INZ-701 prevents ectopic tissue calcification and restores growth in Enpp1 deficient mice

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Inozyme Pharma

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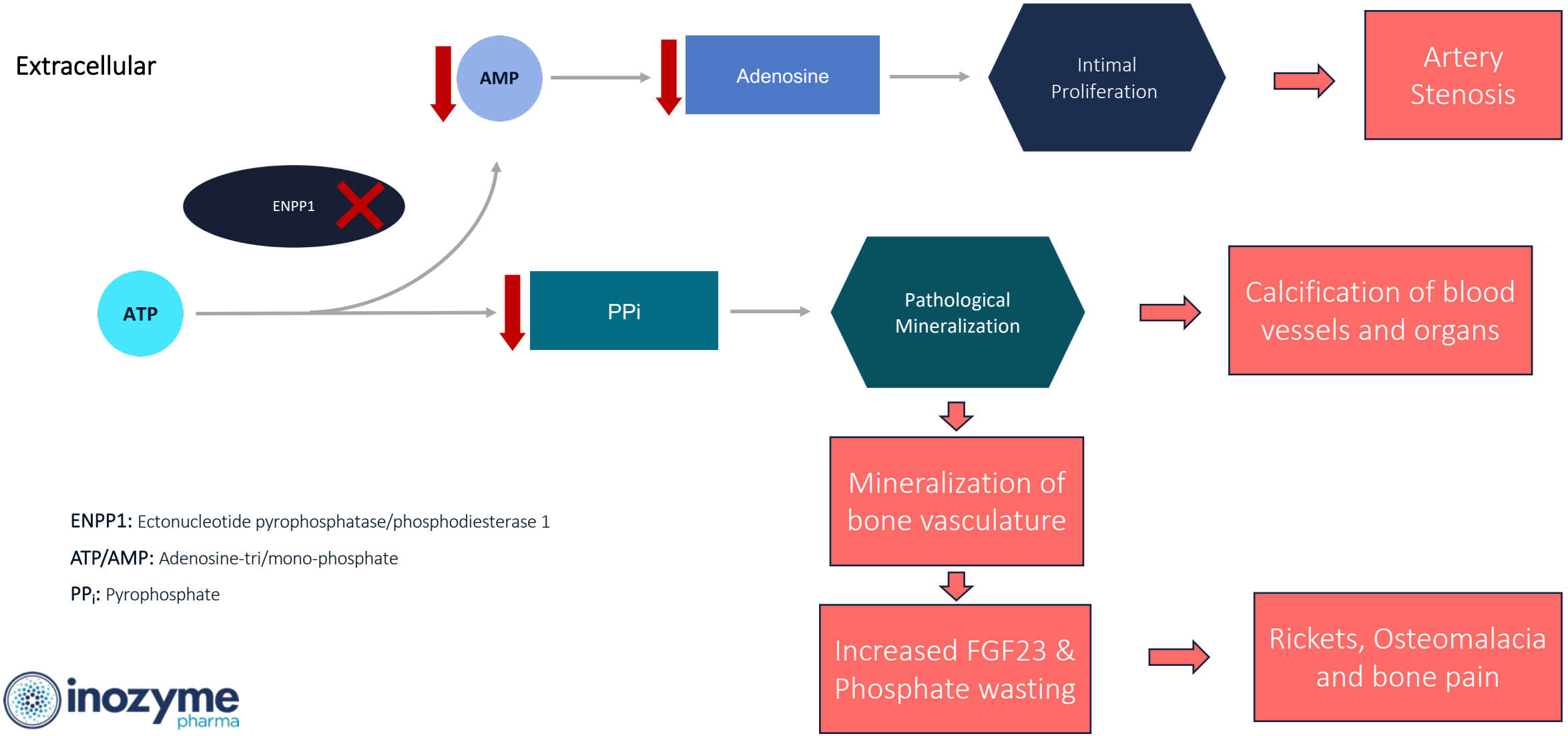
DISCLOSURE

- *The authors are employees of Inozyme Pharma.*
- *The work reported is sponsored by Inozyme Pharma.*

ENPP1 as a key regulator of biological mineralization and intimal proliferation



ENPP1: Ectonucleotide pyrophosphatase/phosphodiesterase 1

ATP/AMP: Adenosine-tri/mono-phosphate

PP_i: Pyrophosphate

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ENPP1 Deficiency is a systemic disease with high mortality and morbidity

Historical Definition

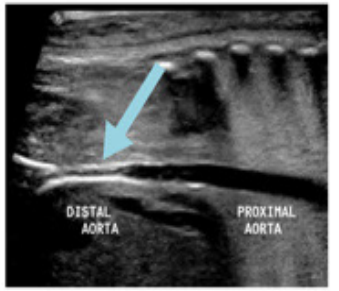
Generalized Arterial Calcification of Infancy (GACI):
Calcification and narrowing of arteries leading to early morbidity and mortality, often resulting in death (45-50% of infants, within 12 months of birth)

Autosomal recessive hypophosphatemic rickets type 2 (ARHR2):
Survivors of the infant stage develop skeletal issues including weak bones/muscles and rickets in children as well as adults

ENPP1 Deficiency - New Definition

COMPLICATIONS

- Calcification
- Narrowing of arteries (stenosis)
- Heart failure
- Cardiomegaly
- Death
- Short stature
- Skeletal deformities
- Weakened bones and muscles
- Fractures
- Bone pain



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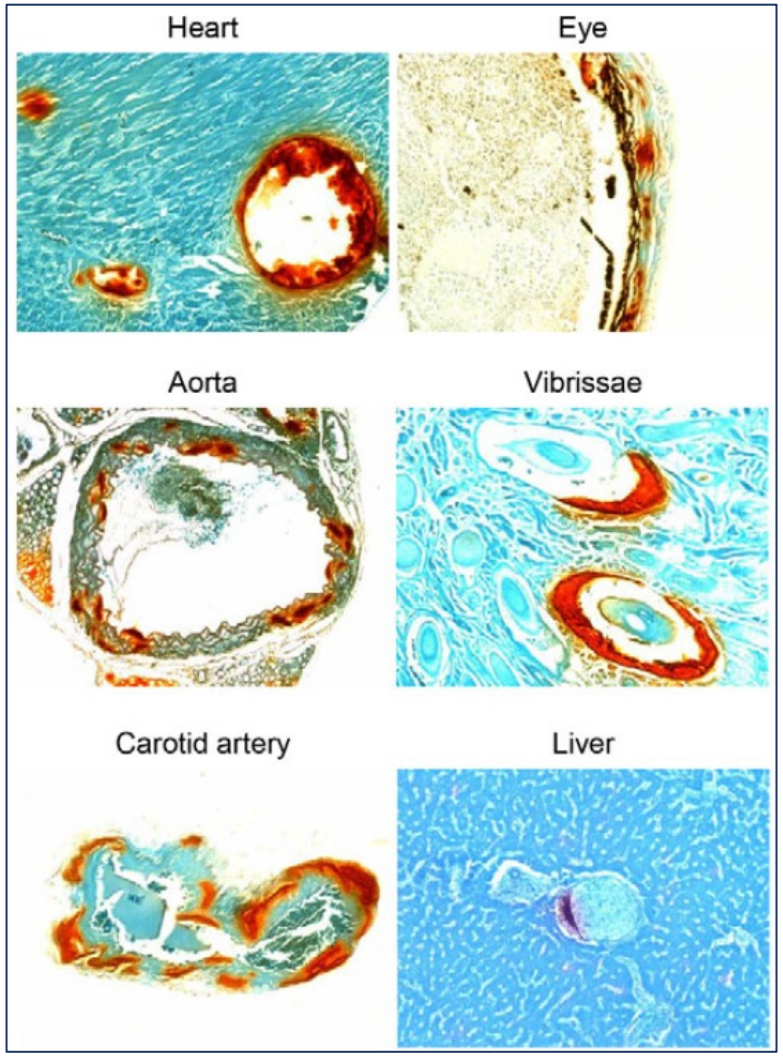
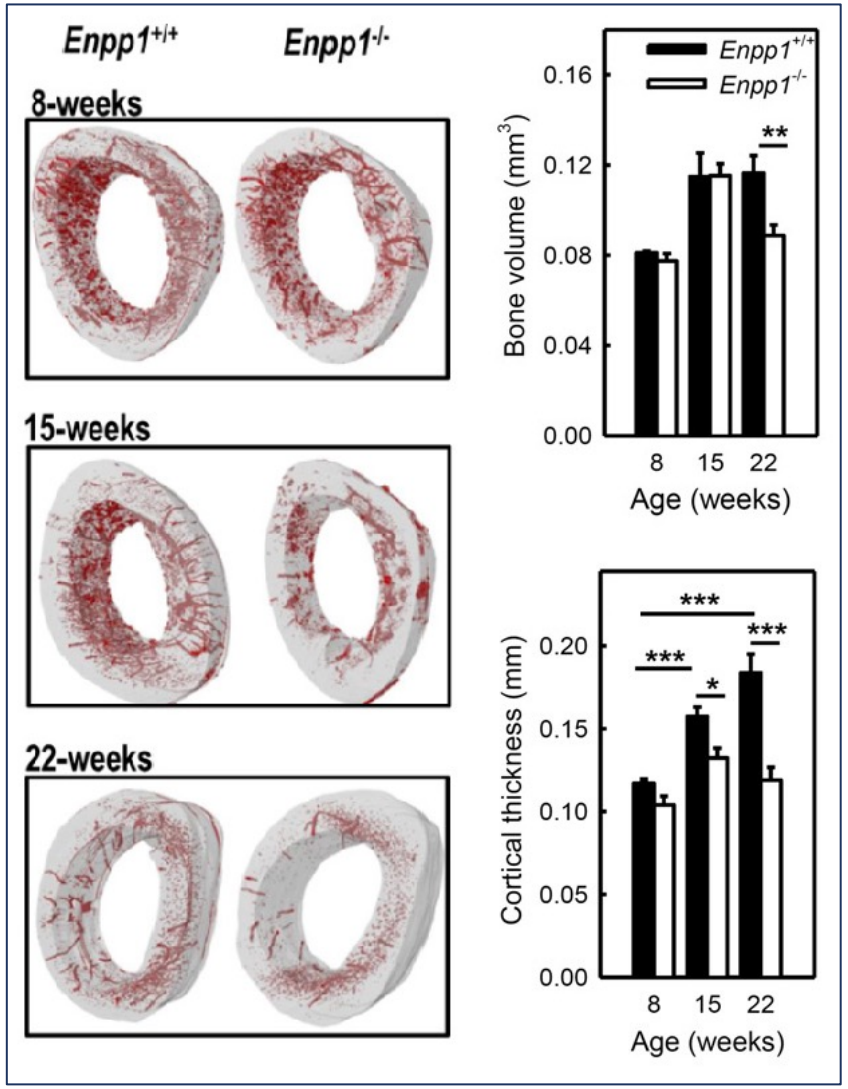
Enpp1 deficient mice recapitulate phenotypes of human disease

Enpp1$^{asj/asj}$ mice develop tissue calcification



Li, 2013

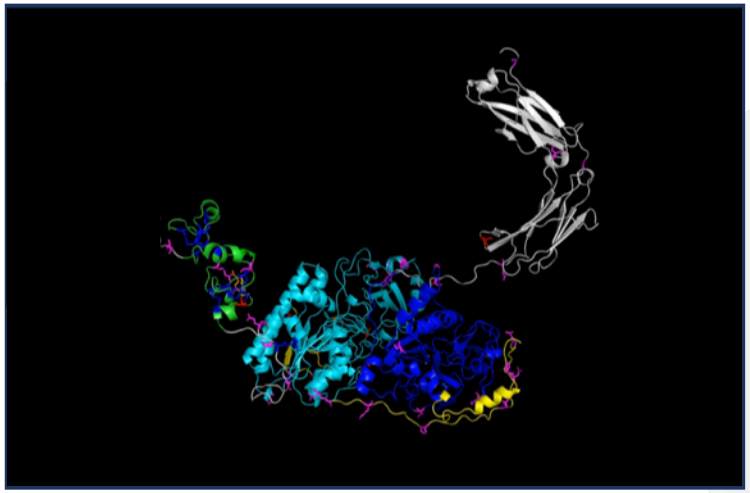
Enpp1$^{-/-}$ mice develop bone defects



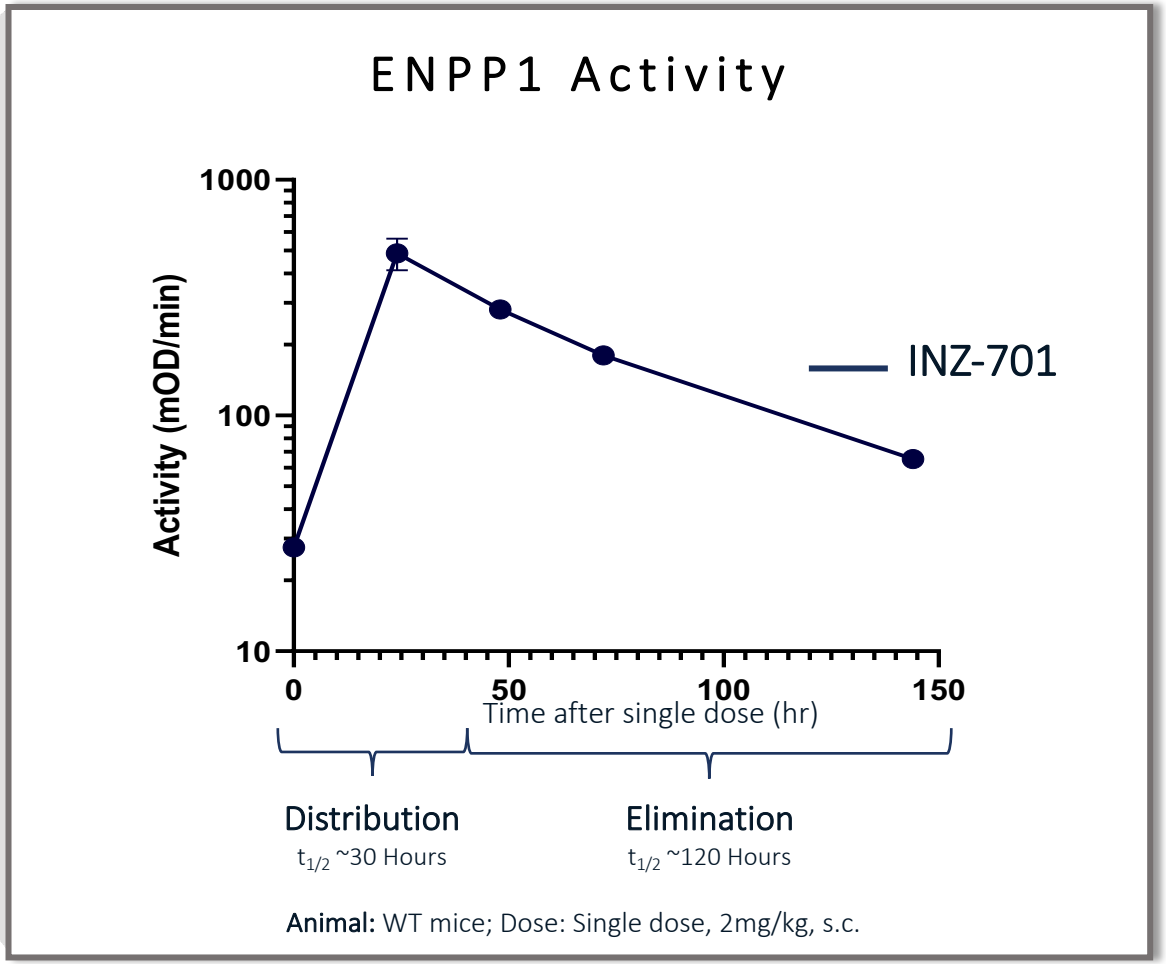
Hajjawi, 2014

INZ-701 as an ERT in development for ENPP1 Deficiency

INZ-701 (ENPP1-Fc)



- **Protein:** Recombinant human ENPP1 (Ectonucleotide pyrophosphatase/phosphodiesterase 1)
- **Construct:** Recombinant Fc fusion protein with soluble extracellular domain of ENPP1
- **Dosing:** TBD
- **Enzymatic Properties:** High catalytic efficiency (Kcat/Km)



Dose response study design

Animal	Diet	Test Article	Dosing	Start	End	Readouts
WT	Acceleration diet* from gestation	vehicle	s.c.; q.o.d	2wk of age (D1)	10wk of age (D56)	• Enpp1 activity • Plasma PPi • Tissue calcium • Body weight • Bone parameters • Clinical signs
Enpp1$^{asj/asj}$		vehicle				
Enpp1$^{asj/asj}$		INZ-701, 0.2mg/kg				
Enpp1$^{asj/asj}$		INZ-701, 1mg/kg				
Enpp1$^{asj/asj}$		INZ-701, 5mg/kg				

*Acceleration diet: high in phosphate and low in magnesium

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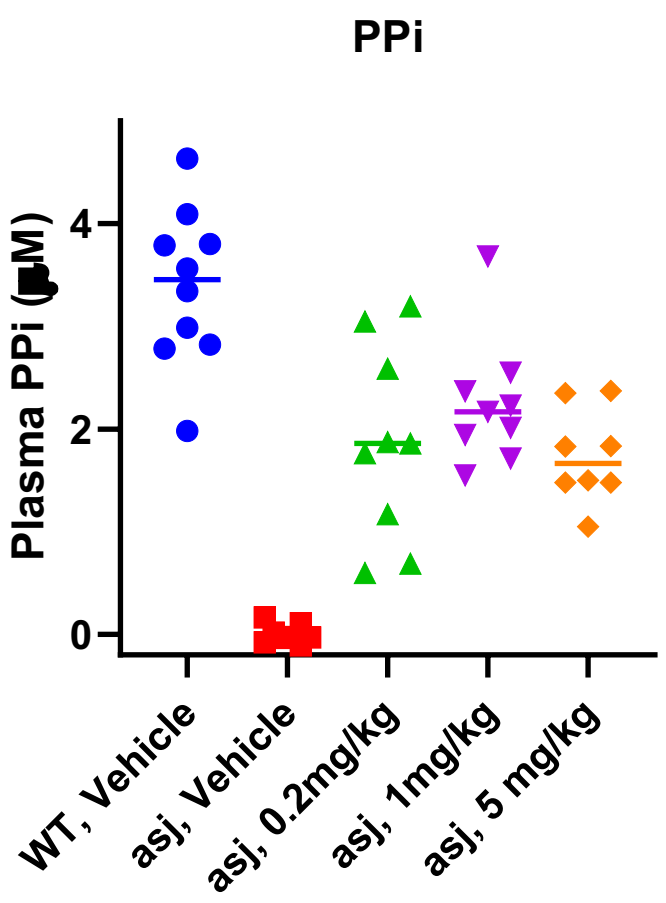
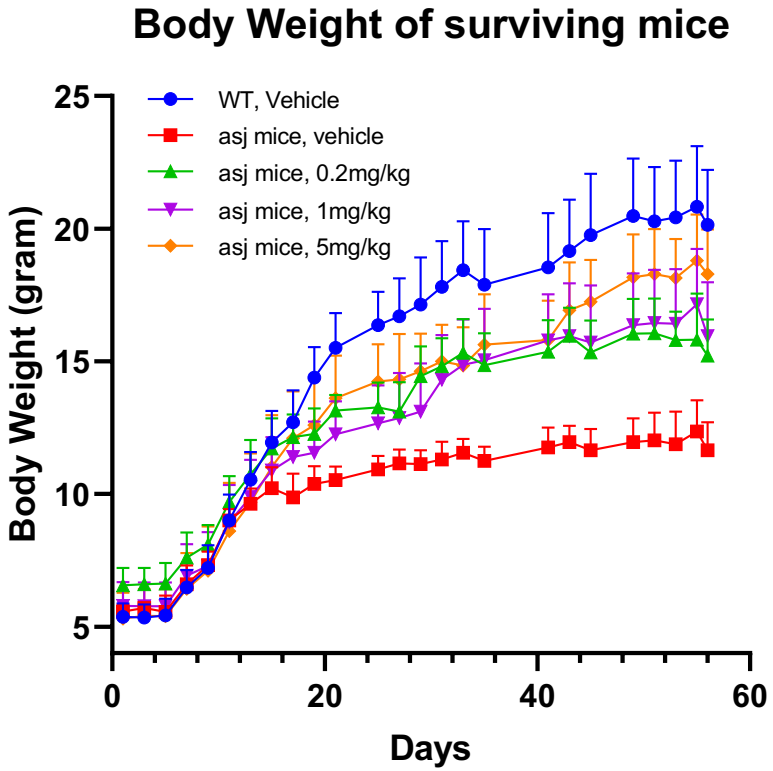
INZ-701 normalizes plasma PPi levels and improves clinical signs



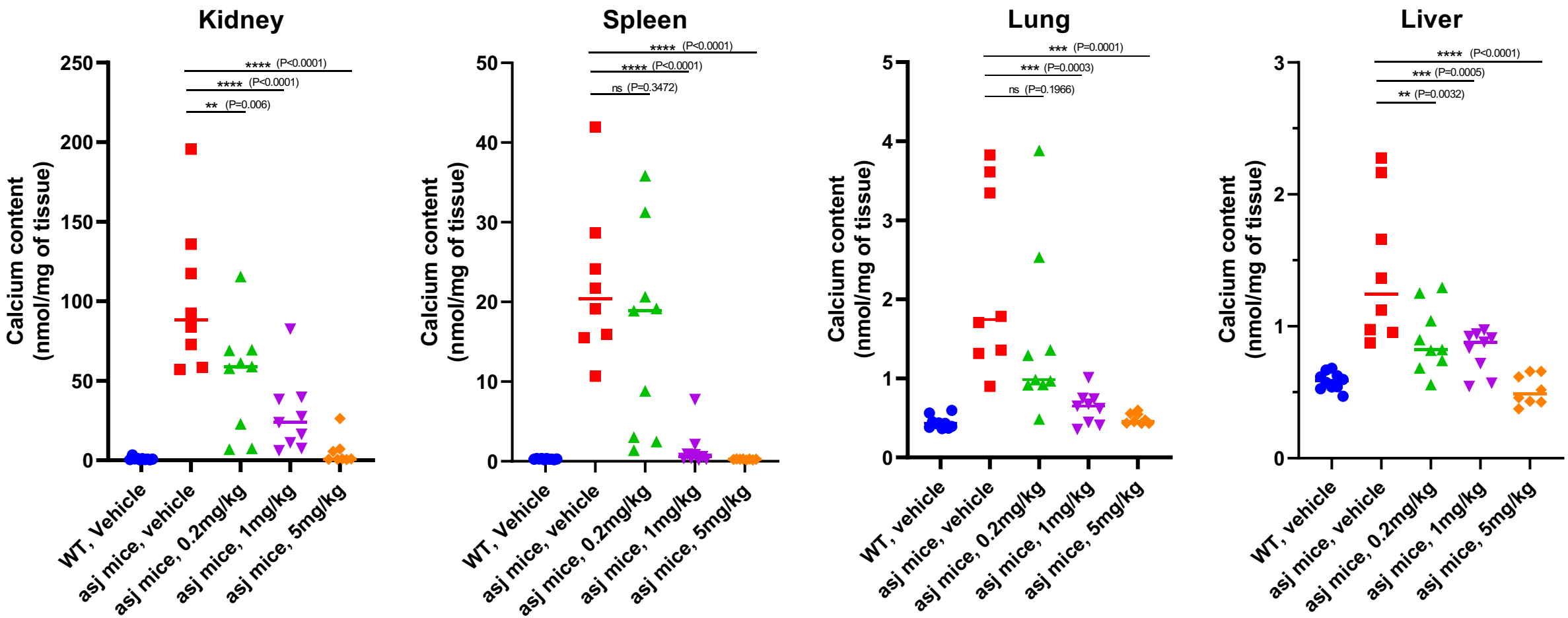


Clinical signs

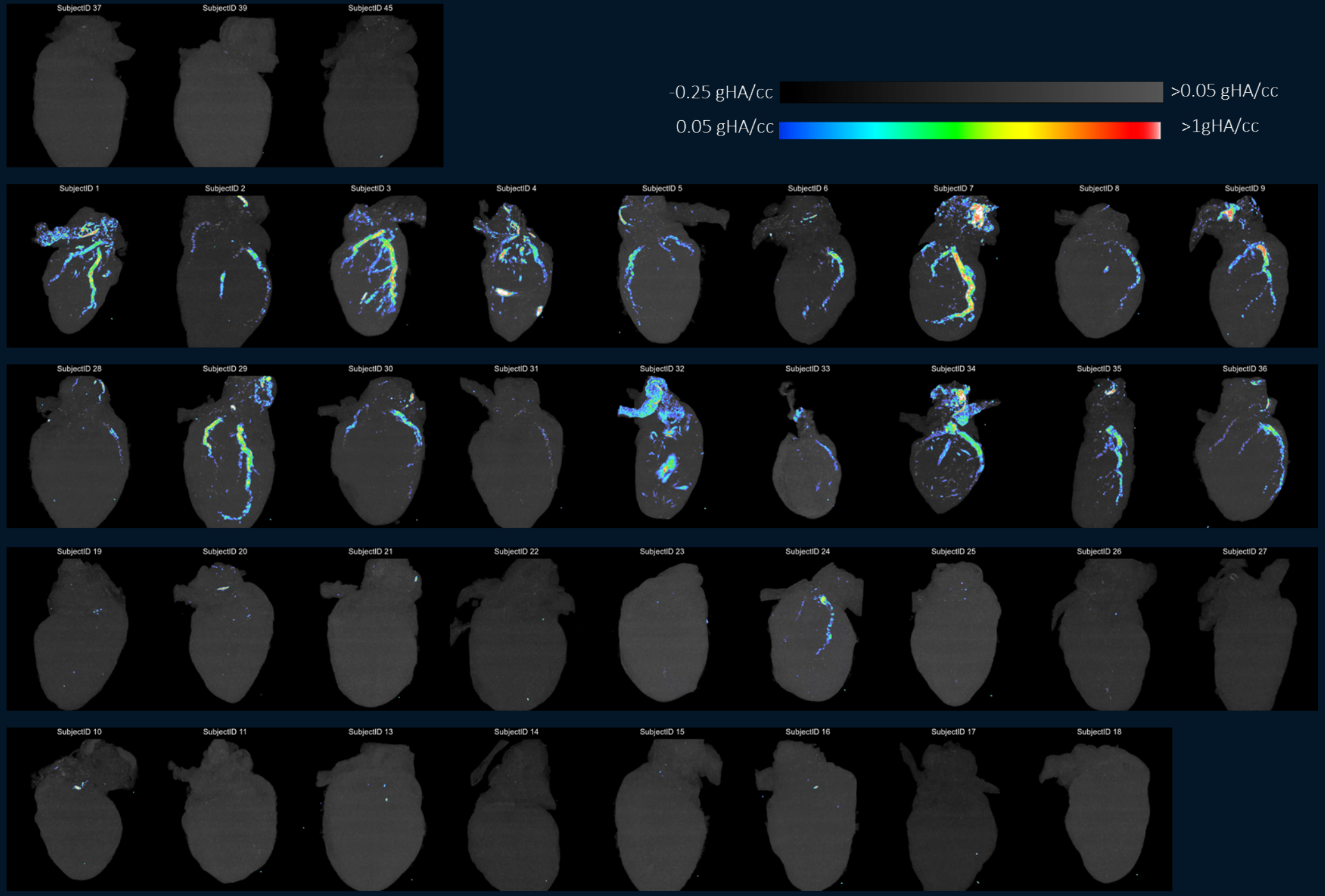
- *Enpp1*$^{asj/asj}$ mice treated with **vehicle** showed pinned ears, stiff legs, stilted gait, hunched back, dehydration

- *Enpp1*$^{asj/asj}$ mice treated with **5mg/kg INZ-701** showed no abnormality

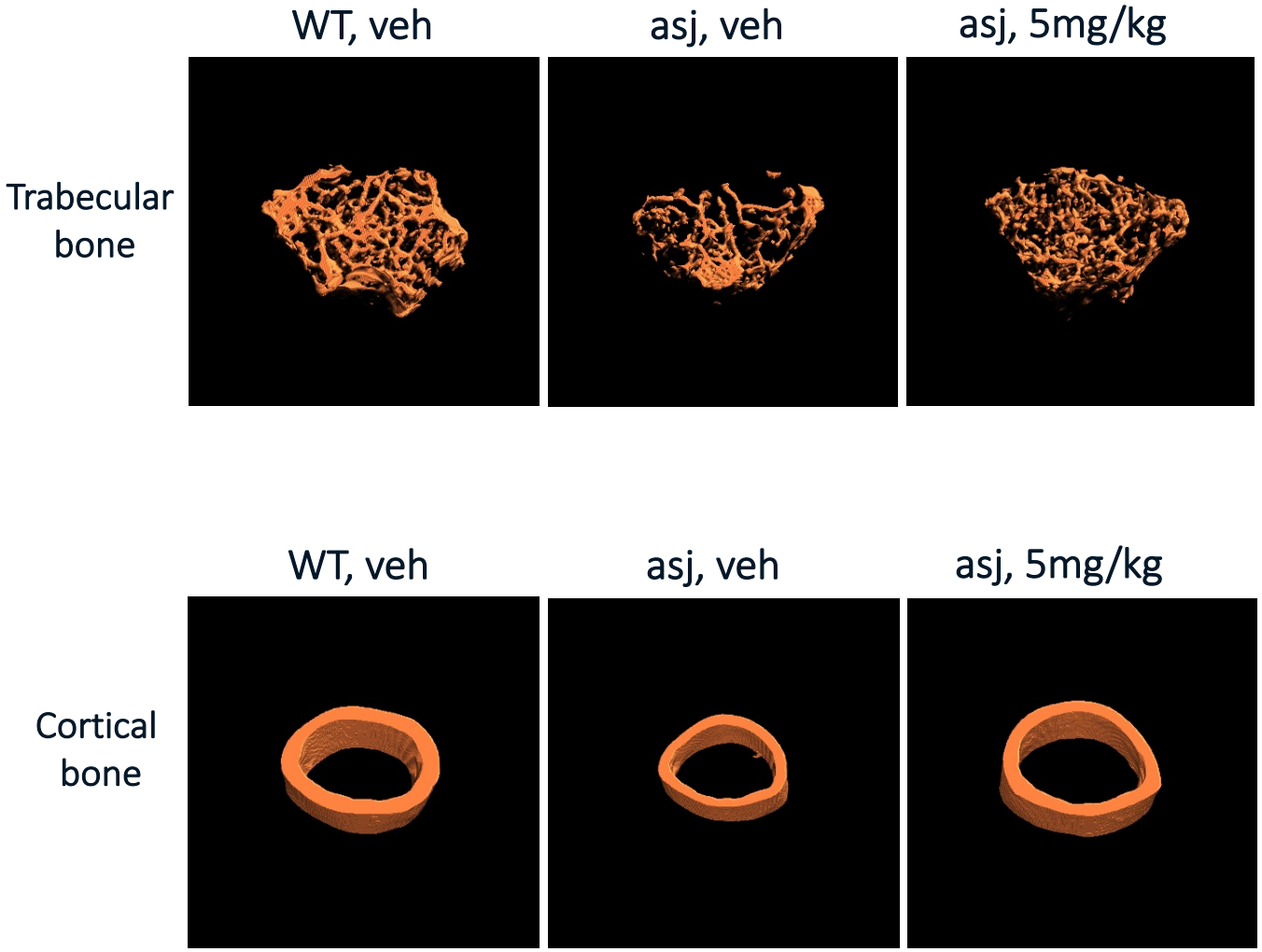
INZ-701 prevents tissue calcification

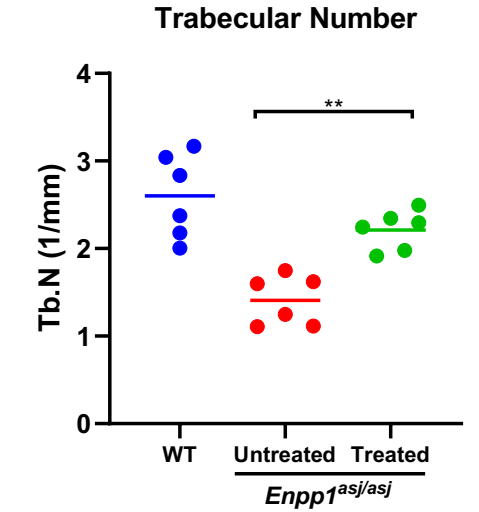


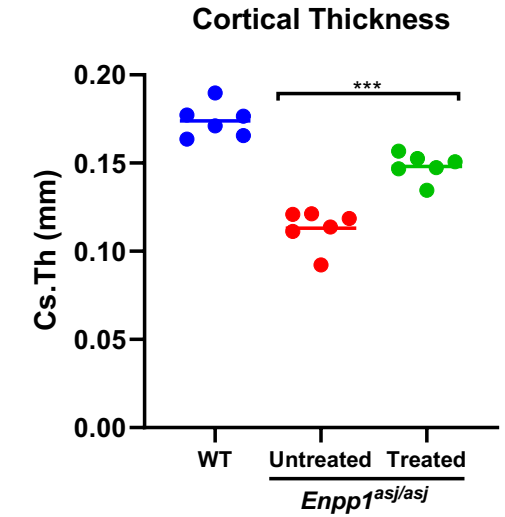
Dose response_µCT of hearts and aorta



hENPP1-Fc corrects bone defects in Enpp1 deficient mice







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Summary

INZ-701, a human ENPP1-Fc ERT, shows dose-dependent therapeutic effects in an Enpp1 deficient mouse model.

- Normalizes plasma pyrophosphate (PPi) levels
- Prevents tissue calcification
- Corrects bone defects
- Restores growth and improves clinical signs

Acknowledgment

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