NEW HORIZONS IN FABRY DISEASE

INTERNATIONAL CONFERENCE ON ADVANCES IN THE TREATMENT OF FABRY DISEASE

pegunigalsidase alfa

Preclinical and clinical

Raphael Schiffmann, M.D., M.H.Sc.

Institute of Metabolic Disease, Baylor Research Institute, Dallas, Texas, USA

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Disclosure

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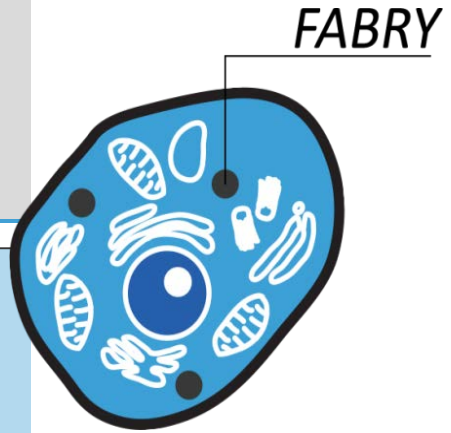
- Amicus Therapeutics
- Protalix Biotherapeutics
- Sanofi Genzyme
- Shire, Inc.

Fabry Disease and Currently Available ERTs

Caused by the loss of function of the lysosomal enzyme α-galactosidase-A (α-Gal-A)

Occurs in most tissues and cell types of: renal, heart, vascular and nervous system

This depends on multifactors including mutation type and gender



Available Treatments

agalsidase beta: Approved in the US & the EU. Administrated IV at 1 mg/kg body weight, EOW *

agalsidase alfa: Approved in the EU. Administrated IV at 0.2 mg/kg body weight, EOW **

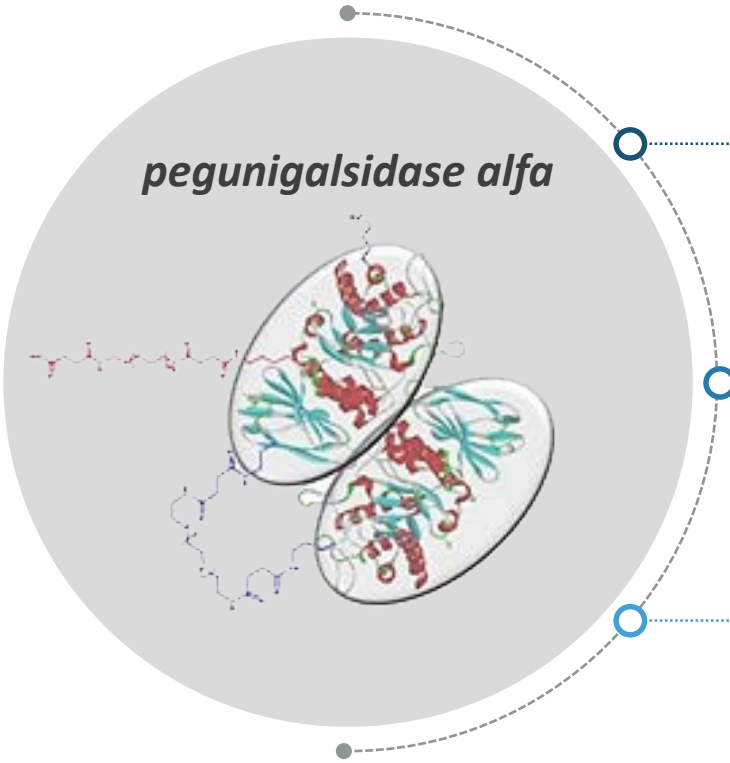
Migalastat: **:** Approved in the EU. Administrated orally, 123 mg hard capsules every other day***

Unmet clinical need

- **Continuous disease progression**
- **Immune response**
- **Infusion reactions**
- **Long-term efficacy**

* agalsidase beta USPI ; ** agalsidase alfa SMPC; *** Migalastat SMPC

pegunigalsidase alfa:
PEGylated, Chemically Modified α-Gal-A Enzyme



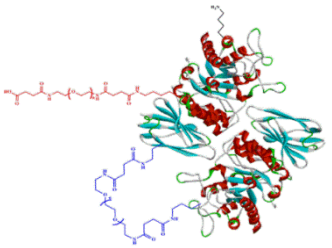
PEGylated covalently-linked homodimer composed of two subunits produced in plant cells

Subunits linked through a **2KDa PEG cross-linker** resulting in 114 kDa enzyme. Contains additional **PEG moieties** bound to only one subunit through a lysine residue

Enzyme maintains its catalytic activity and translocation to the lysosome of target cells

pegunigalsidase alfa is designed for:

- Providing continuous presence of enzyme throughout the 2-week dosing interval by means of a stable homodimer without compromising the enzyme activity and internalization to target organ and cells
  - Extended circulatory half life
  - Enhanced stability in plasma and under acidic lysosomal-like conditions
- Potentially providing increase enzyme exposure and enhanced activity to target organs and sustained degradation and prevention of accumulation and re-accumulation of substrate
- PEGylation potentially reduces immunogenicity

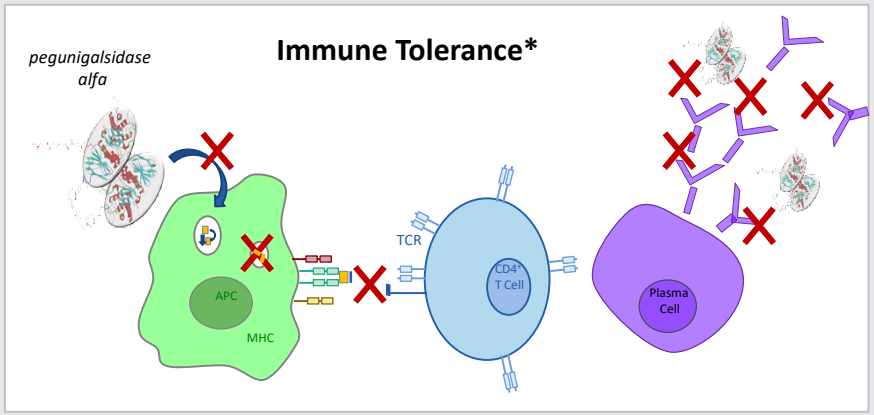


Potential Impact on Immunogenicity

01 **Chemical modification has the potential to hamper the antigen presentation of pegunigalsidase alfa by Antigen Presenting Cells (APC)**
- **Processing**
- **Recognition by T-helper cells**

02 **PEGylation potentially reduces immunogenicity by masking immunogenic epitopes**

03 **Potential induction of immune tolerance due to improved stability and prolonging/continuous exposure**



*Adopted from: M. Ing et al., Cell. Immunol. (2015)

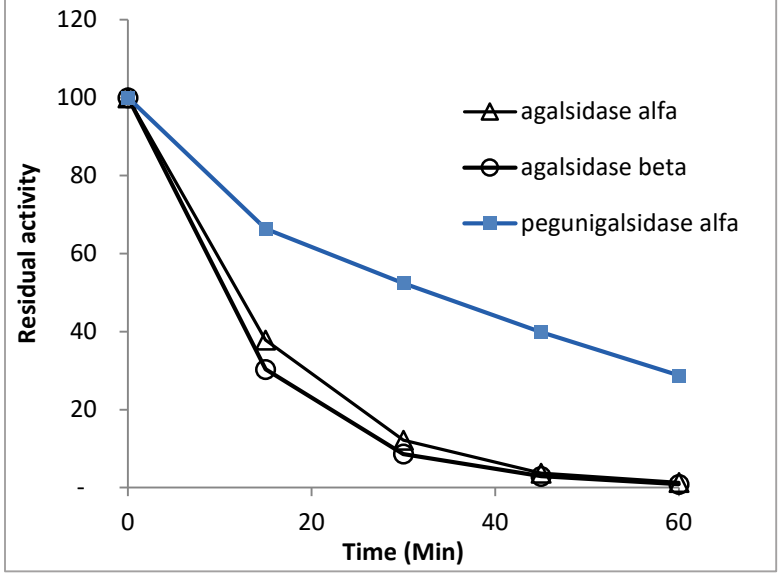
Scientific development and preclinical data

pegunigalsidase alfa
specific characteristics and attributes

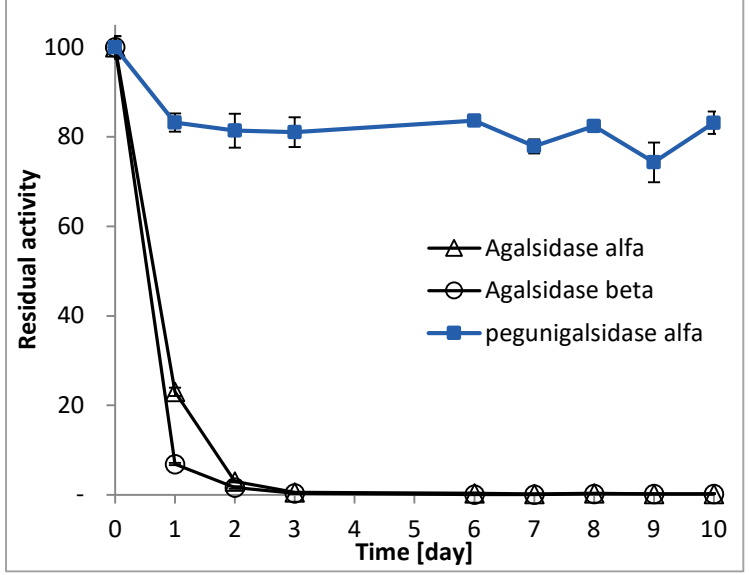
Prolonged Stability in Biological Matrices

Compared to the other ERTs

Stability in human plasma at 37°C (pH=7.4)



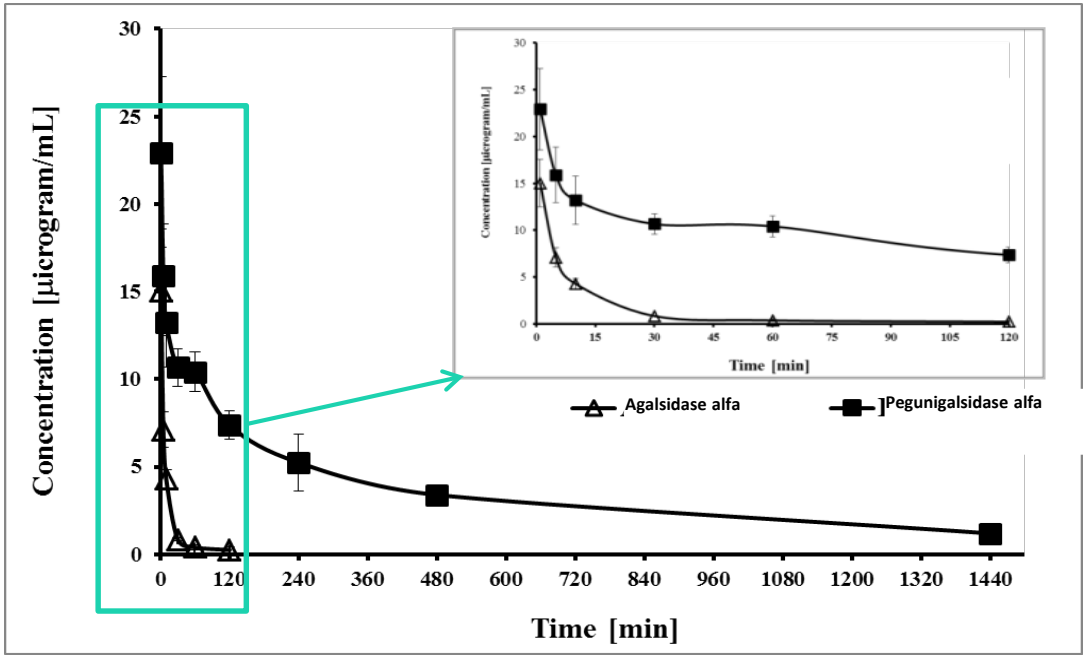
Stability in lysosomal-like conditions (pH=4.6)



pegunigalsidase alfa demonstrates improved stability, implicating for higher potential to deliver an active long-functional enzyme to its site of action

Extended Circulatory Half Life ($t_{1/2}$) - in Fabry Mice Model

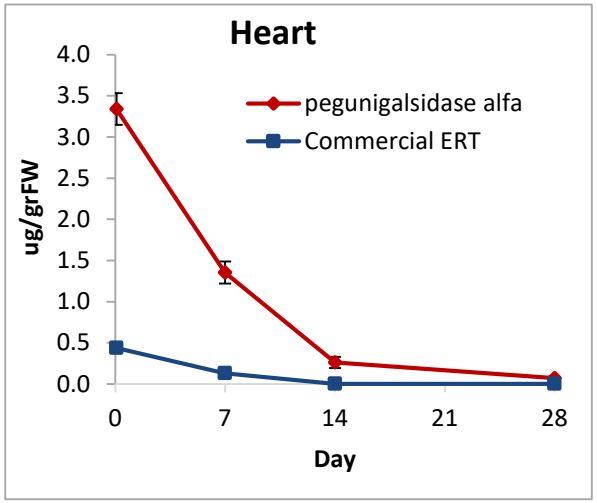
Pharmacokinetic Studies in Fabry Mice Model

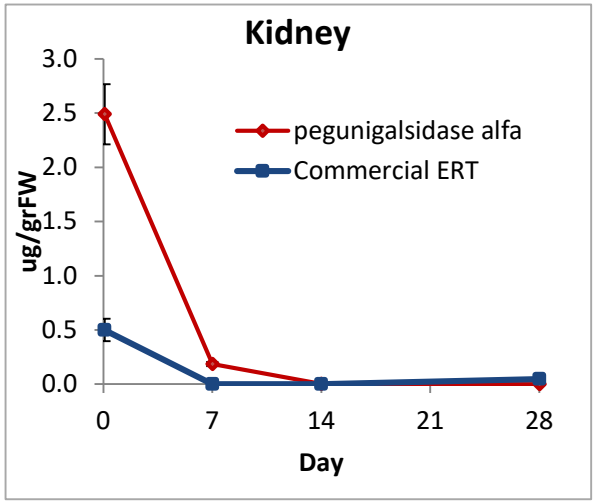


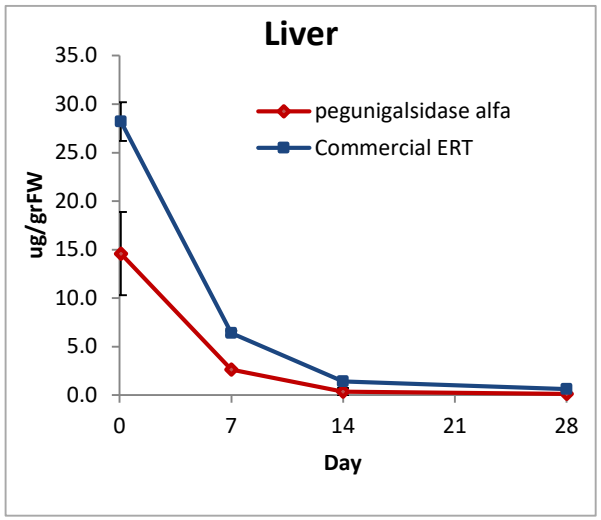
Enhanced Delivery & Prolonged Activity in Target Organs of Fabry Mice. Enzyme quantities were assessed by an activity assay

Increased delivery of the active enzyme to the target organs

Reduced clearance by Liver



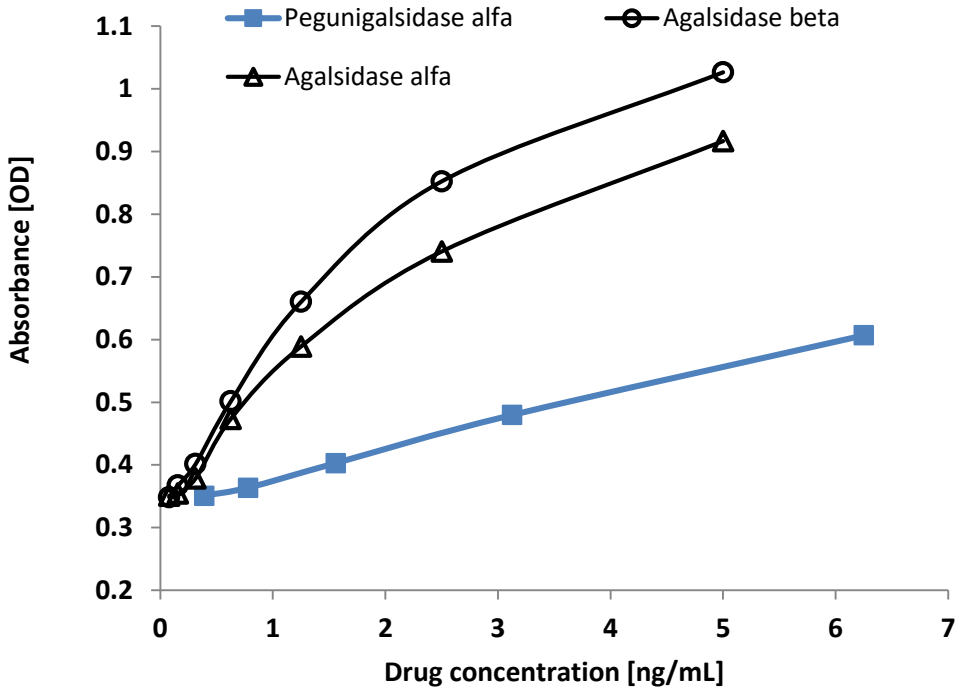




µg/gr FW = amount of enzyme [µg] per gr of tissue fresh weight [FW], assessed by activity

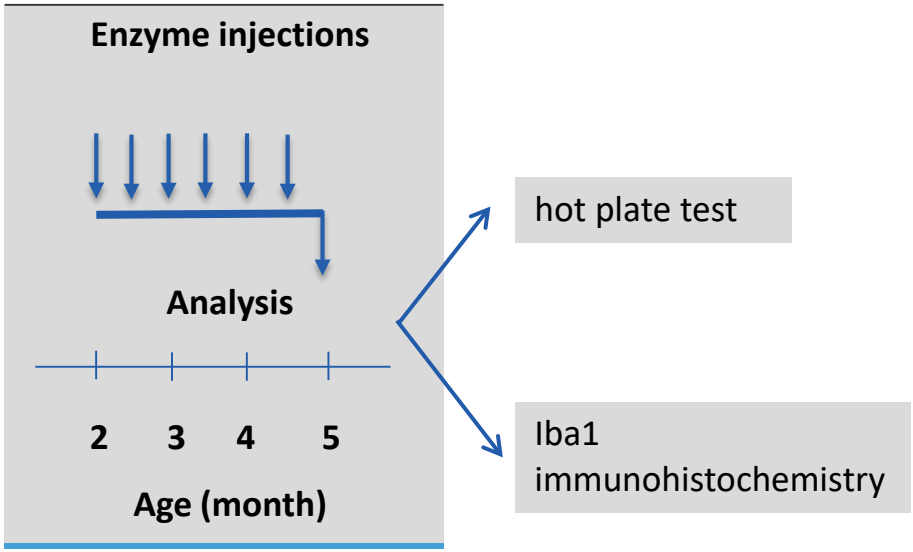
Improved/Reduced Antigenicity

- Antibodies generated by immunization of rabbits with α-Gal-A, recognized pegunigalsidase alfa to a lesser extent than agalsidase alfa or beta



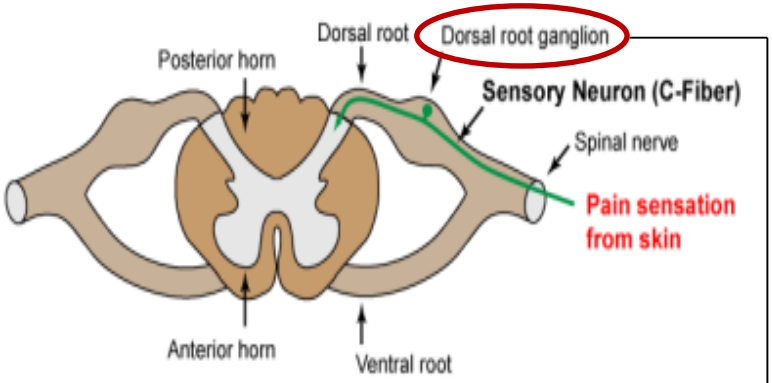
- Patients who develop antibodies on treatment with agalsidase alfa or beta has the potential to benefit from switching to pegunigalsidase alfa due to a lower recognition of pegunigalsidase alfa by existing antibodies to agalsidase beta and alfa

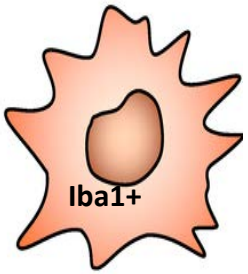
Small-fiber neuropathy in Fabry mice - Biomarkers and Functional measures of Neuropathy (hot plate sensitivity testing)



hot plate test

Iba1 immunohistochemistry



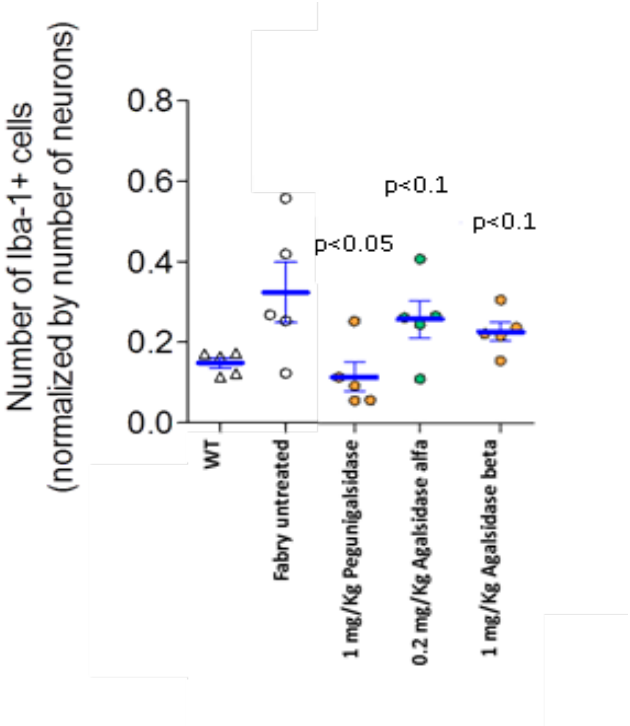


Activated microglia/macrophage

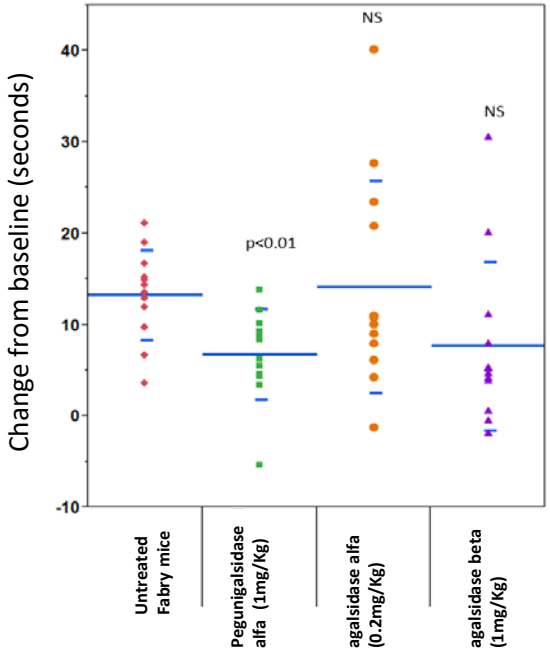
In collaboration with Jinsong Shen, M.D., Ph.D.
Institute of Metabolic Disease, Baylor Research

Protective effect on neuropathy, including peripheral nerves

Biomarker:
Change in number of Iba1⁺ cells in DRG



Function:
Change in time to response to heat stimulus following 6 injections EOW



Statistical significance shown on top of each group indicates the p-values vs. untreated Fabry mice

In collaboration with Jinsong Shen, M.D., Ph.D. Institute of Metabolic Disease, Baylor Research

The data support the potential for improved efficacy of pegunigalsidase alfa compared to existing ERTs with regards to a protective effect on peripheral nerves

Phase I/II

Clinical Experience in studies PB-102-F01/F02/F03 with Fabry patients.

2 years Interim report

Phase I/II, Open Label, Dose Ranging

General Design

Adult Fabry Patients

Three dose groups:

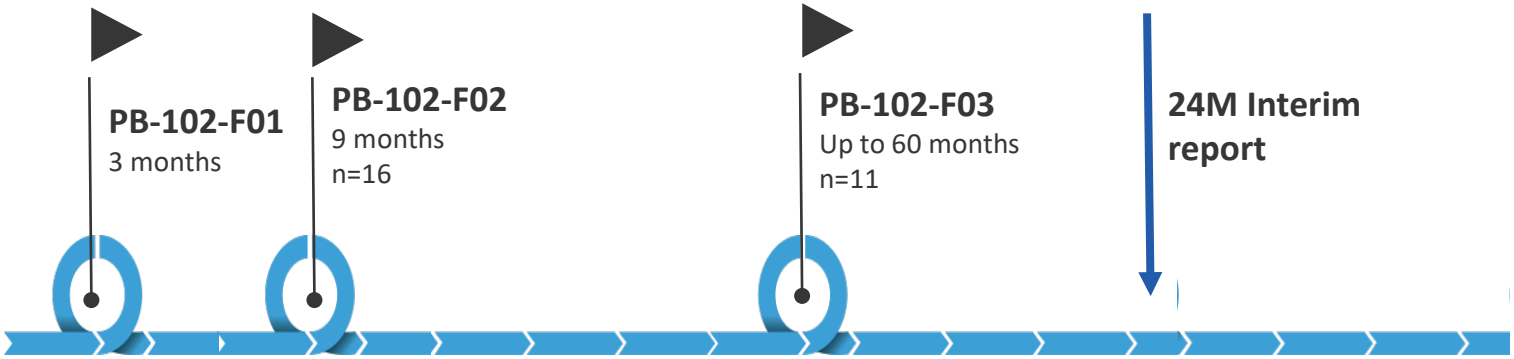
Intravenously, every 2 weeks

Main Inclusion Criteria:

- Symptomatic Fabry patients
- ERT naïve or patients who are off ERT in the last 6 months; negative IgG anti PRX-102 antibody
- eGFR ≥ 60 mL/min/1.73m2

Main Exclusion Criteria:

- Chronic kidney disease stages 3-5
- Severe myocardial fibrosis by MRI
- Pregnant or nursing
- Known allergies to ERT



Reasons for early discontinuation:

- Female-pregnancy
- Female –planned pregnancy
- Male- Patient declined to further participate in a clinical study
- 2 pts (a mother and son) withdrew consent due occupational constrains

Demographics & Baseline Enzymatic Activity

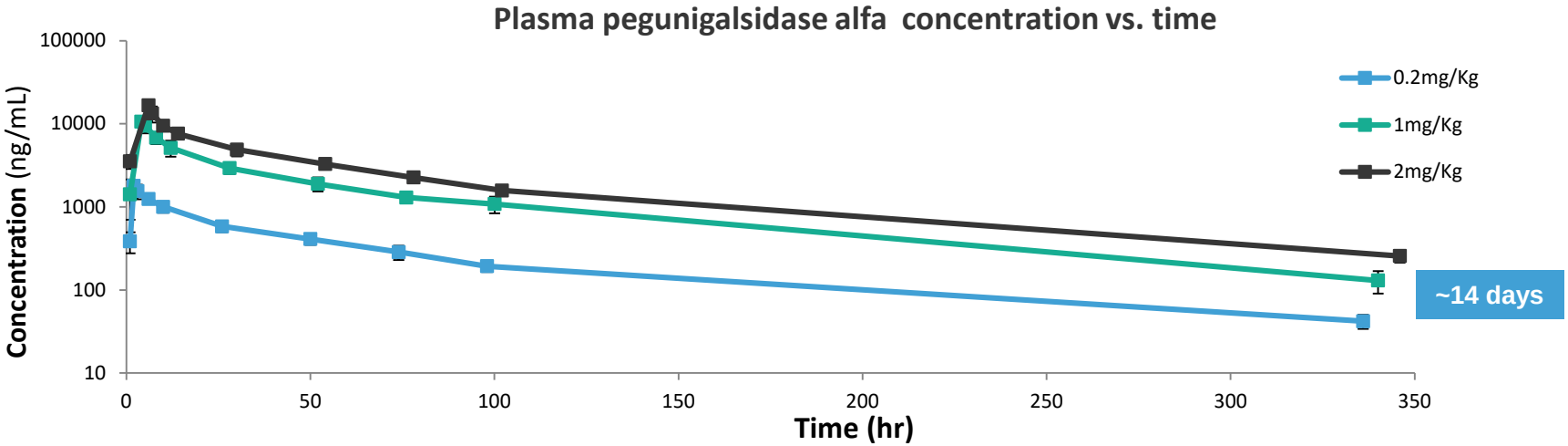
	0.2 mg/kg (n=6)	1 mg/kg (n=8)*	2 mg/kg (n=4)
Mean age (years) ± SD (range)	30.0 ± 10.8 (21-50)	34 ± 9.7 (17.5-52.5)	40.6 ± 9.5 (21-54)
Male : Female	4:2	6:2	1:3
Ethnicity			
Caucasian	4	4	4
African American	1	2	0
Asian	0	0	0
Other	1	0	0

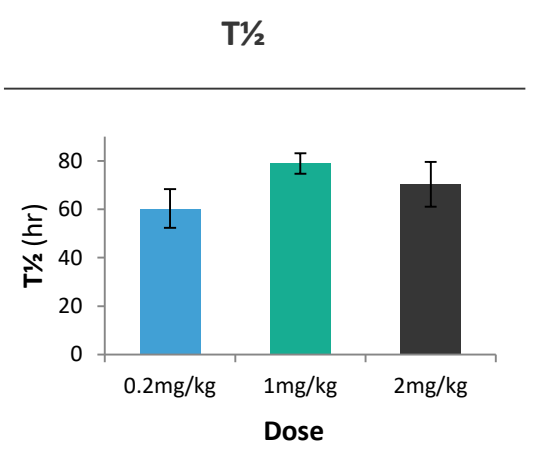
Mean Enzymatic Activity	**0.2 mg/kg (males=4, females=2)**	**1 mg/kg (males*=6, females=2)**	**2 mg/kg (males=1, females=3)**
In leucocytes (range) (normal 33-134 nmol/hr/mg prt.)	Males: 3.15 (1.6-5) Females: 27.5 (15-40)	Males: 2.67 (0-7.8) Females: 69.5 (67-72)	Male 0.56 Females: 42.66 (33-53)
In plasma (range) (normal 4-21.9 nmol/hr/ml)	Males: 0.22 (0-0.4) Females: 3.15 (2-4.3)	Males: 0.28 (0.05-0.44) Female: 6.8 (5.8-7.8)	Male: 0.4 Females: 4.80 (2.52-7.8)

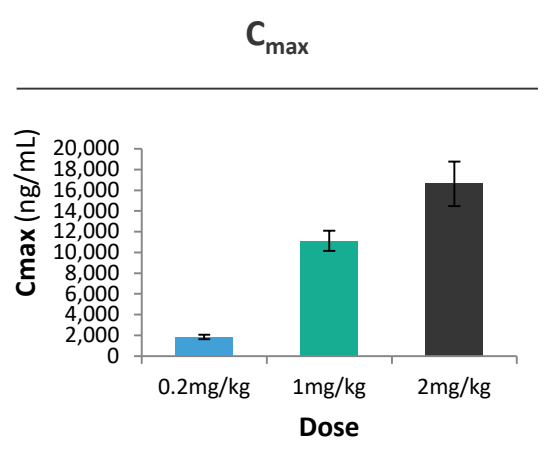
* one subject discontinued due to AE; one subject discontinued due to non compliance

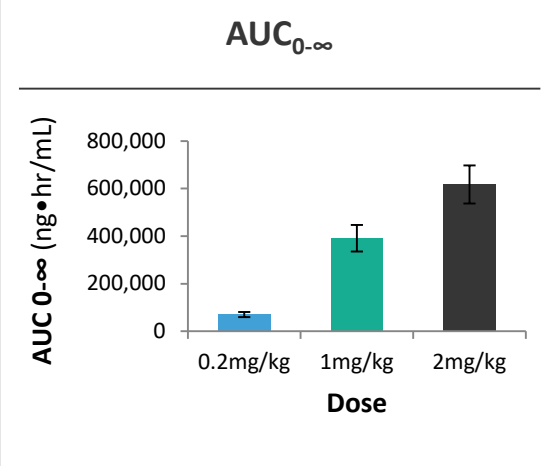
Pharmacokinetics - Available Enzyme Throughout 2-Week Interval

PK sampling was done throughout the 1Y treatment

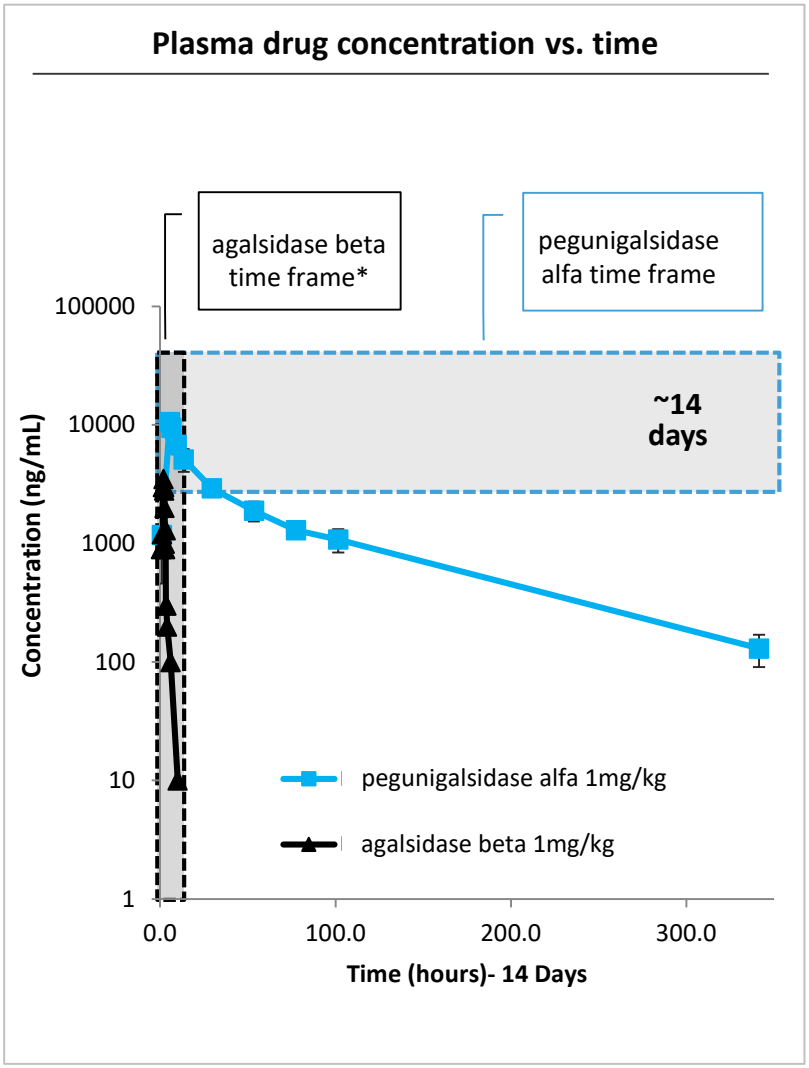




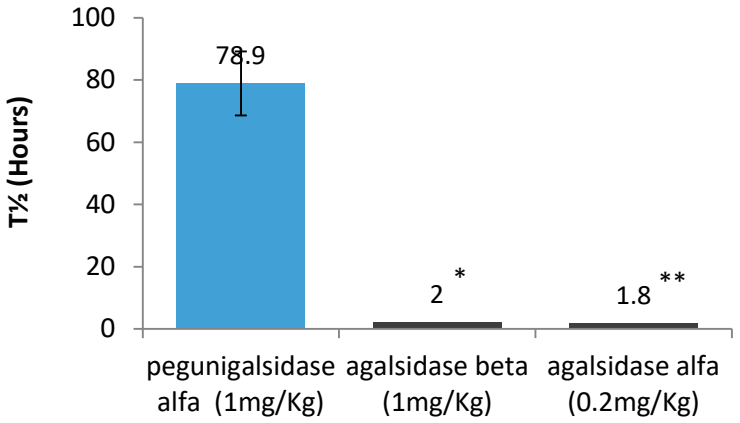




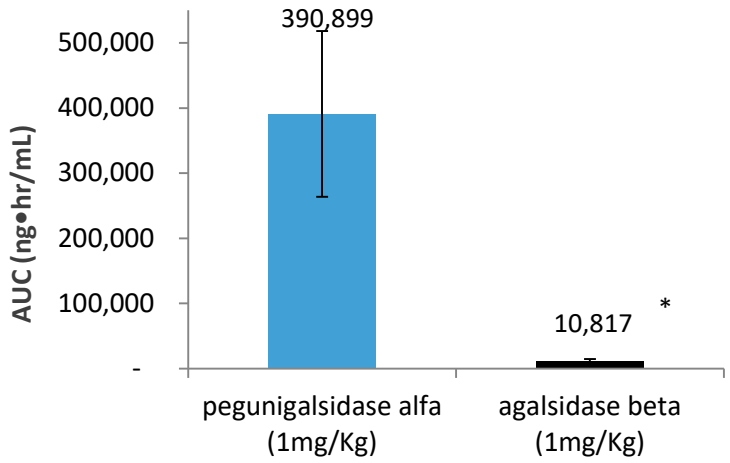
Substantially greater enzyme exposure than current ERTs*,**



T½: Approx. 80 hours



AUC (0-∞): >35 fold from current ERTs (Both drugs at 1mg/kg)



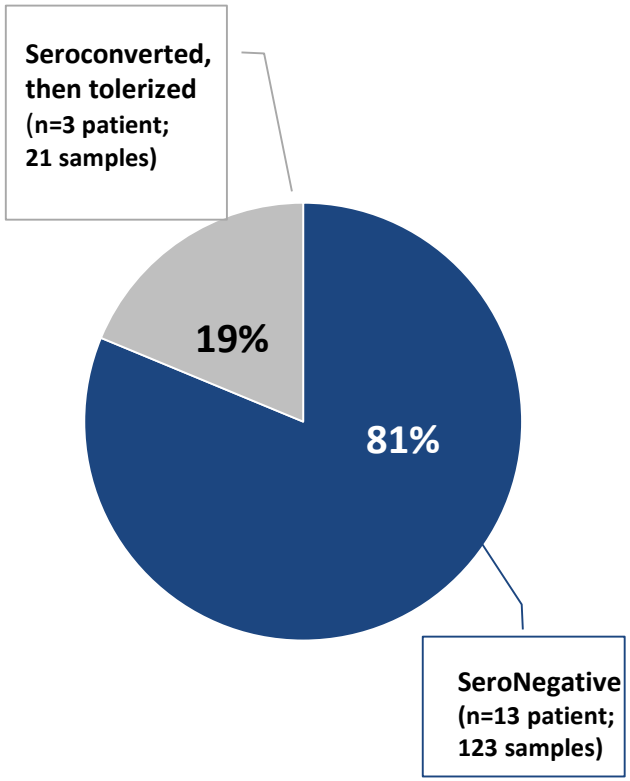
*agalsidase beta – USPI ; ** agalsidase alfa –SMPC; AUC units: ng•hr/mL; 1ng•hr/mL = 0.06 μg•min/mL

Immunogenicity Evaluation – Current Clinical Experience
Low incidence of treatment induced Anti Drug Antibodies (ADA)

Anti-Drug Antibodies (ADA) multi-tier assessment *
Screening
Confirmatory
Confirmed positive samples further characterized for:
- Titer
- Neutralizing activity

Results
- Serum samples were drawn once a month for 4 first months and then once every 2 months
- 123/144 samples (16 patients) tested negative for ADA

Incidence of treatment induced ADA



Low incidence of ADA:
3/16 patients→19%
2 in the 0.2mg/kg
1 in the 1mg/kg
None in the 2mg/kg

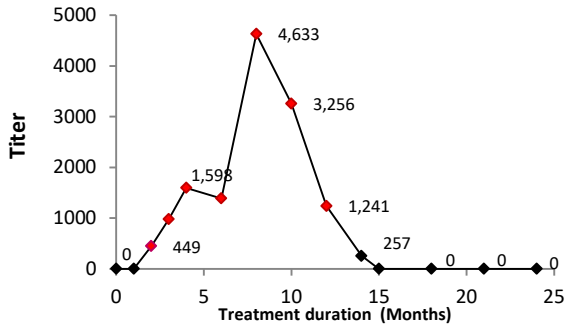
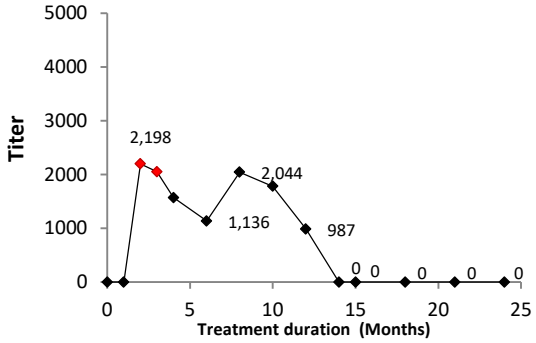
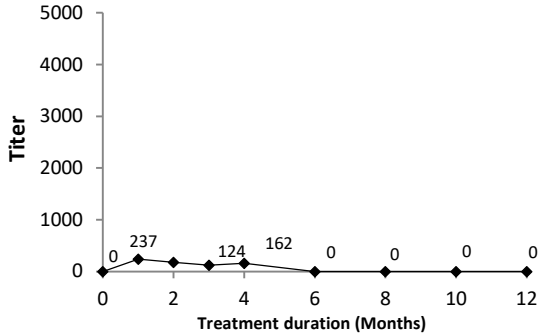
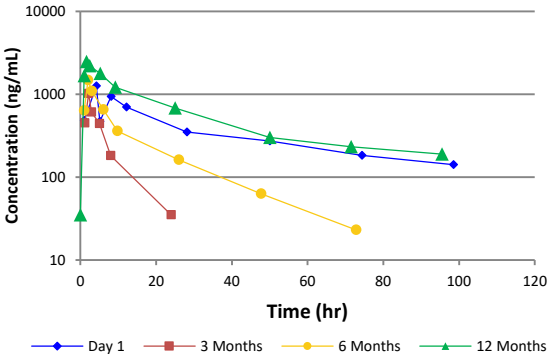
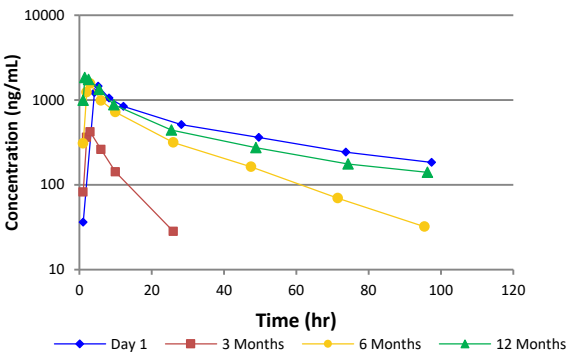
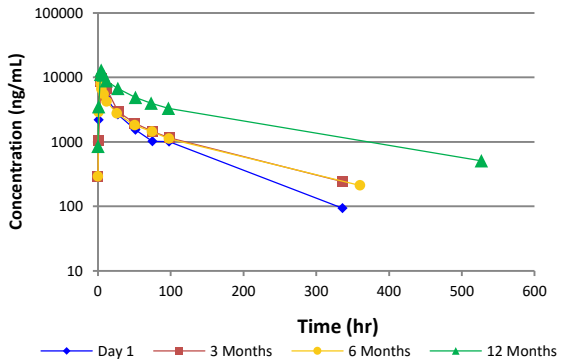
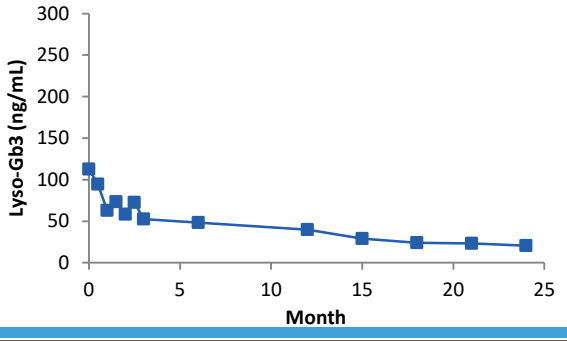
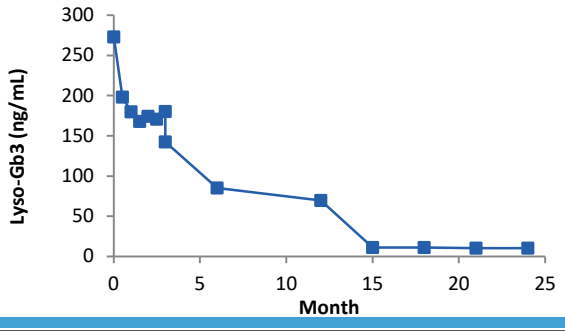
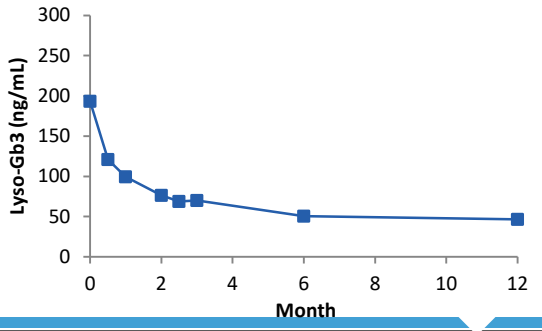
Low titers
Max titer 4633

Neutralizing ADA:
2 of 3 positive patients had neutralizing activity in some samples

Immune tolerization
All 3 ADA positive patients turned to be negative for ADA after 12M of treatment

* With accordance to the crurent regulatory guidelines, using sensitive and validated methods

Reduced Immunogenicity combined with longer enzyme coverage
No effect on continues Biomarkers reduction in ADA positive (including Nab) pts.

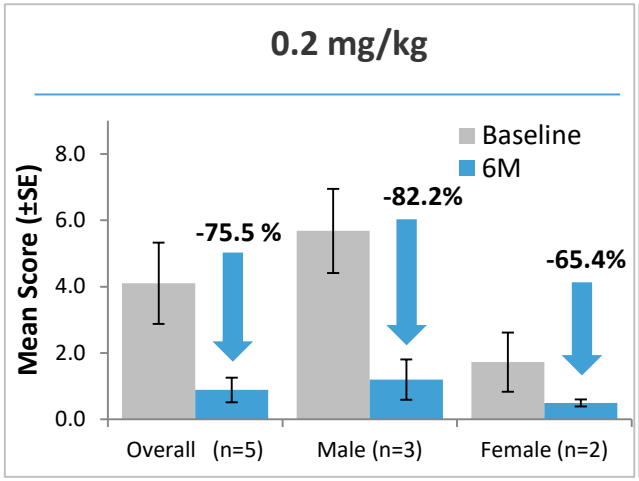
	Subject 15-F106; 0.2mg/kg	Subject 17-F105; 0.2mg/kg	Subject 07-F113; 1mg/kg
ADA⁺: IgG Titers			
PK profiles			
Biomarker			

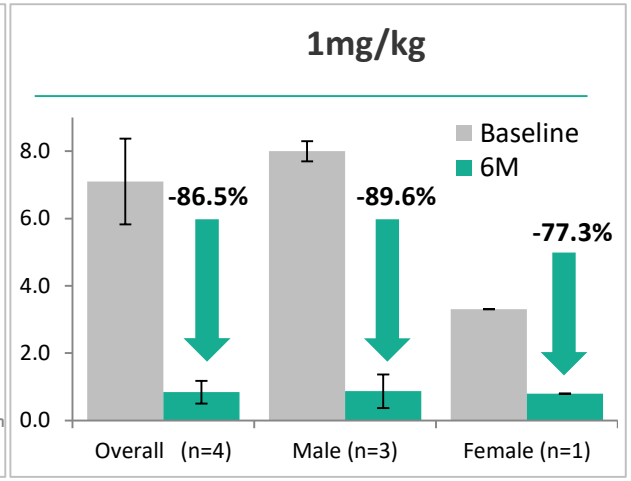
nAb positive samples are indicated in red

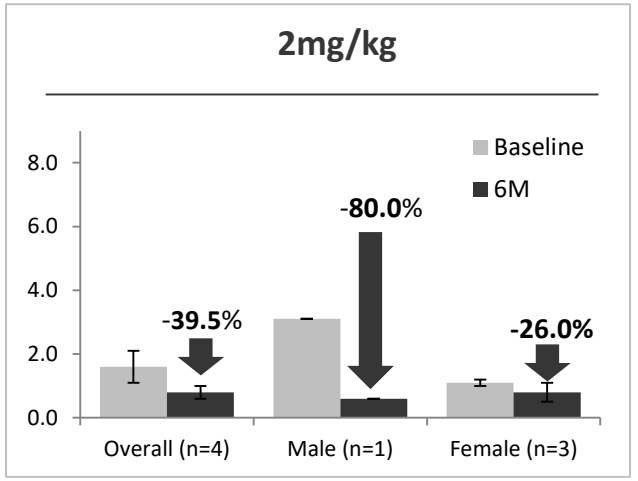
Efficacy

Reduction of Gb3 in Kidney Peritubular Capillaries

Quantitative BLISS Score





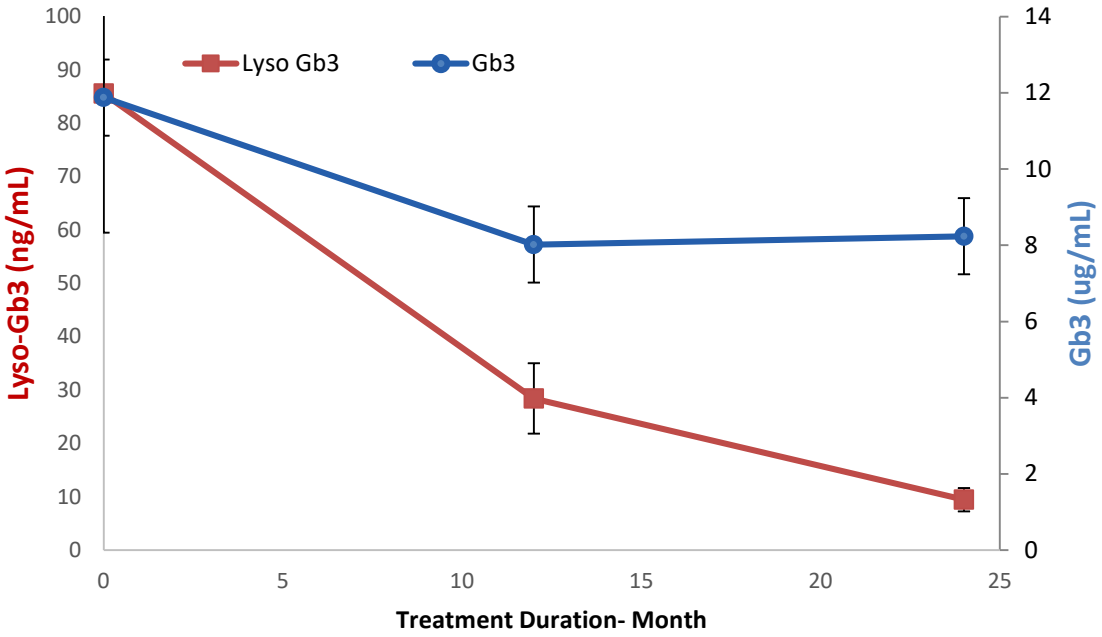


	% change ±SE
All Patients (n=13)	**-67.8±8.9**
Classic Patients (n=8)	**-84.1±3.3**

- >300 PTCs were scored for Gb3 inclusions in each biopsy
- Slides underwent digital imaging before scoring
- Images were distributed in a random and blinded manner for annotation by 1 pathologist, and subsequent scoring by 2 other pathologists

Continuous Reduction of Biomarkers – 24 months

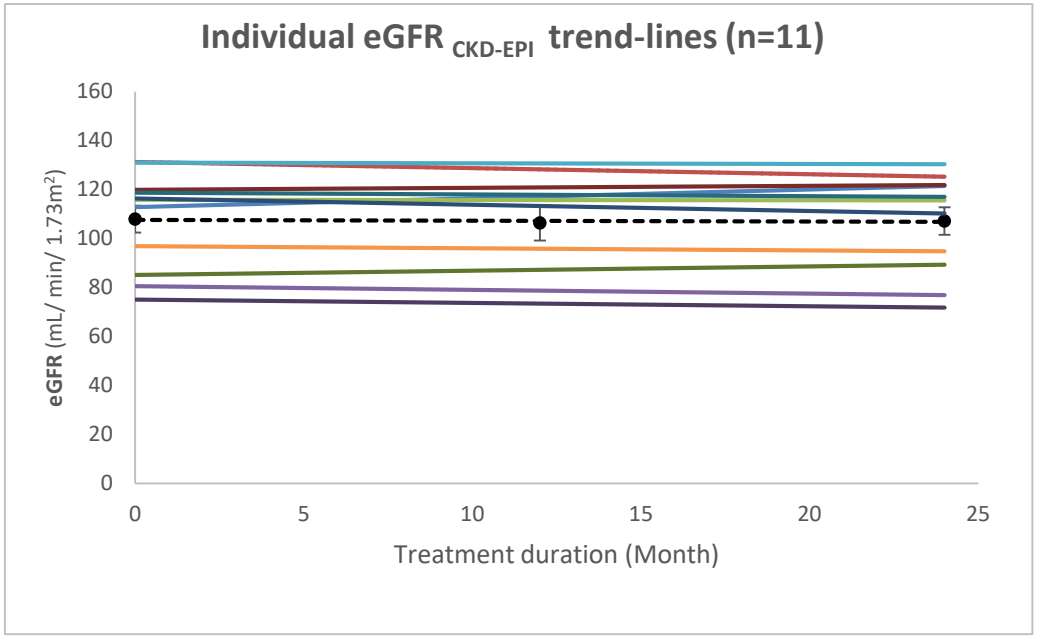
Plasma Gb3 and Lyso-Gb3 (N=11)



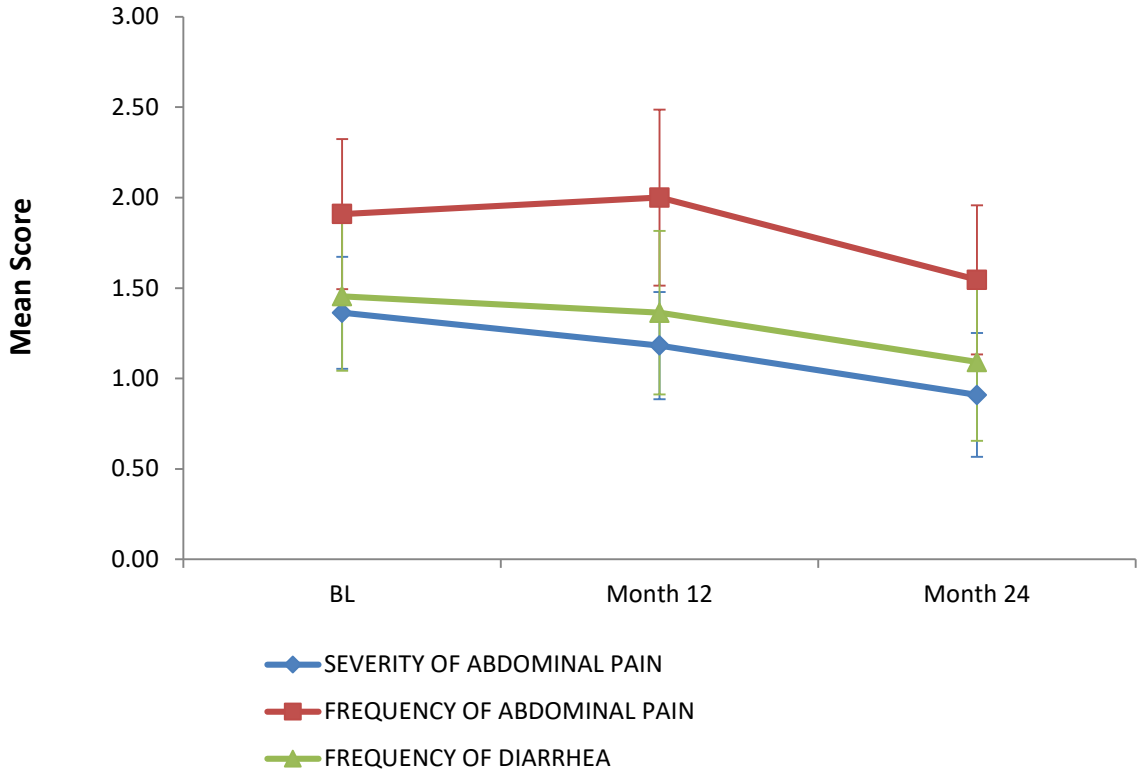
Continuous Stability of Renal Function- 24 months (N=11)

Individual $eGFR_{CKD-EPI}$ absolute values

PID	Sex	eGFR at Base line	eGFR at 12M	eGFR at 24M
51-F102	F	113	116.8	121.6
12-F103	M	127.5	135.8	121.6
15-F106	M	112.4	122.6	112.1
26-F104	M	82.4	75.1	78.8
17-F105	M	131	130.9	130.3
07-F113	M	102	85.9	99.9
09-F108	M	114.3	117.7	108.1
15-F116	F	120.5	119.7	122.6
15-F117	F	88.2	81.1	92.4
17-F118	F	77.7	68.3	74.4
09-F119	M	119.2	117.2	117.5
Mean		**108.02**	**106.46**	**107.20**
SD		18.10	23.98	18.63

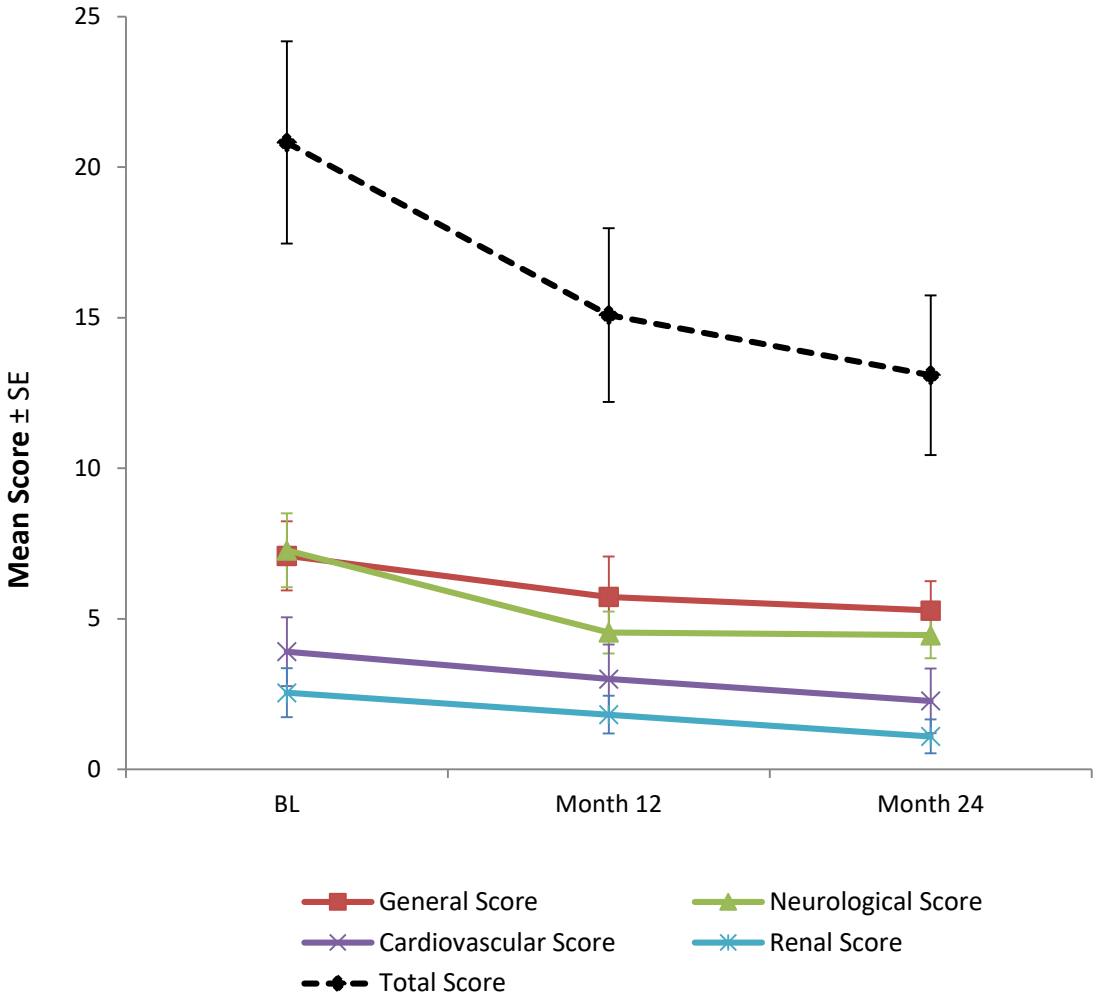


Improvement in Gastrointestinal Symptoms- 24 months (N=11)



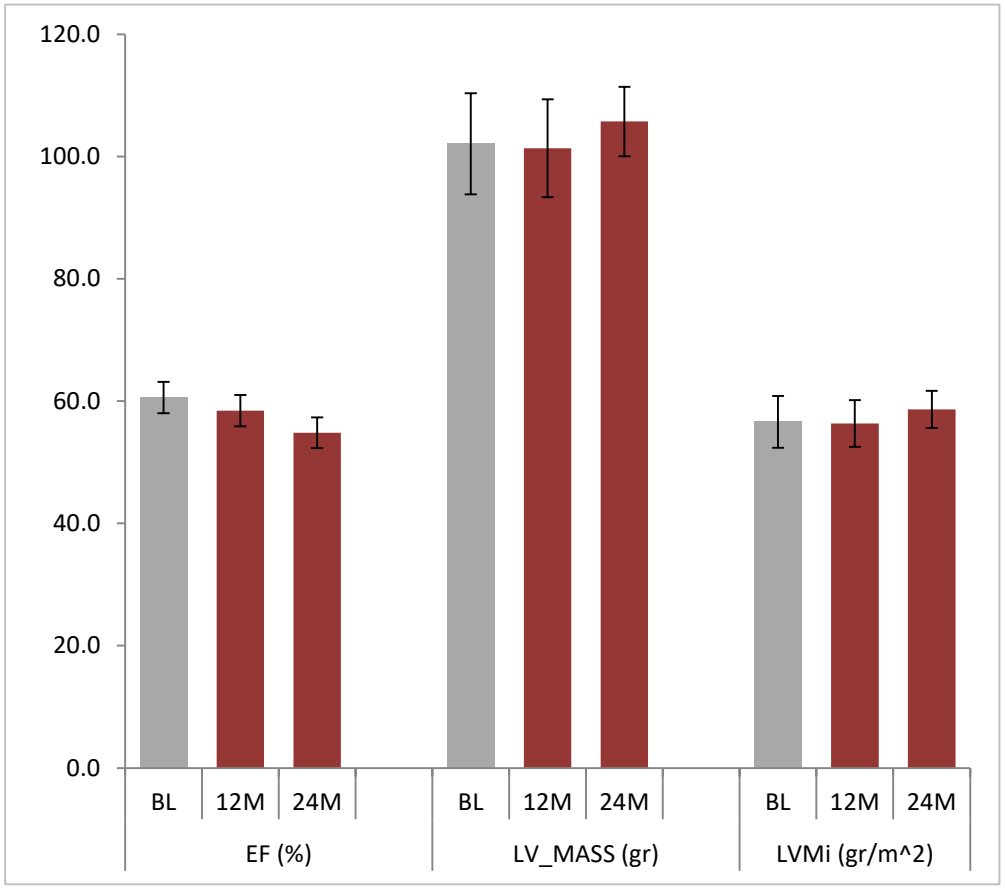
Scoring legends:	
Severity of abdominal pain	0 (no pain) to 4 (very severe pain)
Frequency of abdominal pain	0 (never) to 4 (daily) at least once a day
Frequency of diarrhea	0 (never) to 4 (daily) at least once a day

Mainz Severity Score Index (MSSI)- 24 months (N=11)



Stable Cardiac Parameters (by MRI) - 24 months (N=11)

Mean LVM, LVMI and EF



Normal Ranges (MRI)	Male	Female
LVM(g)	85-181	66-115
LVMI (g/m^2)	46-84	37-67
EF (%)	55-74	54-74

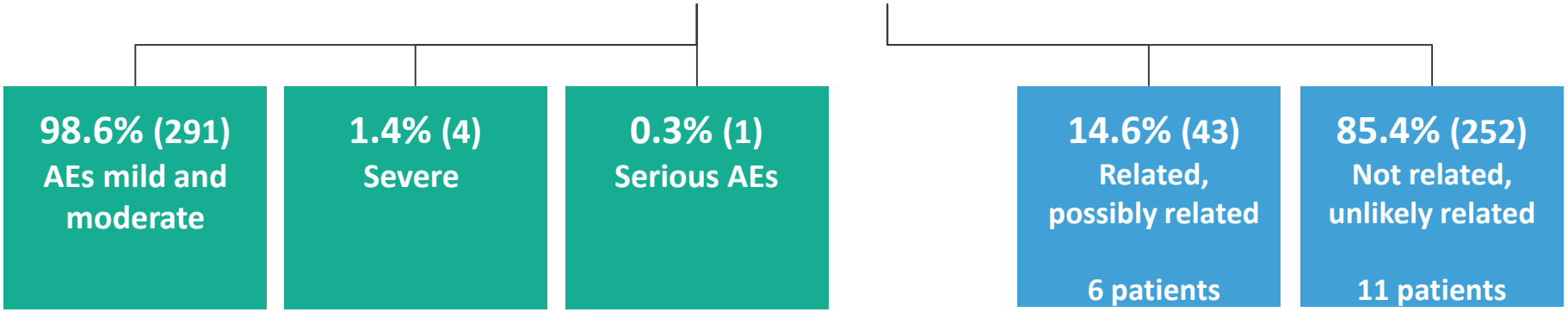
- No cardiac fibrosis developed throughout the 24 months of treatment

Safety

Safety in 906 Infusions (=34.8 patient years)

100% (295)

Total AEs in 11 patients completing 2 years of treatment



- 2 Severe treatment related, 1 pt.. (Migraine, Headache)
- 2 Severe not treatment related in 2 other pts. (Renal Hematoma, Pain in Extremity)

- Kidney hemorrhage post biopsy, not treatment related*

*28 year old male, pre treatment renal hematoma post kidney biopsy- Not related.

Treatment Related AEs -24 months (N=11)

- 9 patients experienced 70 Adverse Events at the day of the infusion
- 22/70 (31.4%) Adverse Events were reported as treatment related
- All recovered without sequelae
- Infusion Treatment Related Adverse Events;
  - Abdominal pain (7)
  - Nausea (2)
  - Chest discomfort (2)
  - Infusion related reaction (2)
  - Chest Pain (1)
  - Diarrhea (1)
  - Oedema (1)
  - Oedema peripheral (1)
  - Dizziness (1)
  - Nervousness (1)
  - Paranasal sinus hypersecretion (1)
  - Sneezing (1)
  - Pruritus (1)

*at the fay of PRX-102 Infusion

Overall Conclusions- Interim 24 month

pegunigalsidase alfa (PRX-102)

pegunigalsidase alfa – PEGylated covalently-linked recombinant alpha-GAL-A enzyme, stable homodimer, produced in plant cells

PK:

pegunigalsidase has a longer half-life and a substantially higher AUC

- Available enzyme throughout 2-week infusion intervals
- Markedly extended circulatory half-life compared with other ERTs

Safety:

pegunigalsidase is well tolerated

- Majority of adverse events – mild and moderate in severity
- Low incidence of treatment induced ADA with reversible & transient effect on PK
- ADA response was transient and tolerization was observed
- ADA positivity had no observed impact on safety and efficacy

Efficacy:

Demonstrated effectiveness, in various disease endpoints including:

- Stable kidney and cardiac function
- Reduction of Gb3 inclusions in kidney peritubular endothelial cells
- Continuous reduction of plasma Gb3 and Lyso-Gb3
- Improvement in Gastrointestinal Symptoms- parameters

Special thanks to:

- **The Patients and their families**
- **Phase I/II Investigators:**

  - Derralynn Hughes
  - Pilar Giraldo
  - Derlis Gonzales
  - Myrl Holida
  - Simeon Boyd
  - Mohamed Atta

  - Derralynn Hughes
  - Kathy Nicholls
  - Ahmad Tuffaha
  - Ozlem Goker- Alpan
  - Gustavo Maegawa

- **Martha R. Charney for PK analysis and projections**
- **Study site clinical teams and co-authors**

EU Positive opinion for orphan drug designation (ODD) for pegunigalsidase alfa – Obtained- November 2017

- ODD was based on medically plausible evidence that pegunigalsidase alfa will provide a significant benefit over existing approved therapies in the European Union

- Significant benefit of pegunigalsidase alfa with a clinically relevant advantage was based on data compared to other authorized treatments in the EU:

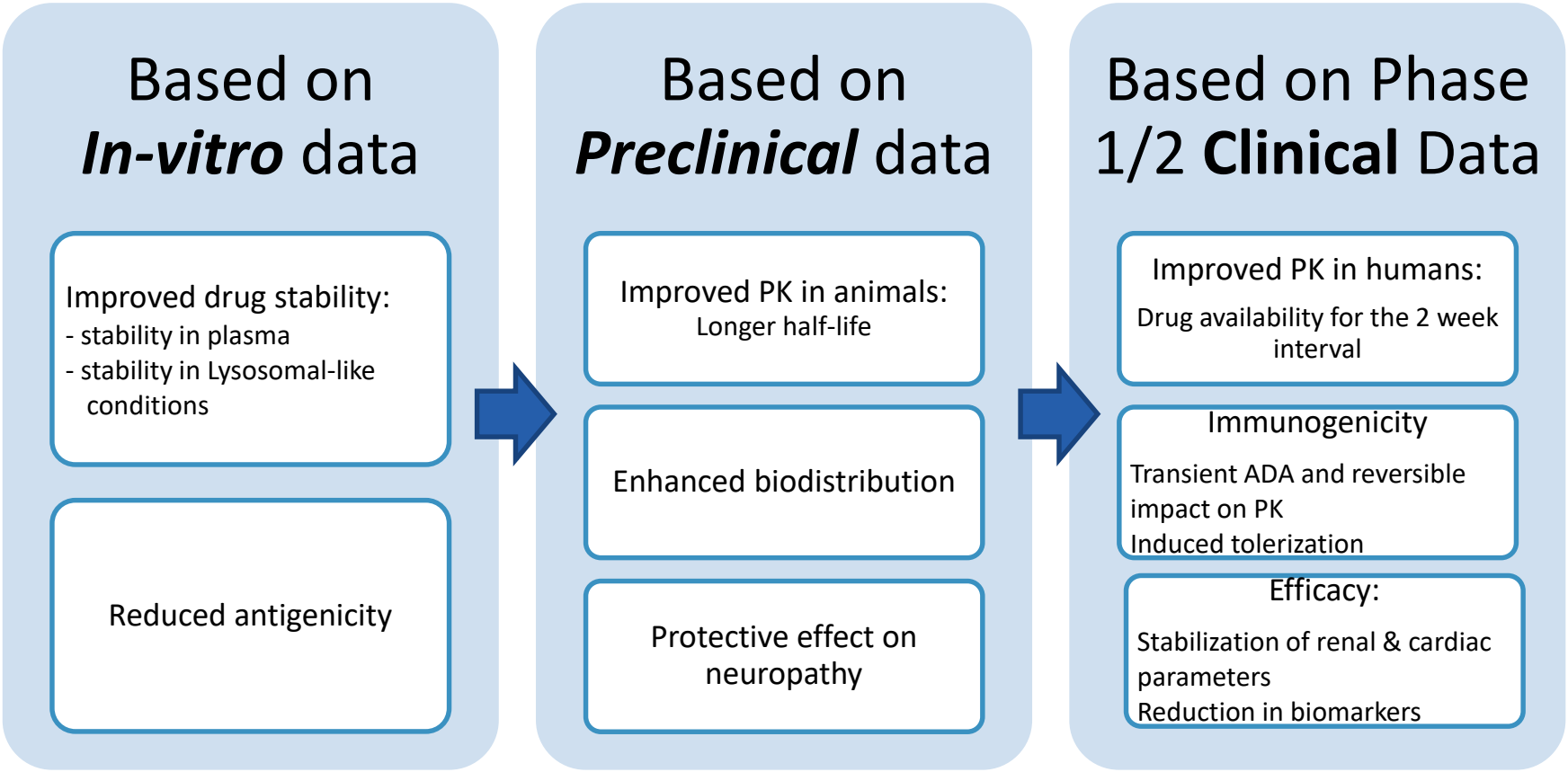
Non clinical

- Reduced accumulation of toxic metabolites (Gb3) in relevant tissues
- Reduced peripheral neuropathy

Clinical

- Stabilization of kidney function
- Reduced immunogenicity

Following FDA & EMA discussions Phase 3 Program initiated
Data supporting design of on-going pegunigalsidase alfa Phase 3 program



On Going Phase 3 Studies

balance a Fabry clinical study

- A randomized, double blind, active control study
- Evaluate the safety and efficacy of *pegunigalsidase alfa* compared to agalsidase beta in patients with FD previously treated with agalsidase beta with rapidly declining renal function
- 2 years treatment duration
- Extension study will be offered to patients at the end of the study

ClinicalTrials.gov Identifier:NCT02795676

bridge a Fabry clinical study

- An open label switch over study from agalsidase alfa
- Assess the safety and efficacy of *pegunigalsidase alfa* patients with FD treated with agalsidase alfa for at least 2 years
- 1 year treatment duration
- Extension study will be offered to patients at the end of the study

ClinicalTrials.gov Identifier:NCT03018730

bright A Fabry clinical study of once-monthly ERT

An open label, switch over study from agalsidase alfa and beta

Assess the safety, efficacy and PK of *pegunigalsidase alfa* 2 mg/kg IV administrated every 4 Weeks in FD patients currently treated with ERT

1 year treatment duration

Extension study will be offered to patients at the end of the study

ClinicalTrials.gov Identifier:NCT03180840

Thank You