A Phase 1/2 Open-Label, Multiple Ascending Dose Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of INZ-701 Followed by an Open-Label Long-Term Extension Period in Adults with ABCC6 Deficiency Manifesting as Pseudoxanthoma Elasticum (PXE): An Interim Analysis

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Introduction

Pseudoxanthoma elasticum (PXE; OMIM no. 264800) is a genetic disorder inherited in an autosomal recessive mode. It is characterized by late-onset yet progressive ectopic calcification in the skin, eyes, and arterial blood vessels. Most PXE patients carry loss-of-function mutations in the *ABCC6* gene.[1-3] *ABCC6* mutations can also cause generalized arterial calcification of infancy type 2 (GACI2; OMIM no. 614473), an exceedingly severe autosomal recessive disorder characterized by congenital calcification of arterial blood vessels.[4,5] These patients with GACI type 2 are clinically indistinguishable from GACI type 1 patients carrying loss-of-function mutations in *ENPP1* (GACI1; OMIM no. 208000). The two clinical entities, PXE and GACI, manifest overlapping phenotypic characteristics due to converging pathomechanistic pathways.[6,7] The *ABCC6* gene encodes ABCC6, a hepatic protein and transmembrane efflux transporter without known substrate(s). Several studies established the pivotal role of ABCC6 in preventing soft tissue calcification; ABCC6 mediates adenosine triphosphate (ATP) release from hepatocytes to the extracellular space where ATP is converted by ENPP1, an ectonucleotide pyrophosphatase/phosphodiesterase, to adenosine monophosphate and inorganic pyrophosphate (PPi),[8,9] the latter being a potent physiologic inhibitor of ectopic calcification.[7,10] ENPP1 is the principal enzyme generating extracellular PPi, as *Enpp1*-deficient mice and patients with ENPP1 Deficiency have minimal plasma PPi and present with extensive vascular calcification.[11-14] In PXE, ABCC6 deficiency impairs the hepatic release of extracellular ATP, the precursor of PPi.

The deficiency of PPi is the underlying cause of systemic ectopic calcification in PXE, suggesting that pharmacologic approaches increasing plasma PPi concentrations are expected to counteract ectopic calcification leading to clinical stabilization and improvement of the disease. INZ-701, a soluble recombinant ENPP1 enzyme, normalized plasma PPi levels by utilizing circulating ATP as a substrate.

INZ-701 is a recombinant human ENPP1-Fc fusion protein is the principal PPi-generating enzyme and used as an enzyme replacement therapy for the treatment of ENPP1 and ABCC6 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 ABCC6 Deficiency

Study Population: *Adults*

Eligibility Criteria:

- Age 18-69 years
- Confirmed clinical and genetic diagnosis

10 patients enrolled

Primary Goals

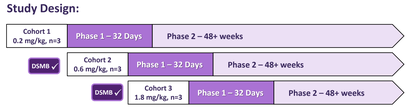
- Safety and tolerability
- Immunogenicity
- Pharmacokinetic properties
- Pharmacodynamics (PPi)

Secondary Goals

Evaluate potential endpoints for pivotal study

- Ophthalmologic disease, ectopic calcification, cardiovascular disease, 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

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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=4)
Age (years)	Median	40	63	49
	Range	29-56	52-67	48-55
Gender	Male (n=4)	2	0	2
	Female (n=6)	1	3	2
Race	White (n=10)	3	3	4

Patients have a heavy lifetime disease burden:

Medical Condition	INZ-701 Dose Cohort			
	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=4)	Total (n=10)
Retinal disease	3	3	4	10
Other ophthalmologic disease	2	1	4	7
Gastrointestinal symptoms	3	1	1	5
Arthritis/arthralgia	0	2	2	4
Hypertension	1	1	2	4
Dental disease	2	2	0	4
Cardiovascular disease	0	2	2	4
Peripheral vascular disease/claudication	0	1	2	3
Vascular calcification	0	0	3	3
Nephrocalcinosis/nephrolithiasis	0	1	1	2
Soft tissue/ligamentous calcification	1	1	0	2
Migraine headache	1	1	0	2
Orthopedic surgery/bone deformity	0	2	0	2
Vascular malformation	0	1	1	2
Autoimmune disease	0	0	1	1

INZ-701 Exhibits a Favorable Safety Profile

Events	INZ-701 dose cohort – No. of patients with at least one event			All patients (n=10)
	0.2 mg/kg biweekly n=3	0.6 mg/kg biweekly n=3	1.8 mg/kg biweekly n=4	
Adverse Event	3	3	4	10
Adverse Event Related to INZ-701	1	3	3	7
Serious Adverse Event	0	0	0	0

All adverse events were mild or moderate in severity

- 7/10 patients experienced mild to moderate adverse events related to INZ-701
  - Injection site reactions (discoloration, discomfort, erythema, induration, pain, pruritus, warmth) occurred in 7/10 patients and were all mild
  - Other related adverse events were mild to moderate and included fatigue, night sweats and urticaria

No serious or severe adverse events

One adverse event led to discontinuation of INZ-701 during Phase 1

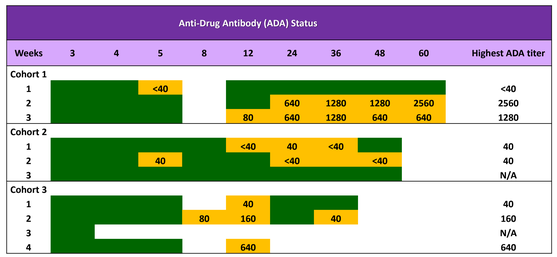
- Moderate erythema and urticaria in one patient in 1.8 mg/kg cohort
- 1 patient withdrew from the study during Phase 2; not related to an adverse event

8 patients remain on treatment and 7 continue on self-administration

- Time on study range: 18-518+ days; total time on treatment across all patients ~9.1 patient-years

Favorable Immunogenicity Profile Observed

- Low, non-neutralizing ADA titers detected
- ADAs were transient in 3 patients



Data cut Aug 15, 2023; ADA titer range measured as dilution factor.

STRENSIQ® ADA titers: 2,048[15]; patients with ADA: 89%[18]

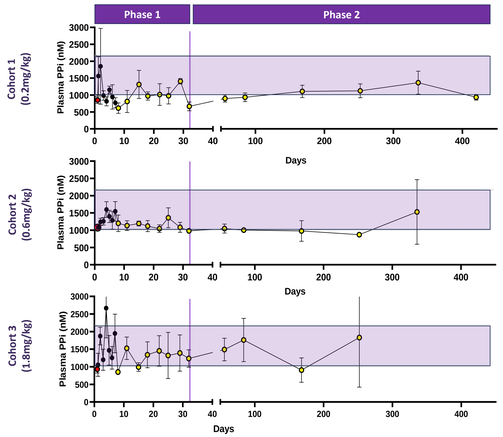
ALDURAZYME® ADA titers: 31,972[16]; patients with ADA: 97%[18]

LUMIZYME® ADA titers: >51,200[17]; patients with ADA: 89%[18]

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

Pyrophosphate Measurements

Rapid, significant and sustained increase in PPi observed at 1.8 mg/kg dose

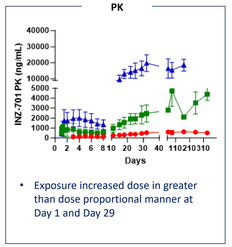


- Rapid increase observed after the 1st dose
- PPi levels reached the healthy volunteer range after the 1st dose

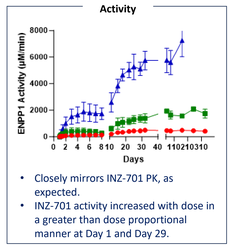
Data expressed as cohort mean ± SEM; Data cut Aug 15, 2023

Pharmacokinetic Properties

PK properties consistent with those observed in adult ENPP1 trial



- Exposure increased dose in greater than dose proportional manner at Day 1 and Day 29



- Closely mirrors INZ-701 PK, as expected.
- INZ-701 activity increased with dose in a greater than dose proportional manner at Day 1 and Day 29.

Data expressed as cohort mean ± SEM; Data cut Aug 15, 2023

Exploratory Endpoints

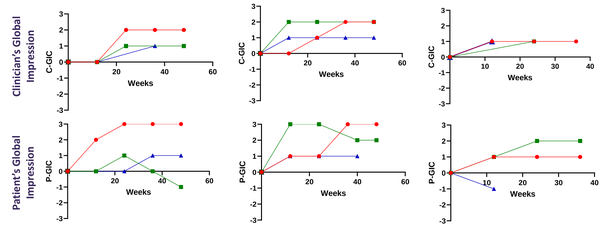
Global Impression of Change Scale (GIC) is an exploratory endpoint in ongoing Phase 1/2 Trial

Assesses overall health compared to baseline

Very much worse	Much worse	Minimally worse	No Change	Minimally improved	Much improved	Very Much improved
-3	-2	-1	0	1	2	3

- Assessment is performed by clinician (C-GIC) and patient (P-GIC)
- Early indicator of potential clinical outcomes

Majority of timepoints showed improvement in C-GIC and P-GIC in all dose cohorts



Colors represent individual patients in respective cohorts

Conclusions: From Interim Data Readouts

✓ **Safety**
- INZ-701 was generally well-tolerated, and exhibited a favorable safety profile
- ADA titers generally low, with no evidence of neutralizing ADA

✓ **Pharmacokinetics**
- Consistent PK observed in all patients as measured by immunoassay and enzymatic activity

✓ **Pharmacodynamics**
- Rapid increase in PPi in all patients to levels comparable to those observed in healthy subjects
- Most sustained increase observed at highest dose level

✓ **Identify clinically meaningful outcome measures to inform design of future study in adults**
- Global impression of change (GIC): improvement noted in 9/9 (C-GIC) and 7/9 (P-GIC)
- Concordance between C-GIC and P-GIC