

1st Canadian Symposium on Lysosomal Diseases

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**pegunigalsidase alfa
for Fabry disease**

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Disclosures

Dr. West has received research funding, honoraria and/or consultant fees from the following:

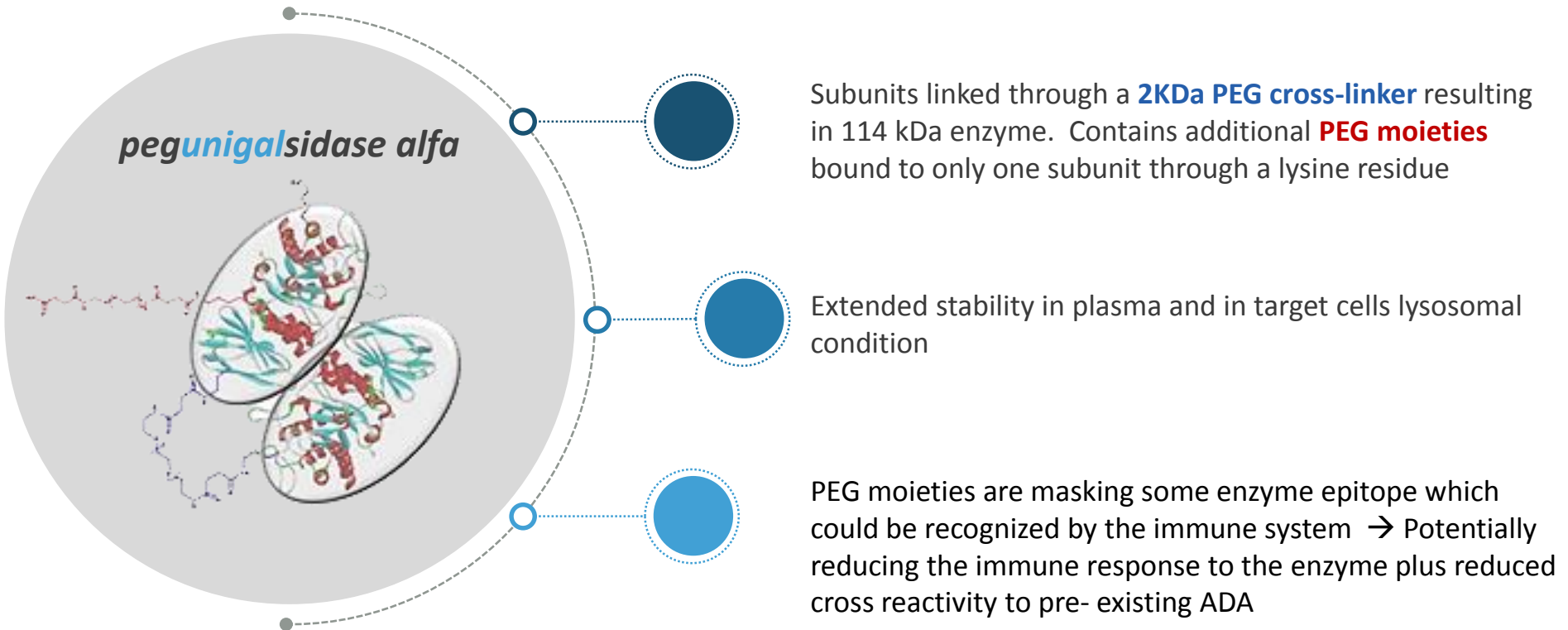
Alexion
Amicus Therapeutics
AvroBio
Excelsior Pharma
Idorsia
Protalix
Sanofi-Genzyme
Shire
Sumitomo Pharma

Pegunigalsidase alfa- Novel Enzyme Replacement Therapy for the Treatment of Patients with Fabry Disease

- A recombinant PEGylated enzyme expressed by Protalix's proprietary plant cell-based expression system, ProCellEx®.
- Phase I/II in naïve Fabry patients has successfully completed
 - B-102-F01/F02- NCT01678898/NCT01769001
- Phase III program – 3 studies are on going world wide
 - PB-102-F20 NCT02795676
 - PB-102-F30 NCT03018730
 - PB-102-F50 NCT03180840
- Has received
 - FDA - Fast Track Designation - 2018
 - EMA - Orphan Drug Designation - 2017

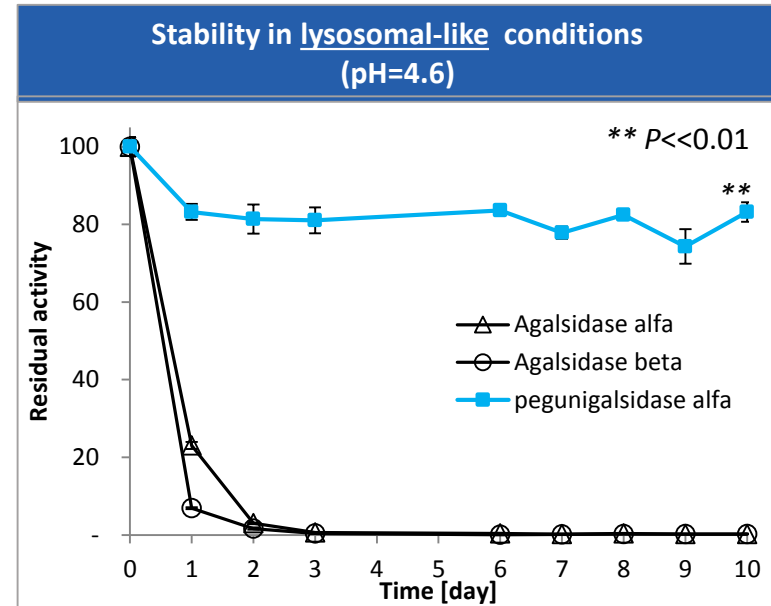
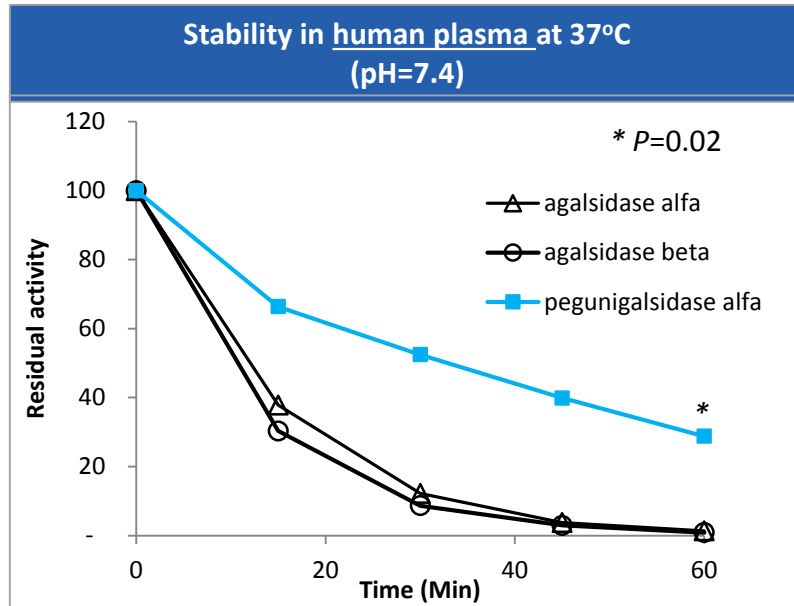


Pegunigalsidase alfa: PEGylated, Chemically Modified α -Gal-A Enzyme



Prolonged Stability in Biological Matrices – *in vitro*

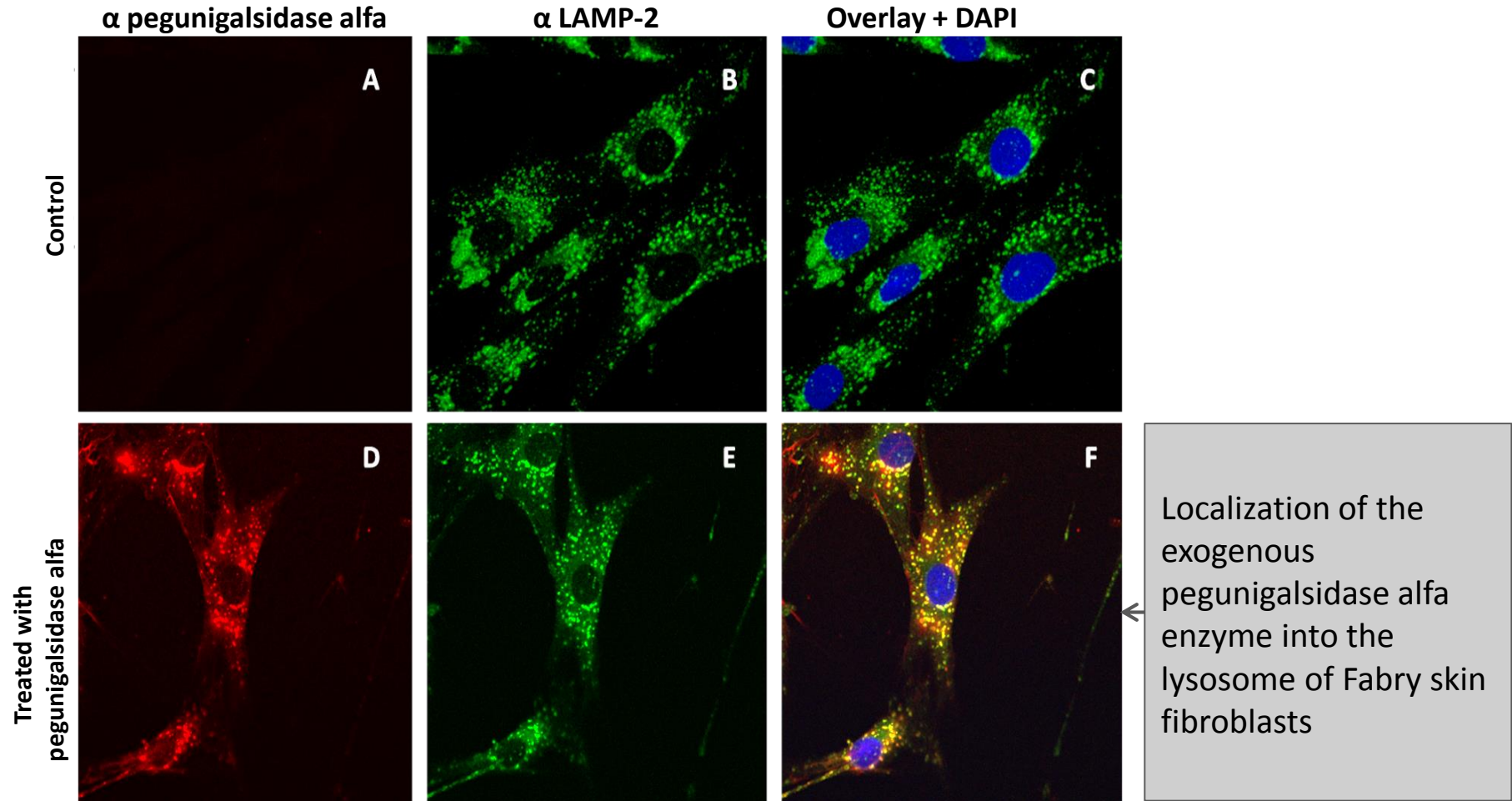
Compared to Other ERTs-Quantified by an Activity Assay



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

Higher stability in plasma and lysosomal-like conditions implicating for higher potential to deliver an active long-functional enzyme to its site of action

Ex Vivo: Internalization and lysosomal localization of pegunigalsidase alfa into skin fibroblasts derived from Fabry patients

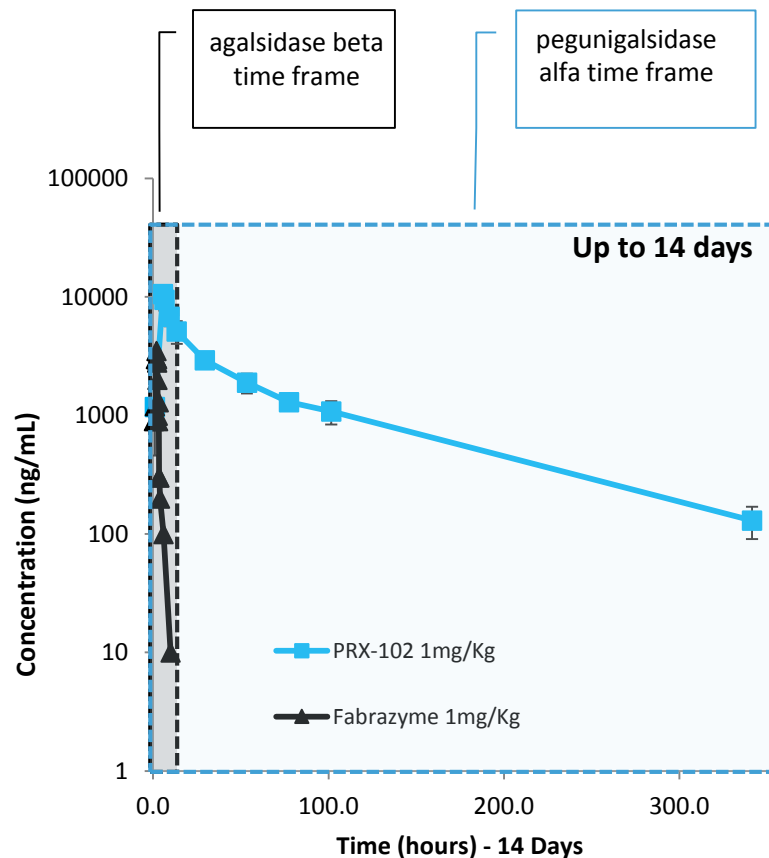


Cells were incubated for 24 h in the absence (panels A–C) or presence (panels D–F) of PRX-102 (160 µg/mL). PRX-102 was labeled with anti PRX-102 antibodies (red fluorophore). Lysosome labeling was achieved with anti LAMP-2 antibody (green fluorophore). Cellular nuclei were labeled using DAPI (blue fluorophore). The overlap is represented in yellow when the images are superimposed (panel F).

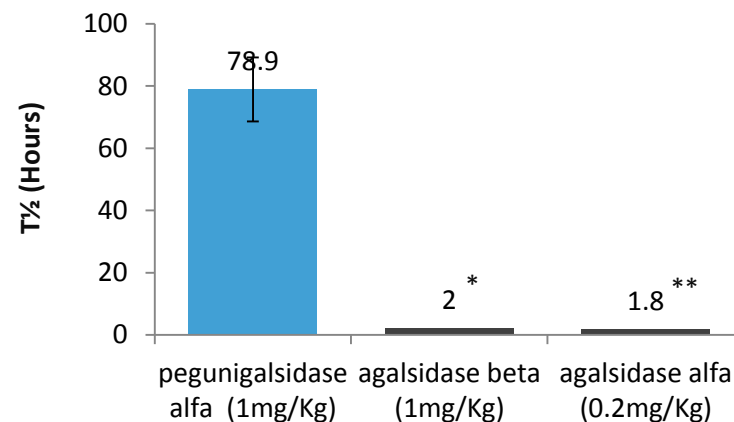
Pharmacokinetics: pegunigalsidase alfa

Longer half life and higher exposure compared to other ERT

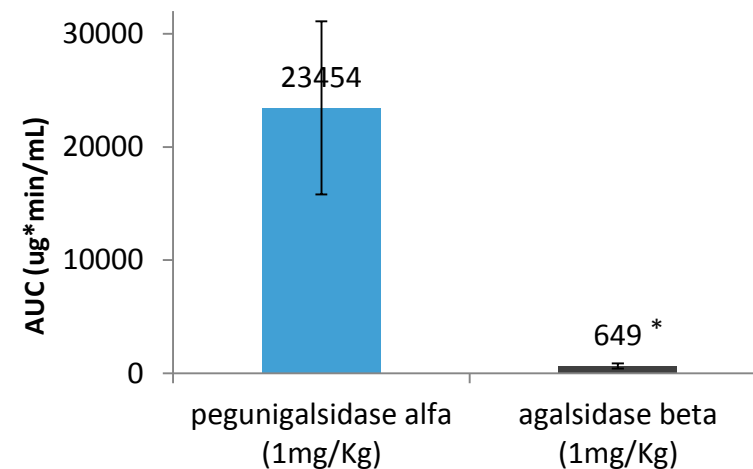
Plasma drug concentration vs. time



$T_{1/2}$: Approx.
80 hours



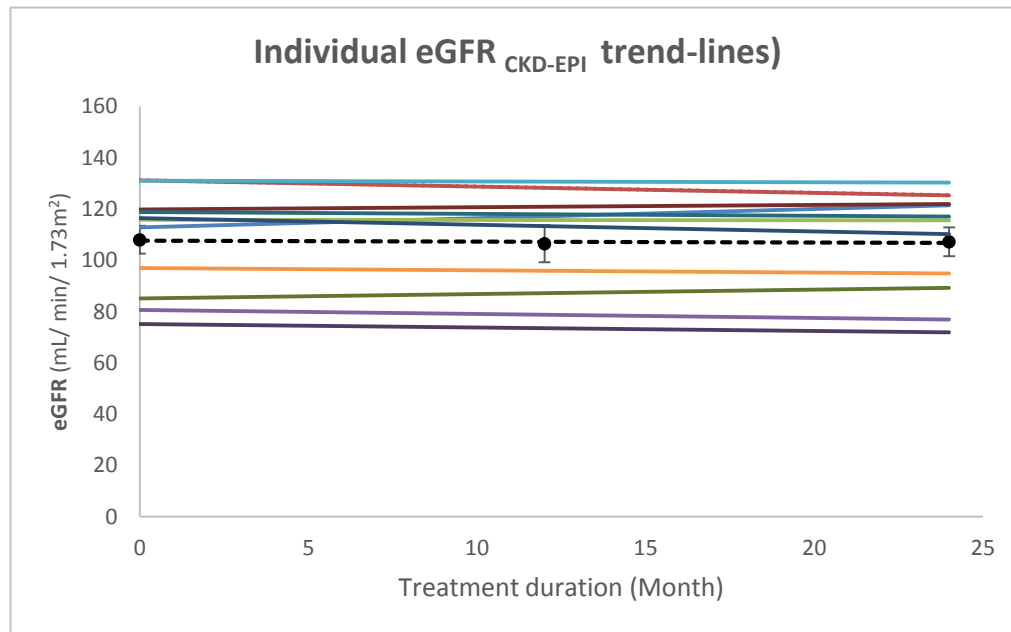
AUC (0- ∞):
>35 fold from
current ERTs



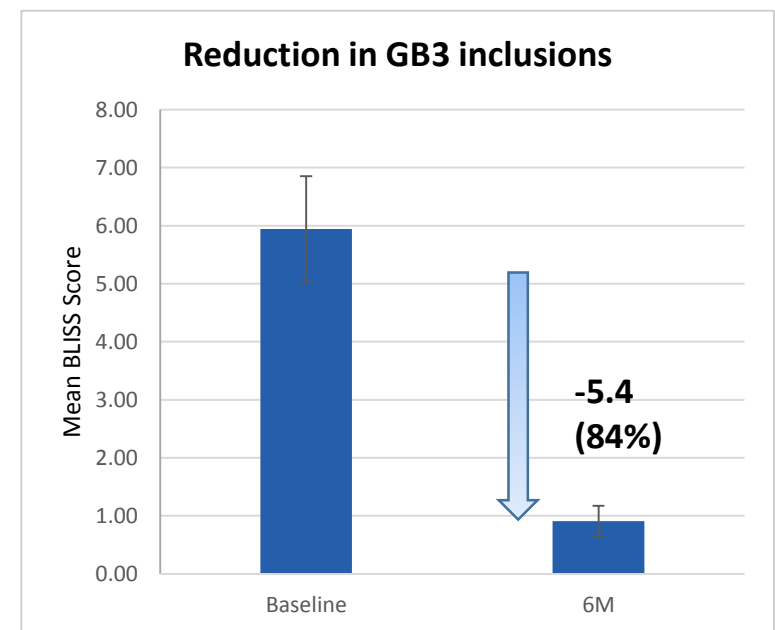
Phase I/II- Naïve Fabry Patients

Stabilization of renal parameters & Reduction of Gb3 inclusion in Kidney Peritubular Capillaries

Renal Function- 24M



Kidney Biopsies- 6M

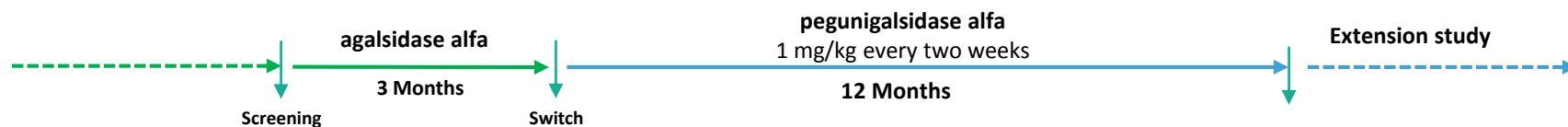


Study Objective and Design

PB-102-F30 NCT03018730- Ongoing in Canada, Europe and Australia (Ex-US Study)



- Multicenter, open label switch over study to evaluate the safety and efficacy of switching from agalsidase alfa to pegunigalsidase alfa
 - 22 adult FD patients (male and female)
 - Previously treated with agalsidase alfa for at least 2 years
- Main Safety and efficacy endpoints
 - Safety
 - Clinical laboratory tests
 - Electrocardiogram
 - Treatment-emergent adverse events
 - Ability to taper off infusion premedication throughout the first 2 months of the study
 - Requirement for use of premedication overall to manage infusion reactions
 - Treatment-emergent anti-PRX-102 antibodies
 - Efficacy
 - Mean annualized change in $eGFR_{CKD-EPI}$
 - Biomarkers (Plasma Lyso-Gb3, Plasma Gb3, Urine Lyso-Gb3)
 - Frequency of pain medication use
 - Short Form Brief Pain Inventory (BPI)
 - Mainz Severity Score Index (MSSI)
 - Quality of life EQ-5D-5L



Study Main Inclusion and Exclusion Criteria



Main inclusion criteria

- Age: 18-60 years
- A documented diagnosis of Fabry disease.
- Treatment with agalsidase alfa for at least 2 years and on a stable dose for at least 6 months
- eGFR ≥ 40 ml/min/1.73 m² by CKD-EPI
- Availability of at least 2 historical serum creatinine evaluations since starting agalsidase alfa treatment and not more than 2 years

Main exclusion criteria

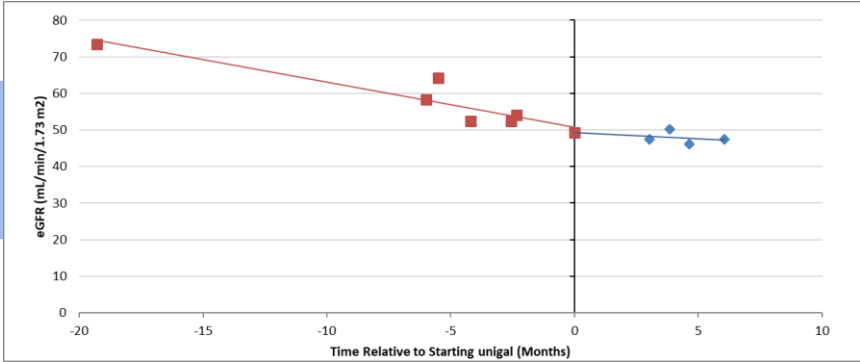
- History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase alfa/beta
- History of renal dialysis or transplantation
- History of Acute Kidney injury in the 12 months prior to screening
- Start or change in dose of ACEi or ARB in the 4 weeks prior to screening
- Urine protein to creatinine ratio (UPCR) > 0.5 g/g and not treated with ACEi or ARB
- Cardiovascular and/or Cerebrovascular event in the 6 months before randomization
- Congestive heart failure NYHA Class IV

Baseline characteristics of first 16 patients (9 males and 7 females)

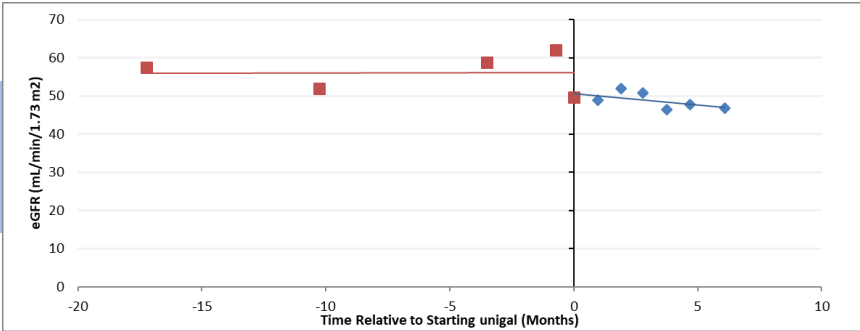
Parameter	ALL (Mean)	All (SD)	Female (Mean)	Female (SD)	Male (Mean)	Male (SD)
Number of patients	n=16		n=7		n=9	
Age at screening years	46.3	10.1	47.1	12.4	45.7	8.6
Age started ERT years	37.9	10.9	39.9	11.5	36.4	10.9
Residual enzyme activity – leucocytes %	15.5	13.1	27.9	10.2	5.9	2.6
Residual enzyme activity – plasma %	14.1	15.6	28.5	12.7	2.9	3.9
Number of patients with proteinuria UPCR≥500 mg/gr	3		1		2	
Number of patients treated with ACEi/ARB	8		4		4	
Plasma Lyso-Gb ₃ nM; (normal ≤ 2.4 nM)	36.18	47.16	13.81	6.11	53.57	58.01
Plasma Gb ₃ nM; (normal ≤ 4961 nM)	6049	2219	5468	1875	6501	2464
Urine Lyso-Gb ₃ pM/mM creatinine; (normal 0 pM/mM)	47.29	40.99	45.48	31.11	49.11	51.63
eGFR _{CKD-EPI} at Baseline (V1) - mL/min/1.73m ²	80.0	21.8	86.0	17.8	75.4	24.5
Annualized Slope on Replagal (~2Y , including V1) - mL/min/1.73m ² /year	-6.8	7.4	-5.1	4.4	-8.0	9.2

Individual eGFR values

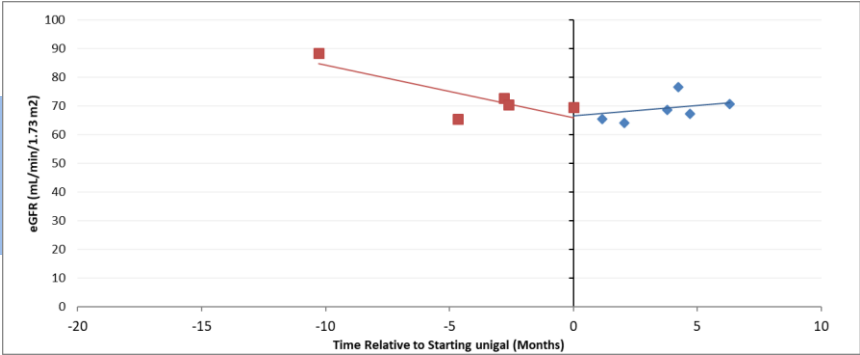
Pt.# 1(M)



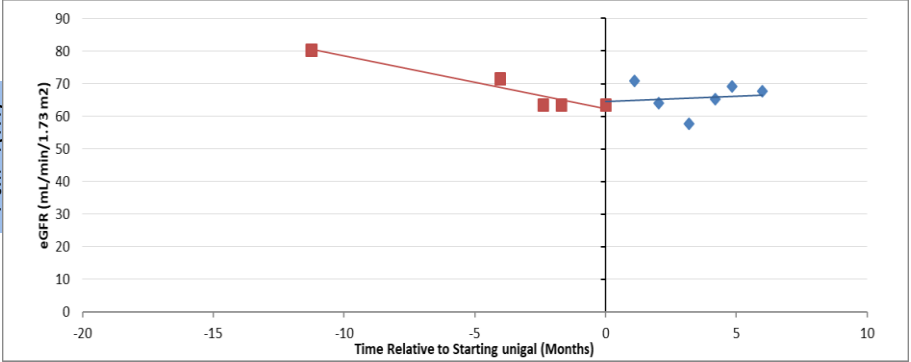
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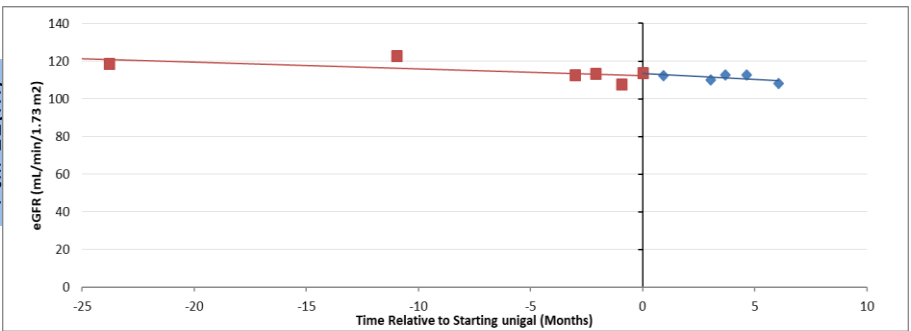
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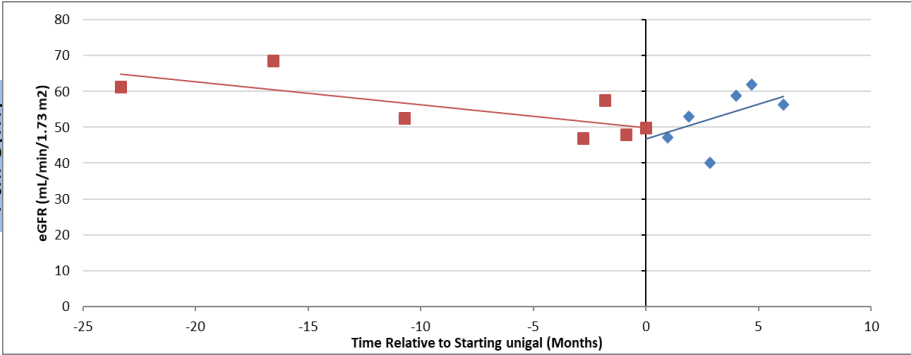
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Pt.# 11(M)

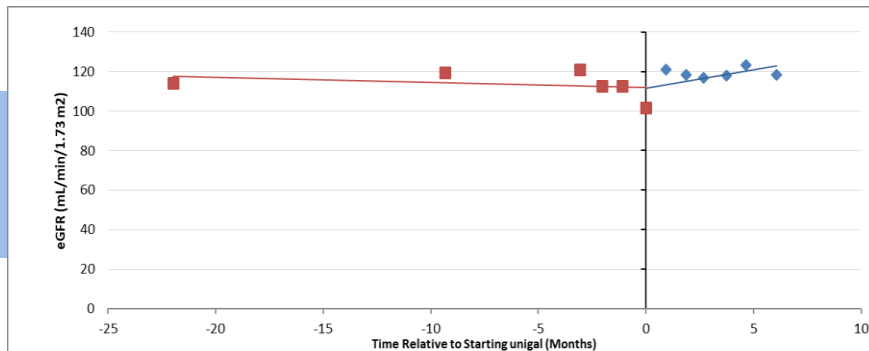


Pt.# 8(M)

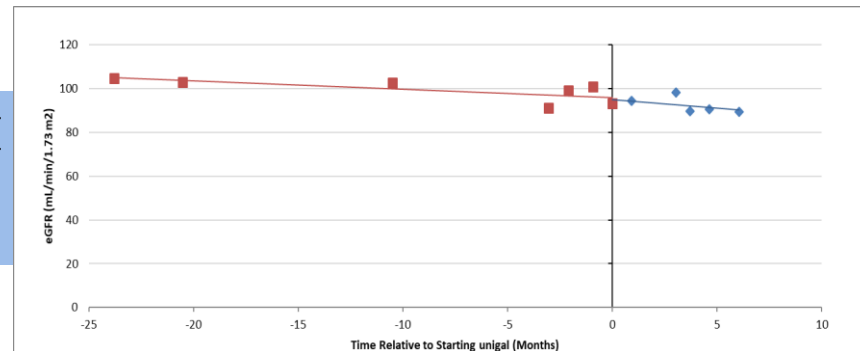


Individual eGFR values (continued)

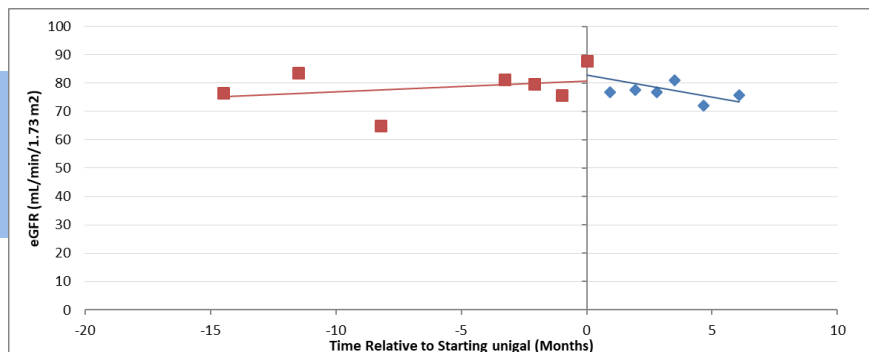
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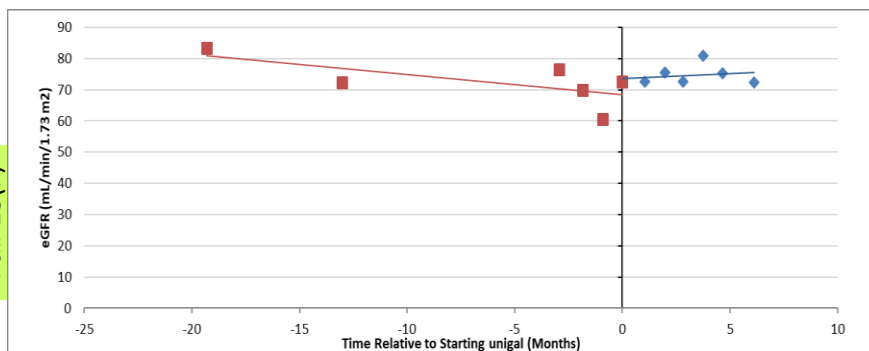
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Pt.# 16(M)

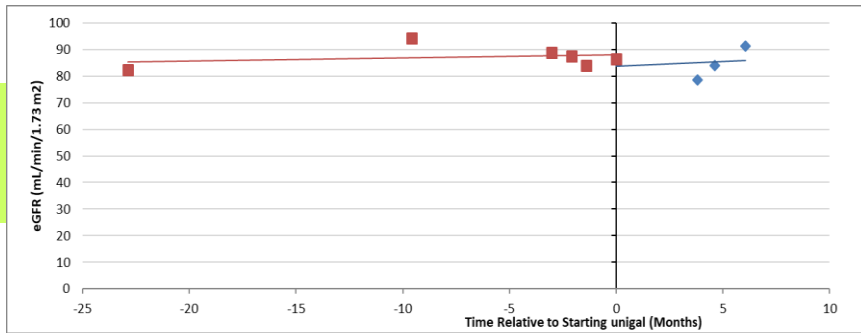


Pt.# 13(F)

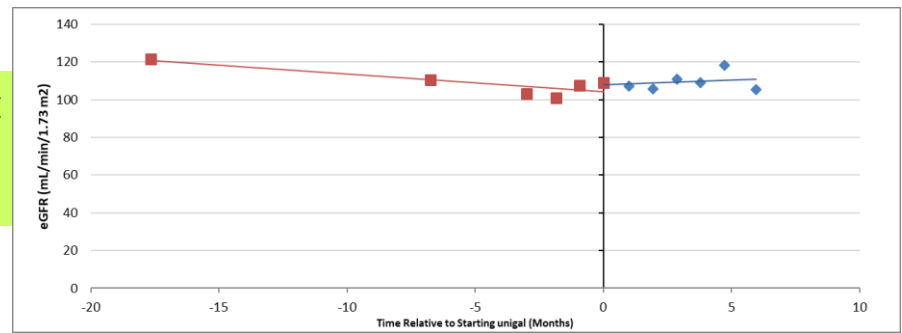


Individual eGFR values (continued)

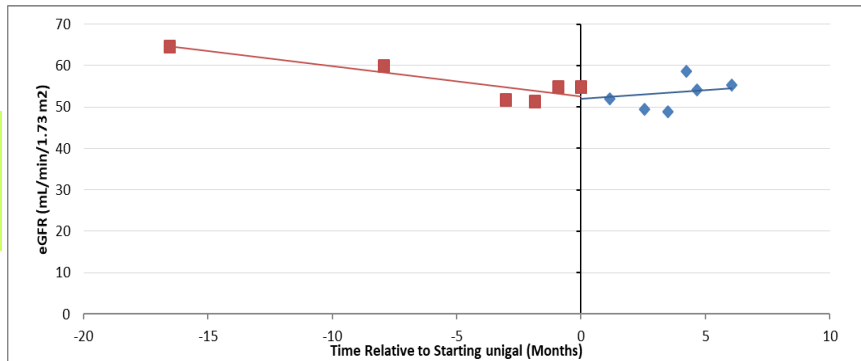
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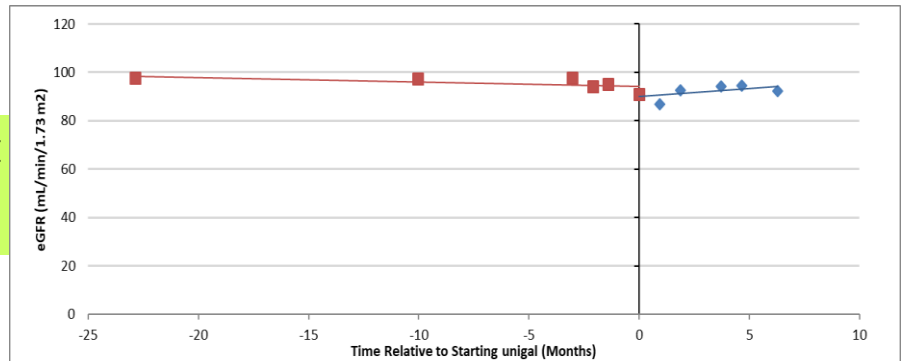
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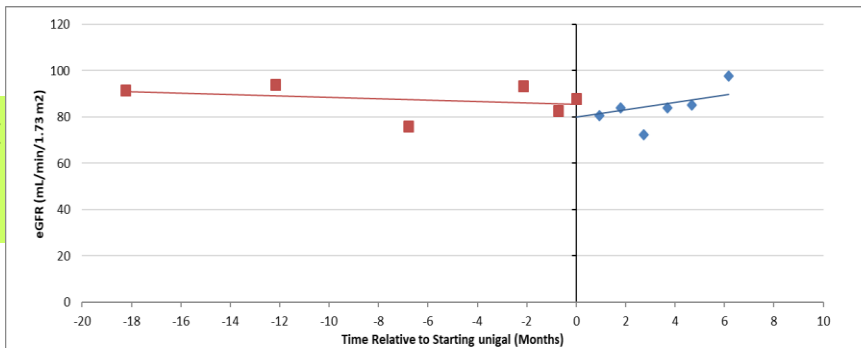
Pt. # 6(F)



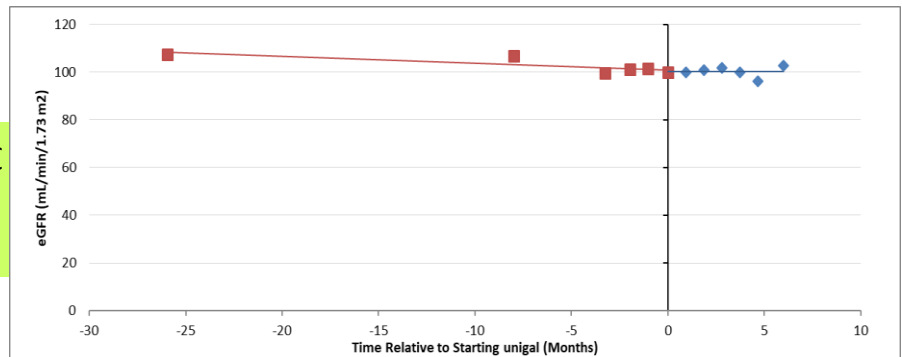
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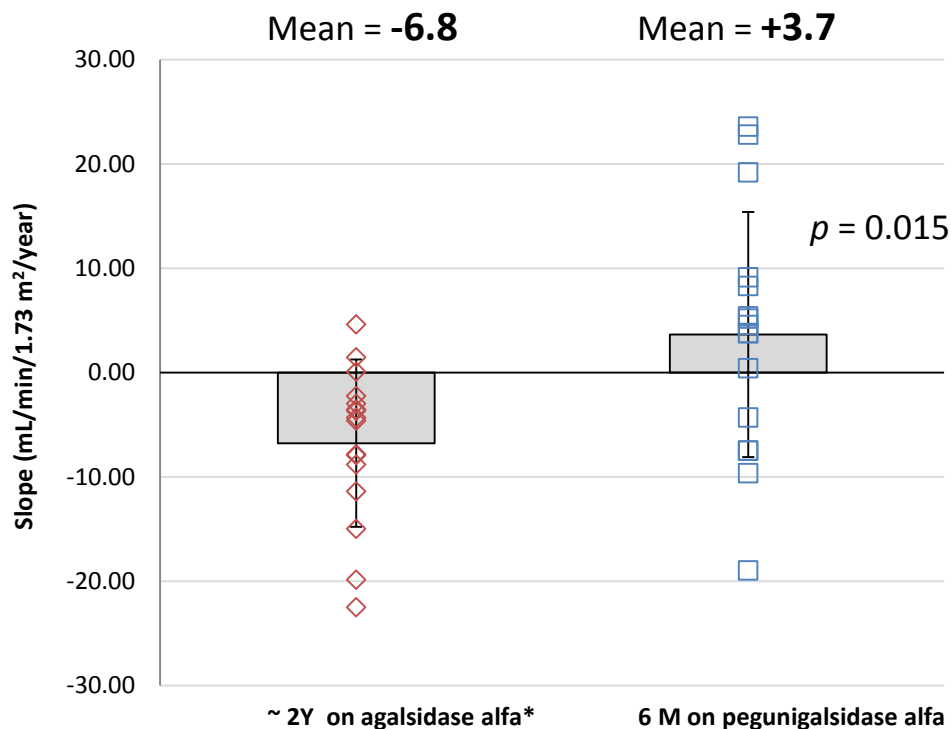
Pt. # 9(F)



Pt. # 12(F)



Mean and individual annualized eGFR slopes pre- and post-treatment with pegunigalsidase alfa (6 M on Unigal; n=16)-preliminary results



	Males (n=9)	Females (n=7)
eGFR _{CKD-EPI} - Mean Baseline (range)	75 (49-111)	86 (54-100)
Mean annualized eGFR slope on Replagal	-8.04	-5.13
Mean annualized eGFR slope on pegunigalsidase alfa	1.29	6.71

* Based on available historical serum creatinine for approximately 2 years and study 3 month screening period values

eGFR mL/min/1.73 m² is calculated using CKD-EPI formula

eGFR Slope = mL/min/1.73 m²/year

Summary

- Pegunigalsidase alfa is a PEGylated enzyme with unique biochemical characteristics
 - Higher stability in plasma and lysosomal-like conditions
 - Prolonged half-life and higher exposure in FD patients
- Reduction of Gb3 inclusion in PTC derived from kidney biopsies was observed in Naïve treated Fabry patients
- Preliminary results from BRIDGE study indicate improvement in kidney function in patients switched from agalsidase alfa

Acknowledgements

Special thanks to:

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