Impact of INZ-701 on Bone and Mineral Metabolism Biomarkers and Clinical Outcomes in Adults with ENPP1 Deficiency – Results from 48-week Phase 1/2 Open Label Study

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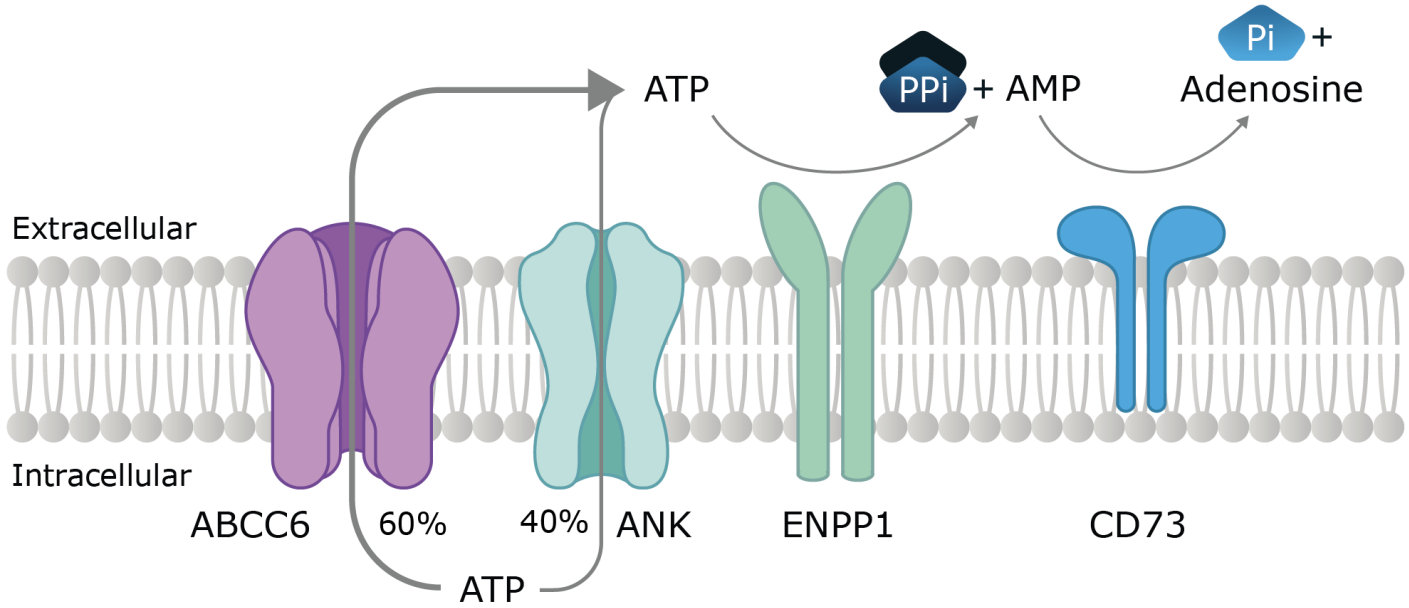
Disclosures

This study was funded by Inozyme Pharma.

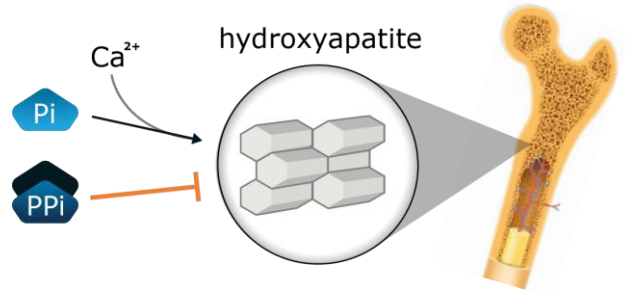
- YS and KG are employees of and stockholders in Inozyme Pharma.
- DW is a former employee of Inozyme Pharma.
- RF is an employee of Parexel, the sponsor’s CRO for study conduct.
- RW, DS and AB have nothing to disclose.

ENPP1 is a key component of the pyrophosphate-adenosine pathway[1-3]

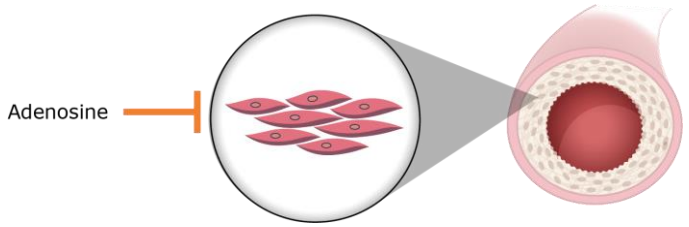
1. ABCC6 and ANK transport ATP from intracellular to extracellular space
2. ENPP1 metabolizes ATP into PPi and AMP
3. CD73 metabolizes AMP into Pi and adenosine



Pyrophosphate (PPi) regulates skeletal mineralization[1]



Adenosine inhibits vascular smooth muscle cell proliferation[1-3]



ABCC6, ATP binding cassette subfamily C member 6; AMP, adenosine monophosphate; ANK, progressive ankylosis protein; ATP, adenosine triphosphate; Ca, calcium; CD73, ecto-5'-nucleotidase; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; HA, hydroxyapatite; Pi, inorganic phosphate; PPi, inorganic pyrophosphate.

1. Ralph D, et al. *Am J Pathol*. 2022;192:762–770. 2. Nitschke Y, et al. *Exp Mol Med*. 2018;50(10):1–12. 3. Albayrak G, et al. *Vascular*. 2015;23:124–131.

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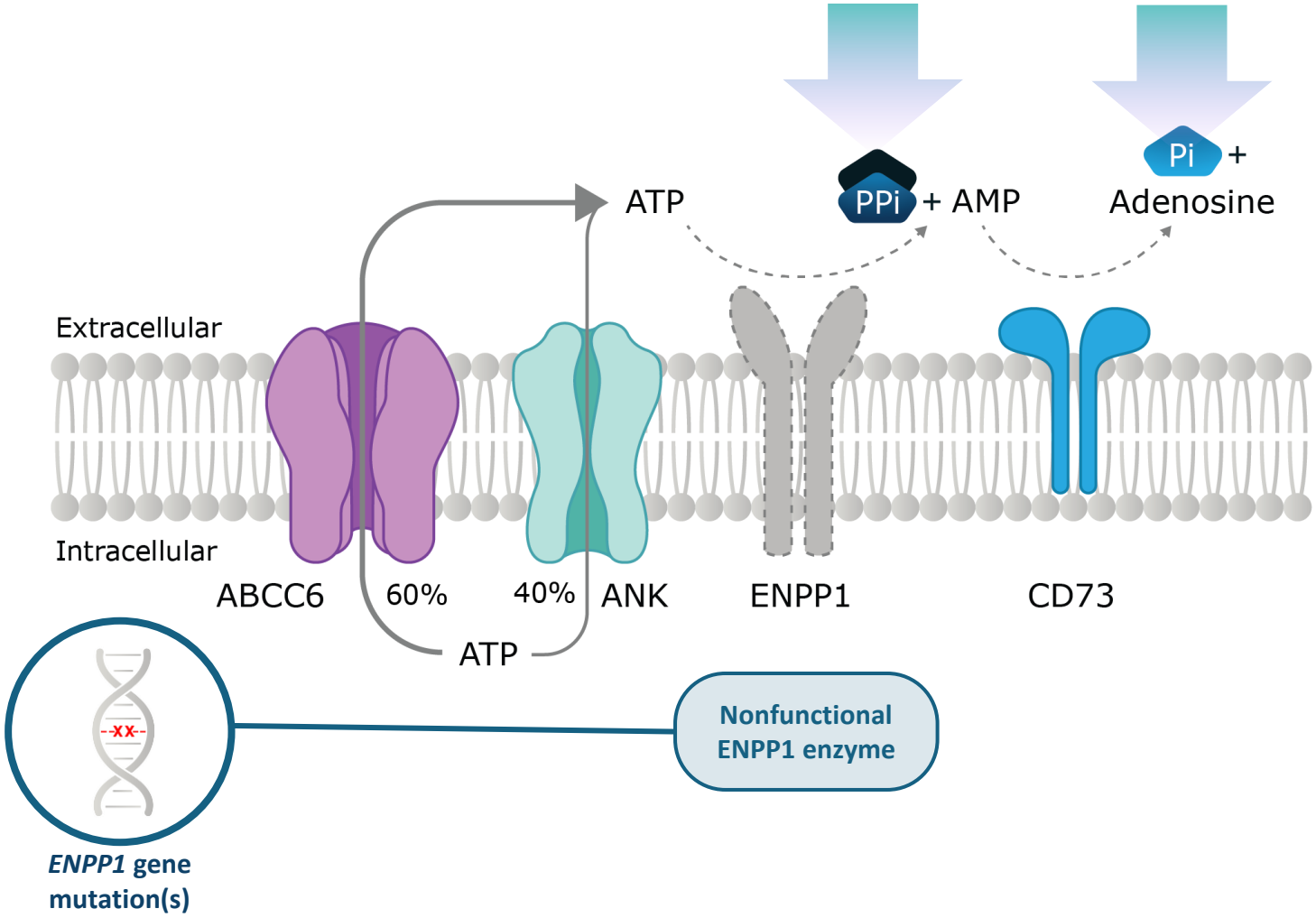
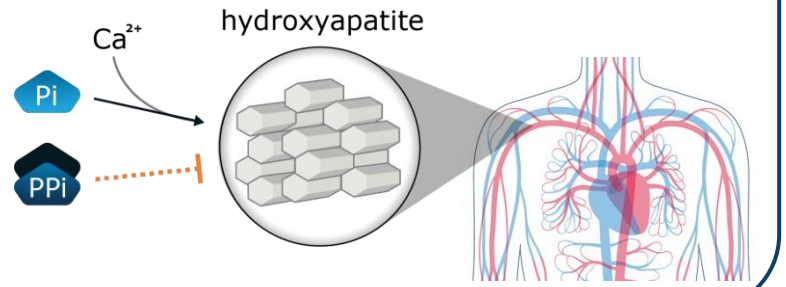
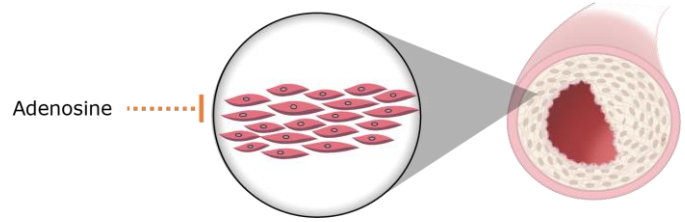
Low PPi and low adenosine due to ENPP1 Deficiency lead to ectopic calcification and arterial intimal proliferation[1-3]



Low PPi levels lead to **soft tissue mineralization**[1]



Low adenosine levels lead to intimal proliferation and **artery lumen narrowing**[1-3]



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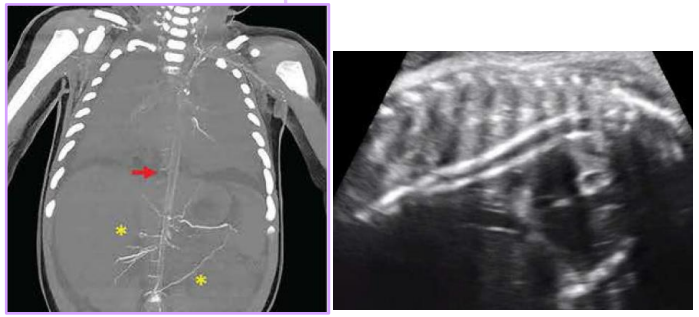
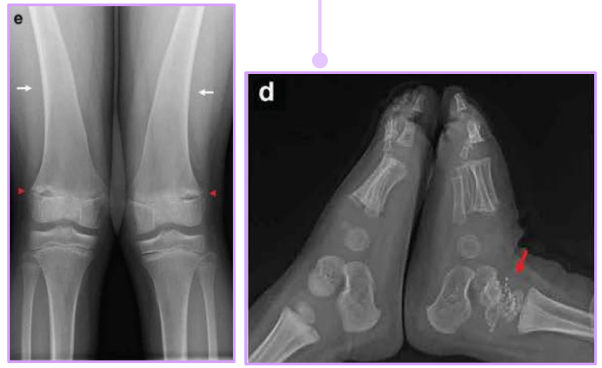
The Natural History of ENPP1 Deficiency[1-5]

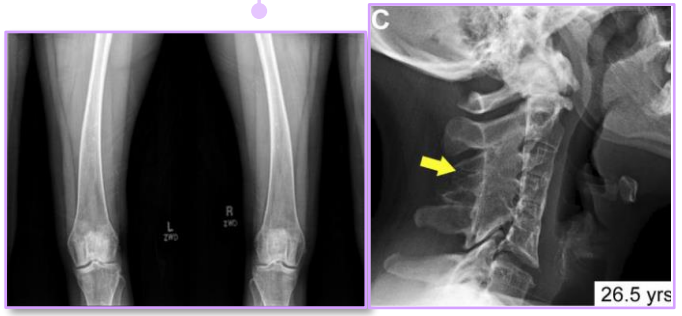
INFANCY*

CHILDHOOD/ ADOLESCENCE

ADULTHOOD







Findings	Arterial calcification (CT, US) Arterial stenosis (CTA, US)	Rickets (Xray) Hypophosphatemia, inc. FGF23 (labs) Joint/ ligament calcification (X-ray, CT)	Osteomalacia (Xray) Hypophosphatemia, inc FGF23 (labs) Joint/ ligament calcification (X-ray, CT)
Signs/Symptoms	• Severe cardiovascular complications • >50% mortality by 6 months of age[1-2]	• Bone deformities • Impaired growth • Hearing loss	• Bone and joint pain • Mobility impairment
Phenotype	**Generalized Arterial Calcification of Infancy (GACI)**	**Autosomal Recessive Hypophosphatemic Rickets Type 2 (ARHR2)**	

Biallelic Genetic Prevalence[6]: 1:64, 000

Not all patients with ENPP1 Deficiency have medical history of GACI.
Patients may first present in childhood-adulthood with musculoskeletal problems[5]

ECHO, echocardiography; CT, computed tomography; US, ultrasound

1. Ferreira CR, et al. *J Bone Miner Res*. 2021;36(11):2193-2202. 2. Rutsch F, et al. *Circ Cardiovasc Genet.* 2008;1(2):133-140 3. Ferreira CR et al. *Genet Med*. 2021;23(2):396-407.; 4. Boyce AM et al. *Curr Osteoporos Rep*. 2020;18(3):232-241.; 5. Kotwal A et al. J Bone Miner Res. 2020 Apr;35(4):662-670.; 6. Ferreira et al. Orphanet Journal of Rare Diseases

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Adult ENPP1 Deficiency Phase 1/2 trial

A Phase 1/2, open-label, multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of INZ-701 followed by an open-label long-term extension period in adults with ENPP1 Deficiency

Study Population:
Adults

Eligibility Criteria:

- Age 18-64 years
- Confirmed clinical and genetic diagnosis
- PPi < 1300 nM

Primary Goals

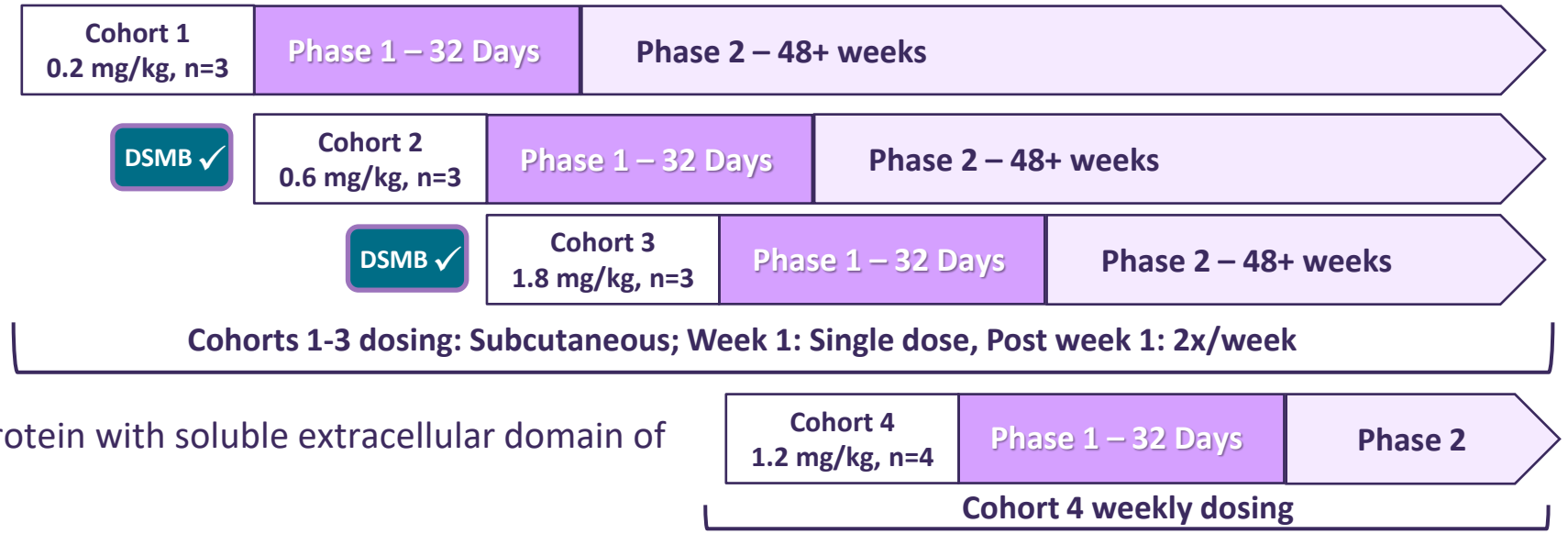
- **Safety** and **tolerability**
- **Immunogenicity**
- **Pharmacokinetic properties**
- **Pharmacodynamics (PPi)**

Secondary Goals

Evaluate potential endpoints for pivotal study

- **Ectopic calcification**, **skeletal**, **vascular** and **physical function**, and **patient reported outcomes**
- Exploratory **biomarkers**

Study Design:



INZ-701: Recombinant Fc fusion protein with soluble extracellular domain of ENPP1

DSMB = Data Safety Monitoring Board.
Clinicaltrials.gov: NCT04686175 .

Purpose:

To describe the **safety** and **exploratory efficacy** of INZ-701 in adults with ENPP1 Deficiency through the end of the phase 2 study period (**week 48**).

Results: Baseline Demographics

		Cohort 1 0.2 mg/kg biweekly (n=3)	Cohort 2 0.6 mg/kg biweekly (n=3)	Cohort 3 1.8 mg/kg biweekly (n=3)	Cohort 4 1.2 mg/kg weekly (n=4)
AGE (YEARS)	**Median**	31	43	25	29
	Range	23-40	30-58	22-29	20-58
GENDER	**Male (n=5)**	0	1	2	2
	Female (n=8)	3	2	1	2
RACE	**White (n=9)**	3	3	2	1
	Asian (n=2)	0	0	0	2
	Not reported (n=2)	0	0	1	1

Results: Medical History

MEDICAL CONDITION	Cohort 1 0.2 mg/kg biweekly (n=3)	Cohort 2 0.6 mg/kg biweekly (n=3)	Cohort 3 1.8 mg/kg biweekly (n=3)	Cohort 4 1.2 mg/kg weekly (n=4)	Total (n=13)
Rickets/osteomalacia	3	2	3	4	12
Cardiovascular disease	2	3	2	3	10
Arterial calcification/stenosis/surgery	2	3	1	3	9
GACI	3	1	1	3	8
Soft tissue/joint calcification	1	2	2	3	8
Bone deformity/orthopedic surgery	0	1	3	3	7
Hearing loss	0	2	2	3	7
Nephrocalcinosis/nephrolithiasis	0	2	2	2	6
Arthritis/arthralgia	2	2	0	1	5
Hypertension	1	2	1	1	5

INZ-701 exhibited a favorable safety profile across dosing cohorts

Event	INZ-701 dose cohort – No. of patients with at least one event				Total patients (n=13)
	0.2 mg/kg biweekly n=3	0.6 mg/kg biweekly n=3	1.8 mg/kg biweekly n=3	1.2 mg/kg weekly n=4	
Adverse event (AE)	3	3	2	3	11
Adverse event related to INZ-701	2	1	1	3	7
Serious adverse event	0	2	0	0	2

Most adverse events were mild or moderate in severity

- 7/13 patients experienced adverse events related to INZ-701, all mild in severity
  - Injection site reactions occurred in 5 patients
  - Other related adverse events included decreased appetite, extremity pain and fatigue

2 serious adverse events - not related to INZ-701

- Patella fracture (motor vehicle accident), cardiac surgery complication

No adverse events led to discontinuation of INZ-701

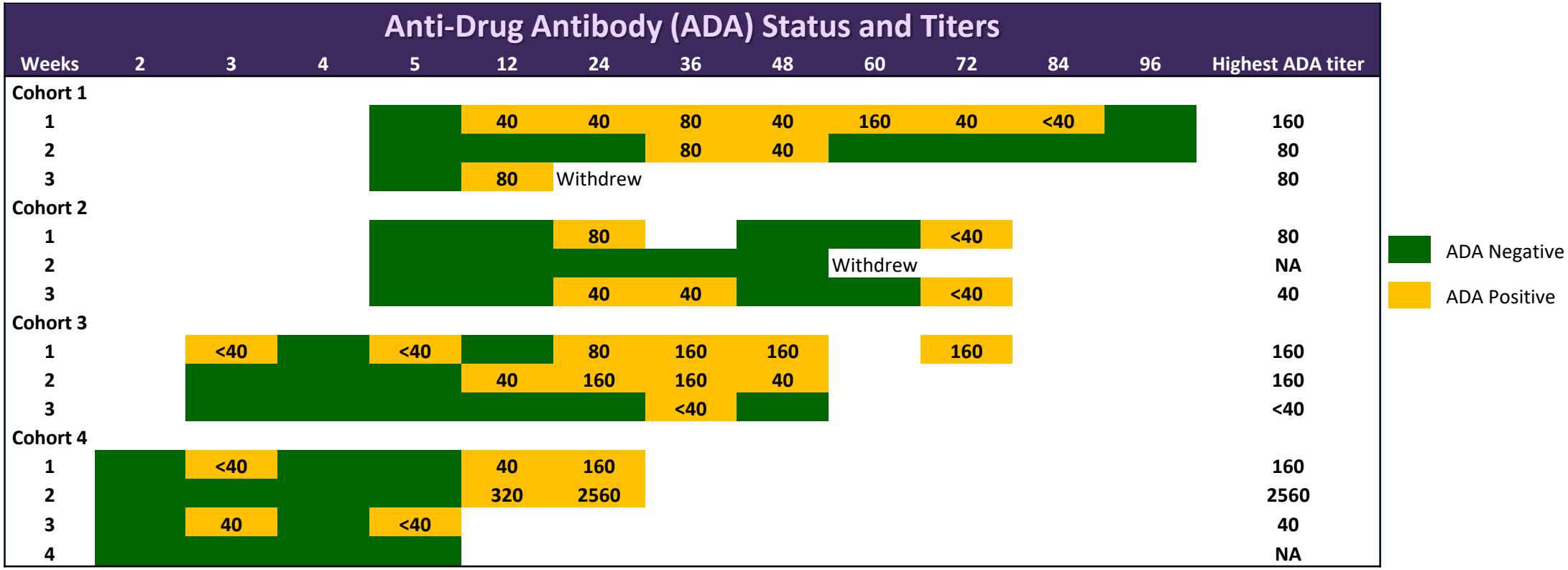
No adverse events led to study withdrawal from Phase 1

- 2 patients withdrew from Phase 2 (1 from cohort 1 and 1 from cohort 2); not related to adverse events
- 11 patients remain on study; 10/11 transitioned to self-administration
- Time on study range: 22-742+ days; 12+ patient-years

Data cut – 4 Jan 2024

Favorable immunogenicity profile observed

Low, non-neutralizing anti-drug antibodies (ADAs) were detected; Transient in at least 3 of 11 patients



ADA titers for other enzyme replacement therapies were observed in previously conducted trials by other companies

STRENSIQ® ADA titers: 2,048[1]; patients with ADA: 89%[4]

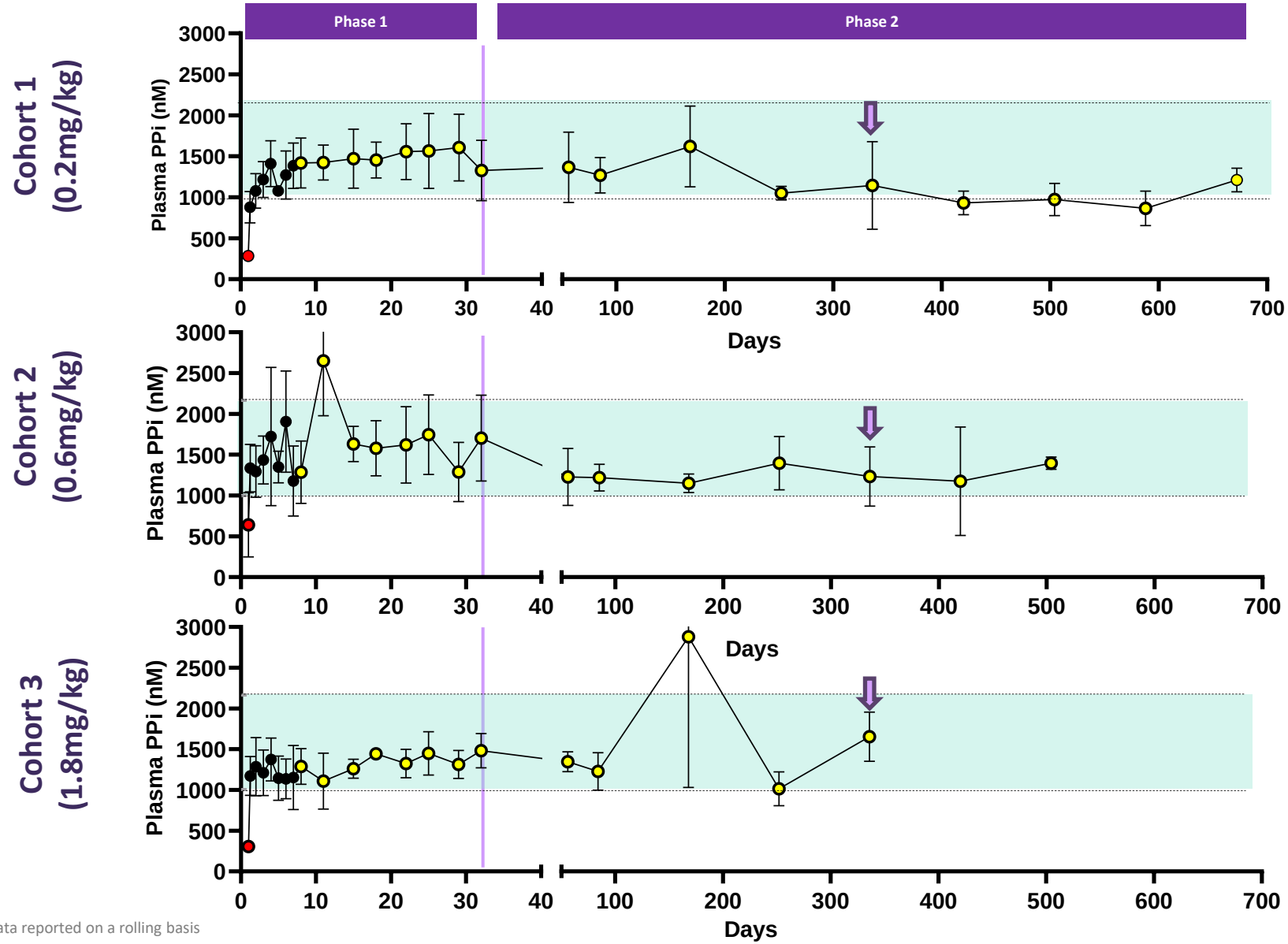
ALDURAZYME® ADA titers: 31,972[2]; patients with ADA: 97%[4]

LUMIZYME® ADA titers: >51,200[3]; patients with ADA: 89%[4]

Data cut Mar 4, 2024; ADA titer range measured as dilution factor

1. Hofmann et al, JCEM 2019; 2. Xue et al, Mol Genet Metab 2016; 3.Kazi et al, JCI 2017; 4. Product USPI 23

Results: Plasma PPi by Dosing Group



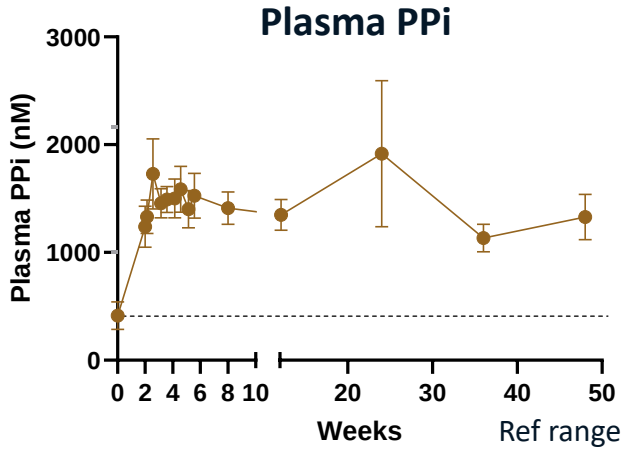
- Rapid increase observed after the 1st dose
- PPi levels reached the healthy volunteer range after the 1st dose

Baseline PPi (pre-dose) + 1st INZ-701 dose
PPi measurement (post-dose)
PPi measurement (pre-dose)
Healthy subject PPi levels; n=10
Data presented as mean ± SEM
48-week timepoint

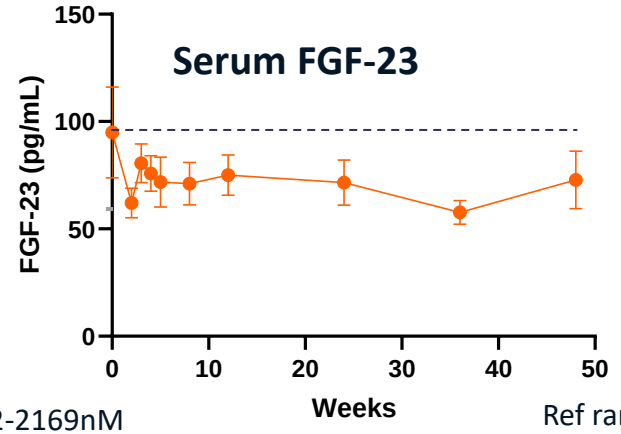
Data reported on a rolling basis

Results: Pooled Plasma PPi, Serum FGF-23, and Serum Pi

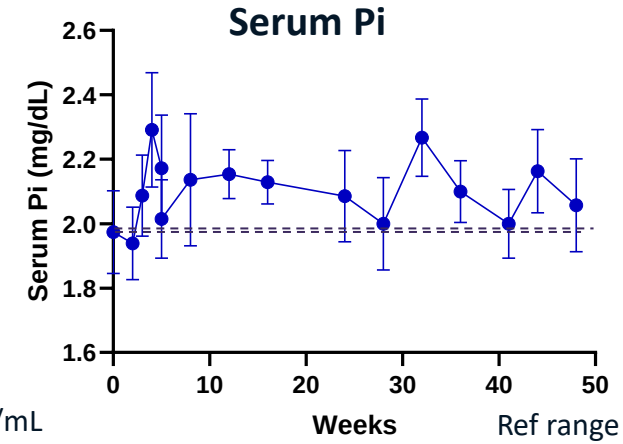
Pooled Cohorts 1-3: Baseline vs mean Week 2-48 PPi, FGF-23, and Pi levels (±SEM)



Ref range : 1002-2169nM



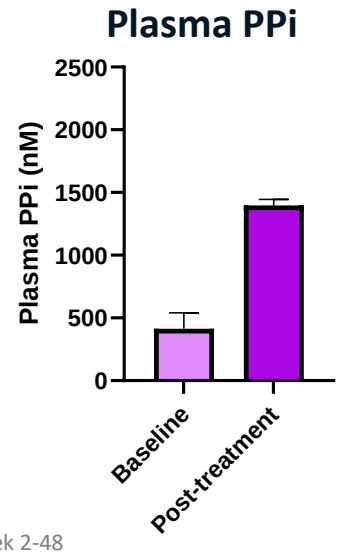
Ref range : <59pg/mL

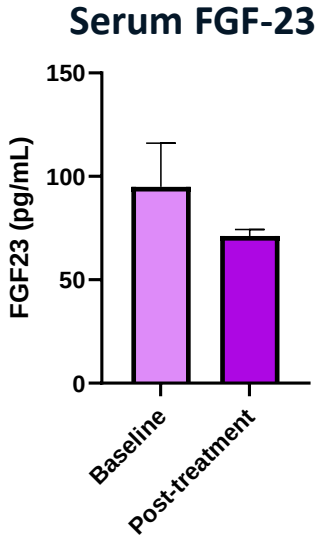


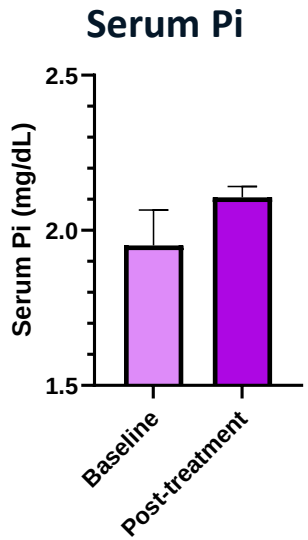
Baseline

Ref range : 2.5-4.5mg/dL

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



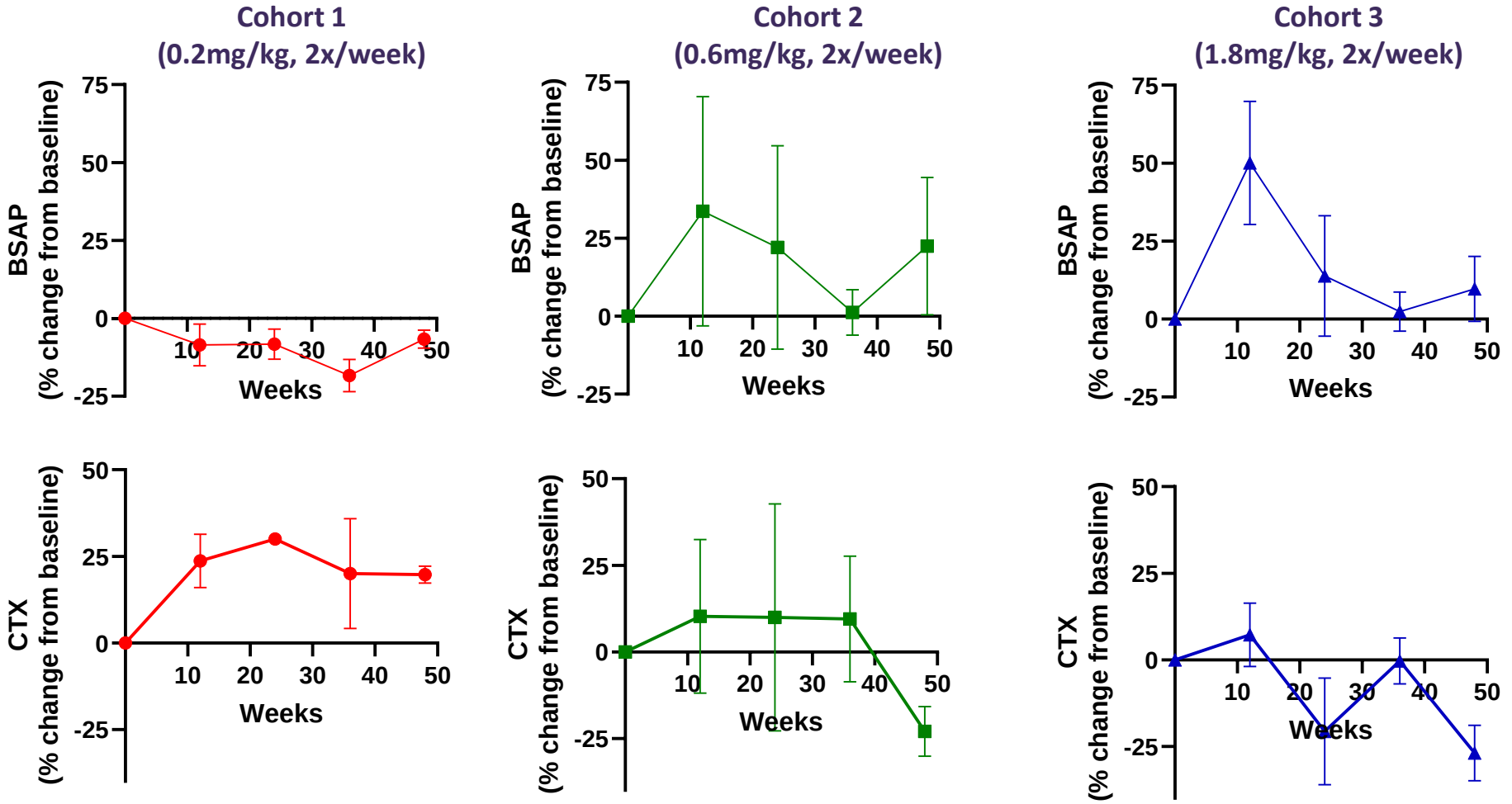




<u>Note</u>: Serum Pi increases observed in absence of phosphate and active vitamin D supplementation

Post-treatment: Week 2-48
Data cut Jan 25, 2024 ; Data presented as mean ± SEM

Results: Bone Mineral Biomarkers by Dosing Group



Bone-specific alkaline phosphatase (BSAP): Key enzyme involved in mineral deposition in bone[1]

- BSAP hydrolyzes PPi and increases local phosphate concentration
- Similar response observed with other treatments of rickets (XLH, VDDR)[2]

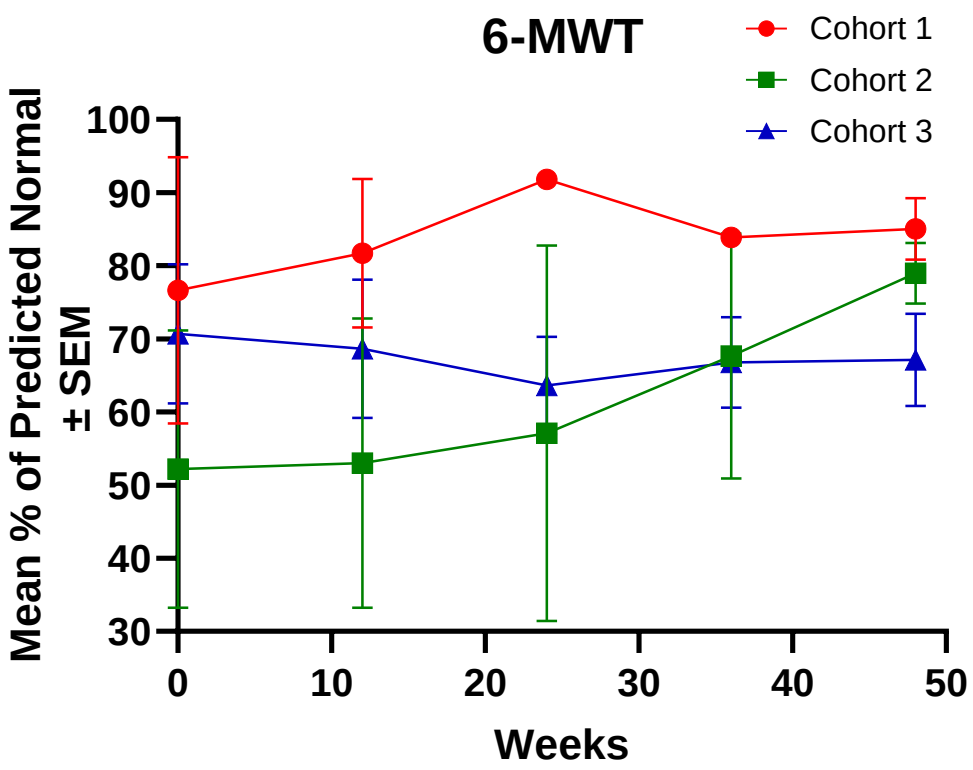
C-telopeptide I (CTX) is a bone resorption marker[1]

- CTX is a product of the breakdown of type I bone collagen

Data cut Jan 25, 2024. Data expressed as cohort mean ± SEM. *XLH – X-linked hypophosphatemic rickets, VDDR – Vitamin D-deficient rickets*

1. Schini M, et al. *Endocr Rev*. 2023;44(3):417-473. 2. Weber TJ et al. *J Clin Endocrinol Metab*. 2022;108(1):155-165.

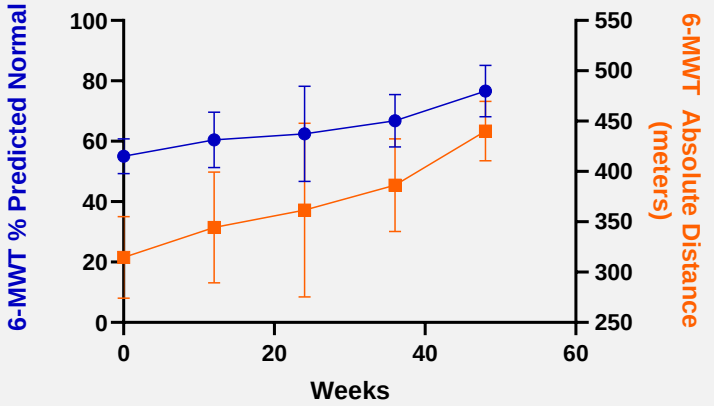
Results: 6-Minute Walk Test (6-MWT) by Dosing Group and by Baseline 6-MWT



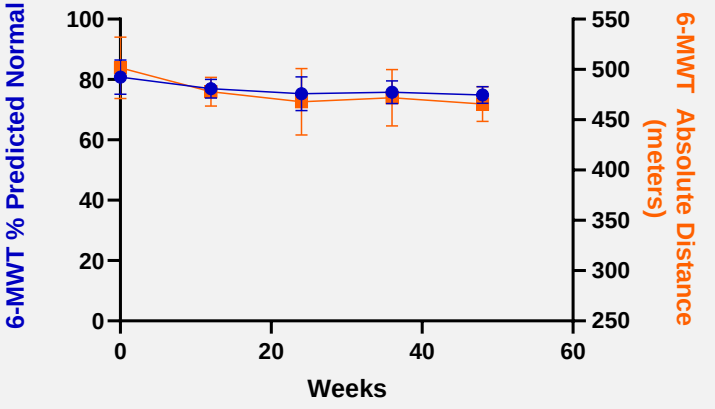
Percent predicted normal adjusts for subject age, sex, height and weight

Greater improvement observed in patients with poor baseline 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)



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

Results: PROMIS Scale (PRO) by Dosing Group

Improvements seen at all dose levels

Pain Intensity	
Cohort	**Responders (n)**
Cohort 1	
Cohort 2	
Cohort 3	
Total	

Pain Interference	
Cohort	**Responders (n)**
Cohort 1	
Cohort 2	
Cohort 3	
Total	

Fatigue	
Cohort	**Responders (n)**
Cohort 1	
Cohort 2	
Cohort 3	
Total	

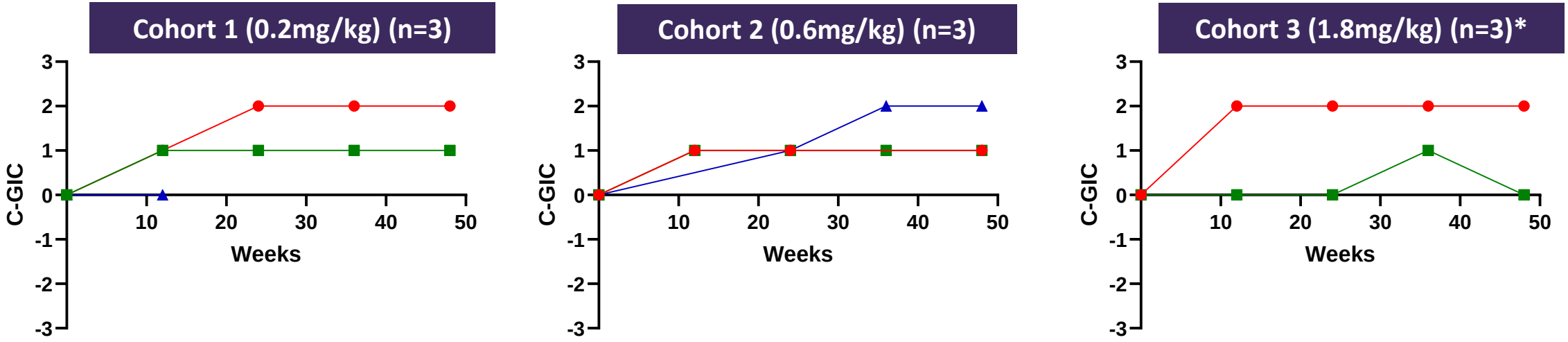
Responder defined as exhibiting improvement from baseline in >50% of timepoints evaluated

Responders
Non responders

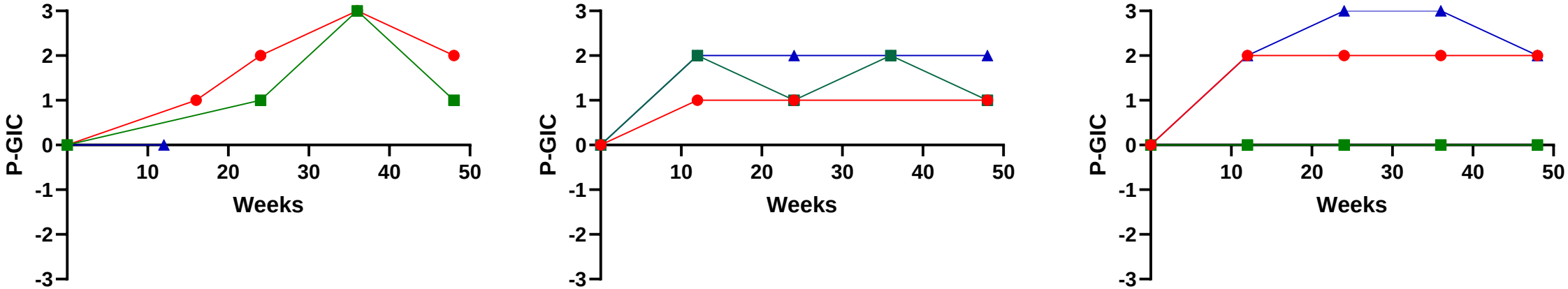
Data cut Jan 25, 2024

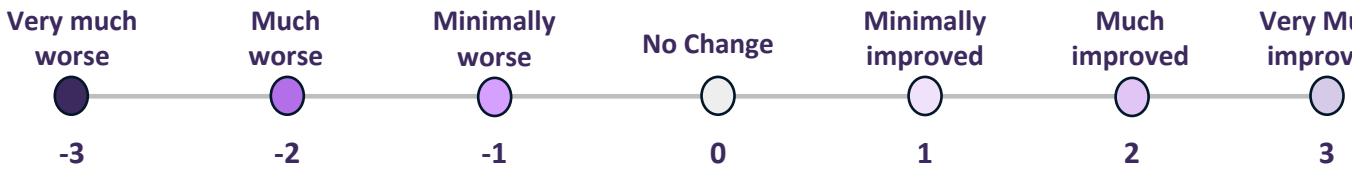
Results: Global Impression of Change Scale

Clinician's Global Impression



Patient's Global Impression





* n=2 for C-GIC

Data cut Jan 25, 2024
Colors represent individual patients in respective cohorts

Conclusions

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

- Study fully enrolled in all 4 cohorts (n=13)
- PK data from cohort 4 support once per week dosing in future clinical studies in ENPP1 Deficiency
- Favorable safety profile was maintained
  - 11 patients remain on study; 10/11 transitioned to self-administration
- PPi remained elevated from baseline and within the normal reference range with long term treatment
- Mechanism of action supported by increase in PPi levels and improvement in serum phosphate and FGF-23
- Bone biomarker response consistent with restoring proper bone mineralization
- Low titer ADAs observed in 11/13 patients with no neutralizing ADAs; ADAs transient in 3/11 patient
- Favorable response on clinical outcomes (6-minute walk test and PRO's) was maintained
- Additional clinical trials are ongoing in infants (ENERGY-1; NCT05734196) and older pediatric patients (ENERGY-3; NCT06046820)

Acknowledgements

The authors would like to thank the patients and their families who took part in this clinical study. We acknowledge the contributions of investigators and study coordinators.