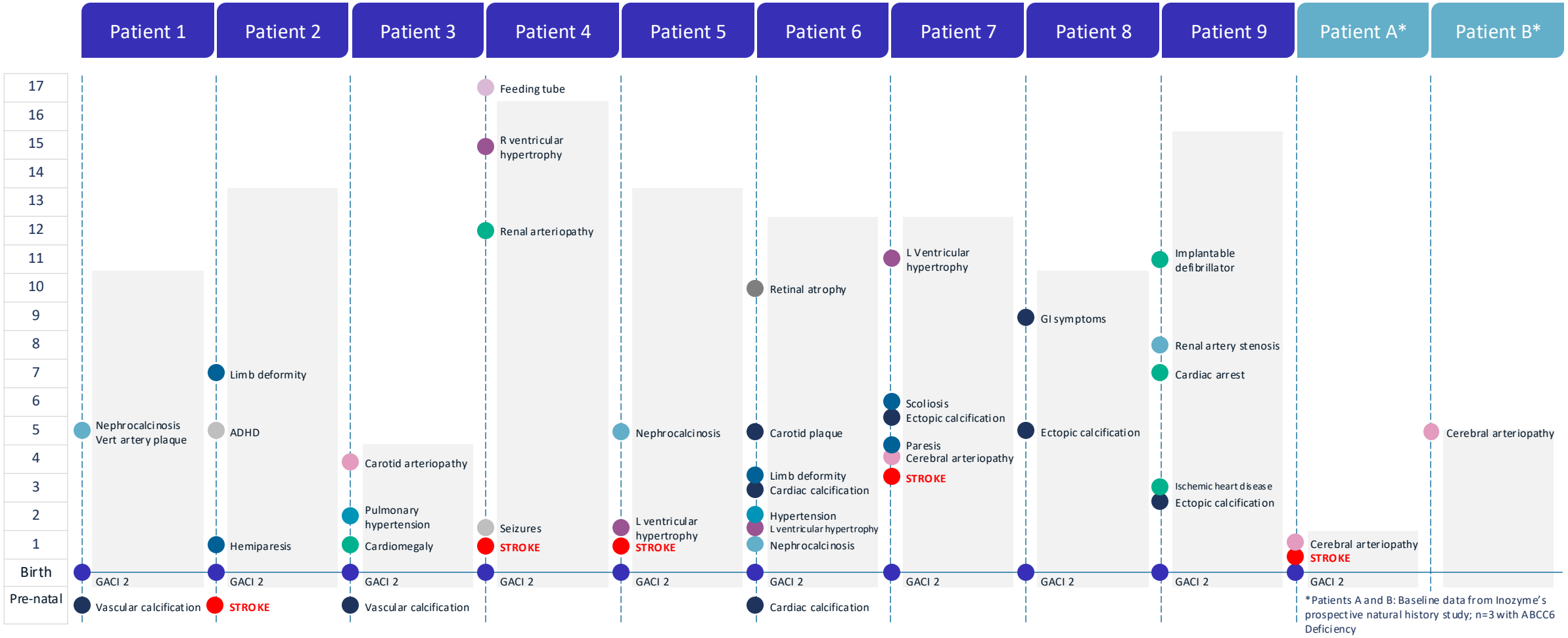
- Market research identified **substantial pediatric population** that represents the most important unmet need in ABCC6 Deficiency

## Regulatory

- Pivotal trial design planning in progress – potential for **approval** with primary and secondary endpoints selected based on serious clinical needs and disease pathology

VFQ-25: Visual Function Questionnaire; PRO: Patient Reported Outcomes; ADA: Anti-drug antibodies

# Retrospective Natural History Study: ABCC6 Deficiency patients had a heavy disease burden early in life




*Patients A and B: Baseline data from Inozyme's prospective natural history study; n=3 with ABCC6 Deficiency

Data cut – 10 Jan 2024

*Shaded area indicates age at time of informed consent*

# Planned roadmap for clinical development of INZ-701 in ABCC6 Deficiency

**ENERGY 1: Infant** (0-12 mos.)
Phase 1b
Single arm

**Pediatric** (0-<18 yrs.)*
Pivotal
Randomized, controlled

**Adult – PXE** (18+)
Phase 1/2
Single arm – MAD

### *Ongoing Study*

- ***Safety*** *and* ***tolerability*** *as primary*
- ***PPi*** *and* ***survival*** *as secondary*

### *Future Studies*

- *Primary and secondary endpoints selected based on* ***serious clinical needs*** *and* ***disease pathology*** *(e.g., death, stroke, myocardial infarction, cardiac hospitalization, retinal disease progression, arterial calcification score, cIMT changes)*

### *Completed Study*

- *Generally safe and well tolerated*
- *Consistently elevated PPi at highest dose*
- *Signals of clinical activity on vascular and ophthalmic for retinal endpoints*

## Basis for Planned Marketing Applications

**1st BLA/MAA**

- Adult Phase 1/2 full data
- ENERGY 1 available data
- Pediatric Pivotal trial data

**Additional filings**

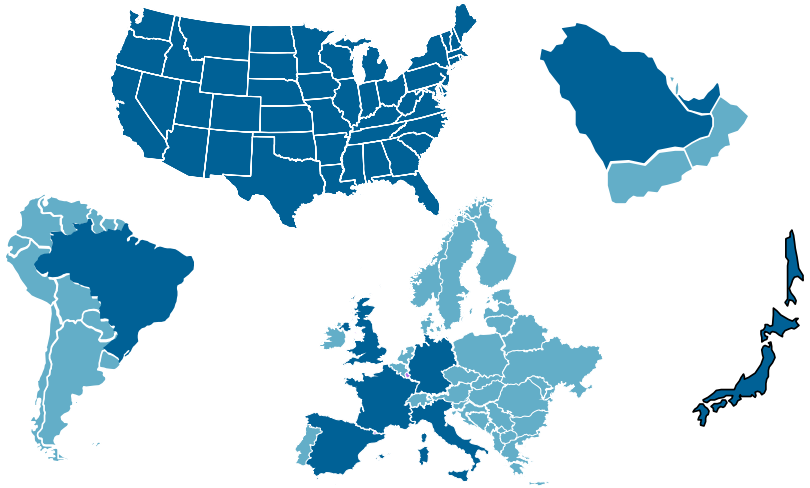
- Adult (18+) study (Supplemental BLA/MAA)
- Japan, Brazil, Middle East

*Subject to regulatory discussions and appropriate financial resources

# Building a Rare Disease Franchise

# Ongoing efforts to increase disease awareness, educate patient and medical communities, and improve access to genetic testing

## Growing Our Global Footprint



**Inozyme is currently conducting disease education in ~15 countries**

## Newborn Screening

**US – Rady Children's Hospital Network**
**UK – Genomics England**
Efforts ongoing to add to other panels across the globe

## Expanding HCP Audience

**Infant and Pediatric ENPP1**
- Fetal and pediatric cardiology
- Neonatology
- Pediatric endocrinology
- Maternal-fetal medicine
- Genetics

**Adult ENPP1**
- Endocrinology
- Nephrology
- Genetics
- Bone specialists

## Increasing Congress Attendance

NeoHeart – Cardiovascular Management of the Neonate
Society for Maternal-Fetal Medicine
PES Pediatric Endocrine Society
ASHG American Society of Human Genetics
ASBMR The American Society for Bone and Mineral Research
Human Growth Foundation
ECTS European Calcified Tissue Society
8th World Congress of Pediatric Cardiology and Cardiac Surgery

## Partnering to Remove Barriers to Diagnosis

GACI Global circulating hope
BeginNGS Newborn Genomic Sequencing to end the diagnostic odyssey
GENOMENON
ipm.ai Part of Real Chemistry
INVITAE
BlueDil int'l
Prevention Genetics
Genomics England
CENTOGENE
Rady Children's

# ENPP1 patient identification activities continue to find new patients and support clinical, medical, and pre-commercial tactics

**1100+** Global patients identified with **confirmed, known, or suspected bi-allelic ENPP1 Deficiency**

**330+**
**Confirmed Patients**

Clinical and genetic diagnoses

**300+**
**Known Patients***

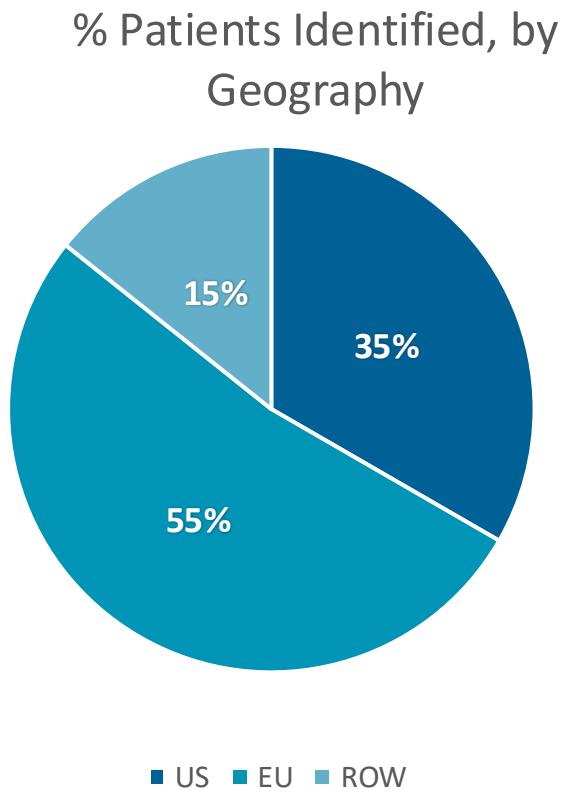
Clinical diagnosis

**440+**
**Suspected Pediatric Patients (US only)**

Identified using AI model of large US claims/EMR database

* Phenotypic findings of disease only

## Confirmed and Known Patients (n=630+)




**40%** of identified patients are between 0 ≤13 years of age

**250+** different physicians are managing identified patients

*Internal data as of 9/23/24; number of confirmed patients expected to increase with patient/physician education, initiation of clinical trials, and progress towards potential regulatory approval*

# ~1,300 likely U.S. pediatric ABCC6 Deficiency patients identified, representing ~70% of estimated genetic prevalence

## Pediatric ABCC6 Deficiency: U.S. Patient estimates

### Ischemic Stroke
**940 patients**

- *Ischemic stroke between ages 1-18*
- *Genetic panel ordered between ages 1 and <18* ***OR*** *mild neurological symptoms occurred prior to stroke*
- *PXE or a phosphorous disorder diagnosis code in all history*
- *Exclusion of differential diagnoses*

### Angioid Streaks
**264 patients**

- *Angioid streaks between ages 1 and <18*
- *Exclusion of differential diagnoses and eye injuries*

### Retinal Imaging/OCT
**60 patients**

- *Optical coherence tomography (OCT) between ages 1 and <18*
- *Genetic panel ordered* ***AND*** *mild neurological symptoms occurred between ages 1 and <18*
- *PXE or a phosphorous disorder diagnosis code in all history*
- *Exclusion of differential diagnoses*

### Cardiovascular Anomaly
**24 patients**

- *Cardiovascular anomaly* ***AND*** *arterial calcification between ages 1-and <18*
- *PXE or a phosphorous disorder diagnosis code in all history*
- *Exclusion of differential diagnoses*

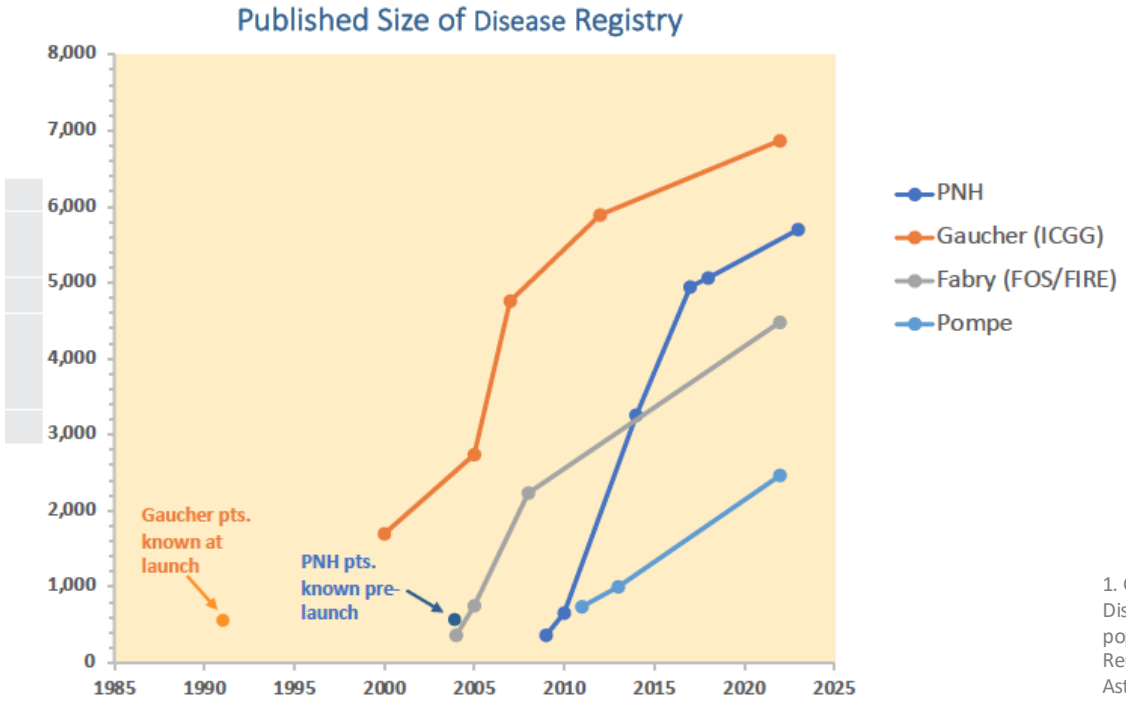
**Identified 1,288 likely U.S. pediatric patients with ABCC6 Deficiency**

Sources: IPM Longitudinal claims database An all-history (2009 – present) lookback period was utilized for clinical profiling Patients with 2+ claims for any one differential diagnosis (sickle cell disorders, Ehlers-Danlos syndrome, Paget's disease) were excluded. Based on 65% medical claims capture rate. No projection factor was used for claims coverage.

# Protein replacement therapies for monogenic rare diseases

***Proven high-value product category***

- High probability of success vs. other disease approaches
  - 88% approval for proteins entering the clinic vs. 19% for all drugs[1]
- History of strong growth in addressable patient numbers with improved diagnosis and awareness post-launch
- Orphan drug status and low payer burden support premium pricing
- Patient-centric commercial strategy linking awareness, diagnosis, and reimbursement has generated multiple high-value markets




| Product | Ann. Tx Cost | 2023 Revenue | US Population Size[2] |
|---|---|---|---|
| Cerezyme[3] | $221K-575K | $743M*[10] | 4,700 |
| Crysvita[4] | $364K | $1,330M** | 16,500 |
| Elaprase[5] | $496K | $610M[11] | 1,100 |
| Fabrazyme[6] | $340K | $1,071M#[10] | 8,250 |
| Myozyme[7] | >$300K | $846M^[10] | 8,250 |
| Strensiq[8] | >$800K | $1,152M[12] | 2,000 |
| Vimizim[9] | >$500K[6] | $701M[13] | 3,300 |

*Competitor Vpriv sales: $342M[11]
**Combined RARE and Kirin sales
#Competitor Replagal sales: $488M[11]
^Next gen (Nexviazyme) sales: $459M[10]

1. Gorzelany, J.A. and de Souza, M.P. (2013)*Sci. Trans. Med.* 5(178): 178fs10; 2. US pop. size based on following prevalence estimates: Gaucher Disease 1/70,000; XLH 1/20,000; Hunter Syndrome 1/150,000; Fabry Disease 1/40,000; Pompe: 1/40,000; HPP: 1/100,000; MPS IV: 1/200,000 and US pop. of 330M; 3. Farabakhshian 2022; 4. Retail cost of $14,071/30 mg; 35 kg pt; 5. WAC of $3,153/50 mg (Takeda US); 70 kg pt; 6. Drugs.com; 7. Reuters; 8. Retail cost $75/mg; 35 kg pt; 9. Retail cost $1505/5 mg, 22.5 kg pt; 10. Sanofi 2023 Annual Report; 11. Takeda 2024 Annual Report; 12. Astra Zeneca 2023 Annual Report; 13. Biomarin 2023 Annual Report

# Calciphylaxis

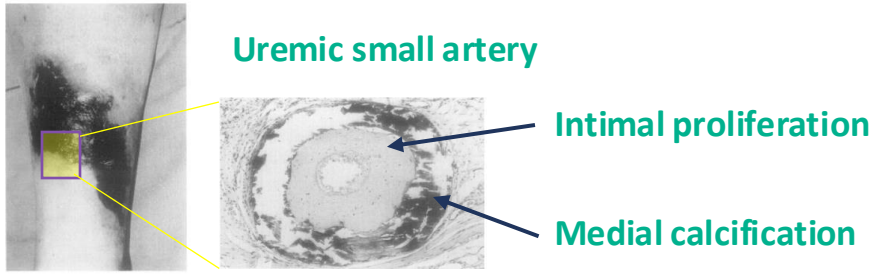
# Calciphylaxis: A severe complication of ESKD with high mortality and morbidity

**Calciphylaxis Incidence: 3.5 : 1,000 ESKD Patients[7]**

**Major Markets Estimate: 5,000 patients/year**

Primarily affects end stage kidney disease (ESKD) patients[2]

**Vascular calcification-mediated disease**

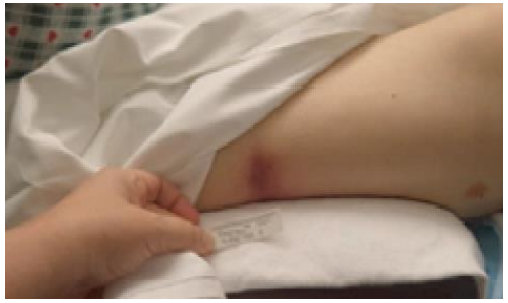



(Hafner et al, JAAD, 1995) (Hafner et al, JAAD, 1995)

Microvascular occlusion of skin arterioles caused by medial calcification, intimal proliferation, and thrombosis; Low PPi

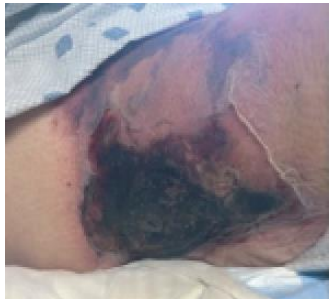
## Significant morbidity and mortality

Initial skin lesions typically present as extremely painful plaques and nodules, and progress to necrotic ulcers



Ghosh T, et al. Int J Dermatol. 2017

**2 months**



Ghosh T, et al. Int J Dermatol. 2017

- **>70%** require hospitalization for severe ulcerations[4]
- **~50%** of patients are bedridden or wheelchair-bound[4]

**~50% mortality**

**1 year after diagnosis[7]**

- Median survival time: 2.6 months[4]
- Sepsis most common cause of death[4-6]

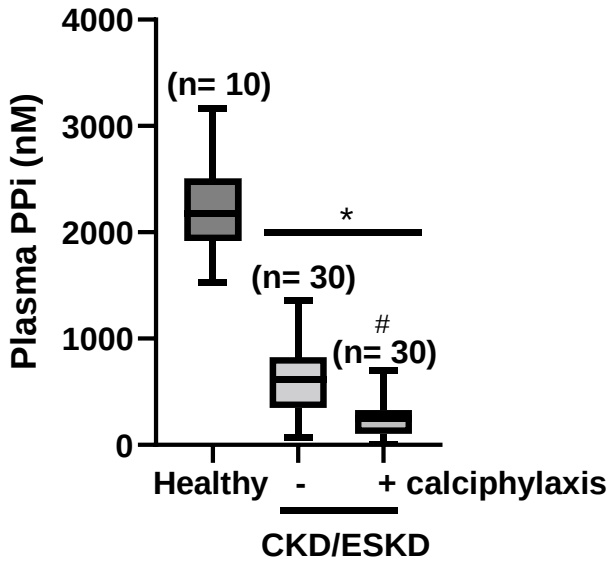
**No approved therapy**

Sources: 1. Nigwekar SU, et al. J Gen Intern Med. 2014; 2. Nigwekar SU, et al. J Am Soc Nephrol. 2016; 3. USRDS Annual Data Report 2021. https://adr.usrds.org/2021/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities ;4. Weenig RH, et al. J Am Acad Dermatol. 2007; 5. Nigwekar SU, et al. Clin J Am Soc Nephrol. 2008; 6. Bazari H, et al. N Engl J Med. 2007; 7. Nigwekar et al. NEJM 2018.

# Growing Evidence: Association of calciphylaxis with PPi deficiency

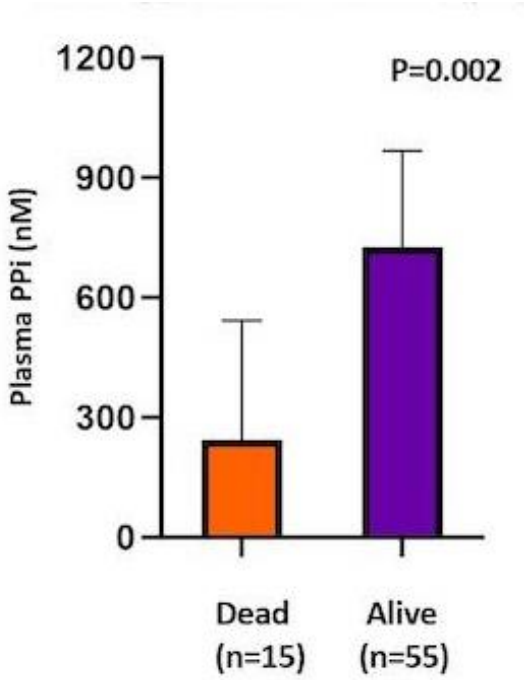
*Arteriolar calcification largely develops due to imbalance between calcification inhibitors and promoters*[1-3]

## PPi levels lower in calciphylaxis

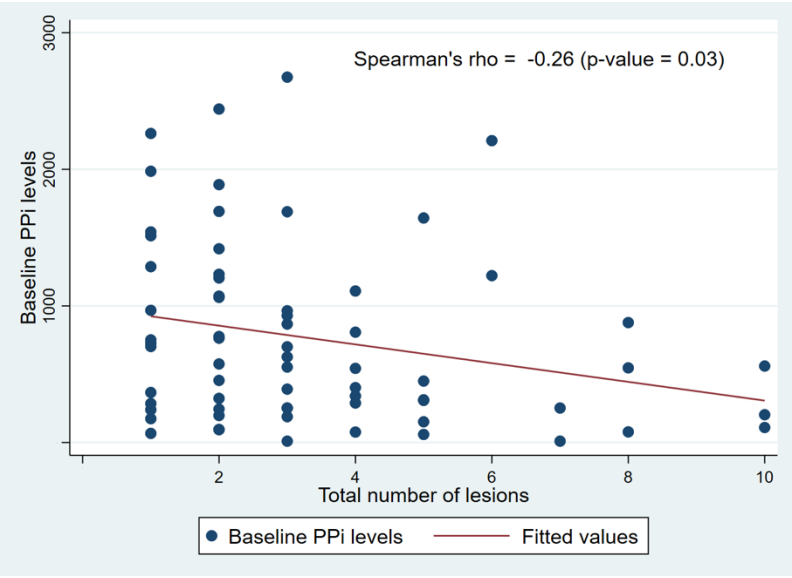



* p<0.0001 vs healthy
\# p=0.0002 vs non-calciphylaxis

## Low PPi levels predicted 6-week mortality




## Low PPi levels correlated with higher numbers of skin lesions

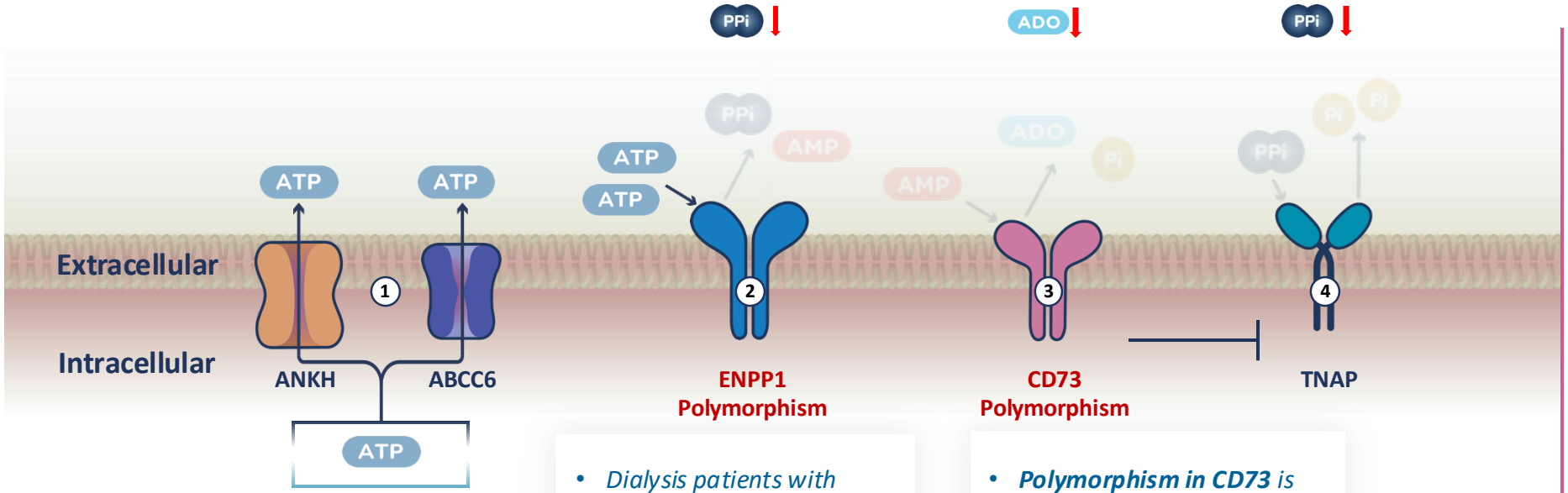



Data presented as median ± interquartile range

- ESKD patients had significantly lower PPi levels compared with healthy subjects[4]
- Calciphylaxis patients had significantly lower plasma PPi levels when compared with non-calciphylaxis ESKD patients[4]
- Published data showed correlation between PPi levels and severity of calcification

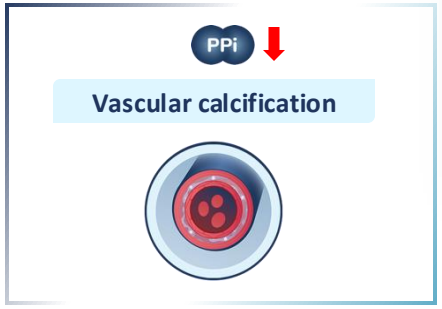
Sources: 1. Kramann R, et al. Nephrol Dial Transplant. 2013; 2. Moe SM, et al . Pediatr Nephrol. 2003; 3. Shroff R, et al. J Am Soc Nephrol. 2013; 4. Internal, Unpublished Data, ECTS 2022 Nigwekar et al; ESKD = End stage kidney disease, CKD = Chronic kidney disease

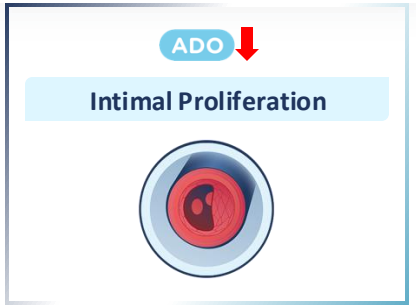
# Genetics strongly support link between PPi-Adenosine Pathway and calciphylaxis



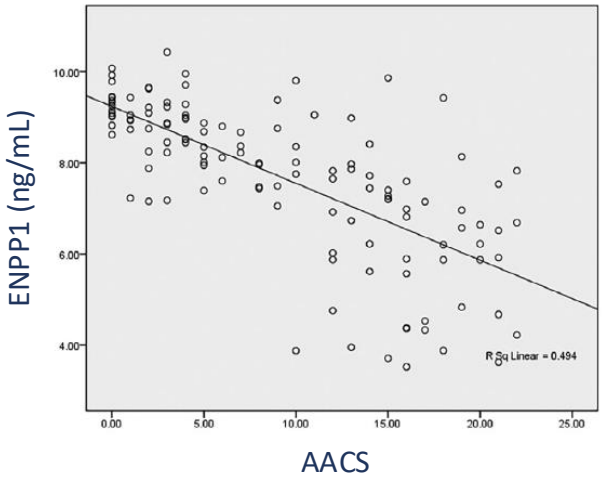

- *Dialysis patients with **ENPP1 K121Q polymorphism** had a significantly higher coronary calcium score and a higher aortic PWV when compared to matched controls*[1]

- ***Polymorphism in CD73** is associated with higher probability of calciphylaxis*[3]




**Relationship of abdominal aortic calcification severity to serum ENPP1 levels in ESKD**




1. Eller *et al*, NDT 20072; 2. Wu *et al*, Hemo Int 2021; 3. Rothe *et al*, PLOS one 2017; 4. Markello *et al*, Mol Genet Metab 2011; 5. Kato *et al*, PNAS 2012;

# SEAPORT 1: Phase 1 trial in patients with end-stage kidney disease (ESKD) receiving hemodialysis

**Study Population: Adults**

**Eligibility Criteria:**

- ≥18 to <70 years
- ESKD and receiving hemodialysis
- Undergoing 3 treatments of HD per week
- Low plasma PPi: <700 nM

**Design: Single arm, Open Label**

**n = 11**

**INZ-701 – 1.8 mg/kg Weekly**
coinciding with dialysis days

**30 days treatment, weekly dosing**

**2 US sites**

**Primary Goals**

- Change from baseline in **plasma PPi** concentration

**Secondary Goals**

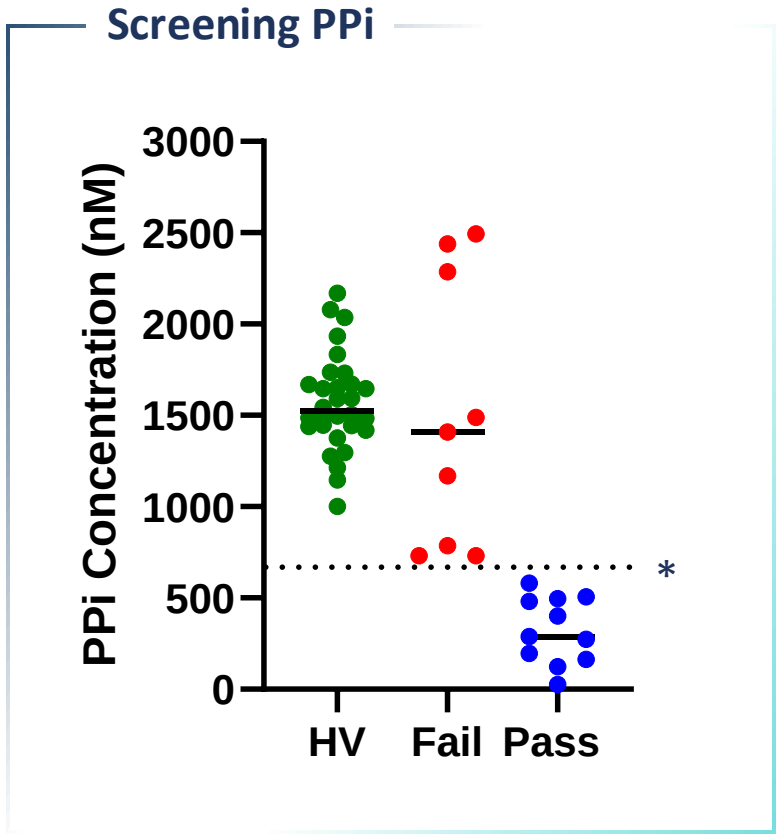
- **Pharmacokinetic (PK)** and **pharmacodynamic (PD)** parameters
- **Safety**

# SEAPORT 1: Patient demographics

*Identified population of ESKD patients with low PPi suitable for enrollment*

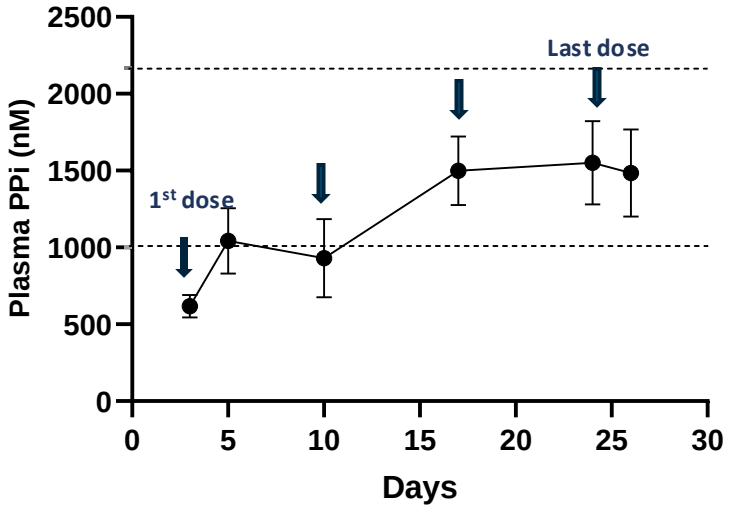
| Patients N=11 | |
|---|---|
| Median age (range) | 66 (28-70)* |
| Gender | |
| Female | 4 |
| Male | 7 |
| Race | |
| Black or African American | 8 |
| White | 3 |
| ESKD Vintage | 4.7 years |

**Screen failures: Mean age – 54*

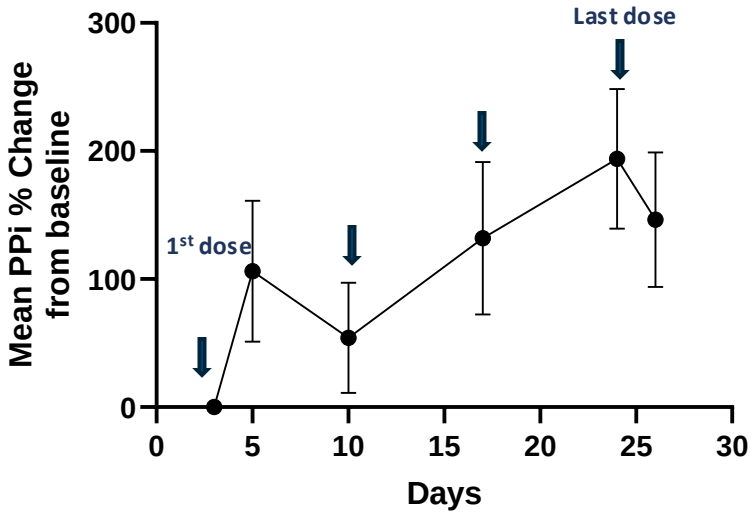


# INZ-701 increased PPi levels in ESKD patients

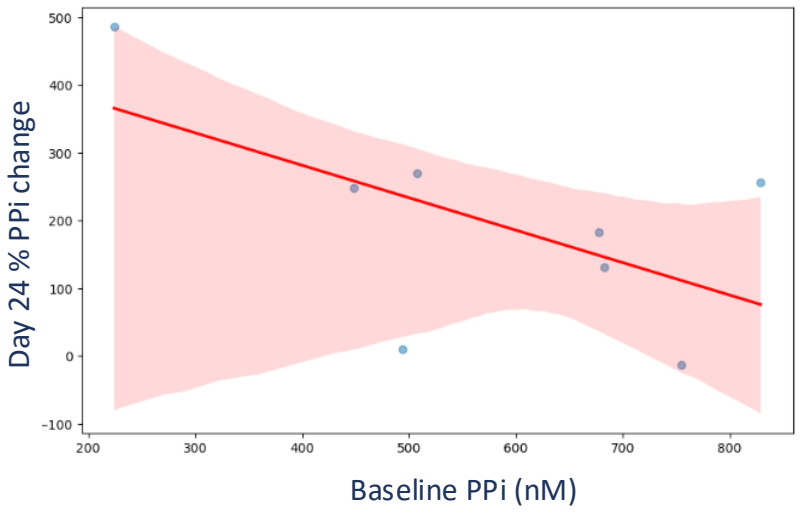
## Mean PPi




## % change in mean PPi




## Baseline PPi vs. % change PPi




Patients reached normal PPi range by third week of four-week dosing schedule

Largest changes occurred in patients with lowest baseline PPi

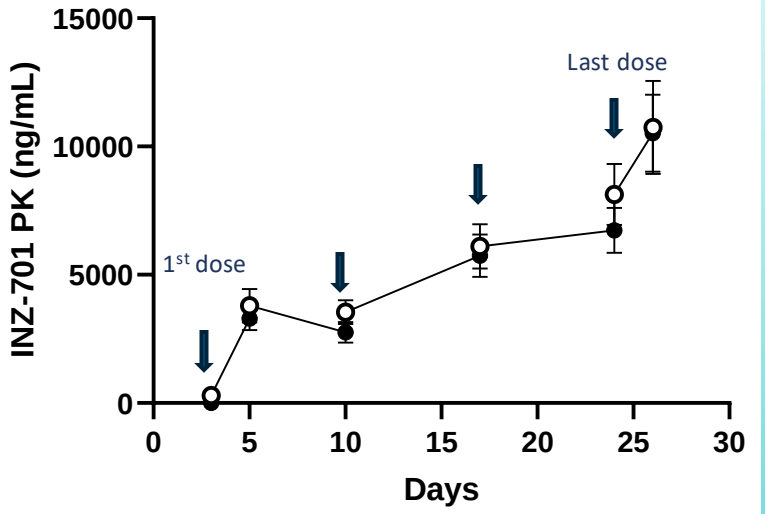
Normal range

INZ-701 dosing

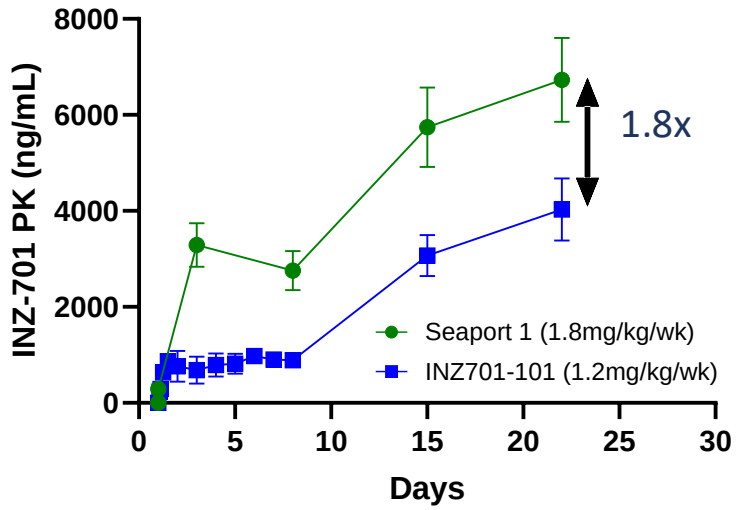
Data presented as mean ± SEM

# INZ-701 exposure in ESKD predictable and consistent with data in non-hemodialysis patients

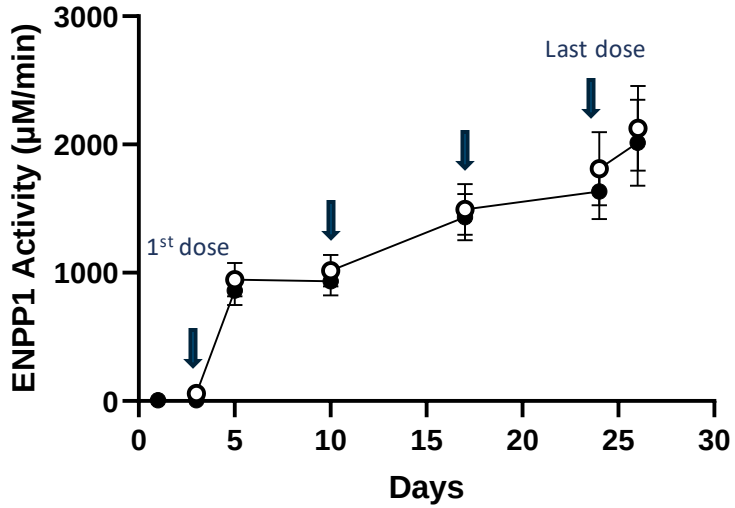
## PK mean




## PK exposure




## ENPP1 activity mean



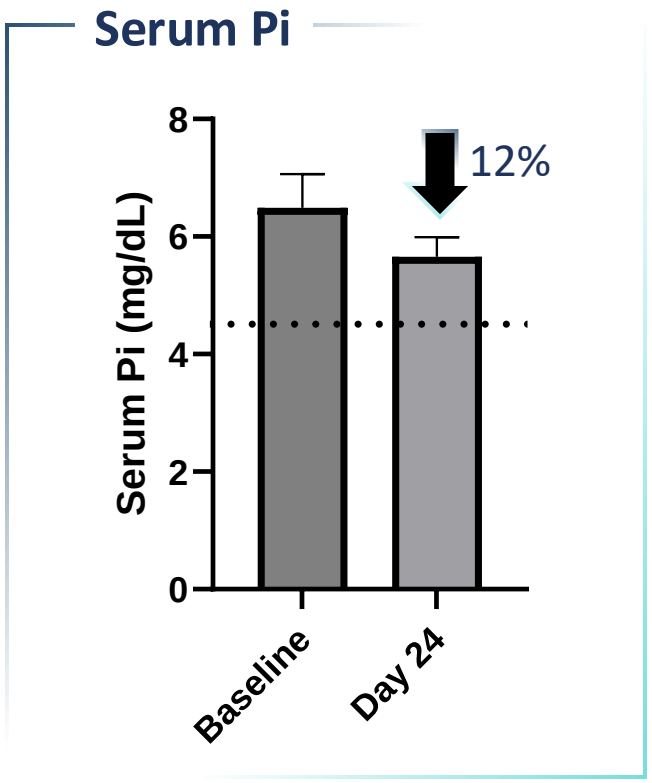

- Exposure as expected for 1.8 mg/kg weekly based on treatment of non-hemodialysis patients
  - 1.2 mg/kg/week (1.5-fold lower than SEAPORT 1) tested in adults with ENPP1 Deficiency (Phase 1/2 Trial): Mean exposure = 3,715 ng/mL
  - SEAPORT 1 mean exposure = 6,732 ng/mL; 1.8-fold difference, confirms dose proportionality
- Increase in mean ENPP1 activity mirrored INZ-701 exposure

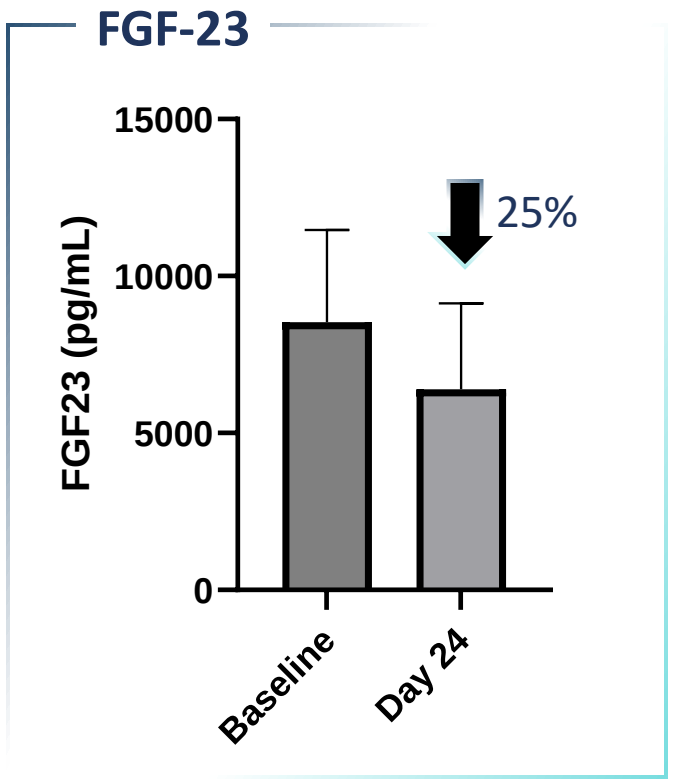
↓ INZ-701 dosing

● Pre-dialysis
○ Post-dialysis

Data presented as mean ± SEM

# Key mediators of mineral metabolism (Pi and FGF-23) decreased during INZ-701 treatment




- Effects on PPi, Pi, and FGF-23 are consistent with reduced propensity for calcification
- Markers associated with bone turnover and CKD metabolic bone disease (CKD-MBD) (PTH< BALP) remain generally unchanged, suggesting longer treatment may be needed to address this syndrome

….. Upper limit of normal

Normal range < 59pg/mL

# SEAPORT 1: INZ-701 was generally safe and well-tolerated

## *No adverse events attributed to study medication*

| Patient ID | AE Preferred Term | Relationship to INZ-701 | Severity (grade) | Outcome | SAE / AESI |
|---|---|---|---|---|---|
| 01 | Hypertension | Not related | 2 | Recovered/resolved with sequalae | SAE |
| | Gastroenteritis viral | Not related | 1 | Recovered/resolved | |
| | Seizure | Not related | 2 | Recovered/resolved | AESI |
| 02 | Hyperkalemia | Not related | 3 | Recovered/resolved | SAE |
| 03 | Hypotension | Not related | 2 | Recovered/resolved | |
| | Loss of consciousness | Not related | 2 | Recovered/resolved | |
| | Thrombocytopenia | Not related | 2 | Ongoing | |

### *Safety Summary*

- 3/11 patients (27%) experienced a TEAE, none of which were attributed to study drug
- TEAE led to temporary drug interruption in one patient (one dose missed)
- No injection site reactions reported

### *Low titers of anti-drug antibodies (ADAs) detected after Day 30*

- No ADA by Day 26 (11/11 patients)
- Low titer of ≤40 at Day 30 post-last dose[#] (3/11 patients*)
  - 60 days post-last dose: 2 are now ADA negative, 1 patient has not yet reached Day 60 post-last dose[#]

Events ongoing at the start of the study were collected as medical history. Only new events were counted as on-study events.
SAE = serious adverse events; AESI = adverse event of special interest
[#] End of study safety follow-up

# SEAPORT 1: Summary

- PPi levels in screened ESKD patients (n=21) were lower than reported in healthy volunteers, with many patients well below the normal range
- Eleven patients with ESKD and PPi <700 nM were treated over four weeks with weekly doses of subcutaneous INZ-701
  - Demonstrated a favorable safety profile, with no drug-related TEAEs
  - Increased mean PPi levels to normal range by week 3
  - Associated with reductions in mineral metabolism biomarkers (Pi and FGF-23)
  - Drug exposure was proportional to the dose received
- Findings suggest
  - INZ-701 may normalize PPi levels in ESKD patients receiving hemodialysis with reduced PPi levels
  - Supports further clinical development of INZ-701 in calciphylaxis

# Anticipated milestones provide robust news flow

| Milestone | Anticipated Timing |
|---|---|
| **ENPP1 Deficiency** | |
| • Complete Enrollment – ENERGY 3 Pivotal Pediatric Trial | **Q4 2024** |
| • Initiate – ENERGY 2 Pivotal Trial in Infants – Ex. U.S. | **Q4 2024** |
| • Interim Data – ENERGY 1 Phase 1 Infant Trial | **Q4 2024** |
| • Topline Data – ENERGY 3 Pivotal Pediatric Trial | **Early 2026** |
| **ABCC6 Deficiency** | |
| • Initiate Pivotal Trial* | **2025** |
| **Calciphylaxis** | |
| • Interim Data – SEAPORT 1 Phase 1 Trial** | ✔ |
| • Initiate Registrational Trial* | **2025** |

*Pending regulatory discussions and appropriate financial resources, **Phase 1 trial in patients with end-stage kidney disease (ESKD) receiving hemodialysis

# Inozyme is at the forefront of developing novel therapies for rare diseases that affect bone health and blood vessel function

**ENPP1 Deficiency, ABCC6 Deficiency and calciphylaxis are serious diseases affecting bone health and blood vessel function linked to dysregulation of the PPi-Adenosine Pathway with no approved therapies**

**Lead product candidate, INZ-701, demonstrated a rapid, significant, and sustained increase in PPi levels, preliminary evidence of efficacy, and a favorable safety profile across multiple clinical trials**

**Currently in pivotal trial for ENPP1 Deficiency; Completed Phase 2 trial for ABCC6 Deficiency and treatment period in Phase 1b trial in calciphylaxis program**

**Experienced team with a track record of success in rare disease**

**In a position of financial strength, with several expected upcoming milestones and a pipeline designed for long-term value creation**

- $131.6M expected to fund operations into Q4 2025 as of 9/30/24
- 64.24M common shares outstanding as of 10/29/24

# Thank you

**Ella**
Living with ENPP1 Deficiency