SEAPORT 1: An Open-label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of INZ-701 in Participants with End-Stage Kidney Disease Undergoing Hemodialysis - Interim Analysis

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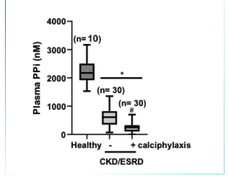
Introduction

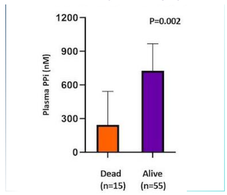
Calciphylaxis is a dire complication of end-stage kidney disease (ESKD) with high mortality and no approved therapies.[1] It is characterized by calcification, as well as intimal proliferation causing occlusion of arterioles in the skin, leading to painful lesions, ulceration, and infection.

Growing evidence associates calciphylaxis with deficiency of inorganic pyrophosphate (PPi), a critical inhibitor of ectopic vascular calcification.[2-3]

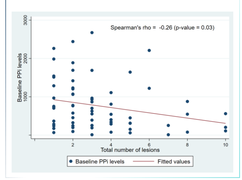
Low PPi levels in ESKD with or without Calciphylaxis[2]



Low PPi levels predicted 6-week mortality in calciphylaxis[2]



Low PPi levels correlated with higher numbers of skin lesions[3]

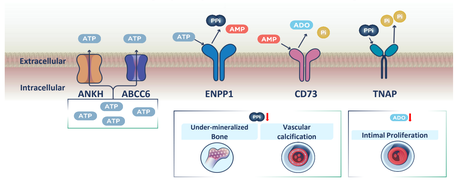


ENPP1, the ectonucleotide pyrophosphatase/phosphodiesterase type 1 enzyme is responsible for generating most of the body's PPi via catalysis of extracellular ATP.[4]

Biochemical and genetic data support a link between the ENPP1 pathway and calciphylaxis.[5-6]

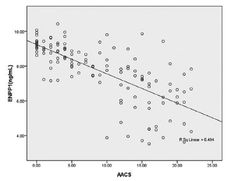
- Dialysis patients with the ENPP1 K121Q polymorphism had a significantly higher coronary calcium score and a higher aortic pulse-wave velocity when compared to matched controls.[5]
- In non-diabetic ESKD patients, levels of serum ENPP1 are strongly negatively correlated to abdominal aortic calcification severity (AACS).[6]
- Polymorphisms in CD73 are associated with an increased risk of calciphylaxis.[7]

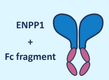
The Pyrophosphate-Adenosine Pathway[4]



- ABCC6, ENPP1, and CD73 act in concert to generate extracellular ATP (ABCC6), process ATP to PPi and AMP (ENPP1), and ultimately process AMP to adenosine and phosphate
- PPi and adenosine are potent inhibitors of calcification and intimal proliferation, respectively

Relationship of abdominal aortic calcification severity to serum ENPP1 levels in ESKD[6]



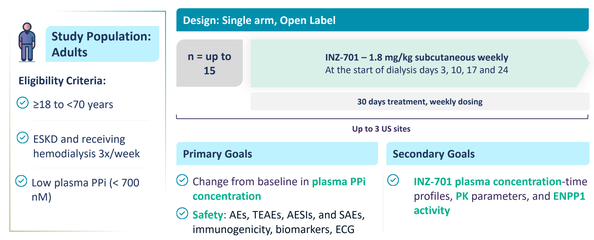


INZ-701 is an investigational soluble fusion protein comprised of functional ENPP1 enzyme fused to the Fc portion of human immunoglobulin 1.

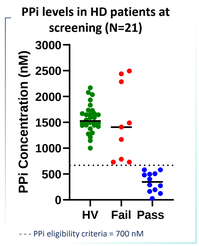
- Treatment of a CKD rat model with INZ-701 prevented or reduced vascular calcification.[8]

Objective, Methods & Study Enrollment

Objective: To evaluate the safety, pharmacokinetics and pharmacodynamics of INZ-701 in adults with ESKD and low pyrophosphate levels receiving hemodialysis (HD) over a 30-day dosing period (SEAPORT 1 Study: **NCT06283589**)



PPi levels in HD patients at screening (N=21)



- Of 21 ESKD patients screened, median PPi levels were 582 nM. Nine patients screen failed with PPi ≥700 nM and 1 passed screening but withdrew before Day 1
- 11 patients completed the four weekly doses of INZ-701. One patient remains in follow-up for safety observation

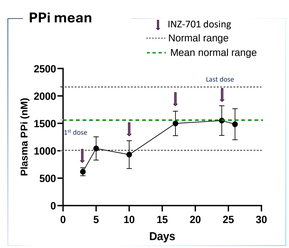
Patient Demographics & Disease History

Patients (N=11)	
Age	
Median (range), years	66 (28-70)
Sex, n (%)	
Female	4 (36%)
Male	7 (64%)
Race, n (%)	
Black or African American	8 (73%)
White	3 (27%)
Dialysis vintage:	
Median (range), months	58.5 (20.7- 117.0)
Cause of ESKD, n (%)	
Type 2 Diabetes Mellitus	7 (64%)
Hypertensive CKD	3 (27%)
Kidney transplant rejection	1 (9%)
Comorbidities, n (%)	
Diabetes Mellitus	9 (81.8%)
Arterial hypertension	7 (63.6%)
Hyperkalemia	11 (100%)

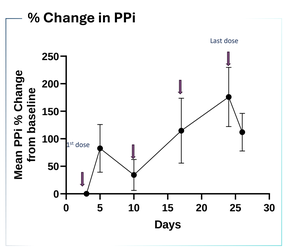
Pharmacodynamics

INZ-701 increases PPi in dialysis patients across the spectrum of PPi deficiency

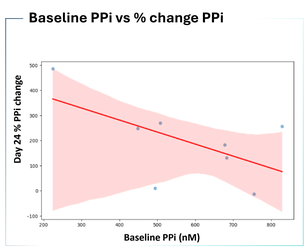
PPi mean



% Change in PPi

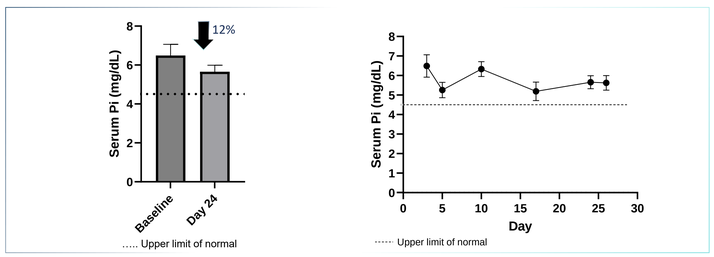


Baseline PPi vs % change PPi



Data presented as mean ± SEM

Key mediators of mineral metabolism (phosphate (Pi) & FGF-23) decreased during INZ-701 Treatment



- Effects on FGF-23 are consistent with reduced propensity for calcification.
- Markers associated with bone turnover and Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) (intact PTH, BSALP; data not shown) remain generally unchanged, suggesting longer treatment may be needed to address this syndrome.

Safety

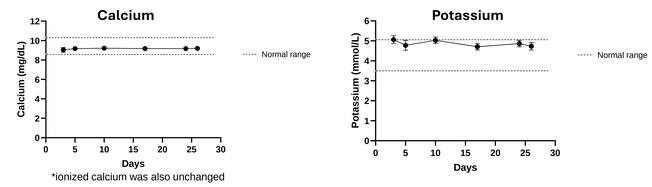
Treatment Emergent Adverse Events (TEAEs) were Unrelated to INZ-701

- 3/11 patients (27%) experienced a TEAE, none of which were attributed to study drug
- TEAE led to temporary drug interruption in one patient (one dose missed)

Patient ID	AE Preferred Term	Relationship to INZ-701	Severity (grade)	Outcome	SAE / AESI
01	Hypertension	Not related	2	Recovered/resolved with sequalae	SAE
	Gastroenteritis viral	Not related	1	Recovered/resolved	
	Seizure	Not related	2	Recovered/resolved	AESI
02	Hyperkalemia	Not related	3	Recovered/resolved	SAE
03	Hypotension	Not related	2	Recovered/resolved	
	Loss of consciousness	Not related	2	Recovered/resolved	
	Thrombocytopenia	Not related	2	Ongoing	

SAE, serious adverse event; AESI, adverse event of special interest

Serum potassium and calcium were unchanged during treatment



*ionized calcium was also unchanged

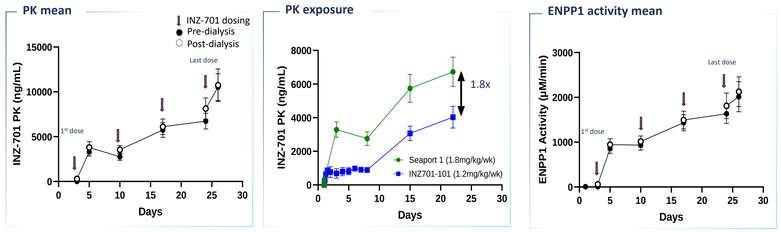
Low titers of anti-drug antibodies (ADA) detected after day 30

- No ADA by Day 26 (11/11 patients)
- Low titer of ≤40 at Day 30 post-last dose (3/11 patients)
  - 60 days post last dose: 2 are now ADA negative, 1 has not yet reached Day 60 post-last dose#

End of study safety follow-up

Pharmacokinetics

INZ-701 exposure was predictable based on previous experience in non-hemodialysis patients



PK was measured using an immunoassay. ENPP1 activity was assessed using an enzymatic assay. Data presented as mean ± SEM

- INZ-701 exposure was as expected for 1.8 mg/kg weekly based on treatment of non-hemodialysis patients.
  - 1.2 mg/kg/week (1.5-fold lower than SEAPORT) tested in adults with ENPP1 Deficiency (INZ701-101 study) showed mean exposure of 3,715 ng/mL.
  - Mean SEAPORT exposure was 6,732 ng/mL, a 1.8-fold difference, confirming dose proportionality.
- Increase in mean ENPP1 activity mirrored INZ-701 exposure.

Conclusions

- PPi levels in screened ESKD patients (n=21) were lower than what has been reported in healthy volunteers
- Eleven patients with ESKD and PPi <700 nM were treated with four weekly doses of subcutaneous INZ-701. INZ-701:
  - Demonstrated a favorable safety profile, with no drug-related TEAEs observed
  - Increased mean PPi levels into the normal range by week 3, and was associated with reductions in mineral metabolism biomarkers (phosphate and FGF-23)
  - Drug exposure was proportional to the dose received
- **These findings suggest the PPi-adenosine pathway is impacted in ESKD patients, and that INZ-701 may normalize PPi levels in those patients, supporting further clinical development in calciphylaxis**

References

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Disclosures & Acknowledgements

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