Impact of the Enzyme Replacement Therapy, INZ-701, in Children with ENPP1 Deficiency: Experience from An Expanded Access Program

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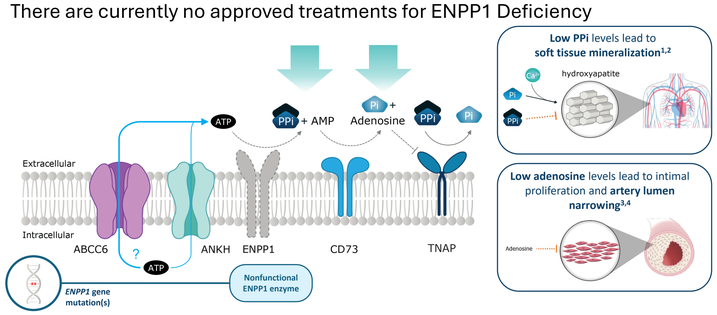
Introduction

- Ectonucleotide pyrophosphatase/phosphodiesterase family member 1 (ENPP1) is a critical enzyme that generates pyrophosphate (PPi), a mineralization inhibitor, and adenosine, a regulator of vascular smooth muscle cell proliferation[1-4]
- Biallelic variants in the *ENPP1* gene lead to 2 age-related phenotypes: Generalized arterial calcification of infancy (GACI) and autosomal recessive hypophosphatemic rickets type 2 (ARHR2), which evolve on a phenotypic continuum[5-6]
- ENPP1 Deficiency typically presents in infancy (GACI) with widespread arterial calcification, severe cardiovascular complications, and high infant mortality (50% in the first 6 months of life)
- All patients with ENPP1 Deficiency who survive beyond infancy develop phosphate-wasting rickets (ARHR2), expected to develop after 1 yr[5-6]
- ENPP1 Deficiency is associated with other multi-system organ complications, with considerable variability in clinical presentation across individual patients[5-6]
- There are currently no approved treatments for ENPP1 Deficiency



Treatment & Methods

- INZ-701 is an investigational enzyme replacement therapy in clinical development for ENPP1 Deficiency. Administered subcutaneously, it is designed to replace deficient ENPP1 activity and restore balance to the PPi-adenosine pathway, thus addressing calcification, phosphate homeostasis, and intimal proliferation
- Here we report experience in 3 children who received INZ-701 in an expanded access program due to the criticality of their disease, ineligibility for a clinical trial, or geographic distance from trial sites
- Patients received INZ-701 at doses ranging from 0.6 mg/kg twice weekly to 2.4 mg/kg weekly
- Patients were followed for safety; clinical assessments performed as part of routine care were collected
- Data are reported as of 13 December 2024

References

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Results

Two infants and a toddler treated with INZ-701 for a median of 13 (10-18) months

Evidence of improved heart function and controlled hypertension

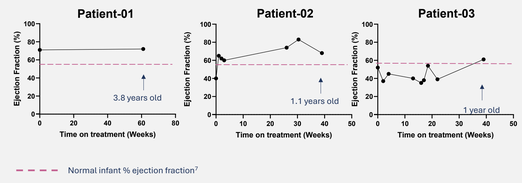
Reduced or stabilized arterial calcifications, a key driver of mortality

Increased or stabilized hypophosphatemia and early evidence of reduced risk for rickets

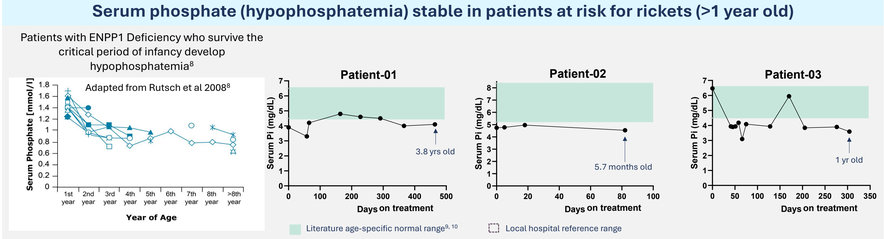
Pt #	Gender	Age at Dx	Age at Tx Start	Time on Tx (mo)	Alive (Y/N)	LVEF		Systemic Hypertension		Arterial Calcifications		Joint/Soft Tissue Calcifications		Hypophosphatemia		Age for Rickets Risk	Rickets
						BL	Tx	BL	Tx	BL	Tx	BL	Tx	BL	Tx	Current Status	
01	Male	1.5 mo	2.5 yr	18	Y	71%	Stable	Yes	Stable on anti-HTN	Yes (M)	Stable	Yes	Stable	Yes	↑ to normal	Yes	No
02	Female	19 d	3 mo	13	Y	40%, CHF	↑ (68%)	Yes	Stable on anti-HTN	Yes (M)	↓↓	Yes	Stable	Near normal*	Stable	No	NA
03	Female	Birth	2 mo	10	Y	52%	↑ (61%)	Yes	Anti-HTN D/C	Yes (M)	↓↓	Yes	Stable	No	Stable	No	NA

Anti-HTN, ant-hypertension medication; BL, baseline; CHF, congestive heart failure; D/C, discontinued; Dx, diagnosis; LVEF, left ventricular ejection fraction; M, multiple; mo, months; NA, not applicable; NR, not reported; Pt, patient; Tx, treatment with INZ-701; yr, year. *Using literature reported age-specific normal ranges for serum phosphate[9,10], the patient is slightly below normal at BL and stable with Tx; using local hospital reference range, patient is slightly above normal at BL and stable with Tx (see serum phosphate graph for patient-02 below).

Ejection fraction stable or improved with INZ-701 treatment



Serum phosphate (hypophosphatemia) stable in patients at risk for rickets (>1 year old)



Favorable safety profile with INZ-701 treatment

Total Adverse Events (AEs) reported (no. participants)	Participants with non-serious AEs related to INZ-701	Participants with non-serious AEs not related to INZ-701	Participants with Serious AEs (SAEs) related to INZ-701	Participants with SAEs not related to INZ-701
12 (2)	2*	Not reported**	0	1#

*9 low grade injection site reactions were the only AEs related to INZ-701 reported

**Limited AE reporting : all SAEs reported regardless of relationship to INZ-701; AEs reported only if related to INZ-701

#3 SAEs: sepsis with myocardial infraction, viral infection, gastrointestinal bleed

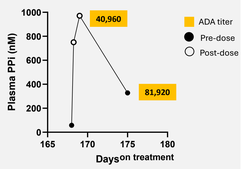
Anti Drug Antibody (ADA) response was not associated with adverse events (AEs)

	Anti-Drug Antibody (ADA) Status/Titers																
Weeks	5	13	19	20	21	24	26	27	29	30	34	37	38	39	43	52	79
Pt-01																	
Pt-02		1,280					40,960	81,920		163,840			163,840				
Pt-03		2,560	5,120	10,240	10,240	20,480			40,960		81,920		163,840				

ADA Negative
ADA Positive

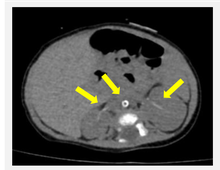
- ADA response was not associated with AEs, but high ADA (2 pts) did result in reduced drug exposure (not shown)
- PPi increased to near normal/normal in patients initially
- In 2 patients, potentially beneficial post-dose PPi elevations were blunted, but not eliminated, due to development of ADAs
  - Patient-02 post-dose PPi increased 13- and 16.7-fold at 6 and 24 hrs post-dose, respectively, on Day 168 of treatment with INZ-701 despite high ADA titer

Patient-02 Post-Dose PPi Response

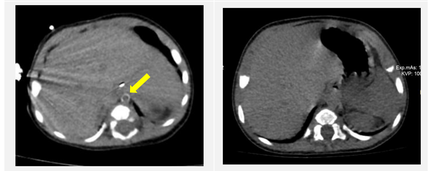


Evidence of complete resolution of arterial calcification (Patient-03)

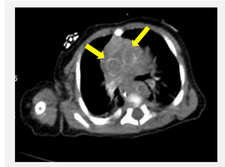
Abdominal aorta and renal arteries



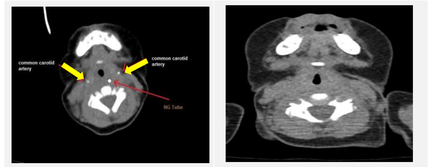
Abdominal aorta



Aorta and pulmonary artery efflux



Carotid artery



Calcification

Key Takeaways

- Children who received INZ-701 under an expanded access program (ongoing) tolerated treatment and showed improvements on disease measures including reduced arterial calcifications, improved heart function and reduced risk for rickets with increased serum phosphate
- There is a critical need for early diagnosis (importantly, genetic testing) and treatment intervention for infants with ENPP1 Deficiency (GACI/ARHR2)

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