



NEW HORIZONS IN FABRY DISEASE

INTERNATIONAL CONFERENCE ON ADVANCES
IN THE TREATMENT OF FABRY DISEASE

pegunigalsidase alfa

Preclinical and clinical

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Disclosure

Research support, travel expenses, honoraria

- 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

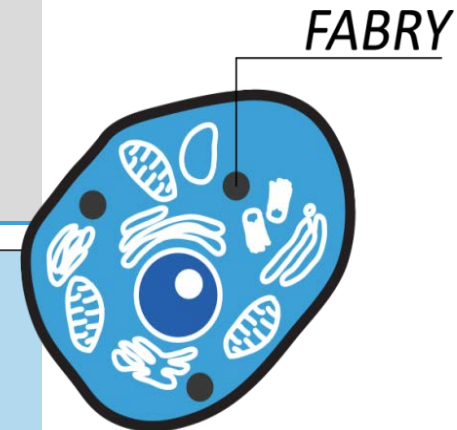
agalsidase beta: Approved in the US & the EU. Administrated IV at 1 mg/kg body weight, EOW *

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

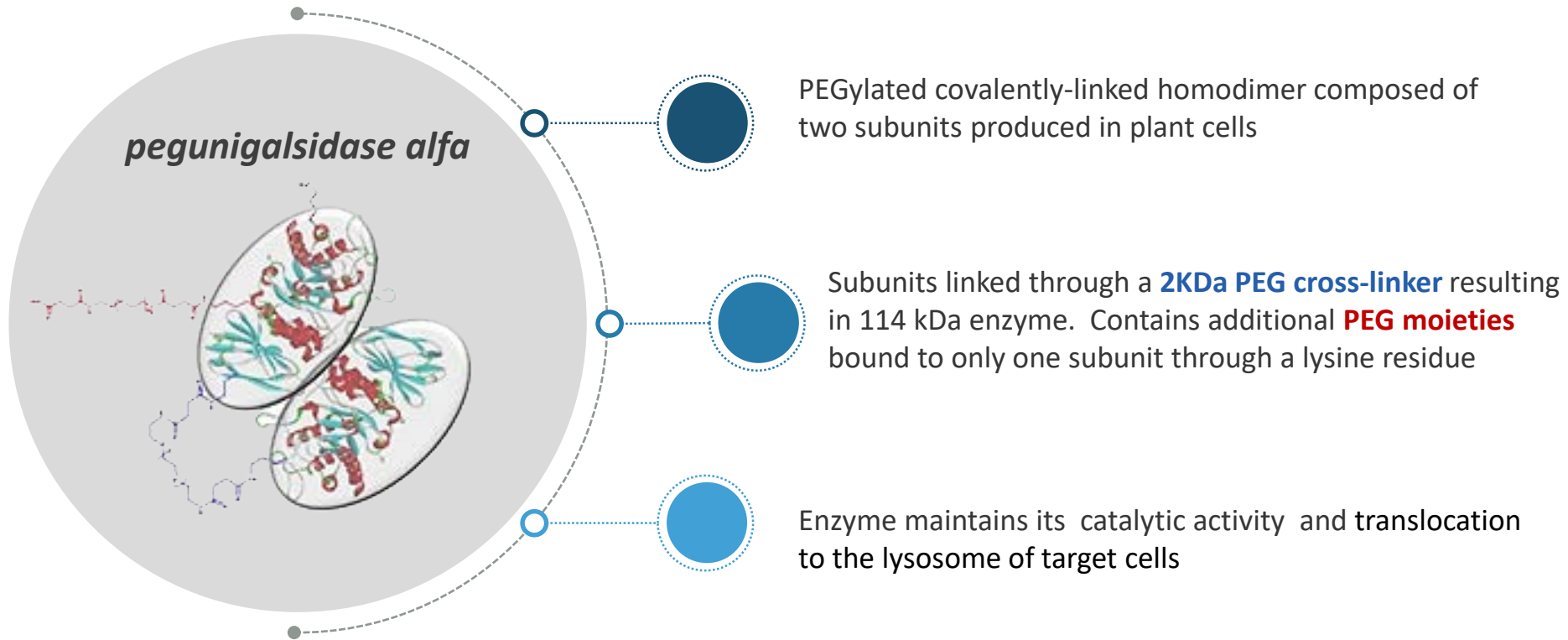
Migalastat: : Approved in the EU. Administrated orally, 123 mg hard capsules every other day***

Unmet clinical need

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

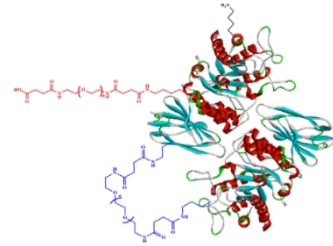


pegunigalsidase alfa: PEGylated, Chemically Modified α -Gal-A Enzyme



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)

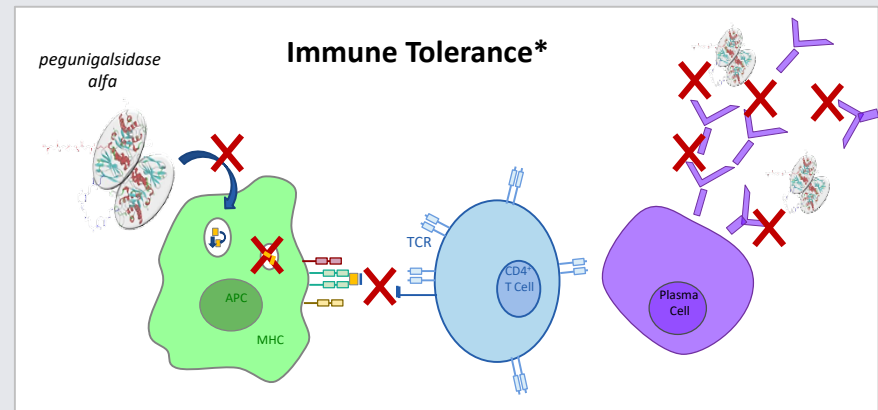
- Processing
- Recognition by T-helper cells

02

PEGylation potentially reduces immunogenicity by masking immunogenic epitopes

03

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





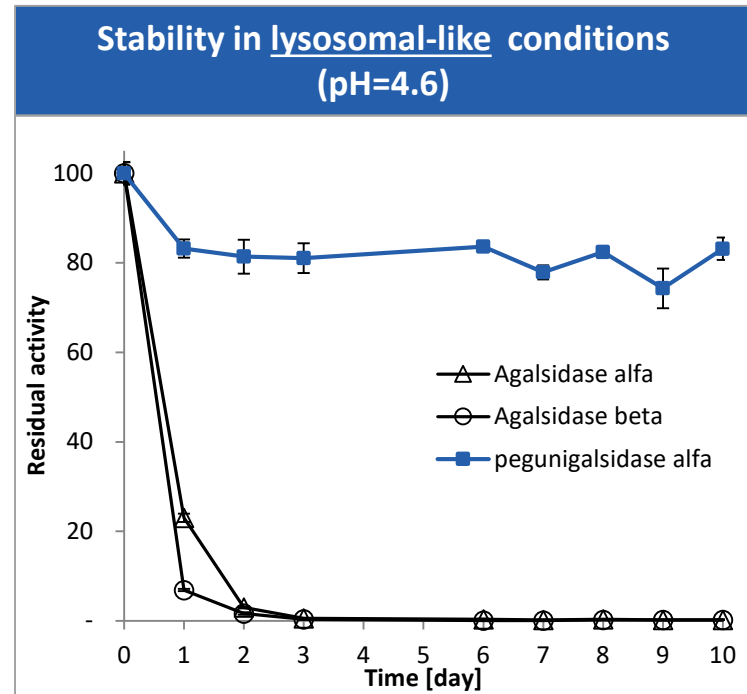
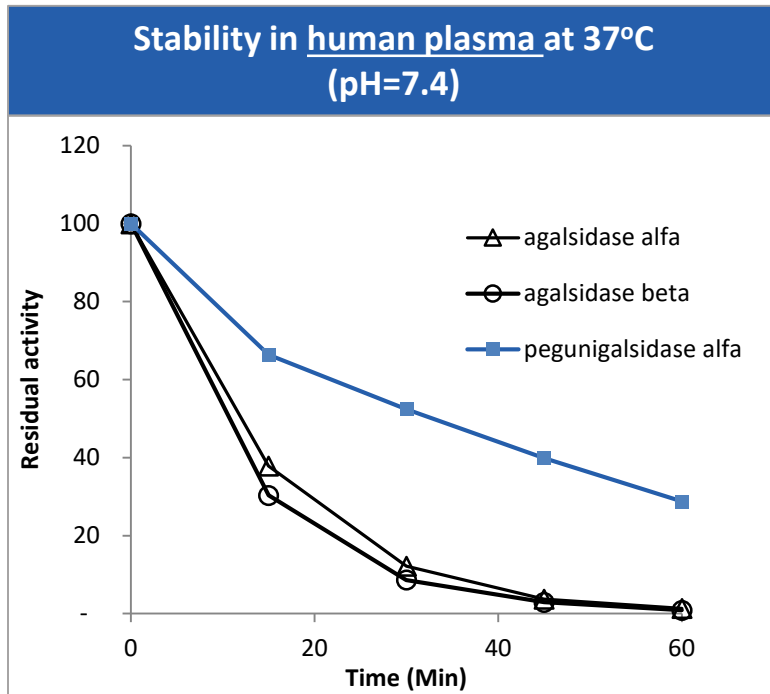
Scientific development and preclinical data

peg**unigalsidase** alfa

specific characteristics and attributes

Prolonged Stability in Biological Matrices

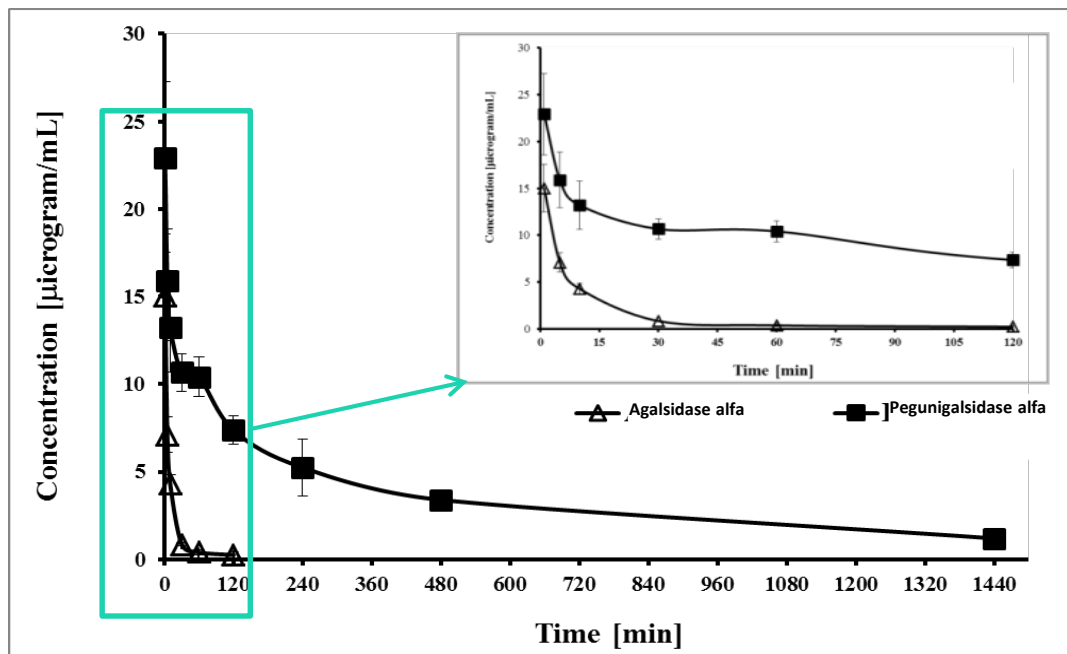
Compared to the other ERTs



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

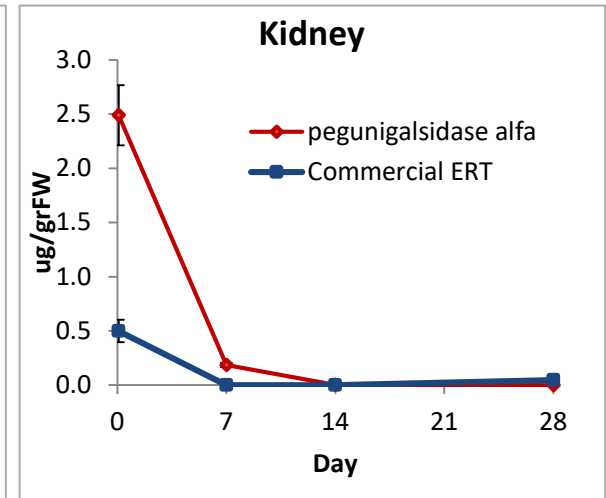
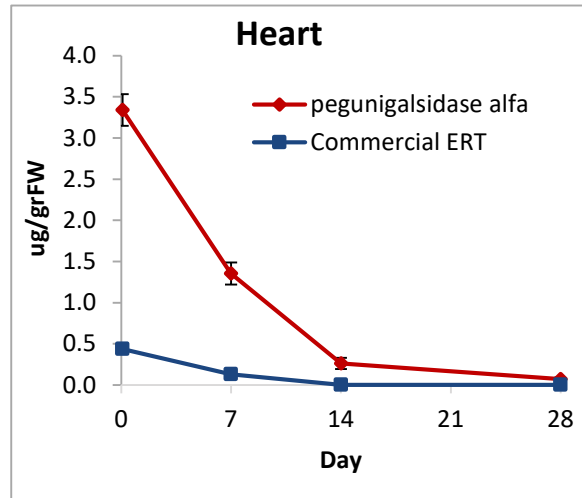
Pharmacokinetic Studies in Fabry Mice Model



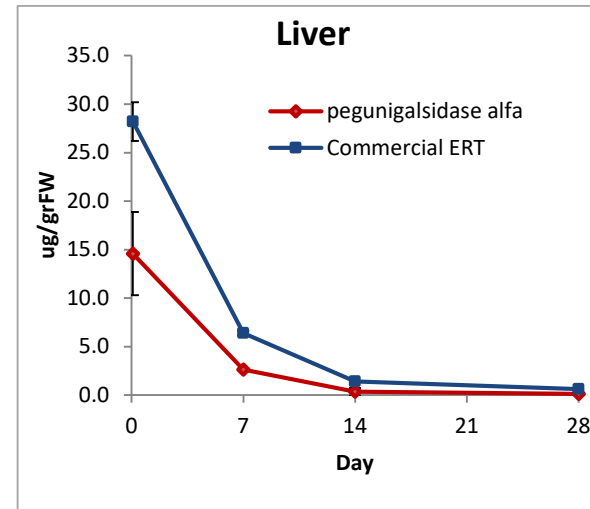
Enhanced Delivery & Prolonged Activity in Target Organs of Fabry Mice.

Enzyme quantities were assessed by an activity assay

Increased delivery of the active enzyme to the target organs

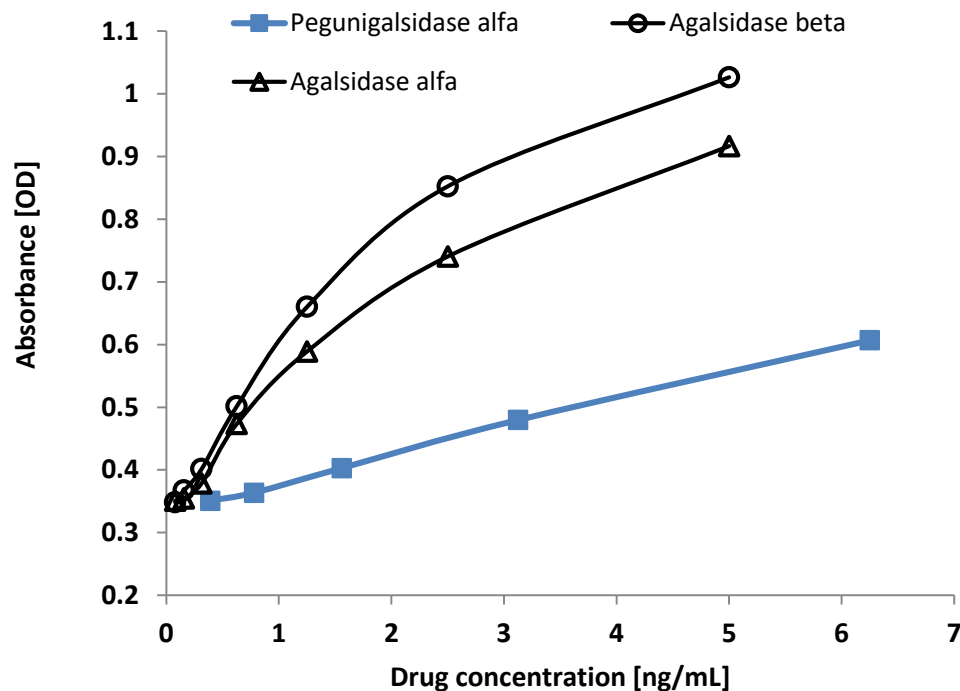


Reduced clearance by Liver



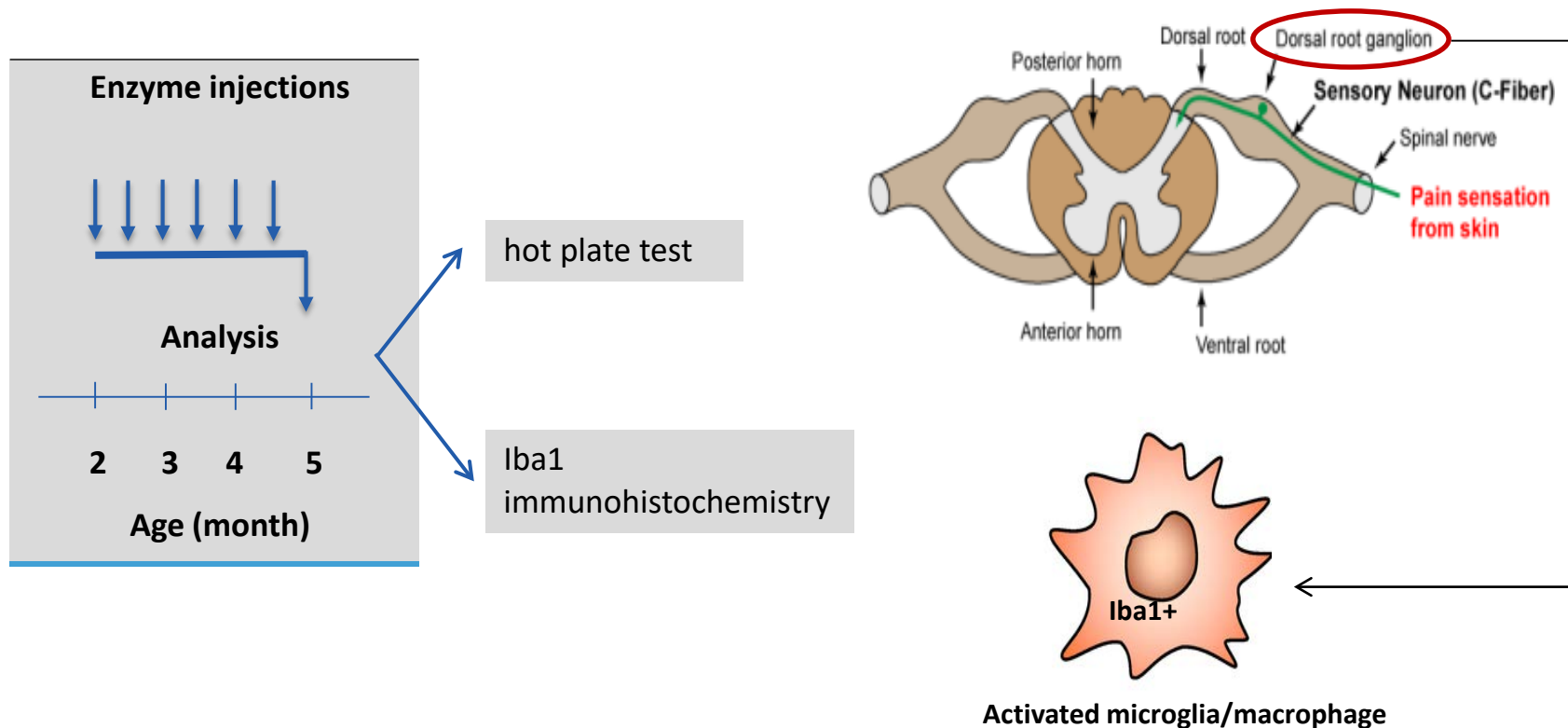
Improved/Reduced Antigenicity

- 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)

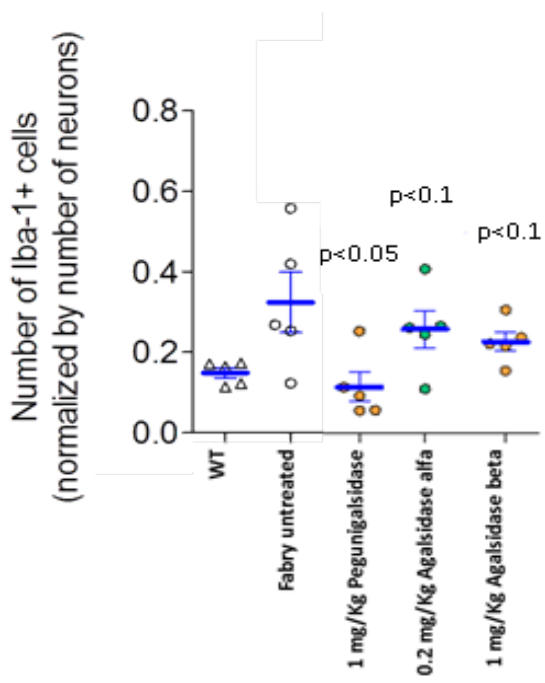


In collaboration with Jinsong Shen, M.D., Ph.D.
Institute of Metabolic Disease, Baylor Research

Protective effect on neuropathy, including peripheral nerves

Biomarker:

Change in number of Iba1+ cells in DRG

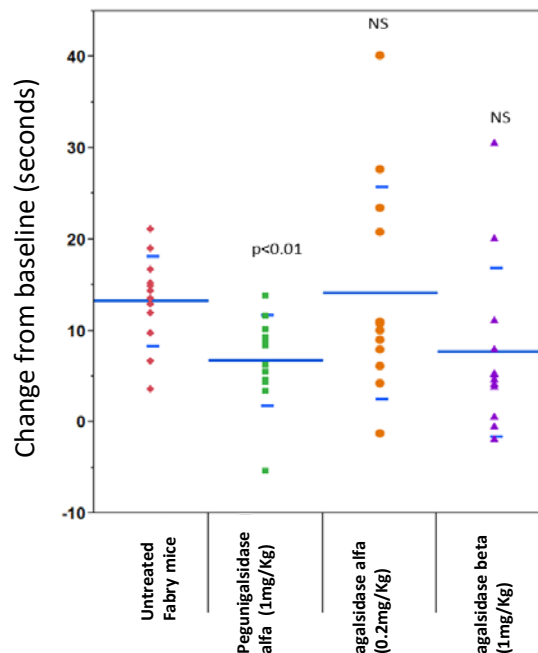


Statistical significance shown on top of each group indicates the p-values vs. untreated Fabry mice

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

Function:

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



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:



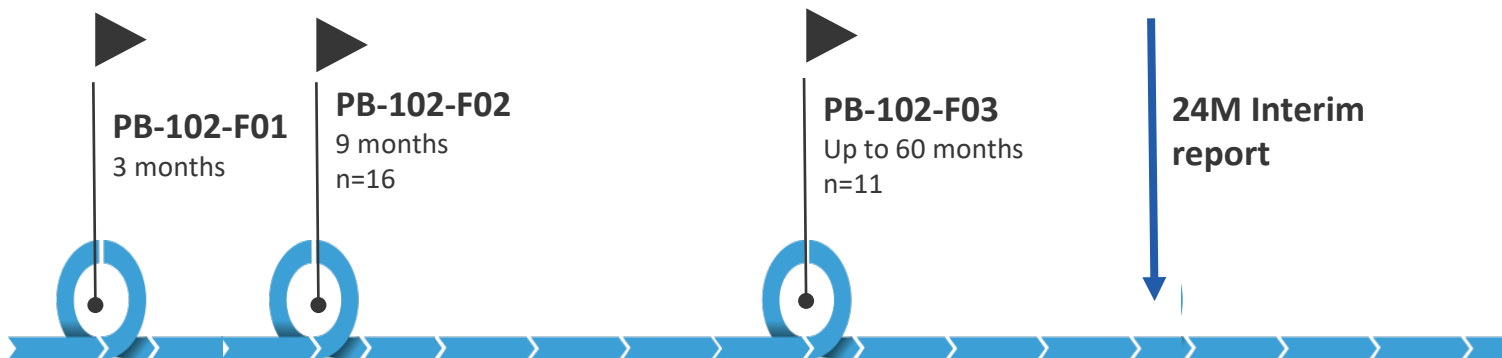
Intravenously, every 2 weeks

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 \geq 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

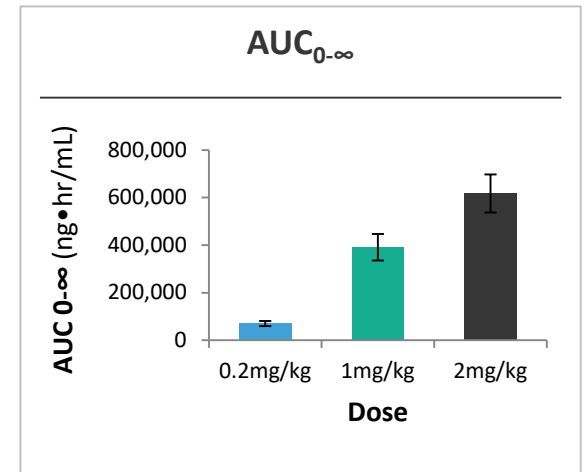
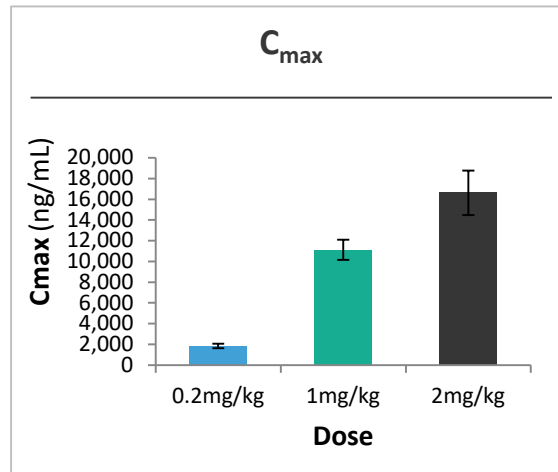
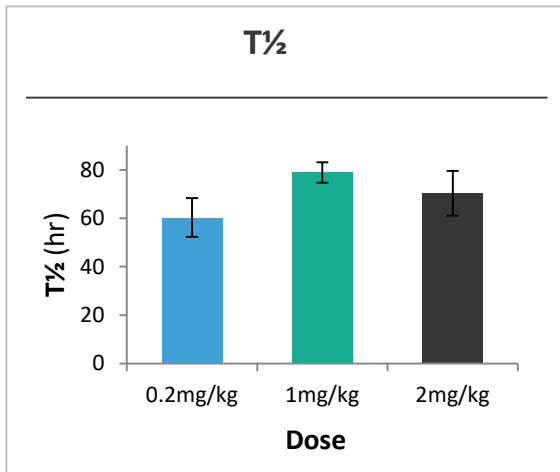
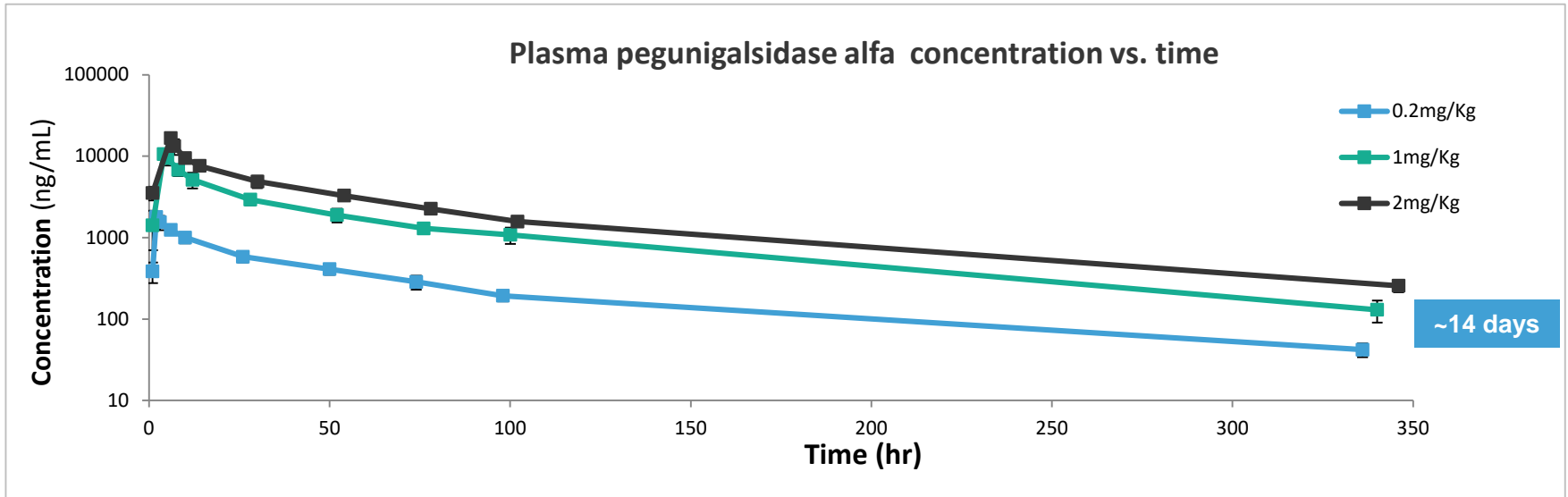
Demographics & Baseline Enzymatic Activity

	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)

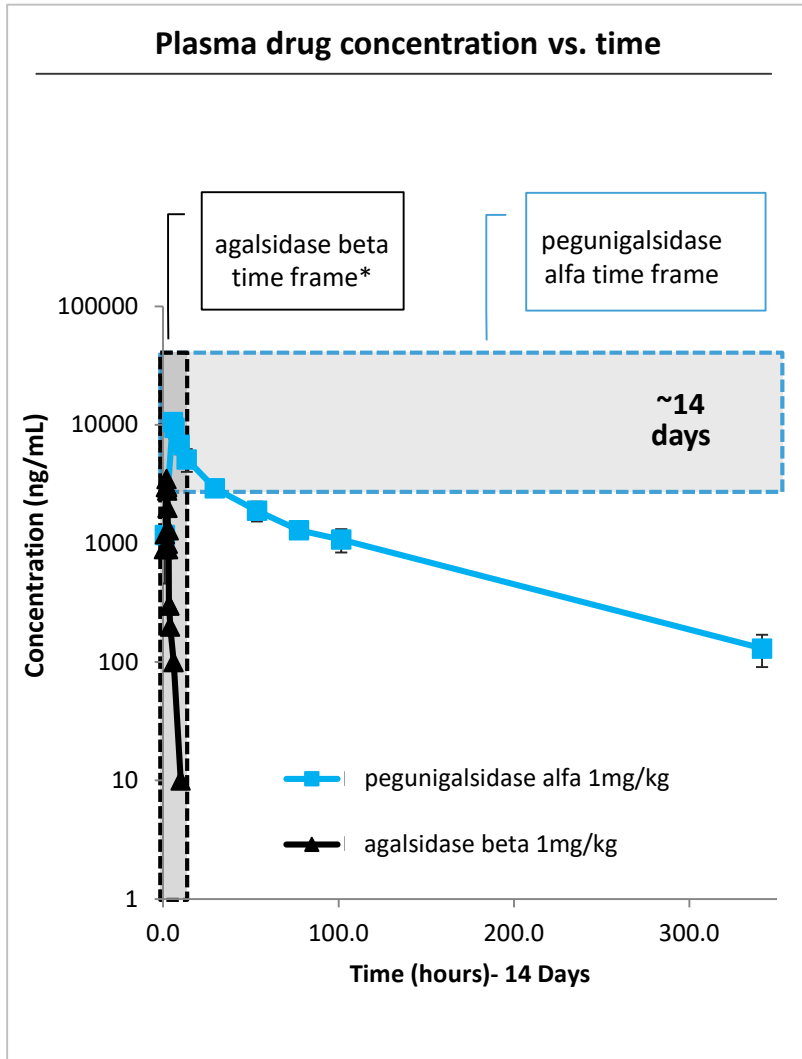
* one subject discontinued due to AE; one subject discontinued due to non compliance

Pharmacokinetics - Available Enzyme Throughout 2-Week Interval

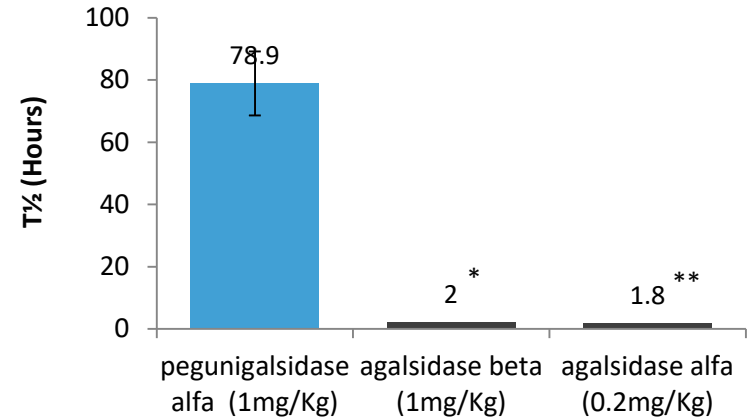
PK sampling was done throughout the 1Y treatment



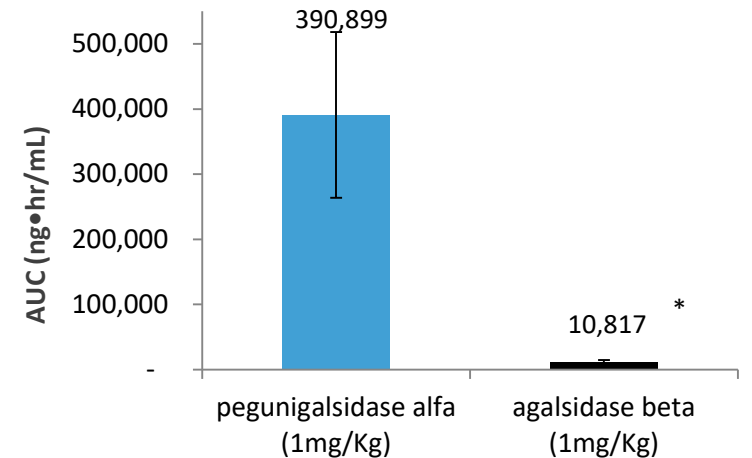
Substantially greater enzyme exposure than current ERTs^{*,**}



T_{1/2}: Approx. 80 hours



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



Immunogenicity Evaluation – Current Clinical Experience

Low incidence of treatment induced Anti Drug Antibodies (ADA)

Anti-Drug Antibodies (ADA) multi-tier assessment *

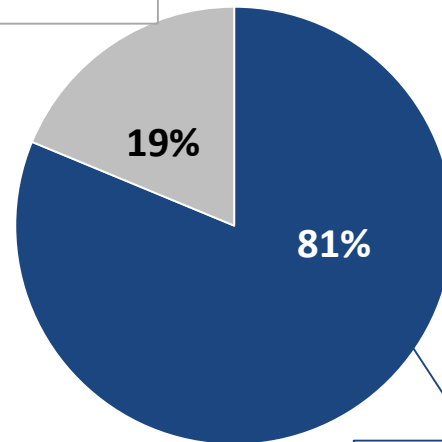
- Screening
- Confirmatory
- Confirmed positive samples further characterized for:
 - Titer
 - Neutralizing activity

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

Seroconverted, then tolerized
(n=3 patient;
21 samples)



SeroNegative
(n=13 patient;
123 samples)

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

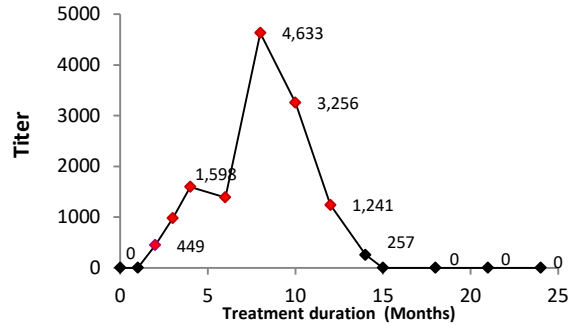
All 3 ADA positive patients turned to be negative for ADA after 12M of treatment

Reduced Immunogenicity combined with longer enzyme coverage

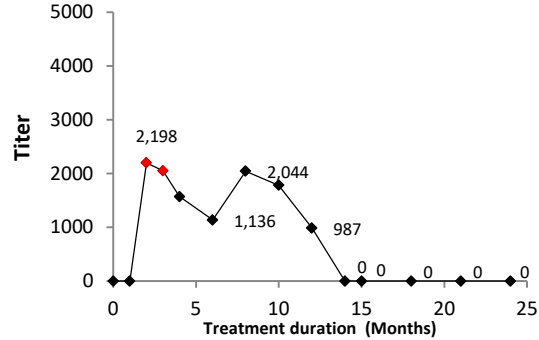
No effect on continues Biomarkers reduction in ADA positive (including Nab) pts.

ADA⁺ : IgG Titers

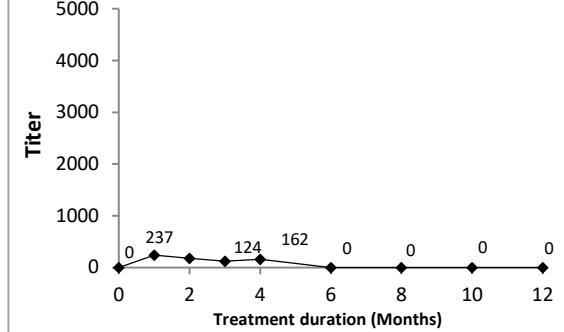
Subject 15-F106; 0.2mg/kg



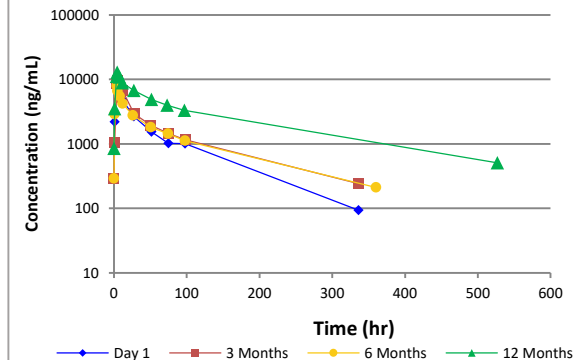
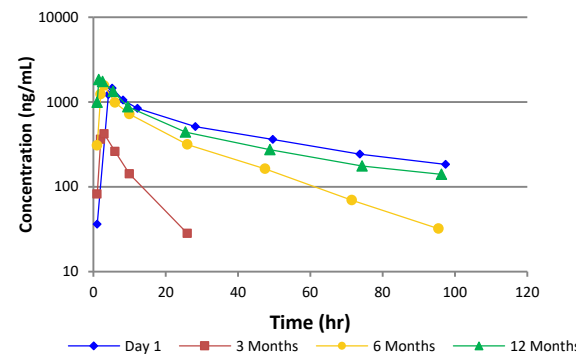
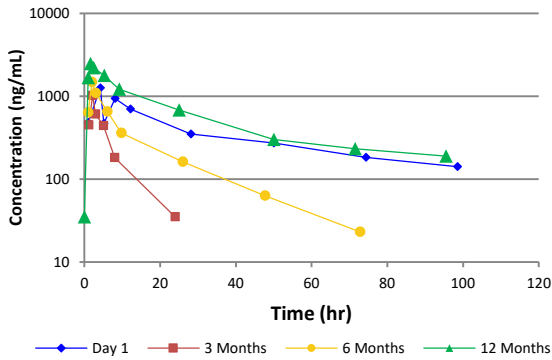
Subject 17-F105; 0.2mg/kg



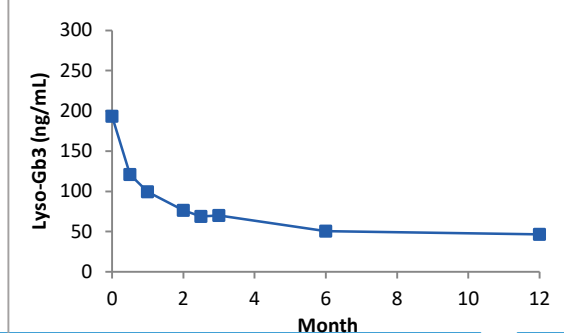
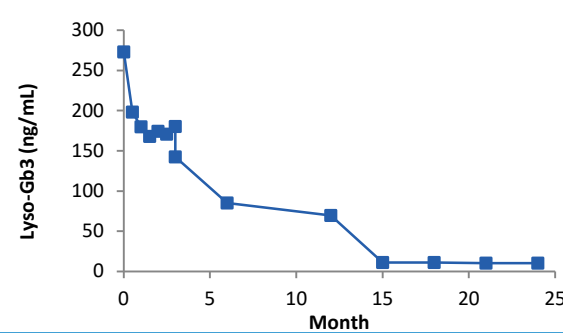
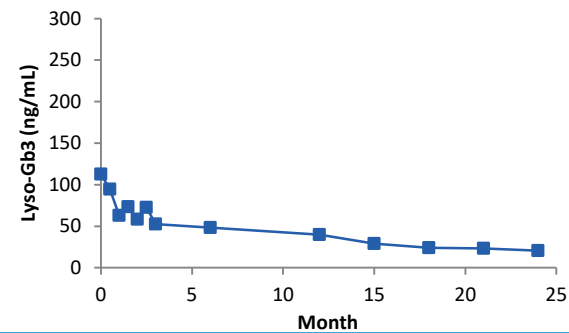
Subject 07-F113; 1mg/kg



PK profiles



Biomarker

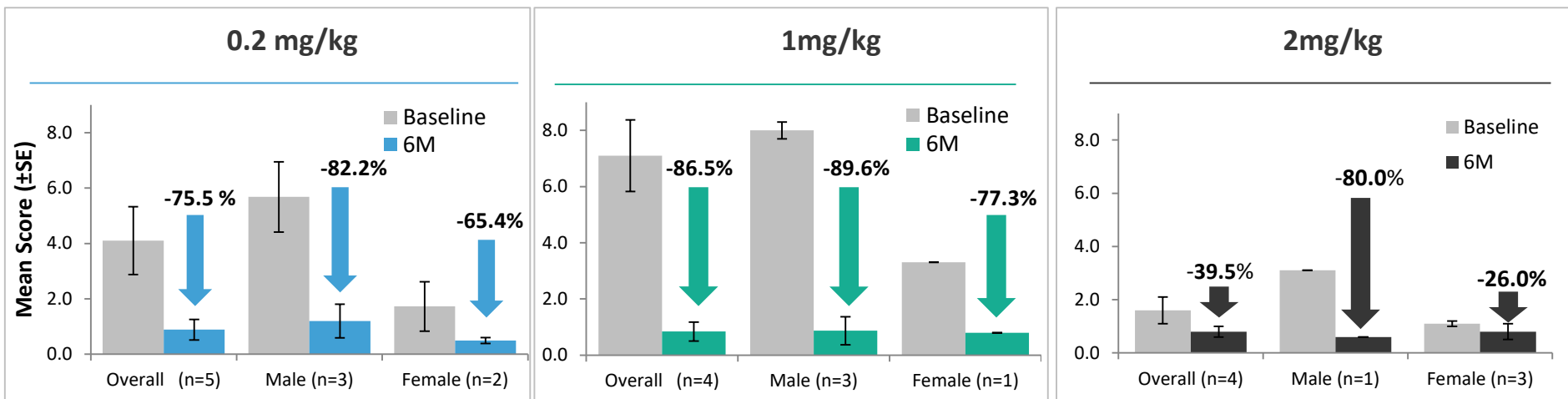




Efficacy

Reduction of Gb3 in Kidney Peritubular Capillaries

Quantitative BLISS Score

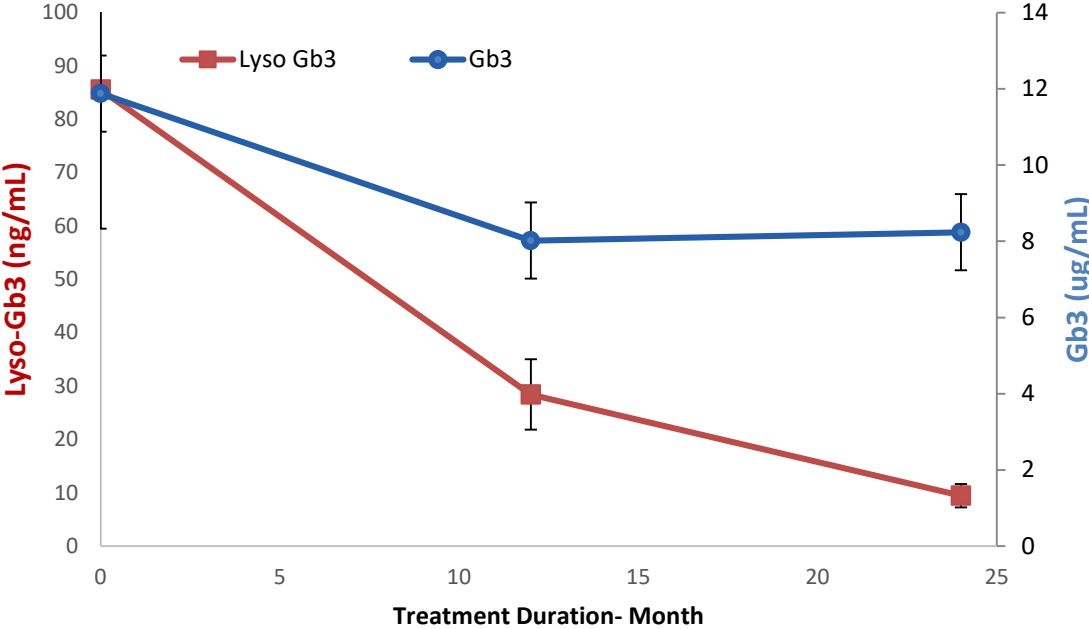


	% change \pm SE
All Patients (n=13)	-67.8 \pm 8.9
Classic Patients (n=8)	-84.1 \pm 3.3

- >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

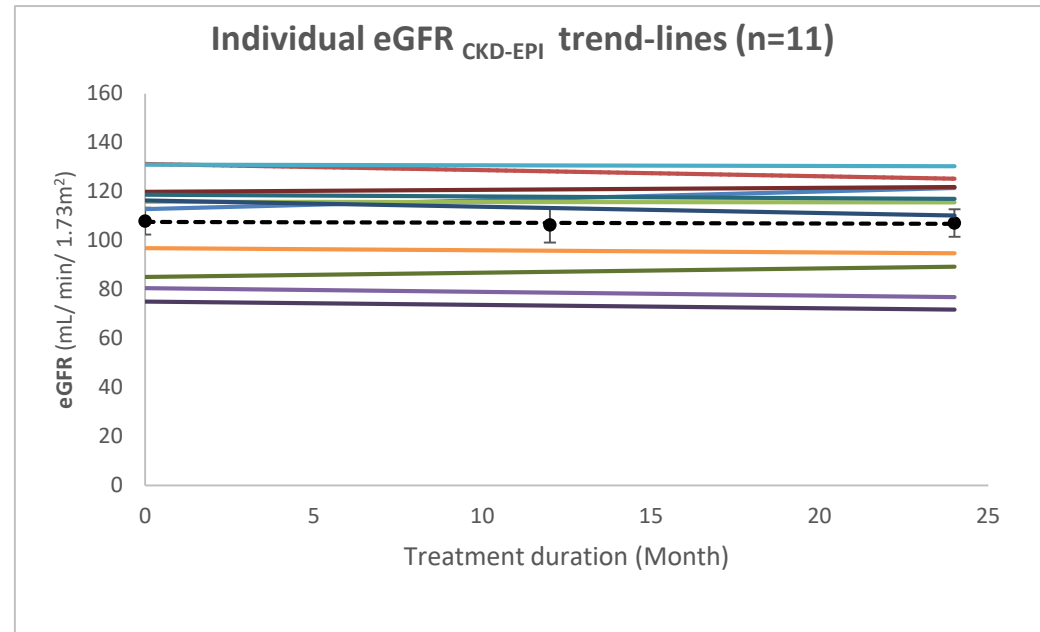
Plasma Gb3 and Lyso-Gb3 (N=11)



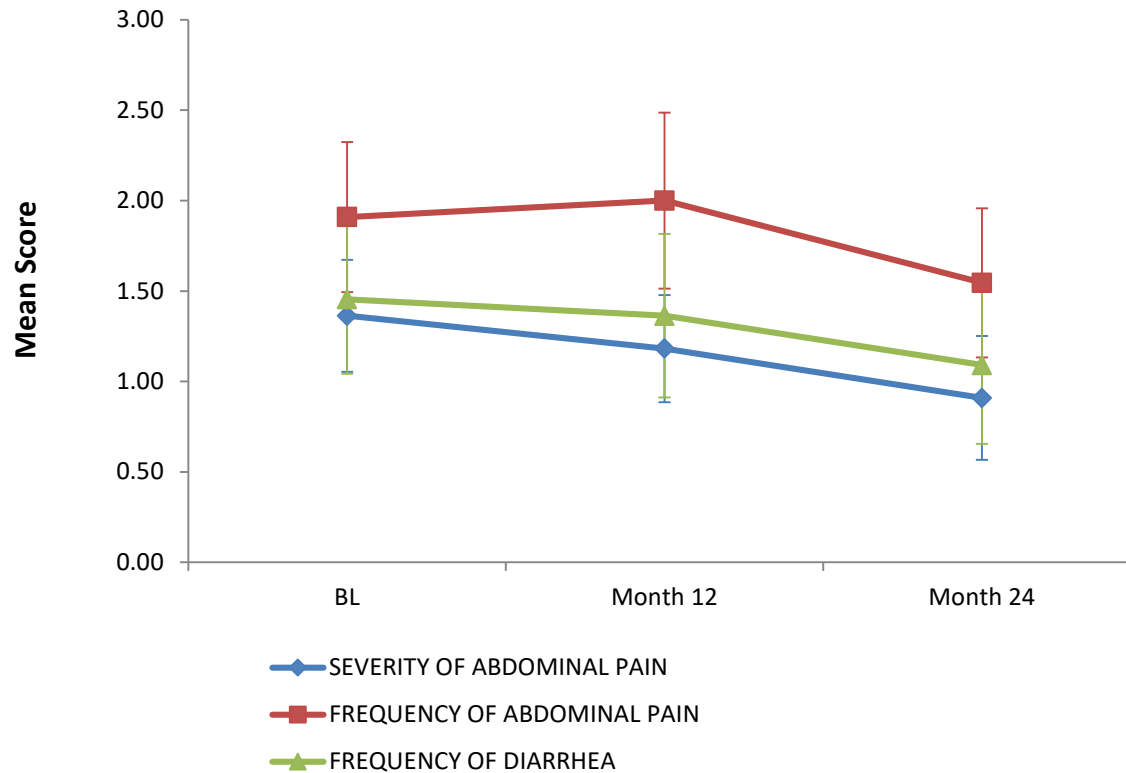
Continuous Stability of Renal Function- 24 months (N=11)

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



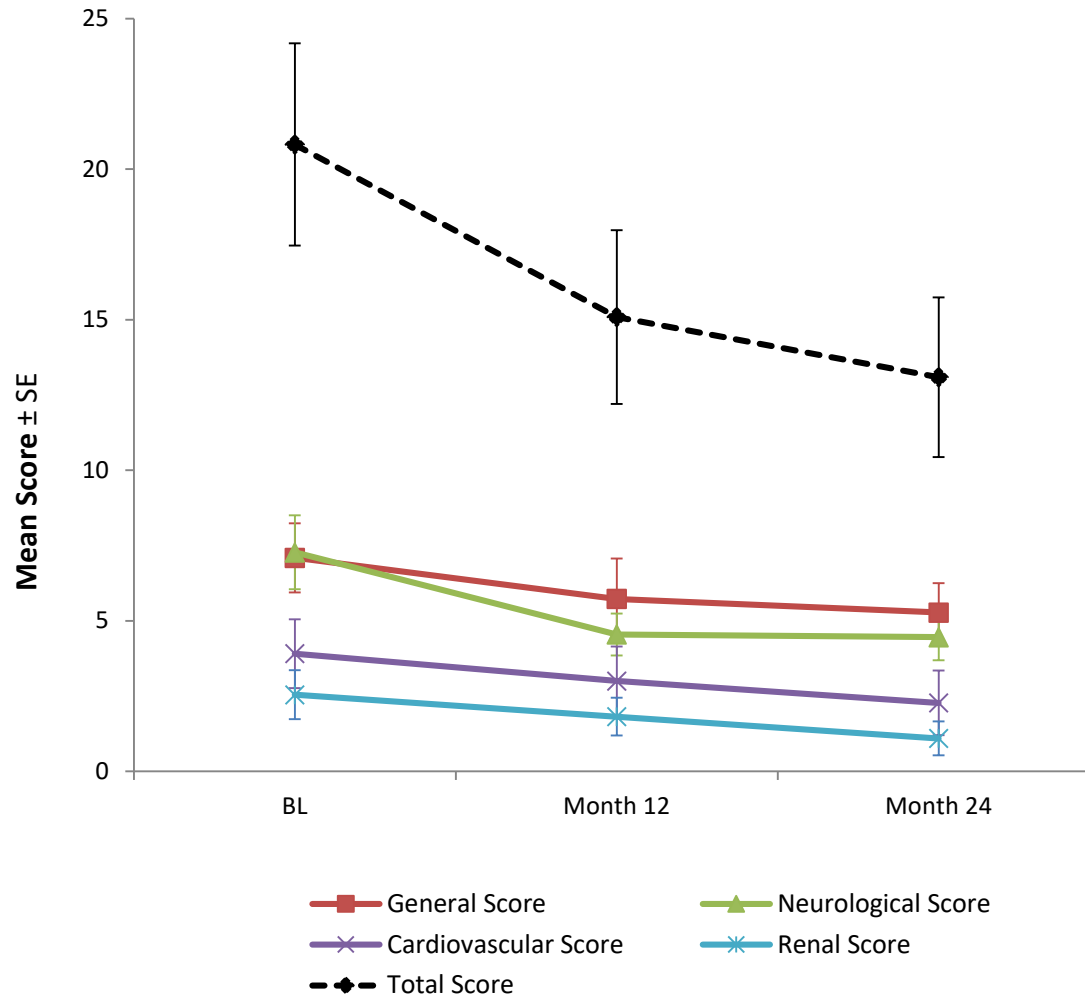
Improvement in Gastrointestinal Symptoms- 24 months (N=11)



Scoring legends:

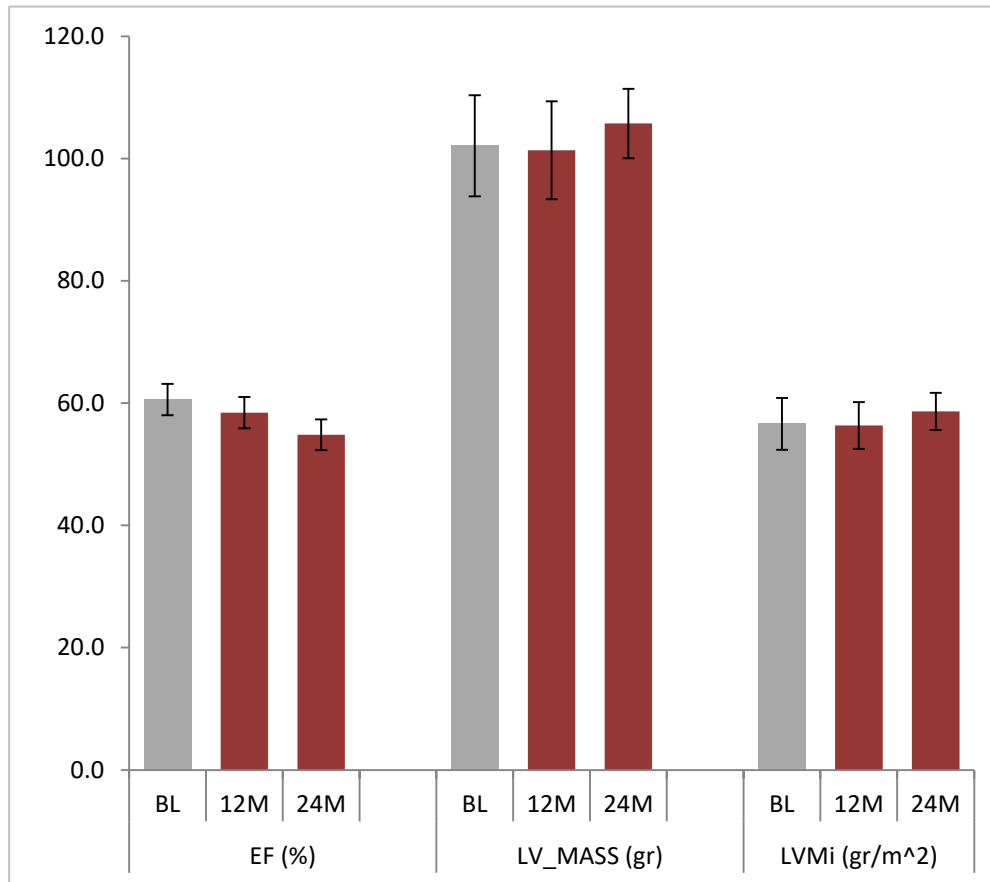
Severity of abdominal pain	0 (no pain) to 4 (very severe pain)
Frequency of abdominal pain	0 (never) to 4 (daily) at least once a day
Frequency of diarrhea	0 (never) to 4 (daily) at least once a day

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

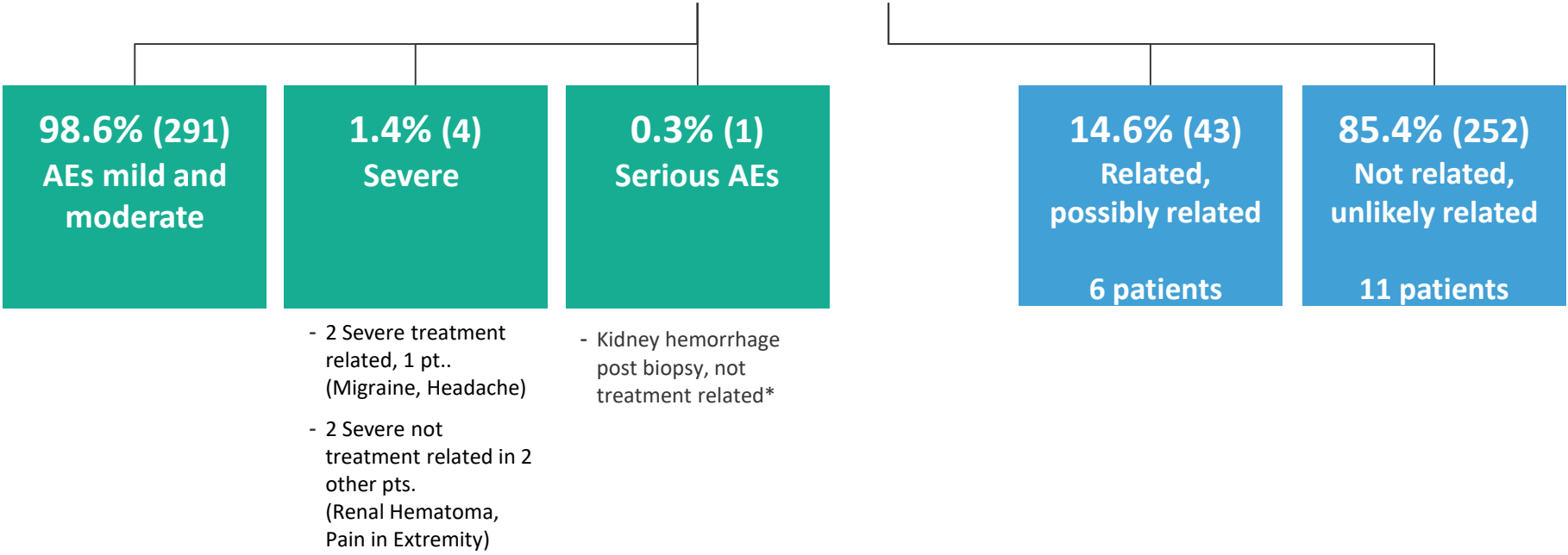


Safety

Safety in 906 Infusions (=34.8 patient years)

100% (295)

Total AEs in 11 patients completing 2 years of treatment



*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)

Overall Conclusions- Interim 24 month



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 Holidá
 - 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

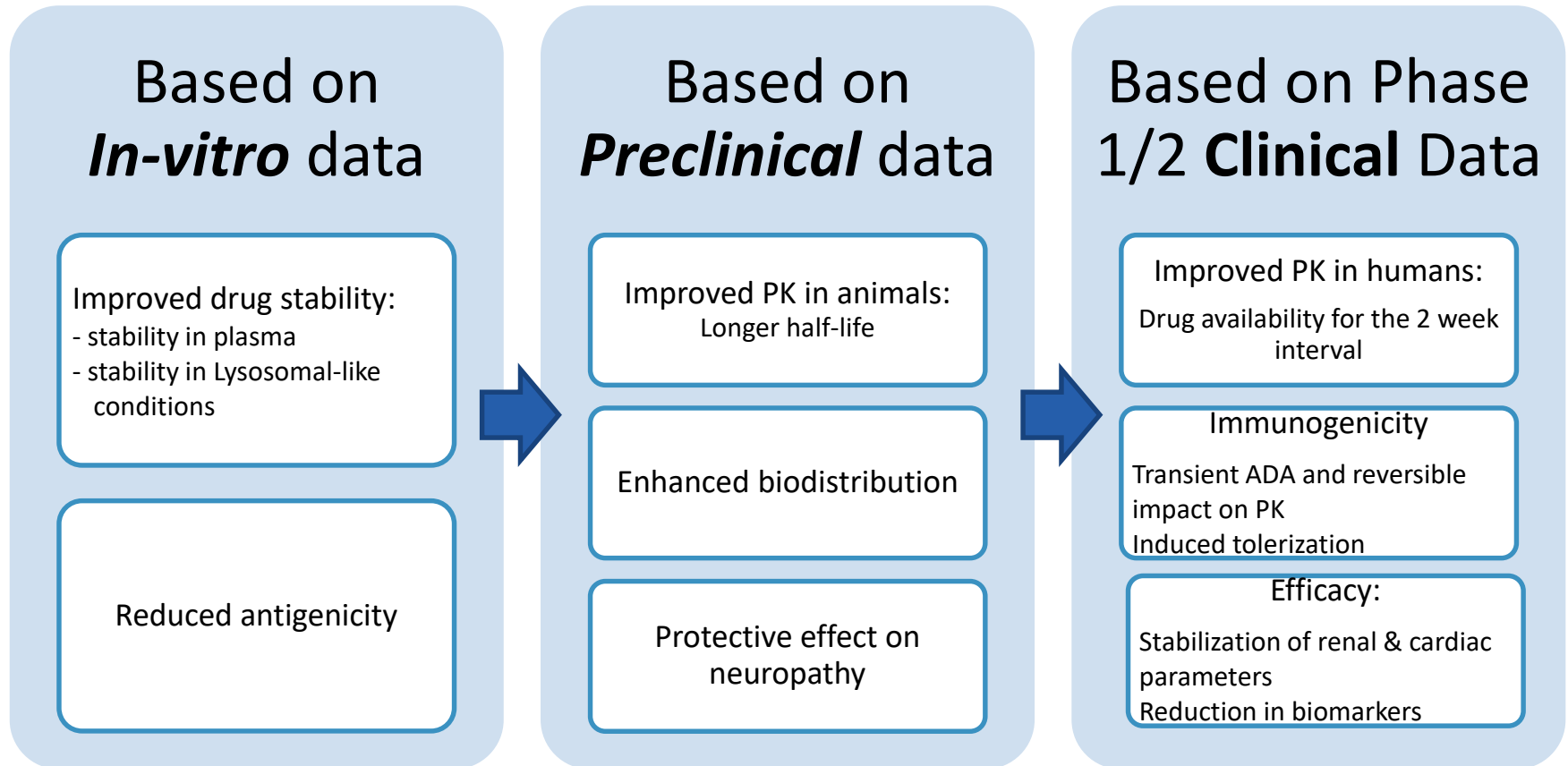
- Reduced accumulation of toxic metabolites (Gb3) in relevant tissues
- Reduced peripheral neuropathy

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



- 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



- 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



- An open label, switch over study from agalsidase alfa and beta
- Assess the safety, efficacy and PK of *pegunigalsidase alfa* 2 mg/kg IV administered 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:NCT02795676](https://clinicaltrials.gov/ct2/show/study/NCT02795676)

[ClinicalTrials.gov Identifier:NCT03018730](https://clinicaltrials.gov/ct2/show/study/NCT03018730)

[ClinicalTrials.gov Identifier:NCT03180840](https://clinicaltrials.gov/ct2/show/study/NCT03180840)



Thank You