A Phase 1/2 Open-Label, Multiple Ascending Dose Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of INZ-701 in Adults with ENPP1 Deficiency: An Interim Analysis

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Introduction

Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) is the major enzyme that generates extracellular pyrophosphate (PPi), an inorganic metabolite with potent anti-calcification activity.[1-3] Loss-of-function mutations lead to a state of ENPP1 Deficiency and hypopyrophosphatemia, which is associated with extensive calcification of the arteries, organs and joints. Infants with ENPP1 Deficiency present with severe cardiovascular complications and over 50% mortality in the first 6 months of life.[5-6] Most patients will develop an FGF-23 mediated hypophosphatemic rickets (Autosomal Recessive Hypophosphatemic Rickets, type 2, ARHR2) by early adolescence, characterized by growth plate abnormalities, bowed legs, short stature, and/or calcification of the joints and ligaments.[4-6]

INZ-701 is a recombinant human ENPP1-Fc fusion protein that is used as an enzyme replacement therapy for the treatment of ENPP1 deficiency.

Phase 1/2 Trial Design and Goals

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

9+ patients enrolled

Primary Goals

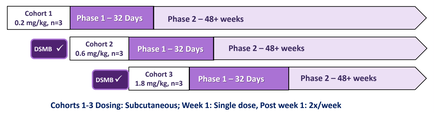
- **Pharmacokinetic properties**
- **Safety and tolerability**
- **Immunogenicity**
- **Pharmacodynamics (PPi)**

Secondary Goals

Evaluate potential endpoints for pivotal study

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

Study Design:



Cohorts 1-3 Dosing: Subcutaneous; Week 1: Single dose, Post week 1: 2x/week

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

Patient Demographics & Baseline Medical Conditions

		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)
Age (years)	**Median**	31	43	25
	Range	23-40	30-58	22-29
Gender	**Male (n=3)**	0	1	2
	Female (n=6)	3	2	1
Race	**White (n=8)**	3	3	2
	Not reported (n=1)	0	0	1
Initial clinical presentation		GACI (3)	GACI (1) ARHR2 2nd decade (2)	GACI (1) ARHR2 1st decade (1) ARHR2 3rd decade (1)

Cohort 2 skewed toward older patients

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)	Total (n=9)
Medical History				
Rickets/osteomalacia	3	2	3	8
Cardiovascular disease	2	3	2	7
Arterial calcification/stenosis/surgery	2	3	1	6
GACI	3	1	1	5
Soft tissue/joint calcification	1	2	2	5
Arthritis/arthralgia	2	2	0	4
Bone deformity/orthopedic surgery	0	1	3	4
Nephrocalcinosis/nephrolithiasis	0	2	2	4
Hypertension	1	2	1	4
Hearing loss	0	2	2	4
Selected Baseline Data				
Average 6-minute walk test (% predicted)	76.7	52.2	70.7	66.5
Average PROMIS pain intensity T score	58.1	54.4	47.4	53.3
Average PROMIS pain interference T score	57.5	53.4	52.5	54.5

Note: higher PROMIS T scores = greater pain or greater interference, respectively; reference mean=50

Each patient had a unique *ENPP1* mutant genotype

INZ-701 Exhibits a Favorable Safety Profile

Event	INZ-701 dose cohort – No. of patients with at least one event			Total patients (n=9)
	0.2 mg/kg biweekly n=3	0.6 mg/kg biweekly n=3	1.8 mg/kg biweekly n=3	
Adverse event	3	3	2	8
Adverse event related to INZ-701	2	1	0	3
Serious adverse event	0	2	0	2

Most adverse events were mild or moderate in severity

- 3/9 patients experienced mild adverse events related to INZ-701
  - Injection site reactions (bruising, hemorrhage, pain, pruritus, swelling) occurred in 2 patients
  - Other related adverse events included decreased appetite and fatigue

2 serious adverse events - not related to INZ-701

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

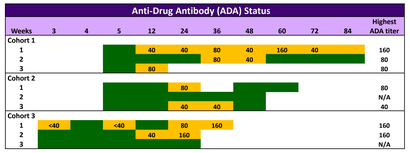
No adverse events led to discontinuation of INZ-701

No adverse events led to study withdrawal from Phase 1

- 2 patients withdrew from Phase 2; not related to adverse events
- 7 patients remain on study; all transitioned to self-administration
- Time on study range: 98-638+ days; total time on treatment across all patients: ~9 years

Favorable Immunogenicity Profile Observed

- **Low, non-neutralizing ADA titers detected**
- **ADAs were transient in 2 patients**



STRENSIQ® ADA titers: 2,048[7]; patients with ADA: 89%[10]

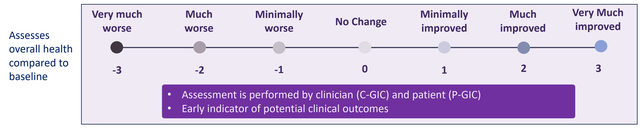
ALDURAZYME® ADA titers: 31,972[8]; patients with ADA: 97%[10]

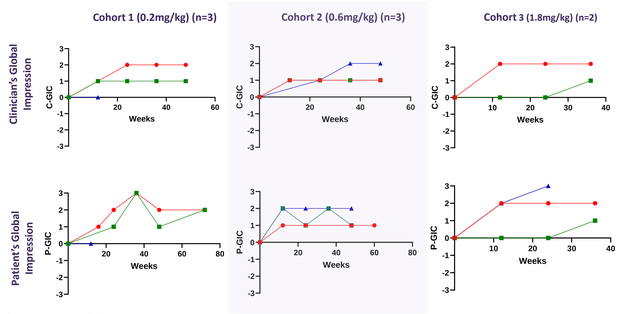
LUMIZYME® ADA titers: >51,200[9]; patients with ADA: 89%[10]

ADA titers for other drugs were observed in previously conducted trials by other companies

Exploratory Endpoints:

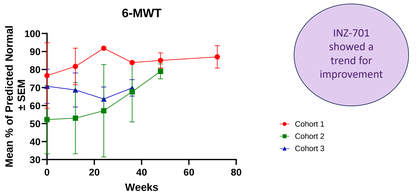
Global Impression of Change Scale (GIC) is an exploratory endpoint in ongoing Phase 1/2 Trial





Colors represent individual patients in respective cohorts

6-Minute Walk Test (6-MWT)

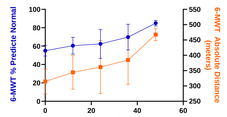


Percent predicted normal adjusts for subject age, gender, height and weight

Data presented as ± SEM; Data cut July 6, 2023

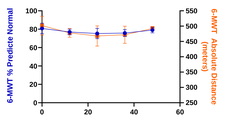
Subgroup analysis: 6-minute walk test

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



Greater improvement observed in patients with poor baseline 6-MWT

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

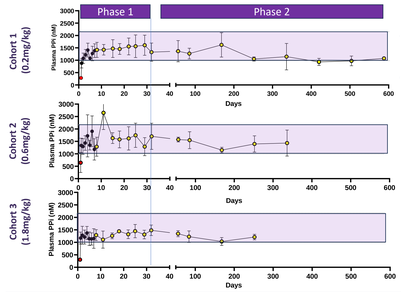


Stable 6-MWT scores observed in patients with higher baseline values

Data presented as ± SEM; Data cut July 6, 2023

PPi and Other Biomarkers

Rapid, significant and sustained increase in PPi observed at all doses



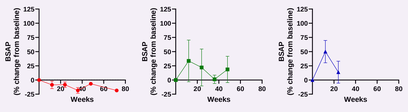
- Rapid increase within 6 hours observed after the 1st dose
- PPi levels reached the healthy volunteer range after the 1st dose

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

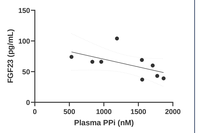
Cohort 1: n=2 post day 84; Cohort 2: n=2 post day 336; Cohort 3: n=2 post day 168

Bone-specific Alkaline Phosphatase (BASP)



- Bone-specific alkaline phosphatase (BSAP): Key enzyme involved in mineral deposition in bone
  - BSAP hydrolyzes PPi and increases local phosphate concentration
  - Similar response observed with other treatments of rickets (XLH, VDDR)

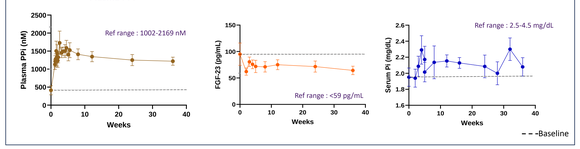
FGF-23 vs. PPi 1-week post-dose



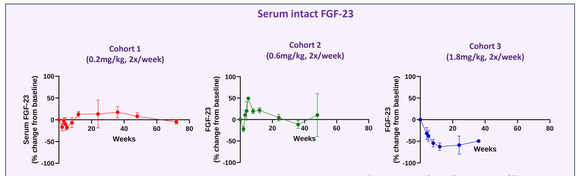
Analysis performed at 1 week post-dose to assess FGF-23 levels at timepoint where PPi levels have not yet plateaued. Each dot represents a patient (n=3/cohort)

Spearman correlation	1-week post-dose
R coefficient	-0.7113
P value	0.0371

Pooled Cohorts 1-3: Baseline vs mean Week 2-36 PPi, FGF-23, and Pi levels (± SEM)

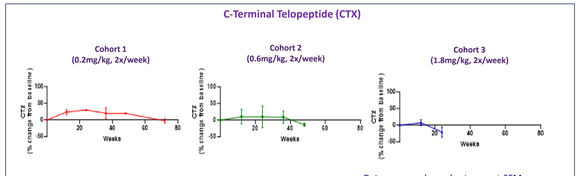


Serum intact FGF-23



Data expressed as cohort mean ± SEM

C-Terminal Telopeptide (CTX)



Data expressed as cohort mean ± SEM

Conclusions: Primary Goals Met

Safety and immunogenicity

- ✓ Well-tolerated, no serious adverse events related to study drug
- ✓ Support for first studies in infants (ongoing) and children (pending)
- ✓ Low, sometimes transient levels of non-neutralizing anti-drug antibodies

Pharmacokinetics

- ✓ 126-hour half-life supports once-weekly dosing
- ✓ Informs and validates PK model

Pharmacodynamics

- ✓ Significant elevation of plasma pyrophosphate (PPi), maintained for over 18 months
- ✓ Changes in key biomarkers (i.e., FGF-23 and phosphate (Pi)) support clinical hypothesis
- ✓ Rapid increase in PPi at 1 week correlated with decreases in FGF-23 levels (p= 0.0371)
- ✓ Dose ranging data support adult dose of 1.8 mg/kg/week

Identify clinically meaningful outcome measures to inform design of future study in adults

- ✓ Functional improvements can be measured by 6-minute walk test and patient-reported outcomes; strongest improvements seen in patients with greatest impairment at baseline
- ✓ Identified areas of bone pathology (low BMC/BMD) may represent locations for radiographic scoring for improvements
- ✓ Subset analyses reveal patient populations most likely to benefit from INZ-701 treatment in future adult studies

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