Interim clinical and safety data of INZ-701 treatment in infants and young children with ENPP1 Deficiency and key program updates

January 2025

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Strong progress advancing INZ-701 across multiple indications and demographics

Milestones to Date

- ✓ Positive clinical effects observed in adults with ENPP1 Deficiency and ABCC6 Deficiency in Phase 1/2 trials
- ✓ Favorable safety profile in adults with ENPP1 Deficiency, ABCC6 Deficiency and calciphylaxis
- ✓ Low, often transient, ADAs detected in some adults in ENPP1 Deficiency and ABCC6 Deficiency Phase 1/2 Trials
- ✓ >5,000 doses of INZ-701 (>57 Patient Years)
- ✓ Convenient at-home dosing regimen

January 2025 Updates

- Clinical improvements in multiple measures of disease from baseline observed in infants and children with ENPP1 Deficiency with INZ-701 treatment
- Favorable safety profile in infants and children
- Enrollment complete in ENERGY 3 pivotal trial in pediatric patients with ENPP1 Deficiency
- Preliminary support from U.S. and EU regulators for ASPIRE pivotal trial in children with ABCC6 Deficiency

Generalized arterial calcification of infancy (GACI): A severe manifestation of ENPP1 Deficiency in infants

Significant morbidity and mortality in infants and children with GACI

~10%

of normal PPi levels

50%

Mortality within the first 6 months due to severe cardiovascular complications

95%

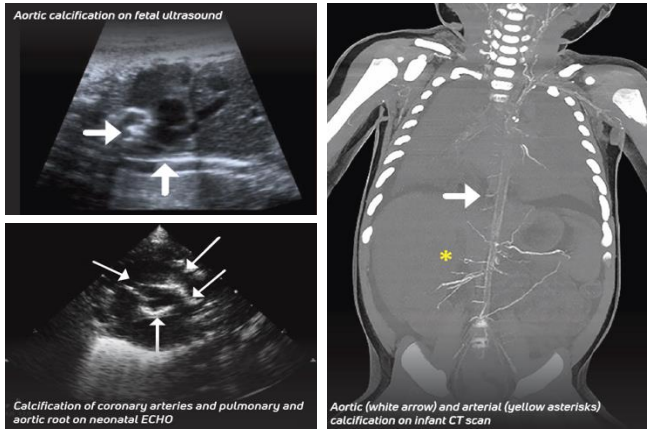
Present with ectopic calcification

100%

Develop hypophosphatemic rickets in childhood

Expected to develop after 1 year

Vascular Calcification



Calcification, intimal proliferation, and stenosis

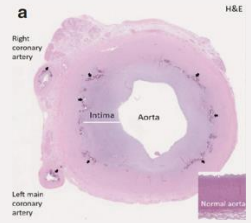


Image reproduced from Ferreira 2021.

INZ-701 treatment in infants and very young children with GACI

Two ongoing programs evaluating safety and clinical effects

ENERGY 1
3 infants treated

- Phase 1b, global, open-label study in patients <1 yr old
- GACI-1 (ENPP1 Deficiency) or GACI-2 (ABCC6 Deficiency)
- No fixed dose; intra- and inter-patient dose escalation over time based on safety and tolerability data

Expanded Access Program
2 infants + 1 toddler treated

- Open-label treatment for ENPP1 Deficiency
  - Patients <1 yr old with unstable conditions where transport is not possible
  - Patients of any age in countries where no trial site is open to new patient accrual

Clinical improvements in multiple measures of disease from baseline observed with INZ-701 treatment

Natural history	INZ-701 treatment
50% Mortality within the first 6 months due to severe cardiovascular complications	**80%** of treated infants thriving beyond 1 year of age Improved survival observed
95% Present with ectopic calcification	Substantial reduction or stabilization of arterial calcifications Evidence of improved heart function
100% Develop hypophosphatemic rickets in childhood Expected to develop after 1 year	**0%** Evidence of rickets in at-risk children Increase/stabilization of serum phosphate levels

ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024

Significant disease burden at baseline in GACI infants and children

Impaired heart function, substantial ectopic calcifications, hypophosphatemia and systemic hypertension are common; Some patients entering age for rickets development

Study Patient ID/ [Time on Tx]	Age at diagnosis	Age at Tx Start	Status	Arterial calcifications		LVEF		Systemic Hypertension		Hypophosphatemia		Joint/soft tissue calcifications		Age for rickets risk	Rickets
			Alive/ Dead	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Current Status	
E1 Pt1 [16 mo]	2.6 mo	8.5 mo		Yes (M)		62%		NR		Yes		Yes		Yes	
E1 Pt2 [15 mo]	4.4 mo	10.5 mo		NR		64%		NR		Yes		Yes		Yes	
E1 Pt3* [3 wks]	26 d	1 mo		Yes (M)		29%		Yes		Yes		Yes		NA	
EAP-01 [22 mo]	1.5 mo	2 yrs 5 mo		Yes (M)		71%		Yes		Yes		NR		Yes	
EAP-02 [14 mo]	19 d	3 mo		Yes (M)		40%, CHF		Yes		Yes		NR		No	
EAP-03 [11 mo]	Birth	2 mo		Yes (M)		52%		Yes		No		Yes		No	

ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024; BL: Baseline; D/C: discontinued; anti-HTN: ant-hypertension medication; M: Multiple; NA=Not applicable; NR: Not reported; CHF: Congestive heart failure; LVEF: Left ventricular ejection fraction, *Patient expired at 3 weeks of dosing, not evaluable

INZ-701 treatment observations in GACI infants and children

Evidence of improved heart function, stabilization or reduction in ectopic calcifications and hypophosphatemia, and prevention of rachitic changes

Study Patient ID/ [Time on Tx]	Age at diagnosis	Age at Tx Start	Status	Arterial calcifications		LVEF		Systemic Hypertension		Hypophosphatemia		Joint/soft tissue calcifications		Age for rickets risk	Rickets
			Alive/ Dead	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Current Status	
E1 Pt1 [16 mo]	2.6 mo	8.5 mo	A	Yes (M)	Stable	62%	Stable	NR	NR	Yes	↑ to/near normal	Yes	Stable	Yes	No
E1 Pt2 [15 mo]	4.4 mo	10.5 mo	A	NR	Stable	64%	Stable	NR	NR	Yes	Stable	Yes	Stable	Yes	No
E1 Pt3* [3 wks]	26 d	1 mo	D	Yes (M)	NA	29%	NA	Yes	Stable on pro-panolol	Yes	↑ to normal/ nr. normal	Yes	NA	NA	NA
EAP-01 [22 mo]	1.5 mo	2 yrs 5 mo	A	Yes (M)	Stable	71%	Stable	Yes	Stable on catopril	Yes	↑ to normal/ nr. normal	NR	NR	Yes	No
EAP-02 [14 mo]	19 d	3 mo	A	Yes (M)	↓↓	40%, CHF	↑ (68%)	Yes	Stable on catopril, pro-panolol	Yes	Stable	NR	NR	No	NA
EAP-03 [11 mo]	Birth	2 mo	A	Yes (M)	↓↓	52%	↑ (61%)	Yes	Anti-HTN tx D/C	No	Stable	Yes	Stable	No	NA

ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024; BL: Baseline; D/C: discontinued; anti-HTN: ant-hypertension medication; M: Multiple; NA=Not applicable; NR: Not reported; CHF: Congestive heart failure; LVEF: Left ventricular ejection fraction, *Patient expired at 3 weeks of dosing, not evaluable

Improved survival in GACI observed:

80% of treated infants thriving with 11+ months of treatment

Study Patient ID/ [Time on Tx]	Age at diagnosis	Age at Tx Start	Status
			Alive/Dead
E1 Pt1 [16 mo]	2.6 mo	8.5 mo	A
E1 Pt2 [15 mo]	4.4 mo	10.5 mo	A
E1 Pt3 [3 wks]	26 d	1 mo	D
EAP-01 [22 mo]	1.5 mo	2 yrs 5 mo	A
EAP-02 [14 mo]	19 d	3 mo	A
EAP-03 [11 mo]	Birth	2 mo	A

ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024

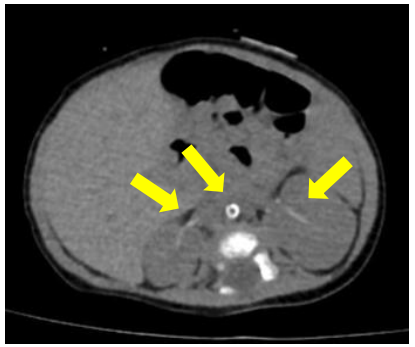
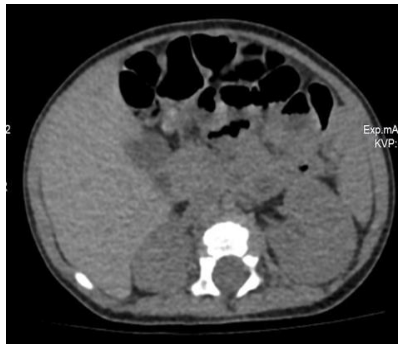
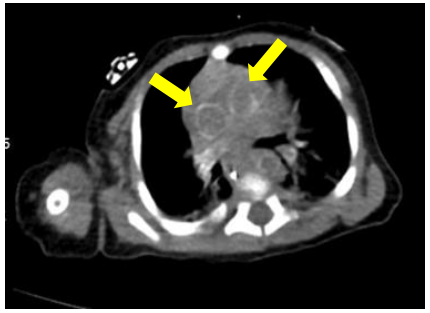
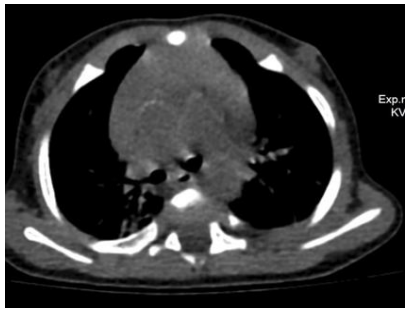
Reduced or stabilized arterial calcifications observed:

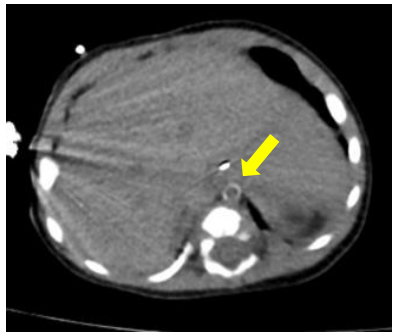
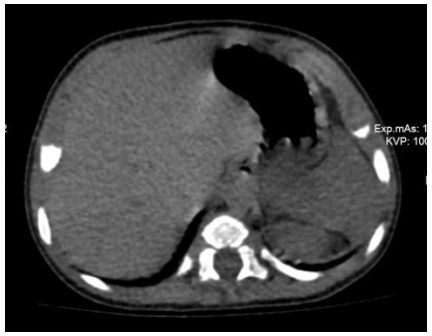
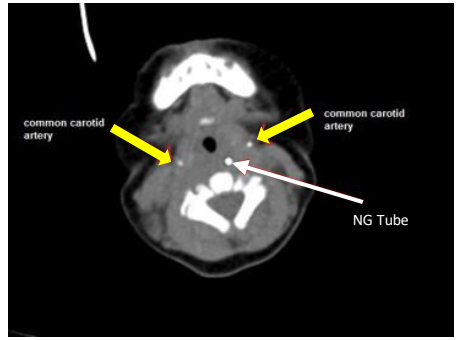
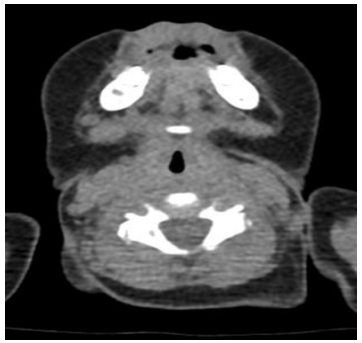
Key driver of morbidity and mortality in GACI addressed

Study Patient ID/ [Time on Tx]	Age at diagnosis	Age at Tx Start	Arterial calcifications	
			Baseline	Treatment
E1 Pt1 [16 mo]	2.6 mo	8.5 mo	Yes (M)	Stable
E1 Pt2 [15 mo]	4.4 mo	10.5 mo	NR	Stable
E1 Pt3 [3 wks]	26 d	1 mo	Yes (M)	NA
EAP-01 [22 mo]	1.5 mo	2 yrs 5 mo	Yes (M)	Stable
EAP-02 [14 mo]	19 d	3 mo	Yes (M)	↓↓
EAP-03 [11 mo]	Birth	2 mo	Yes (M)	↓↓

ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024; M=Multiple sites; NR=Not reported ; NA = Not applicable; Patient expired at 3 weeks of dosing

Case EAP-03: Evidence of complete resolution of arterial calcification observed

	Baseline	6-month follow-up
Abdominal aorta and renal arteries		
Aorta and pulmonary artery efflux		

	Baseline	6-month follow-up
Abdominal aorta		
Carotid arteries		

EAP data cut: 13 Dec 2024

Calcification

Evidence of improved heart function observed:

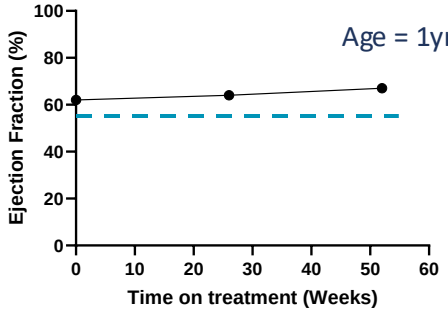
Stabilization or improvement in left ventricular ejection fraction (LVEF) in all surviving patients observed

Study Patient ID/ [Time on Tx]	Age at diagnosis	Age at Tx Start	LVEF	
			Baseline	Treatment
E1 Pt1 [16 mo]	2.6 mo	8.5 mo	62%	Stable
E1 Pt2 [15 mo]	4.4 mo	10.5 mo	64%	Stable
E1 Pt3 [3 wks]	26 d	1 mo	29%	NA
EAP-01 [22 mo]	1.5 mo	2 yrs 5 mo	71%	Stable
EAP-02 [14 mo]	19 d	3 mo	40%	↑ (68%)
EAP-03 [11 mo]	Birth	2 mo	52%	↑ (61%)

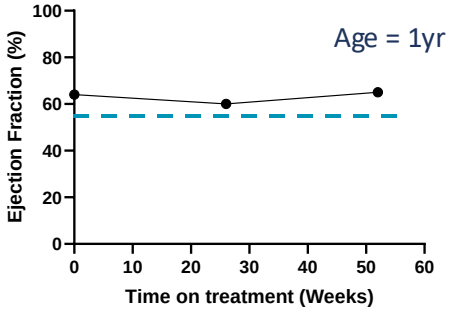
ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024; M=Multiple sites; NR=Not reported; NA = Not applicable, Patient expired at 3 weeks of dosing

Ejection fraction was stable or improved with INZ-701 treatment

E1 Pt1

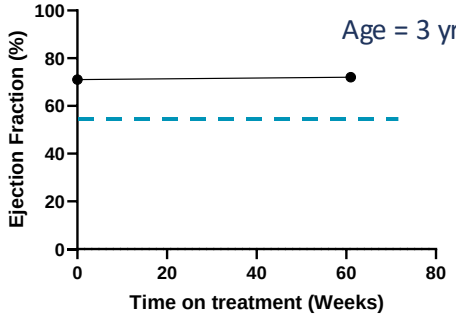


E1 Pt2

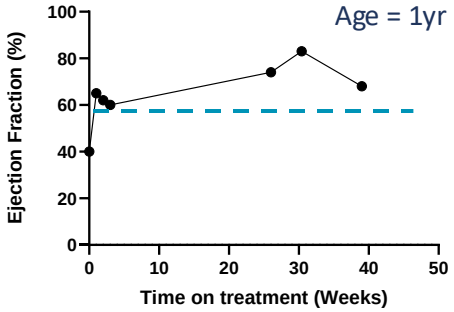


Normal infant EF % (Tissot et al, Front Pediatr. 2018 Apr 4;6:79)

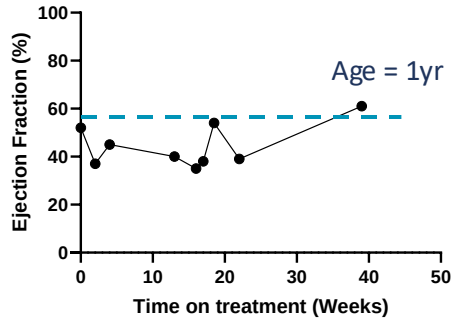
EAP-01



EAP-02



EAP-03



ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024

Reduced risk of rickets observed:

Increased or stabilized phosphate levels in all patients

Study Patient ID/ [Time on Tx]	Age at diagnosis	Age at Tx Start	Hypophosphatemia		Age for rickets risk	Rickets
			Baseline	Treatment	Current Status	
E1 Pt1 [16 mo]	2.6 mo	8.5 mo	Yes	↑ to/near normal	Yes	No
E1 Pt2 [15 mo]	4.4 mo	10.5 mo	Yes	Stable	Yes	No
E1 Pt3 [3 wks]	26 d	1 mo	Yes	↑ to/near normal	NA	NA
EAP-01 [22 mo]	1.5 mo	2 yrs 5 mo	Yes	↑ to/near normal	Yes	No
EAP-02 [14 mo]	19 d	3 mo	Yes	Stable	No	NA
EAP-03 [11 mo]	Birth	2 mo	No	Stable	No	NA

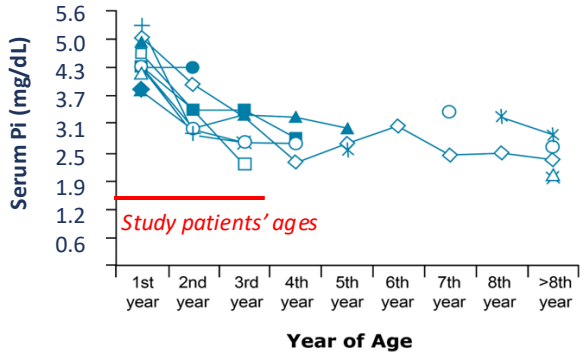
- Radiographic evidence of rickets expected after 1 year of age
- Co-incident with progressive hypophosphatemia
- X-Rays pending for patients EAP-02 and EAP-03

ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024; M=Multiple sites; NA=Not applicable; Patient expired at 3 weeks of dosing; NR=Not reported.

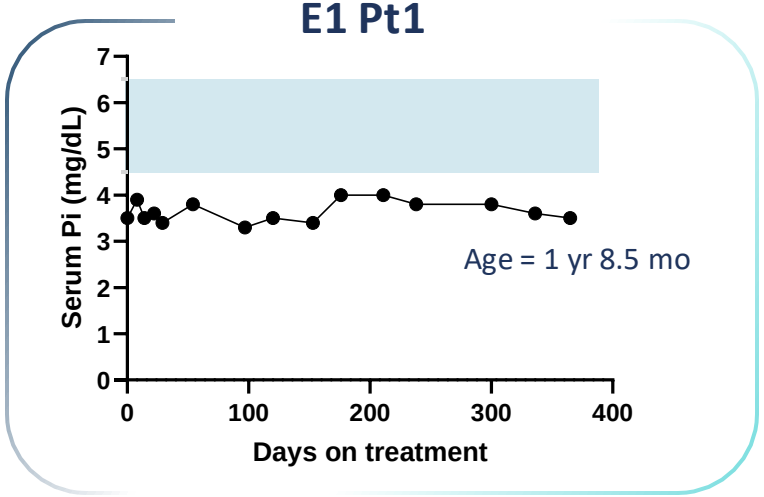
Serum phosphate was stable with INZ-701 treatment in all patients at risk for ARHR2

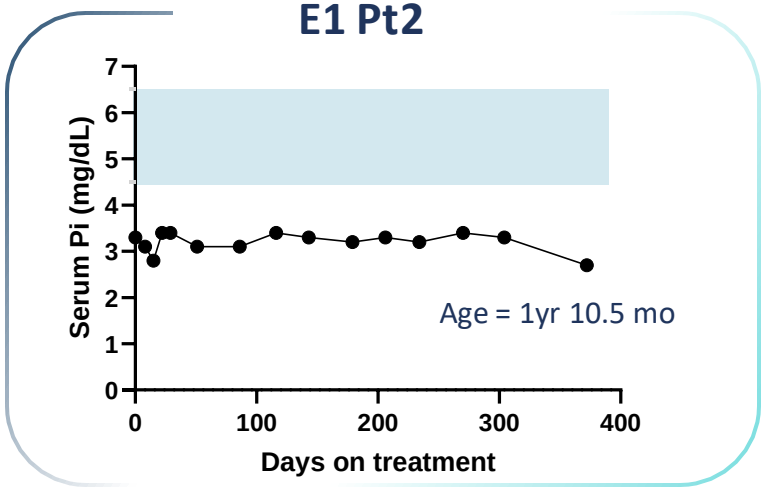
Natural History: Patients with ENPP1 Deficiency who survive the critical period of infancy develop hypophosphatemia

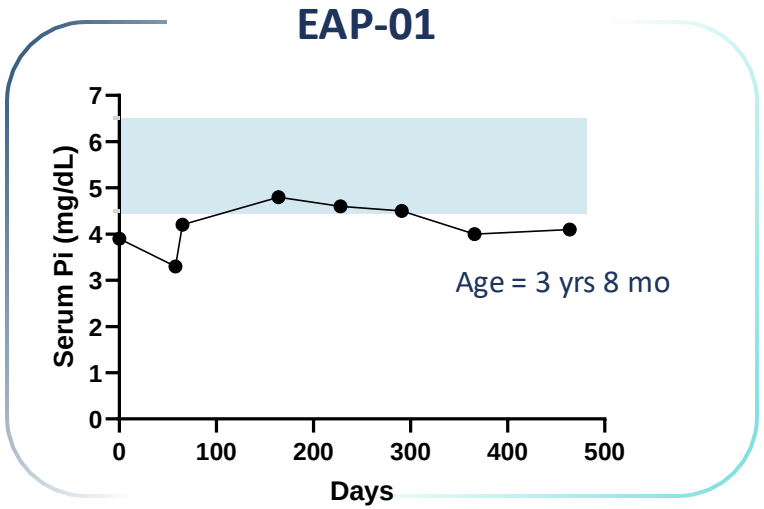
Serum Phosphate Levels

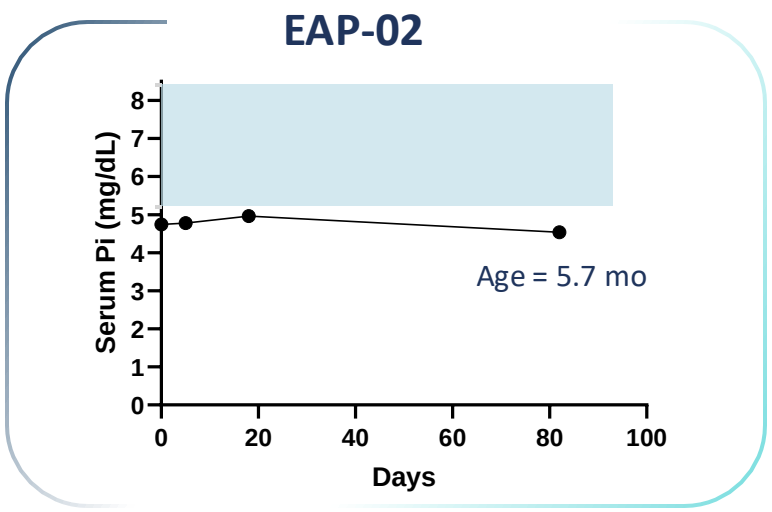


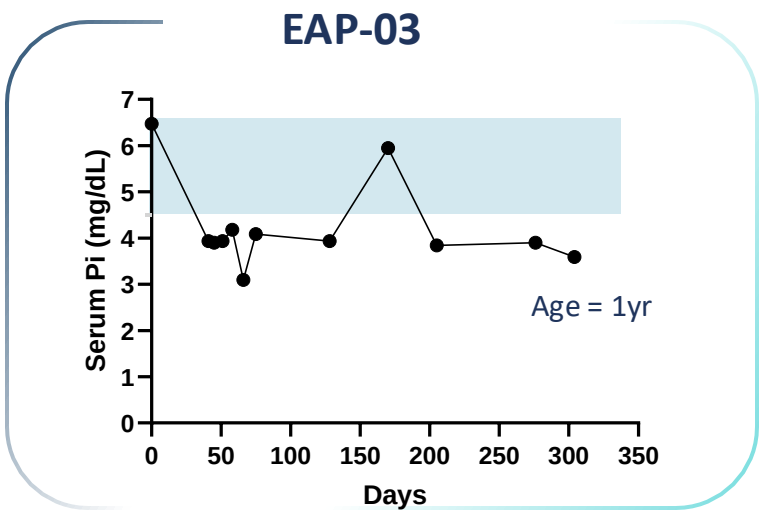
Adapted from Rutsch F, et al. *Circ Cardiovasc Genet*. 2008;1:133–140







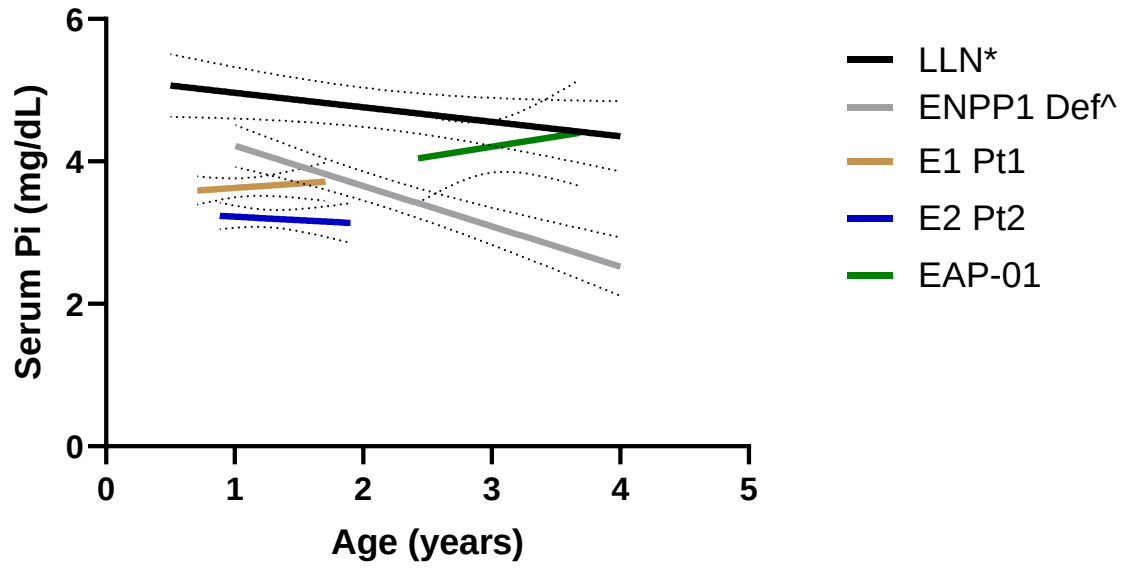




Age-specific normal range*

* Am J Kidney Dis 46: S1-S122, 2005; Pediatrics 77:891-896, 1986, ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024

Serum phosphate was stable or improved with INZ-701 treatment in patients at risk for rickets



- Serum phosphate levels (LLN) decreased slightly over time in healthy individuals (black line)
- By 1 year of age, ENPP1 deficient patients are already hypophosphatemic
- Serum phosphate levels decrease in a more pronounced way over time in ENPP1 deficient patients (grey line)
- **INZ-701 showed stabilization or improvement of serum phosphate levels in infants (brown and blue line) or children (green line)**

* LLN = lower limit of normal: Am J Kidney Dis 46: S1-S122, 2005, Pediatrics 77:891-896, 1986; ^ Adapted from Rutsch F, et al. *Circ Cardiovasc Genet*.1:133–140, 2008, ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024

Data presented as linear regression; ····· 95% confidence interval

INZ-701 exhibited a favorable safety profile in ENERGY 1 and EAP patients

		No. of Patients			
No. of Patients with AEs	Total adverse events (AEs) reported	AEs related to INZ-701	AEs not related to INZ-701	Serious AEs (SAEs) related to INZ-701	SAEs not related to INZ-701
ENERGY 1 (n=3)	34	0	2[2]	0	1[4]
Expanded Access (n=2)	12	2[1]	Not reported[3]	0	1[5]

[1] Includes 9 low grade injection site reactions

[2] All AEs were mild (grade 1)

[3] Limited AE reporting in EAP patients; All SAEs reported regardless of relationship to INZ-701; other AEs reported only if related to INZ-701.

[4] 1 SAE: MI resulting in death

[5] 3 SAEs: Sepsis with MI; viral infection; GI bleed

ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024

ADA response observed in youngest patients

ADAs absent in toddler and transient in one infant

	Anti-Drug Antibody (ADA) Status/Titers																
Weeks	**5**	**13**	**19**	**20**	**21**	**24**	**26**	**27**	**29**	**30**	**34**	**37**	**38**	**39**	**43**	**52**	**79**
Subject ID																	
E1 Pt1		320			80		40			80							
E1 Pt2		2,560			10,240		10,240			10,240				40,960	20,480	81,920	
EAP-01																	
EAP-02		1,280					40,960	81,920		163,840			163,840				
EAP-03		2,560	5,120	10,240	10,240	20,480			40,960		81,920		163,840				

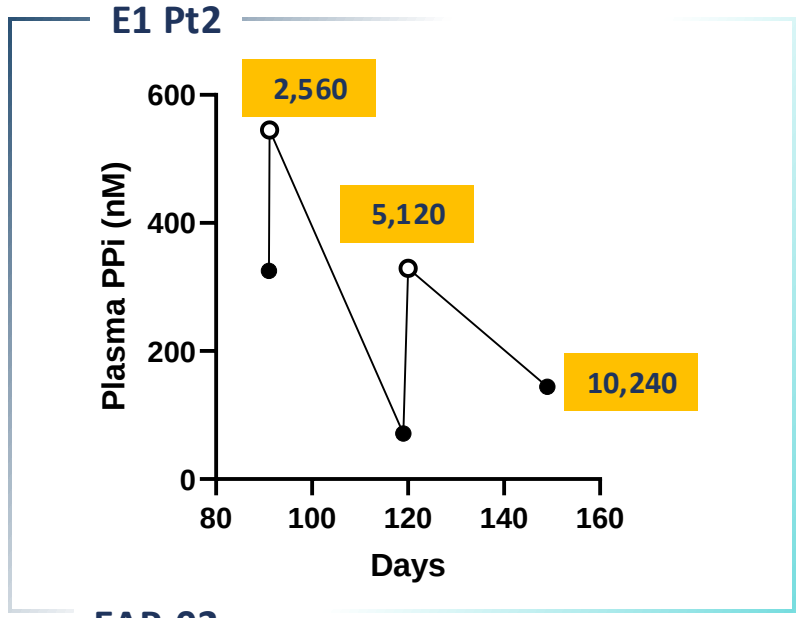
- High ADA titers in some infants significantly affected PK and PD
- ADAs were not associated with adverse events in any patient
- Data collected pre- and post-dosing demonstrated substantial transient increases in PPi and drug exposure following INZ-701 administration, consistent with the clinical effects observed

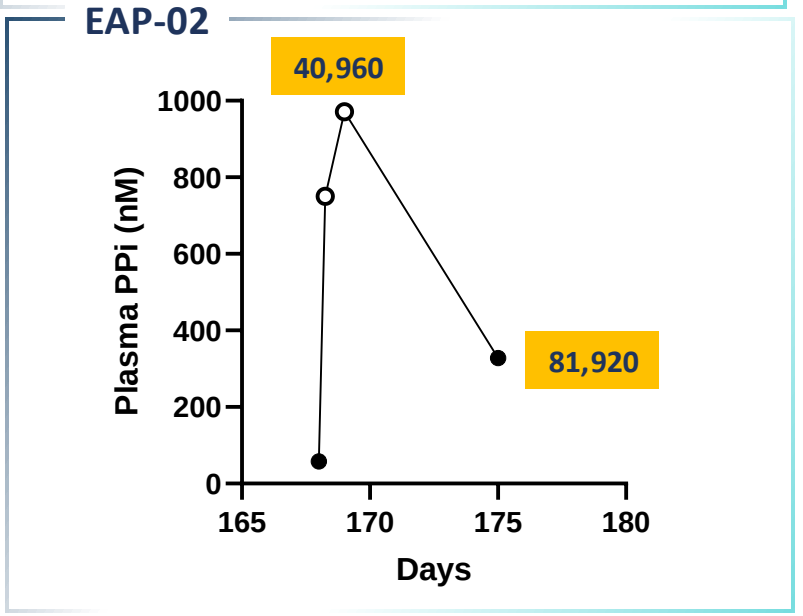
ADA Negative
ADA Positive

ENERGY 1 data cut: 16 Aug 2024; EAP data cut: 13 Dec 2024

ADAs blunt but do not eliminate potentially beneficial post-dose PPi increases

Subject ID	Day	PPi (nM)	Fold change
E1 Pt2	91 pre-dose	325	--
	91+4 hrs post-dose	545	1.7X
	119 pre-dose	71	--
	119 +24 hrs post-dose	329	4.6X
EAP-02	168 pre-dose	58	--
	168 +6hrs post-dose	750	13X
	168 +24 hrs post-dose	971	16.7X





Antibody titers

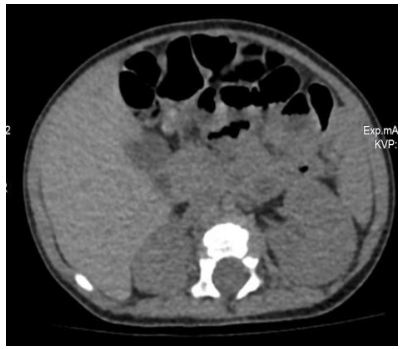
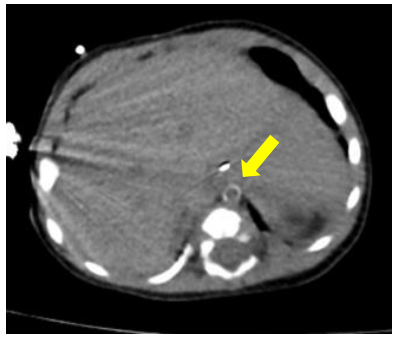
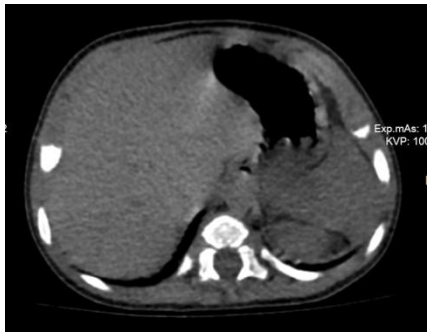
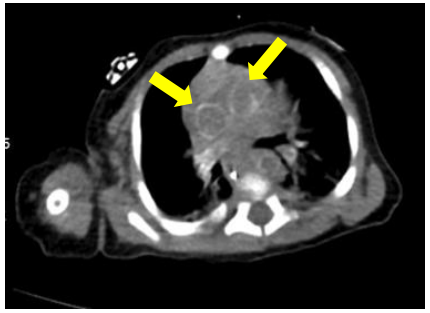
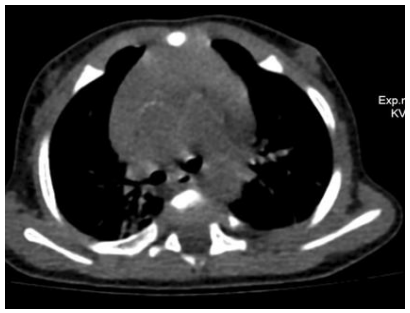
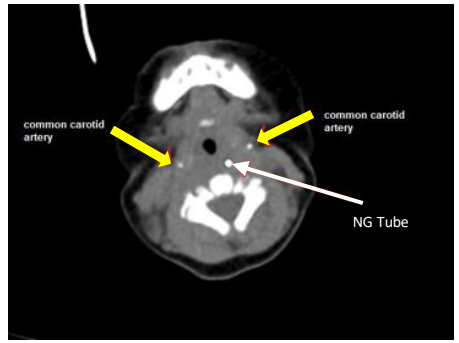
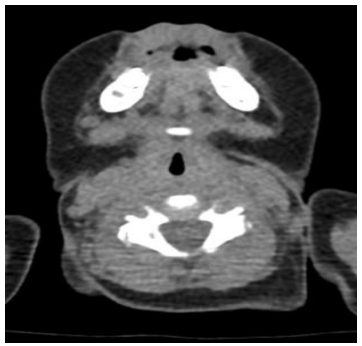
Closed symbols = pre-dose; Open symbols = post-dose

ENERGY 1 data cut: 14 Oct 2024; EAP data cut: 13 Dec 2024

Case EAP-03: Evidence of complete resolution of arterial calcification observed despite ADA detection

JAN'24 | FEB'24 | MAR'24 | APR'24 | MAY'24 | JUN'24 | JUL'24

- JAN'24: 1st INZ-701 dose (1.8 mg/kg)
- FEB'24: Baseline CT
- APR'24: ADAs detected
- MAY'24: INZ-701 dose increase (2.4 mg/kg)
- JUL'24: Follow up CT

	Baseline	6-month follow-up
Abdominal aorta and renal arteries		
Abdominal aorta		
Aorta and pulmonary artery efflux		
Carotid arteries		

EAP data cut: 13 Dec 2024

⇨ Calcification

Five patients continue receiving long-term, home administration of INZ-701

Data Review Committee recommended continuing treatment of all patients following review of interim laboratory and clinical data

- No safety signals
- Transient exposure and PPi response expected following each dose
- Potential for tolerization with long-term exposure

Clinically-relevant ADA response limited to infants

- Most ENPP1 and ABCC6 deficient adults show no ADA response or a transient, low titer response with no impact on PK
- Monitoring of ENPP1 deficient pediatric patients (ENERGY 3 trial) has shown no evidence of hypersensitivity or immune-related adverse events

Positive interim data in infants and very young children supports growing body of evidence for INZ-701 use in all age groups

Positive interim safety and exploratory efficacy data

- Well-tolerated when administered to infants and very young children
- Evidence of improved heart function, stabilization or reduction in ectopic calcifications and hypophosphatemia, and prevention of rachitic changes
  - Absence of rachitic changes support potential benefit in ENERGY 3 pediatric pivotal trial
- ADAs impacting exposure only seen in some patients less than 1 year of age and not observed in older patients

Infant data intended to support approval package for broad commercial label

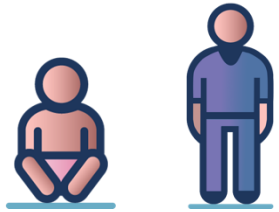
- ENPP1 Deficiency can severely affect patients at all ages
- Clinical studies comprising the INZ-701 development program address ENPP1 Deficiency across all age groups
  - ENERGY 1, ENERGY 2, EAP: Infants
  - ENERGY 3, EAP: Pediatric (1-12 yrs.)
  - 101, ADAPT: Adults
  - ENABLE: >1 yr.

ASPIRE: Planned Pivotal Study in Pediatric Patients with ABCC6 Deficiency

ASPIRE: Planned pivotal study in pediatric patients with ABCC6 Deficiency

Preliminary support from U.S. and EU regulators for ASPIRE pivotal trial in children with ABCC6 Deficiency

Population: Infants and pediatrics birth to <18 yrs



- Mono or biallelic
- At risk for stroke or CV events based on at least 1 of the following:
  - History of GACI or GACI symptoms
  - Prior stroke/TIA
  - History of CV disease
  - Cerebral arteriopathy documented by imaging
  - Family member with ABCC6 variant and GACI, stroke, cardiovascular disease or arteriopathy

Design: Multicenter, multinational, randomized (1:1), open label, conventional therapy control

Sample size estimate: 70 patients (35/arm); 85% Power

Primary

Composite endpoint:

1. Death (any cause)
2. Stroke
3. Myocardial infarction
4. Cardiac hospitalization
5. Severe disease-related AEs

Secondary

- PPi concentration
- Retinal disease progression
- Change from BL: arterial calcium score
- Change from BL: transcranial doppler
- Pediatric PROs
- PK and enzyme activity
- Safety

Thank you