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# Our Mission

Fulfill an unmet medical need with therapeutic breakthroughs in diseases of abnormal mineralization

September 2021

# Legal Disclaimer

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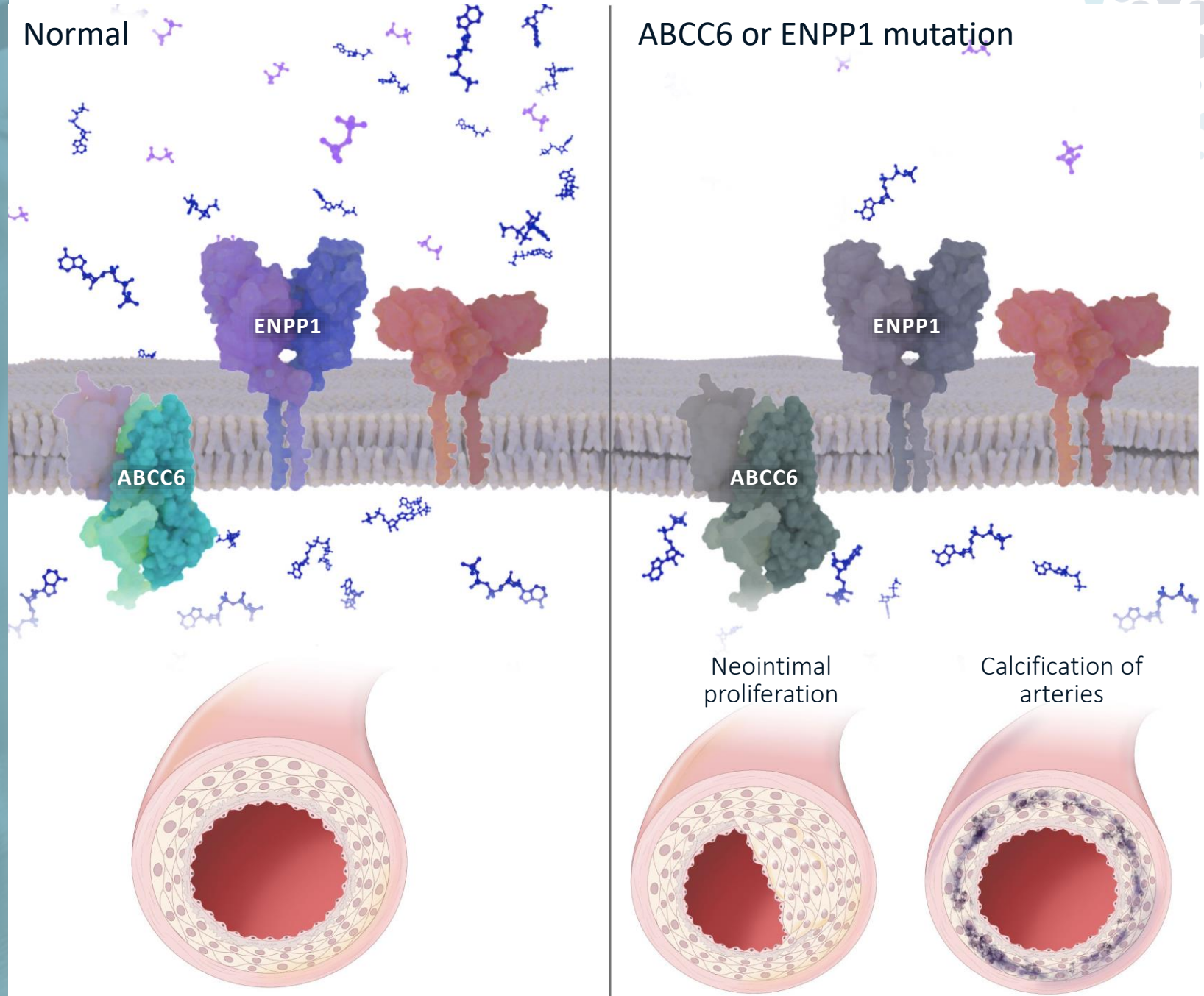
# Abnormal mineralization and intimal proliferation

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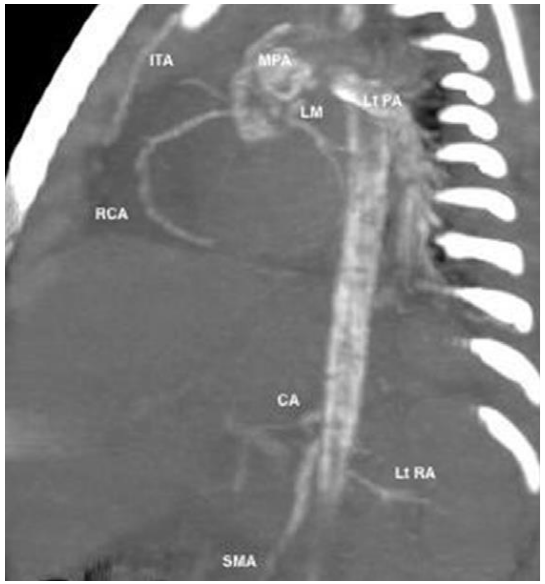
# ENPP1 Deficiency is a disease with high morbidity and mortality

## GACI
0 – 3 YEARS

### CALCIFICATION
*(Bolster et al., Foren. Sci., 2015)*



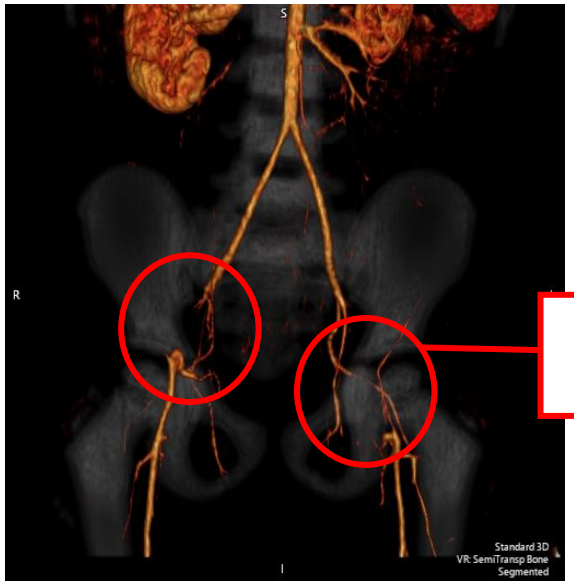

**>40% MORTALITY**
within first 12 months of life, despite intervention

In a retrospective natural history study

**70.8%** develop hypophosphatemic rickets, and experience high treatment burden in patients who survive infancy…

## ARHR2
3 – 18 YEARS

### NEOINTIMAL PROLIFERATION
*(Ferreira et al. Gen. Med., 2020)*



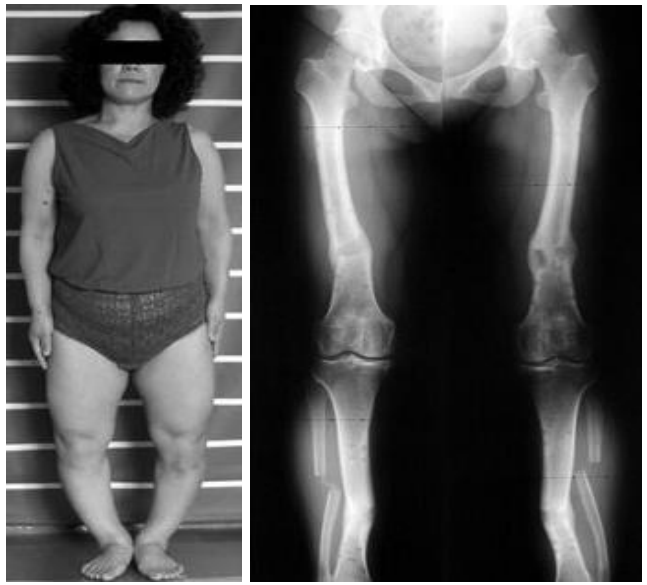

Obstructive Arteriopathy

**>85%** experience morbidity related to: bone/joint pain and/or mobility/fatigue

In a Burden of Illness study in adults (n=7) and children (n=13) with ENPP1 Deficiency

## Osteomalacia
18+ YEARS

### SKELETAL DEFECTS
*(Matsubara et al., Arch. Ortho. Surg., 2008)*



**77.2%** ARTERIAL
**65.8%** ORGAN
**64.4%** JOINT

**PREVALENCE OF CALCIFICATION**
In patients with ENPP1 Deficiency diagnosed with GACI

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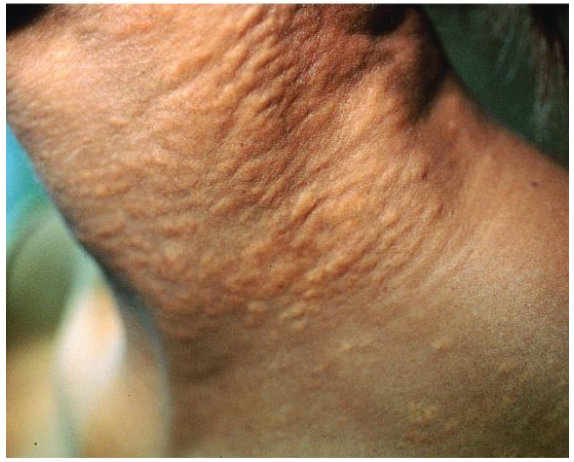
# ABCC6 Deficiency shares biology and symptoms with ENPP1 Deficiency

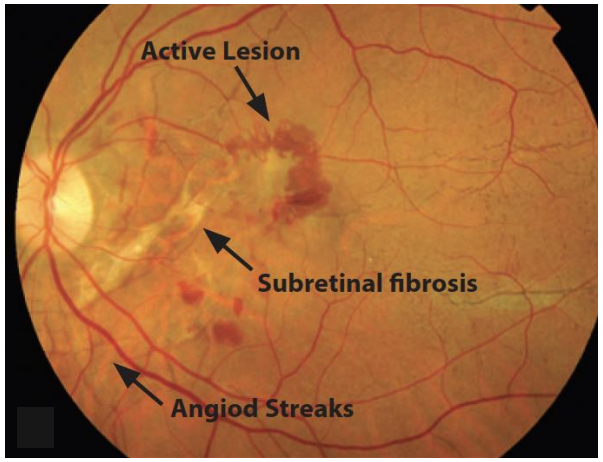
## GACI Type 2
0 – 3 YEARS

## PXE
ONSET IN 20 – 30S | PROGRESSIVELY AFFECTS ADULT POPULATION

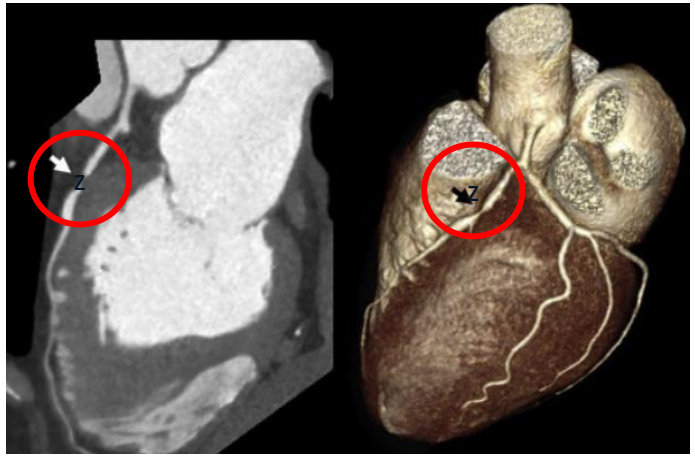
### SKIN LESIONS
*Borst et al. Trends in Biochemical Sciences, February 2019,*



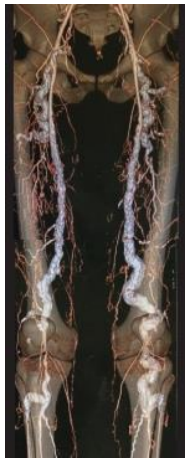
### RETINAL ABNORMALITIES
*Zaria et al. eye news | OCTOBER/NOVEMBER 2015*




### NEOINTIMAL PROLIFERATION
*Karam et al. J Cardio Comp Tomo 2015*



### VASCULAR CALCIFICATION
*Mowafy et al. Vascular & Endovascular Review 2019*



**10.8% MORTALITY RISK**

within first 12 months of life, despite intervention

In patients with ABCC6 Deficiency diagnosed with GACI

**37% VISUALLY IMPAIRED**

**15% LEGALLY BLIND**

In adults over the age of 50[3]:

**45-53%** develop **PERIPHERAL ARTERIAL DISEASE**[4-5]

**3-5x** higher risk of **ISCHEMIC STROKE**[5-6]

**89.5%** **ARTERIAL** **84.2%** **ORGAN**

**PREVALENCE OF CALCIFICATION**

**PREVALENCE OF STROKE/SEIZURE: 21%**

In patients with ABCC6 Deficiency diagnosed with GACI

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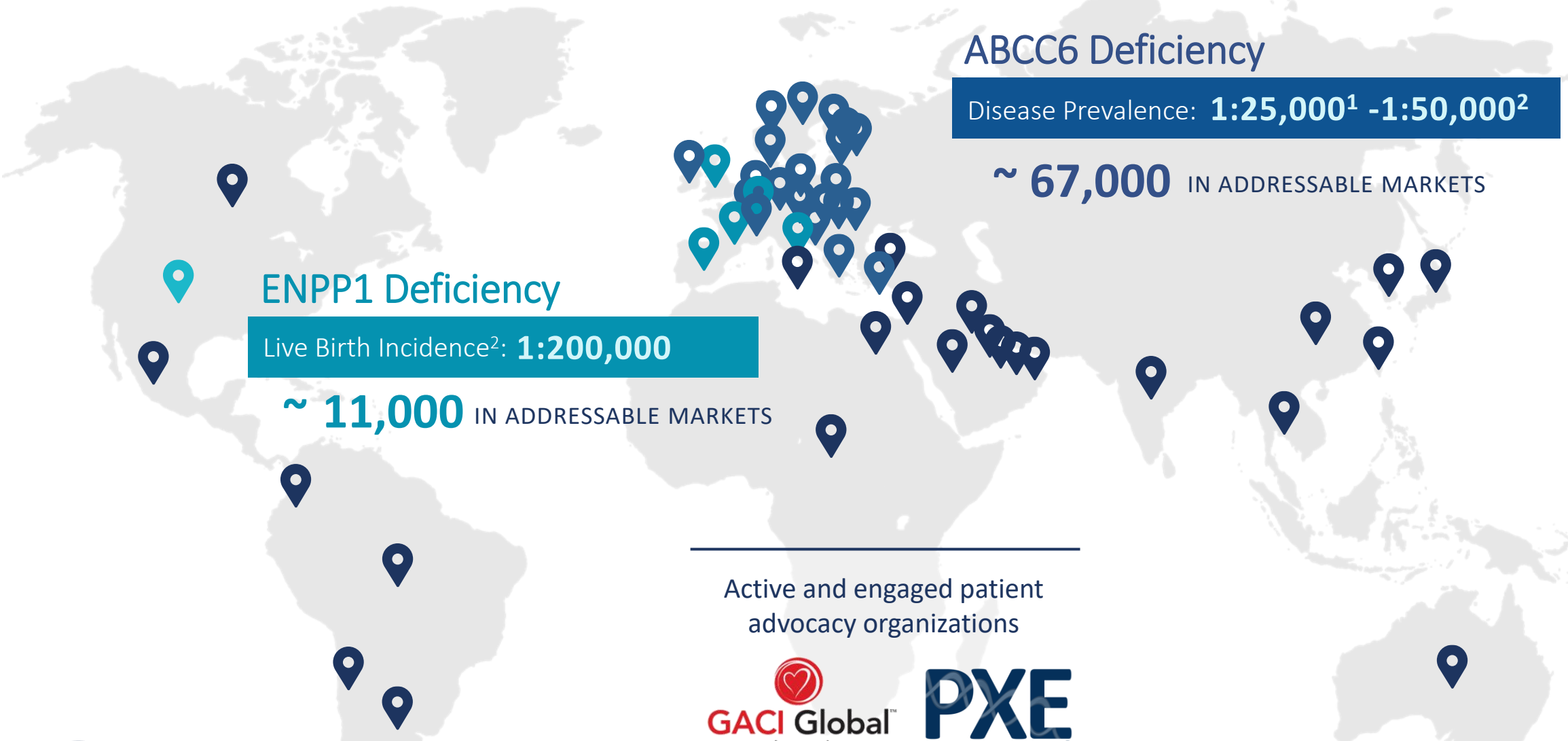
# ENPP1 and ABCC6 market and engaged patient community



## ABCC6 Deficiency

Disease Prevalence: **1:25,000[1] -1:50,000[2]**

**~ 67,000** IN ADDRESSABLE MARKETS

## ENPP1 Deficiency

Live Birth Incidence[2]: **1:200,000**

**~ 11,000** IN ADDRESSABLE MARKETS

Active and engaged patient advocacy organizations

GACI Global™ circulating hope

PXE international

- U.S.
- EU5
- EU6+
- ROW

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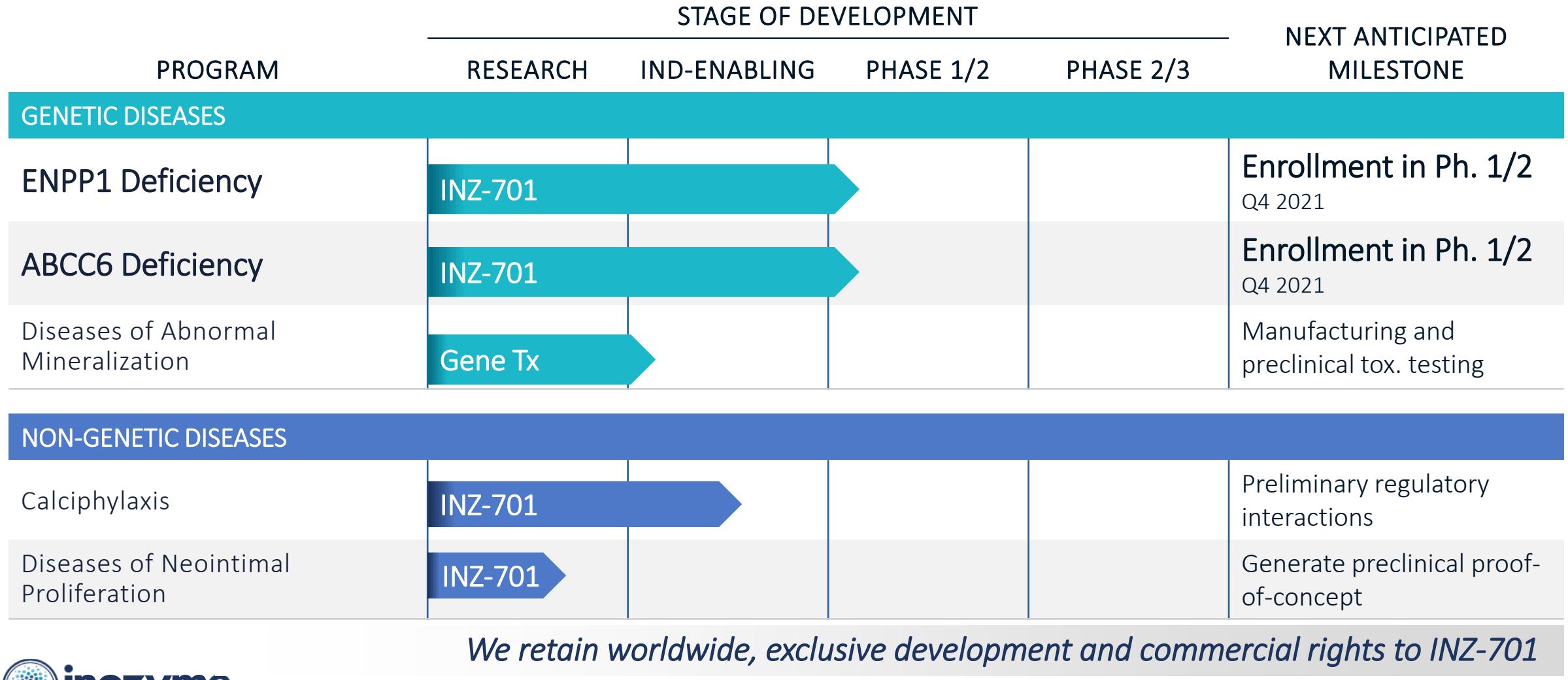
# Abnormal mineralization biology provides untapped therapeutic opportunity

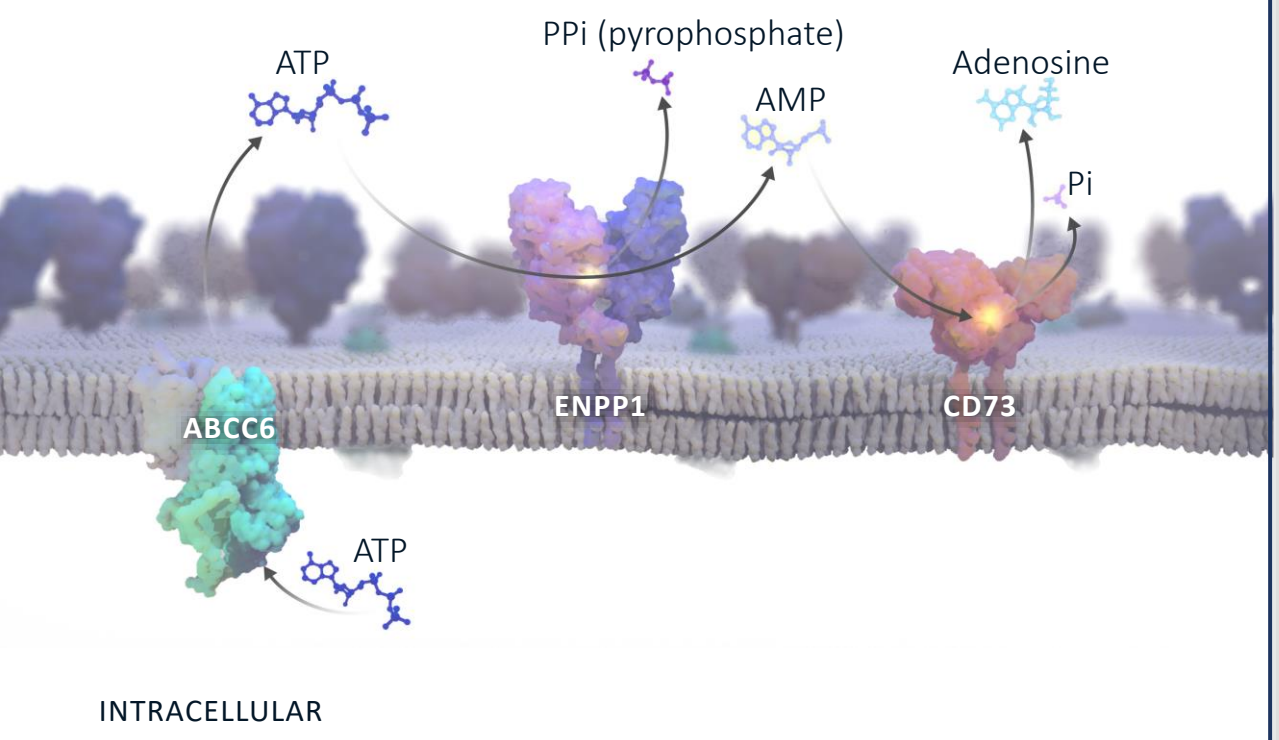
*Initial focus on genetic diseases followed by expansion into non-genetic diseases*




*We retain worldwide, exclusive development and commercial rights to INZ-701*

# Understanding the biology of ENPP1 and ABCC6 is key to changing the treatment paradigm for patients

# ENPP1 and ABCC6: Key Transmembrane proteins regulating mineralization and neointimal proliferation




## PPi maintains healthy mineralization

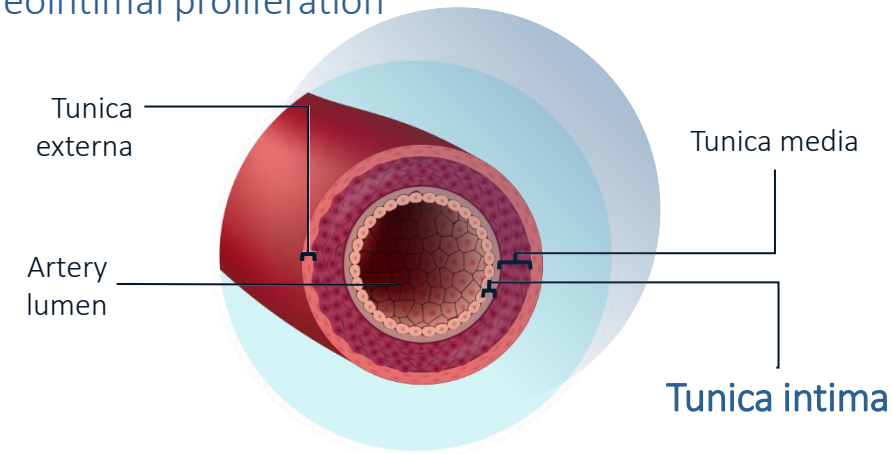
Inhibits growth and formation of hydroxyapatite, which results in:

Maintenance of healthy bones and teeth

Inhibition of pathological ectopic mineralization *(i.e., mineralization of arteries, organs, and joints)*

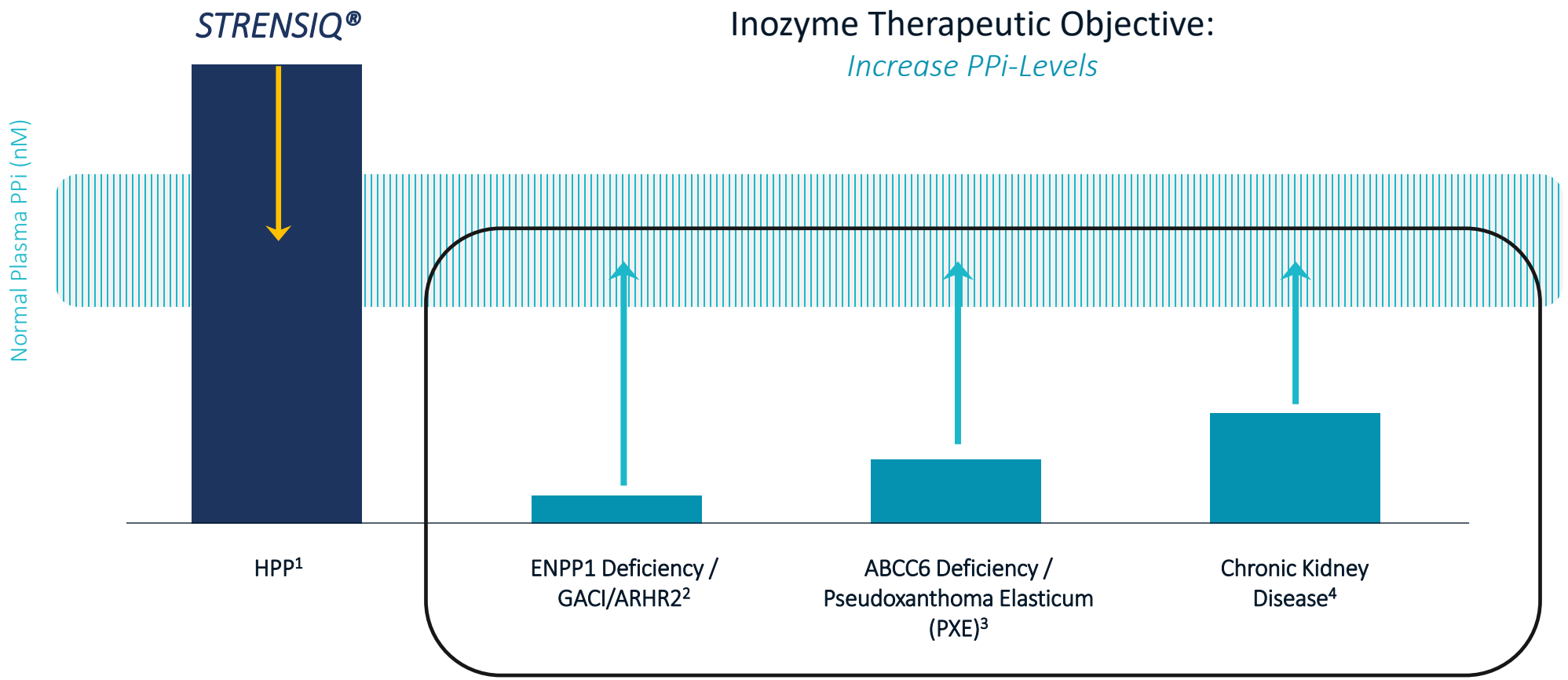
## Adenosine maintains healthy vessel wall thickness

Inhibits neointimal proliferation



# Regulating PPi is a therapeutic objective in several diseases

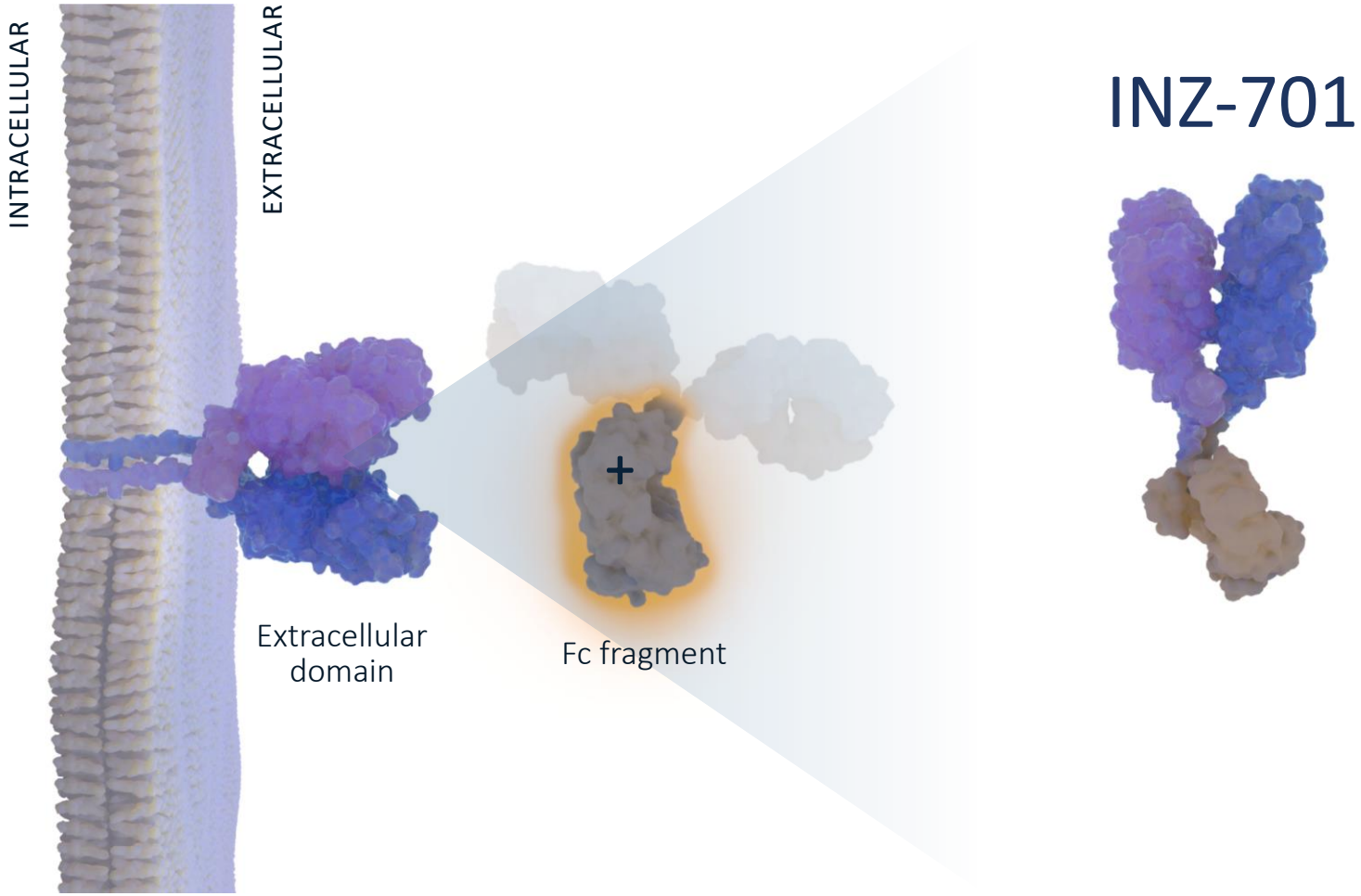
## *Reduction of excessive PPi levels has been achieved by STRENSIQ®*




*Sources:* **1.** *Hypophosphatasia Reported in Whyte et al. JCI Insight. 2016;1(9):e85971.* **2.** *Nitschke et al., 2018.* **3.** *Kauffenstein et al., 2018.* **4.** *O'Neill et al, 2010.*

# INZ-701 has been designed to replace lost enzymatic function of ENPP1

## *Pharmacological properties have been optimized*




INZ-701



**PROTEIN**
Recombinant human ENPP1 (Ectonucleotide pyrophosphatase/phosphodiesterase 1)

**CONSTRUCT**
Recombinant Fc fusion protein with soluble extracellular domain of ENPP1

**DOSING**
SC ; 2x/week in Ph. 1/2 for ENPP1 deficiency

**ENZYMATIC PROPERTIES**
High catalytic efficiency (Kcat/Km)

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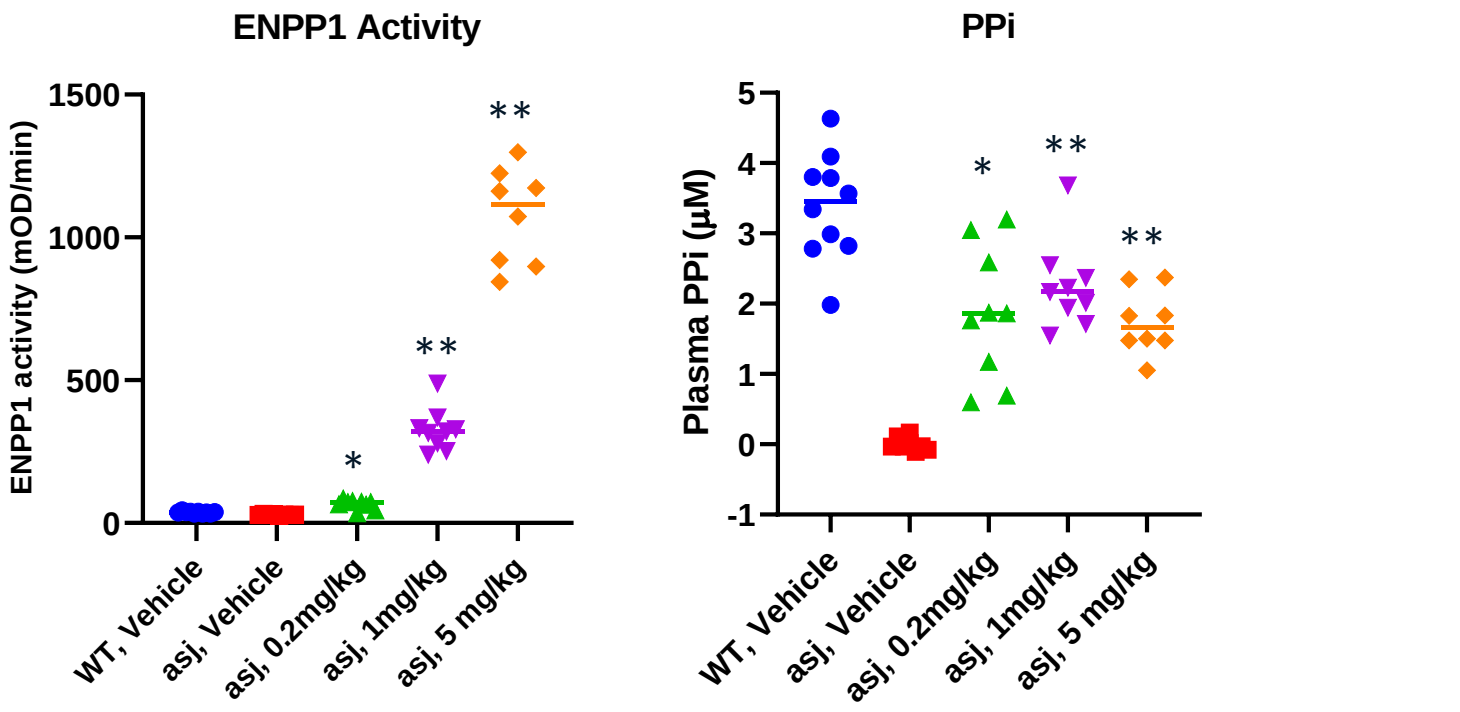
# Our solution: INZ-701 preclinical development

# INZ-701: Increased PPi levels in ENPP1-deficient mice (asj)

## *Biomarker proof-of-concept achieved in mice treated with INZ-701*




* $P \leq 0.01$; ** $P \leq 0.001$

### Asj-mouse Model:

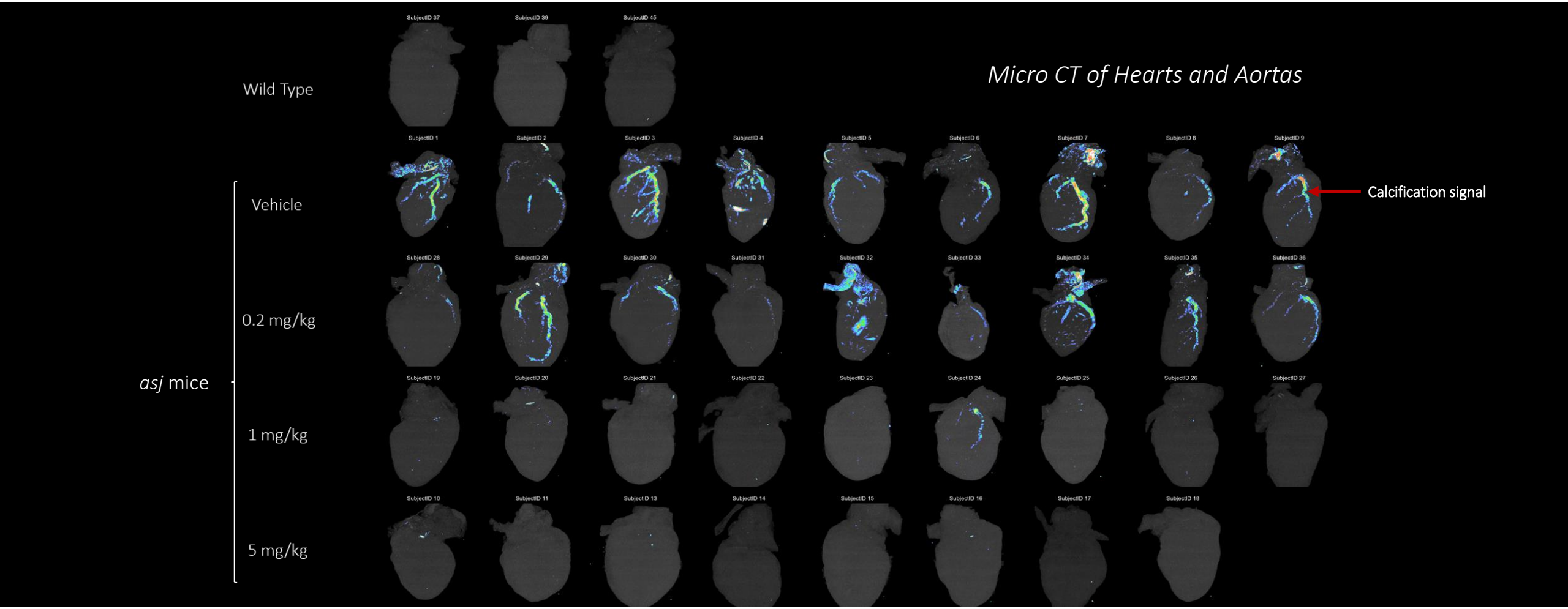
- Failure to thrive and gain weight
- Extensive vascular calcification
- Premature mortality
- Mimics human disease

*Therapy start at age of 2 weeks (D1) and end at 10 weeks (D56)*

Sources: *Cheng et al.* Journal of Bone and Mineral Research, 2021

# INZ-701: Prevented cardiovascular calcification in ENPP1-deficient mice (asj)

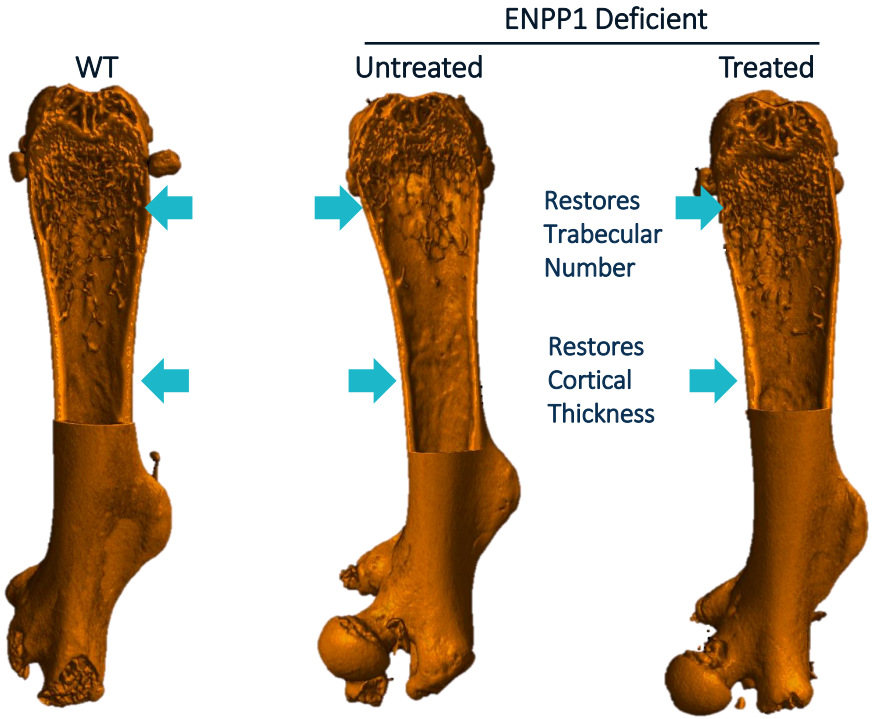
## *Validation of pharmacological effect in representative mouse model*




Sources: *Cheng et al.* Journal of Bone and Mineral Research, 2021

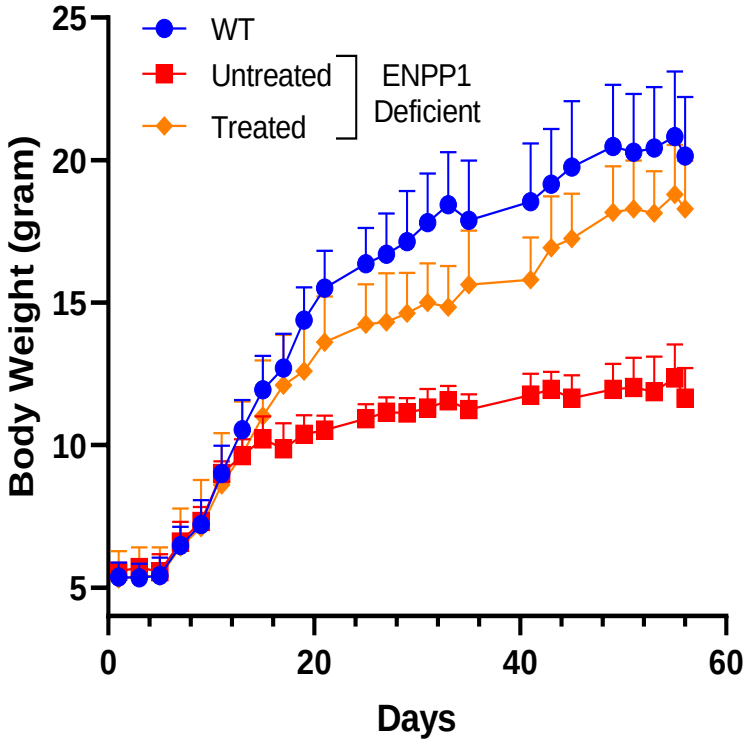
# INZ-701: Prevented bone loss and restored growth in ENPP1-deficient mice (asj)

## Corrected Bone Defects




| | WT | Untreated | Treated |
|---|---|---|---|
| Average Trabecular Number (1/mm) | 2.601 | 1.407 | 2.213 |
| Average Cortical Thickness (mm) | 0.174 | 0.113 | 0.148 |

## Rescued Growth Defect



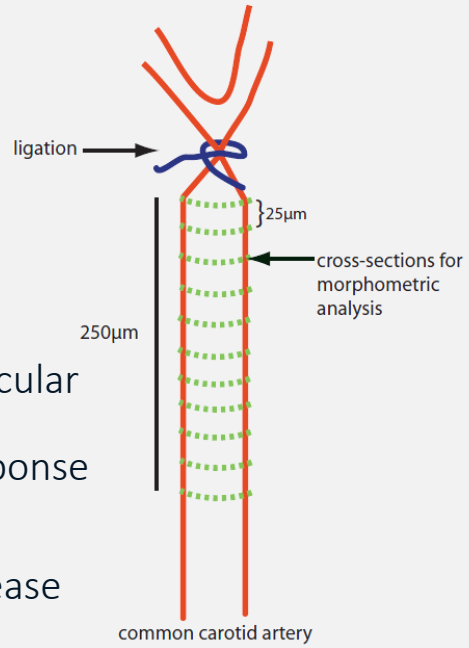

Sources: *Cheng et al.* Journal of Bone and Mineral Research, 2021

# INZ-701: Prevented neointimal proliferation in ENPP1-deficient mice

*Proof-of-concept achieved in mouse model supporting regulation of adenosine pathway*

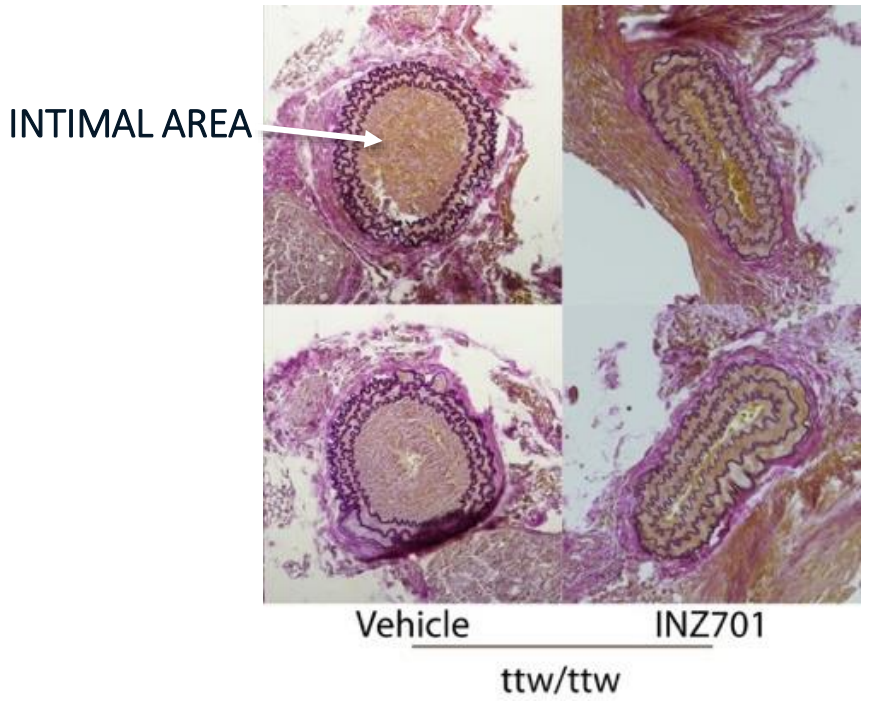
## ttw-Mouse Model:

- Severe calcification of the cartilage and arterial walls
- Marked intimal vascular smooth muscle cell proliferation in response to arterial injury
- Mimics human disease



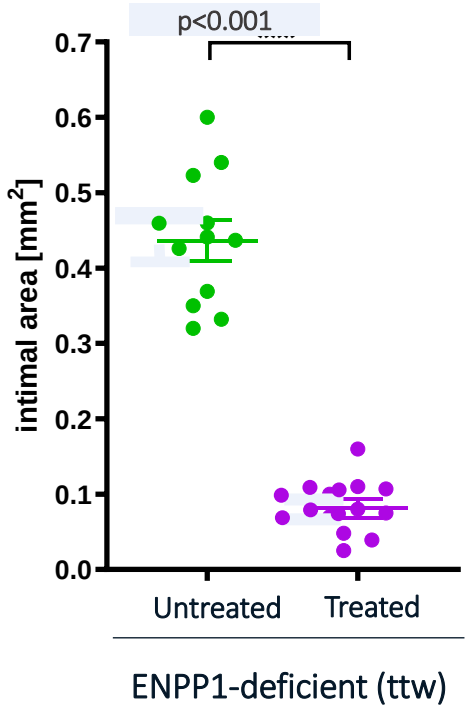

## Histology

**Histological Analysis** of Preventive Treatment in Mice Ligated for 14 Days



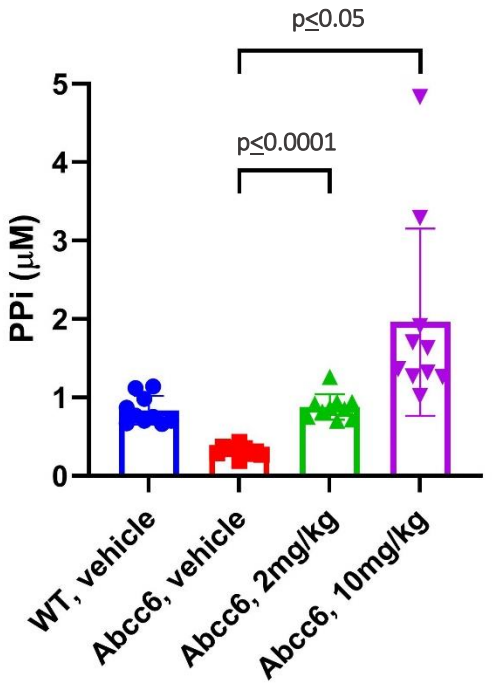

Sources: *Internal, Unpublished Data.*

## Intimal Area

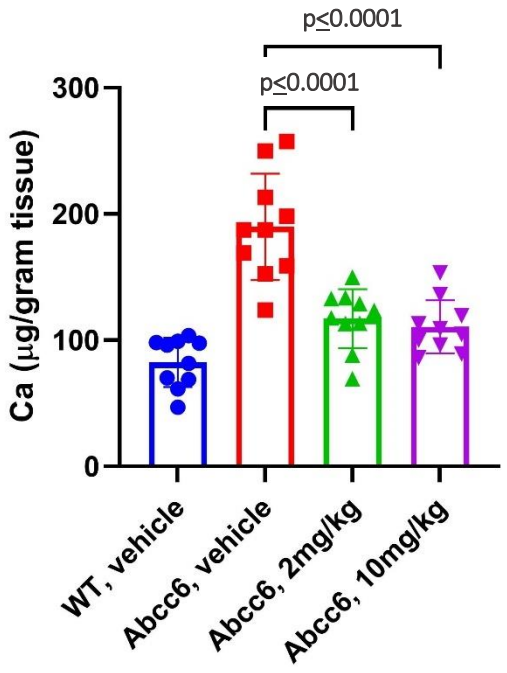


# INZ-701:
# Increased PPi and reduced tissue calcification seen in ABCC6-deficient mice

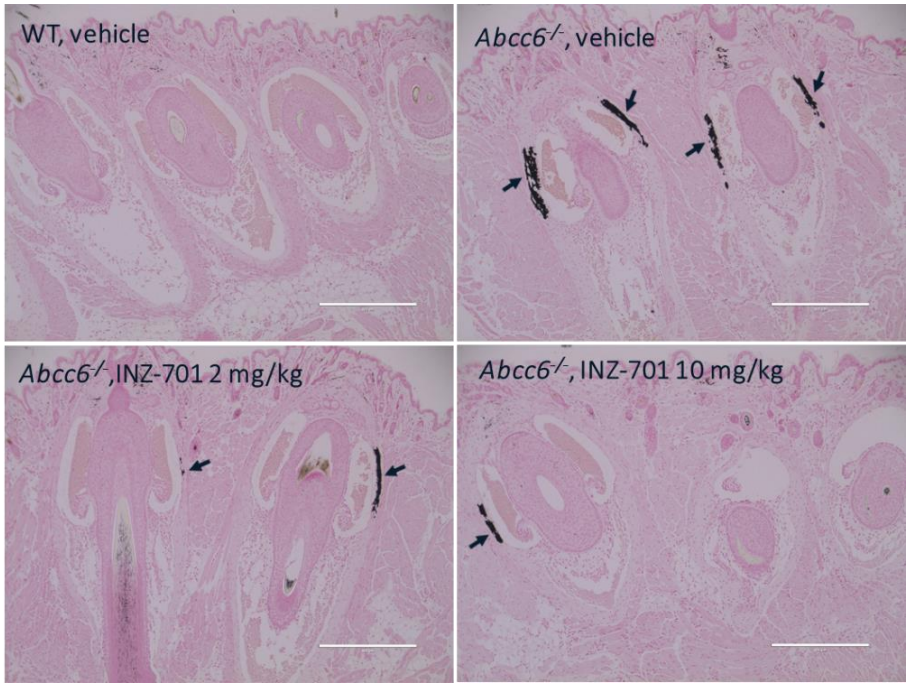
## Plasma PPi




## Muzzle Skin Calcification




## Von Kossa Stain of Muzzle Skin




- Dose: 2 and 10mg/kg, SC, QOD
- Duration: ~4wk of age to ~12 wk of age

- All animals are given anti-CD4
- All animals on normal diet

### *ABCC6 Mouse Model*

- Calcification in aorta and arteries of soft tissues
- Spontaneously developed
- calcification of elastic fibers in blood vessel walls
- Calcification in Bruch's membrane in the eye
- Mimics human disease

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Sources: *Internal, Unpublished Data.*

# INZ-701:
# Clinical development

# Well-positioned to execute two Phase 1/2 clinical trials

## ENPP1 Deficiency

- IND cleared in US
- CTA cleared in Europe
- Phase 1 unit trial site activated in US
- Activating Academic Institution trial sites
- FDA and EMA – Orphan Drug Designation
- FDA - Fast track designation and rare pediatric disease designation


## ABCC6 DEFICIENCY

- IND cleared in US
- CTA cleared in Europe
- Phase 1 unit trial site activated in US
- Activating Academic Institution trial sites
- FDA and EMA – Orphan Drug Designation

# Building comprehensive understanding of ENPP1 and ABCC6 deficiencies

## ENPP1 Deficiency

### Burden of Illness Study

*Understand disease from perspective of ENPP1 patients and caregivers. Data shared in H1 2021*

### Prospective Natural History Study – ENPP1

*Expect initiation Q1 2022*

### Retrospective Natural History Study

*Believed to be largest retrospective, cross-sectional study in ENPP1 Deficiency*

## ABCC6 Deficiency

### Burden of Illness Study

*Understand disease from perspective ABCC6 patients and caregivers. Data shared in H1 2021*

### Prospective Natural History Study – ABCC6

*Expect initiation in 2022*

## Biology

### Healthy Volunteer PPi Study

*Results to be presented at medical conferences in 2021*

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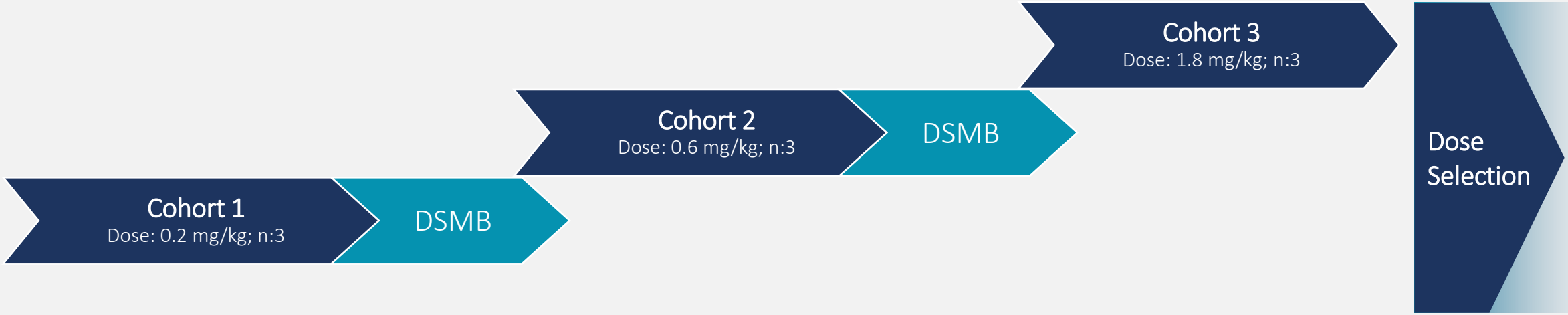
# ENPP1 Phase 1/2 clinical trial design

## Adults

**FIH**




| | |
|---|---|
| **Eligibility Criteria** | • Confirmed clinical and genetic diagnosis<br>• Age 18-65 years |
| **Primary Objective(s)** | • **Safety and tolerability of INZ-701**<br>• Establish dosing regimen for future clinical development |
| **Additional Objectives** | • Plasma PPi<br>• Other disease-relevant biomarkers |
| **Planned Doses** | • 0.2 mg/kg, 0.6 mg/kg, and 1.8 mg/kg; twice weekly subcutaneous |
| **Phase 1 Duration** | • 7 weeks duration per subject; staggered recruitment per cohort (DSMB) |

DSMB = Data Safety Monitoring Board

# ENPP1 clinical development strategy

## Adults

**FIH**

- Cohort 1 Dose: 0.2 mg/kg; n:3
- DSMB
- Cohort 2 Dose: 0.6 mg/kg; n:3
- DSMB
- Cohort 3 Dose: 1.8 mg/kg; n:3

Dose Selection

| | |
|---|---|
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## PIVOTAL

Pending regulatory discussions and approval

Phase 1/2 Extension – 48 weeks | Remain on Drug

Placebo-controlled Expansion Cohort

Adults, Phase 3 – 2:1 Tx:Pbo

| ENDPOINT | MEASUREMENT |
|---|---|
| PPi | Blood biochemistry |
| Calcification | High resolution radiography |
| Pain | Pain Scores |

## Pediatric

### Infants – 0-3 years

Pending regulatory discussions and approval

| ENDPOINT | MEASUREMENT |
|---|---|
| PPi | Blood biochemistry |
| Calcification | High resolution radiography |
| Survival | Alive at 6 months |

### Adolescents – 3-18 years

Pending regulatory discussions and approval

| ENDPOINT | MEASUREMENT |
|---|---|
| PPi | Blood |
| Rickets | RGI-C |
| Growth | Rate |

Infants, Phase 3 Open Label – 48 weeks

Adolescents, Phase 3 Open Label – 48 weeks

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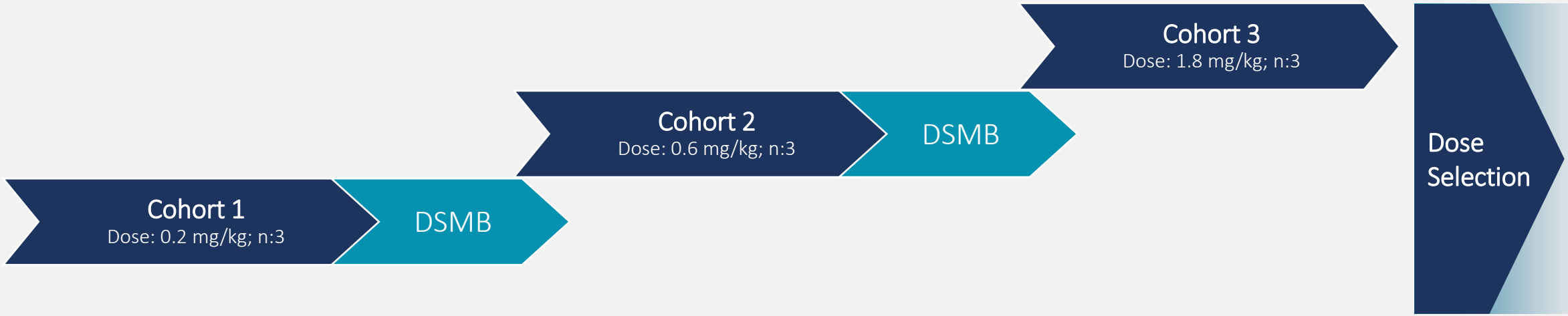
DSMB = Data Safety Monitoring Board

# ABCC6 Phase 1/2 clinical trial design

## Adults

**FIH**

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# ABCC6 clinical development strategy

## Adults

**FIH**

- Cohort 1 Dose: 0.2 mg/kg; n:3
- DSMB
- Cohort 2 Dose: 0.6 mg/kg; n:3
- DSMB
- Cohort 3 Dose: 1.8 mg/kg; n:3
- Dose selection

| | |
|---|---|
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### Infants – 0-3 years

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|---|---|
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| Calcification | High resolution radiography |
| Survival | Alive at 6 months |

## PIVOTAL

Pending regulatory discussions and approval

Phase 1/2 Extension – 48 weeks | Remain on Drug

Placebo-controlled Expansion Cohort

Adults, Phase 3 – 1:1 Tx:Pbo – 48 weeks

| ENDPOINT | MEASUREMENT |
|---|---|
| PPi | Blood biochemistry |
| Vascular calcification progression | High resolution radiography |
| Maintain or slow vision loss | |

Infants, Phase 3 Open Label – 48 weeks

DSMB = Data Safety Monitoring Board

# Financial overview and upcoming anticipated milestones

**$137.5M**

Cash, cash equivalents & investments to fund operations into the fourth quarter of 2022
as of 6/30/2021

**23.4M**

Common shares outstanding
as of 6/30/2021

## ENPP1 Deficiency

- ☑ Clearance of IND and CTAs
  Early 2021
- ○ Enrollment in Phase 1/2 Trial
  Q4 2021
- ○ Initiation of Prospective Natural History Study
  Q1 2022
- ○ Preliminary Safety and Biomarker Data From Phase 1/2 Clinical Trial
  H1 2022

## ABCC6 Deficiency

- ☑ Filing of CTA
  H1 2021
- ☑ Clearance of IND and CTA
  Mid-2021
- ○ Enrollment in Phase 1/2 trial
  Q4 2021
- ○ Preliminary safety and Biomarker Data from Phase 1/2 Clinical Trial
  H1 2022

## New Indications & Pipeline

- ☑ Calciphylaxis
  Preclinical POC
- ○ Neointimal Proliferation
  Preclinical POC
- ○ Gene Therapy Program
  Select development candidate

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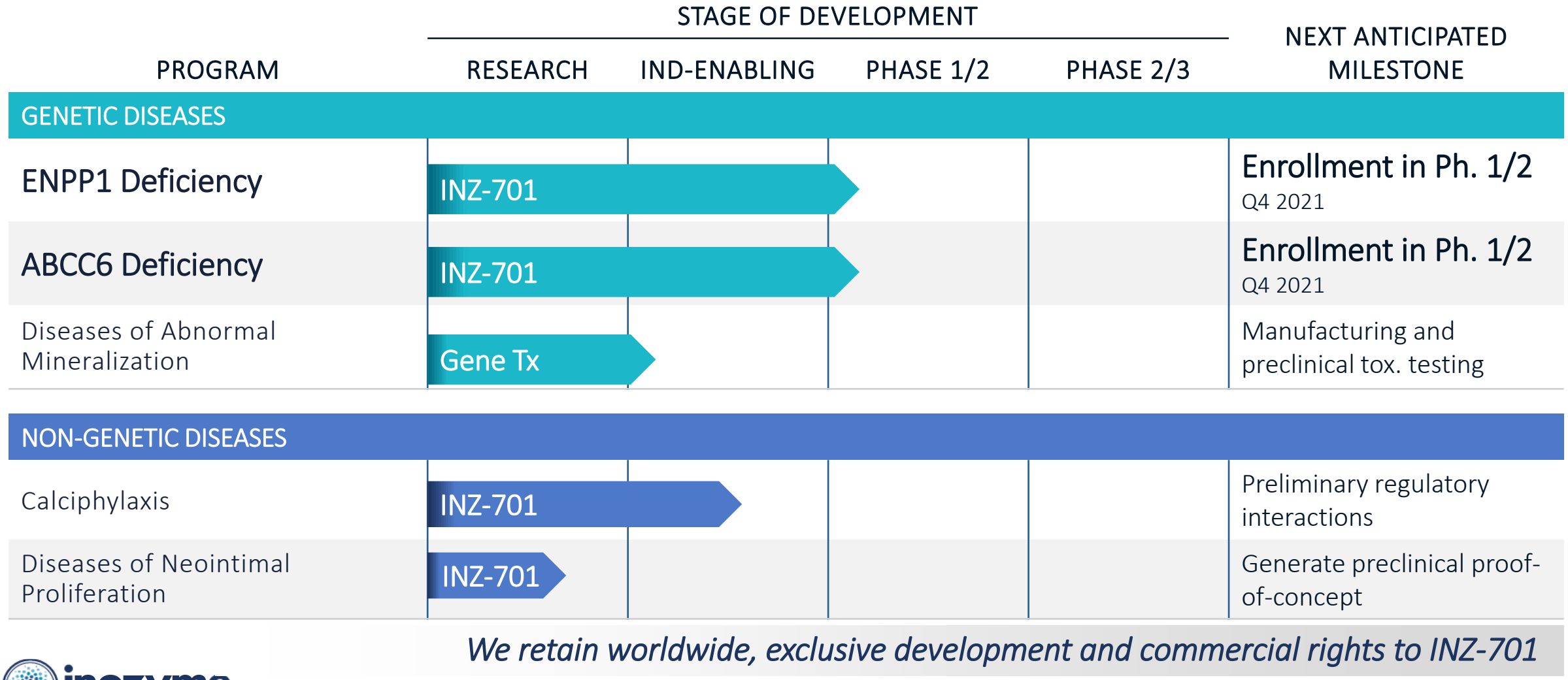
# Abnormal mineralization biology provides untapped therapeutic opportunity

*Initial focus on genetic diseases followed by expansion into non-genetic diseases*

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# Thank You

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investors@inozyme.com