pegunigalsidase alfa

PRX-102 α -Galactosidase-A

Novel PEGylated ERT for Fabry disease - IV administration of plant derived alpha-gal-a enzyme safety and efficacy, 1 year experience

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Disclosure

Research Support: Protalix Biotherapeutics, Shire, Inc., Amicus Therapeutics
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Phase I/II

1 Year Clinical Experience

Phase I/II, Open Label, Dose Ranging

General Design

Adult Fabry Patients

Three dose groups:

0.2 mg/kg | **1** mg/kg | **2** mg/kg

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

Overall Study Design

Demographics & Baseline Enzymatic Activity

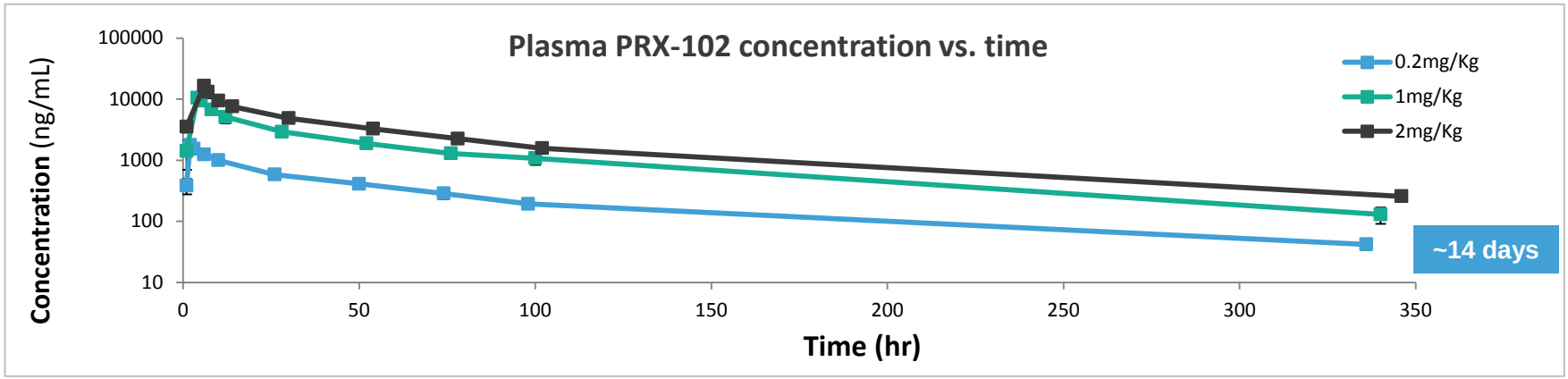
	0.2 mg/kg (n=6)	1 mg/kg (n=8)*	2 mg/kg (n=4)
Mean age (years) ± SD (range)	30.0 ± 10.8 (21-50)	34 ± 9.7 (17.5-52.5)	40.6 ± 9.5 (21-54)
Male : Female	4:2	6:2	1:3
Ethnicity			
Caucasian	4	4	4
African American	1	2	0
Asian	0	0	0
Other	1	0	0

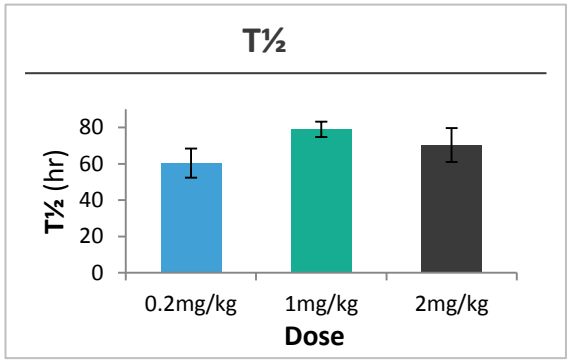
Mean Enzymatic Activity	**0.2 mg/kg (males=4, females=2)**	**1 mg/kg (males*=6, females=2)**	**2 mg/kg (males=1, females=3)**
In leucocytes (range) (normal 33-134 nmol/hr/mg prt.)	Males: 3.15 (1.6-5)	Males: 2.67 (0-7.8)	Male 0.56
	Females: 27.5 (15-40)	Females: 69.5 (67-72)	Females: 42.66 (33-53)
In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

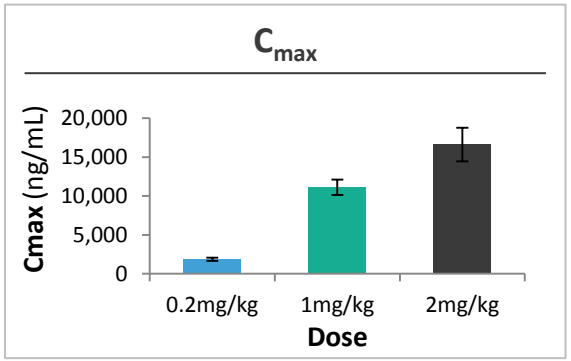
* one subject discontinued due to AE; one subject discontinued due to non compliance

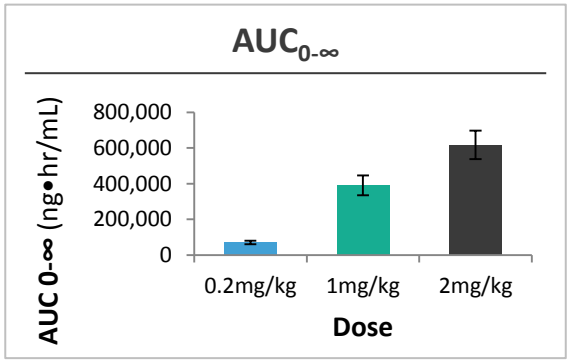
Pharmacokinetics

Available Enzyme Throughout 2-Week Interval









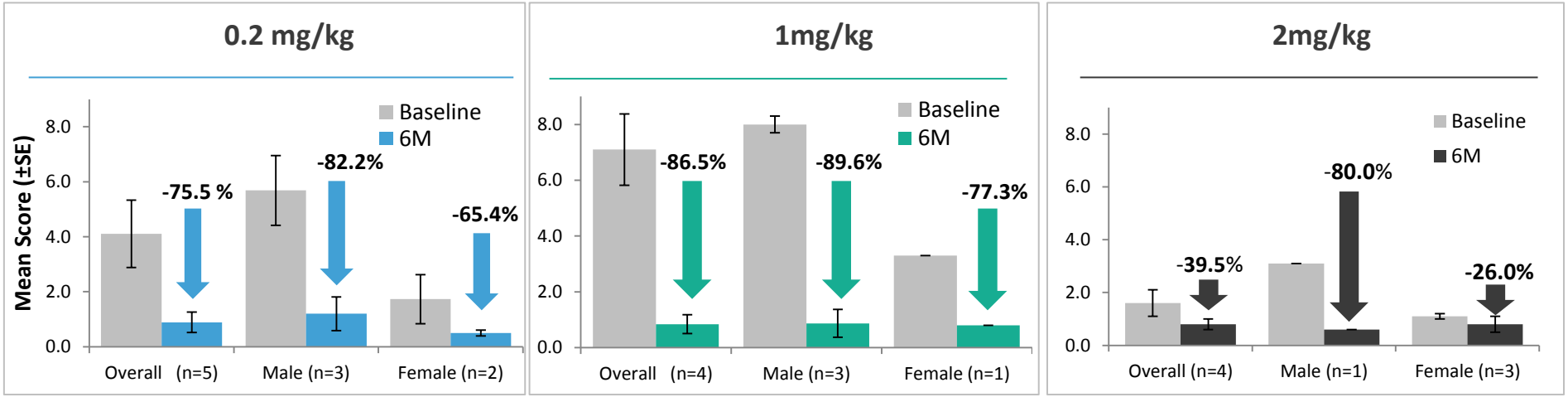
Efficacy

Efficacy analysis presented for:

All patients (n=16)
Classic FD patients (n=10 ; 9M;1F)

Reduction of Gb3 in Kidney Peritubular Capillaries

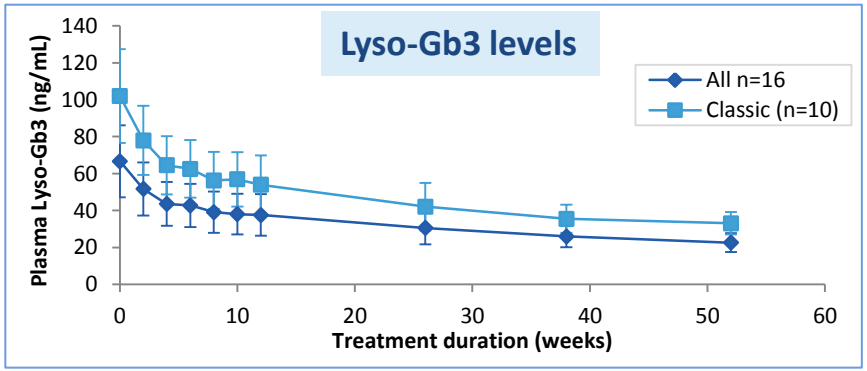
Quantitative BLISS Score

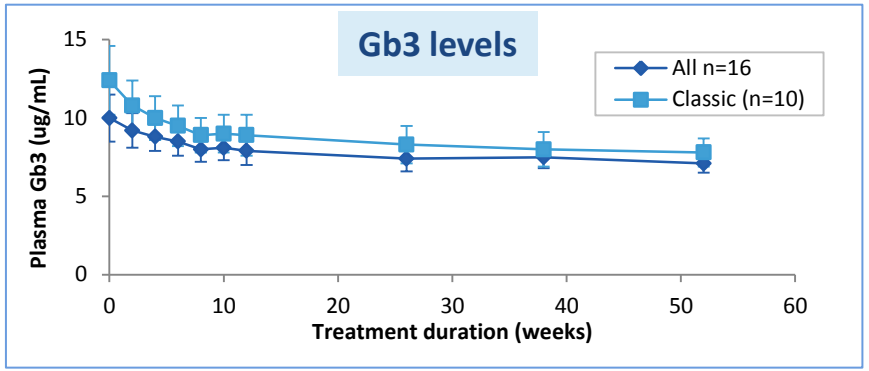


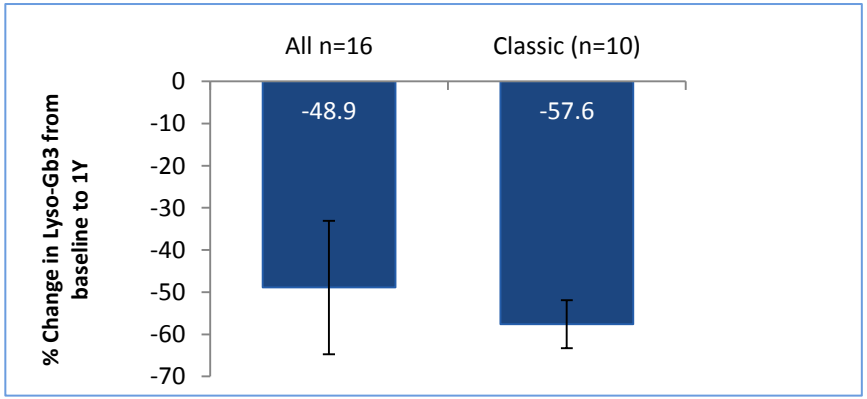
	% change ±SE
All Patients (n=16)	**-67.8±8.9**
Classic Patients (n=10)	**-84.1±3.3**

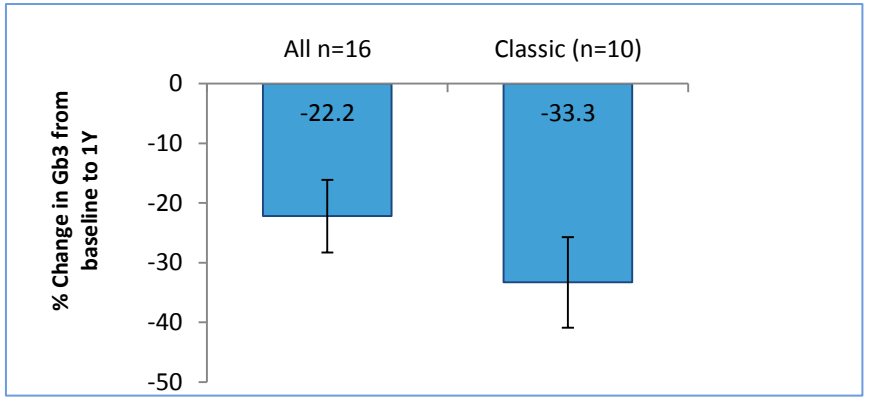
- >300 PTCs were scored for Gb3 inclusions in each biopsy
- Slides underwent digital imaging before scoring
- Images were distributed in a random and blinded manner for annotation by 1 pathologist, and subsequent scoring by 2 other pathologists

Biomarkers -Plasma Gb3/Lyso-Gb3 *(All vs. classic)*



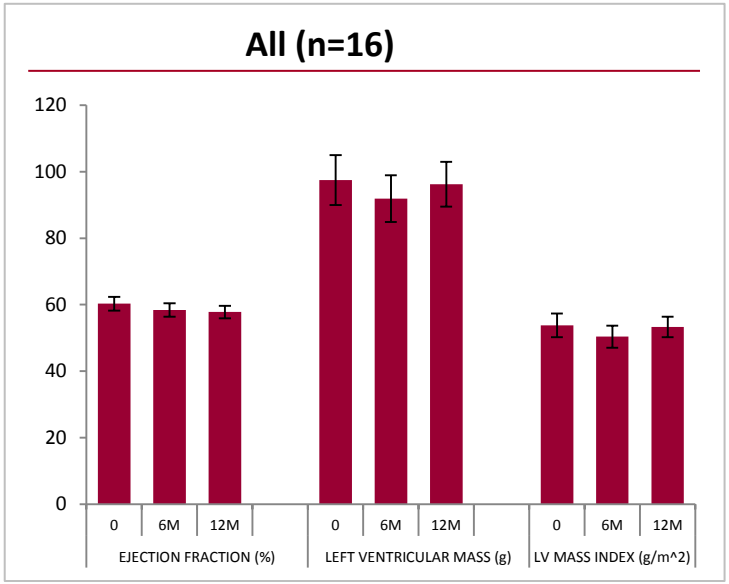


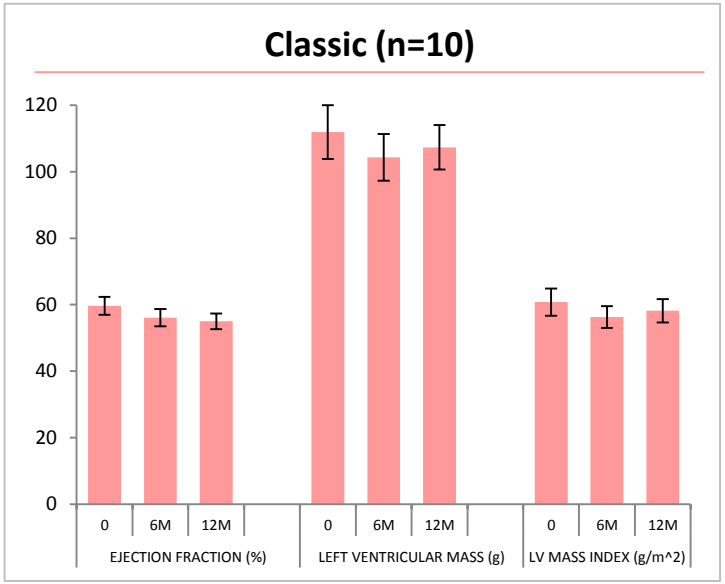




Stable Cardiac Parameters (by MRI)

Mean LVM, LVMI and EF

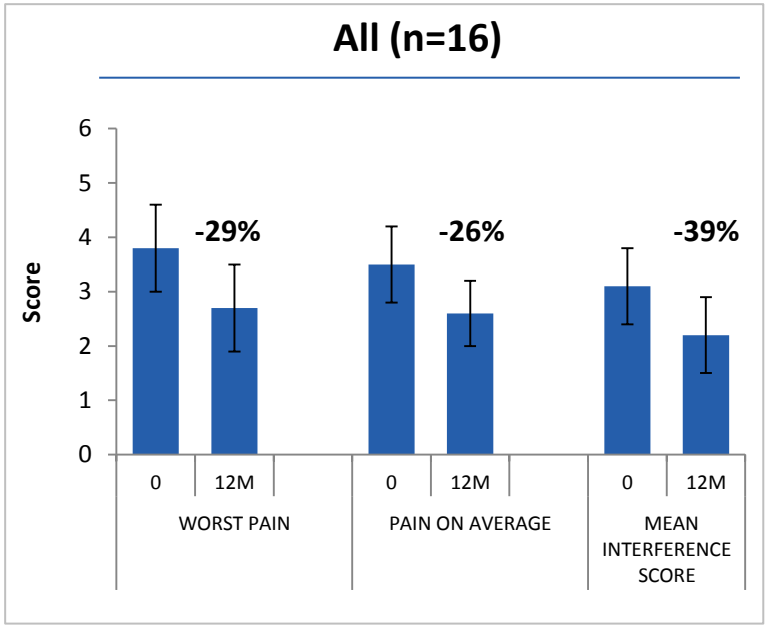


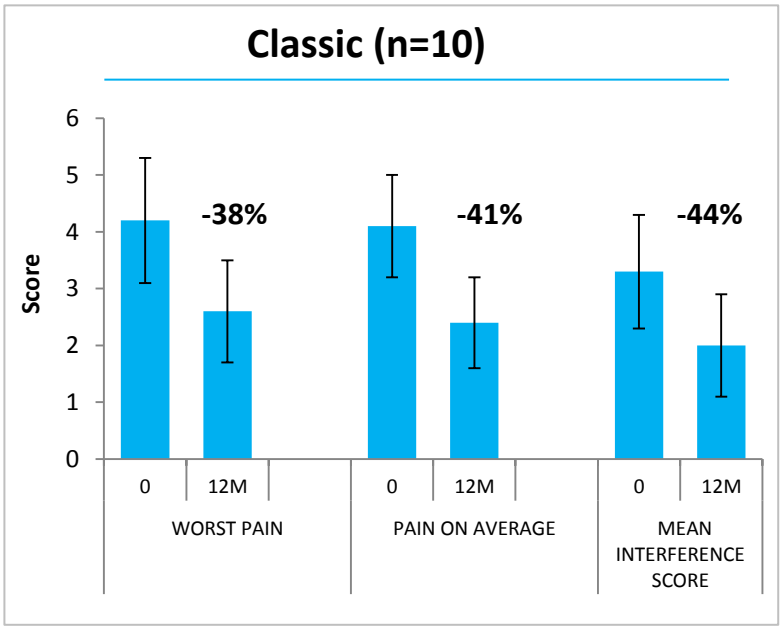


- No cardiac fibrosis observed throughout the year of treatment

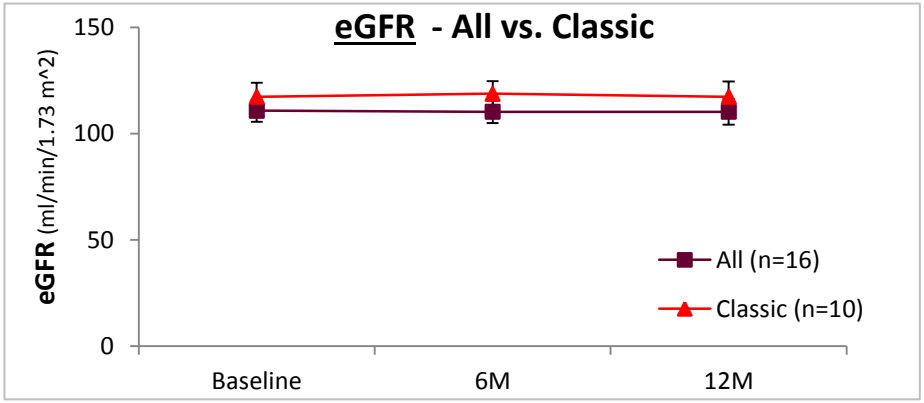
Normal ranges (MRI)	Male	Female
LVM (g)	85-181	66-115
LVMI (g/m2)	46-84	37-67
EF (%)	55-74	54-74

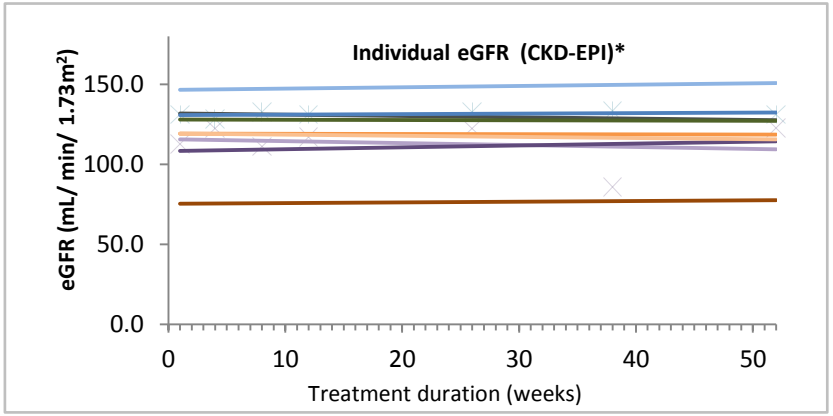
Brief Pain Inventory (BPI)

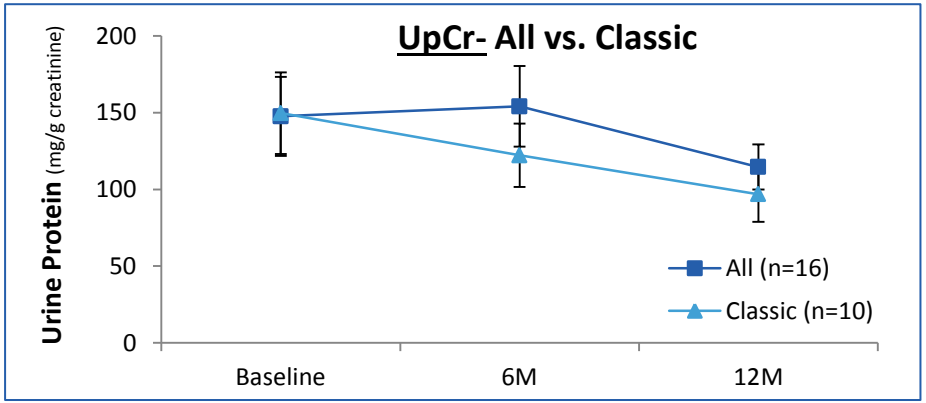




Stable Kidney Functions







* Excluding 1 male patient treated intermittently with doxycycline throughout the year

Safety

Safety in 416 infusions, 16 patient years

223 (100%)

Total AEs in 17/18 subjects

219 (98.2%)
AEs mild and moderate

4 (1.8%)
Severe

- 2 Severe treatment related in 2 pts. (Migraine, Bronchospasm*)
- 2 Severe not treatment related in 2 other pts.

2 (0.9%)
Serious AEs

- Bronchospasm - treatment related*
- Kidney hemorrhage post biopsy, not treatment related**

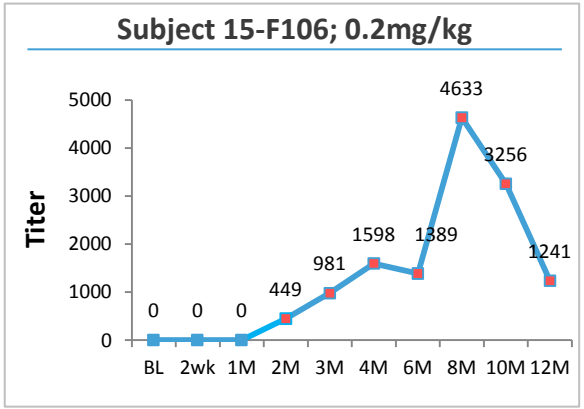
54 (24.2%)
Related, possibly related

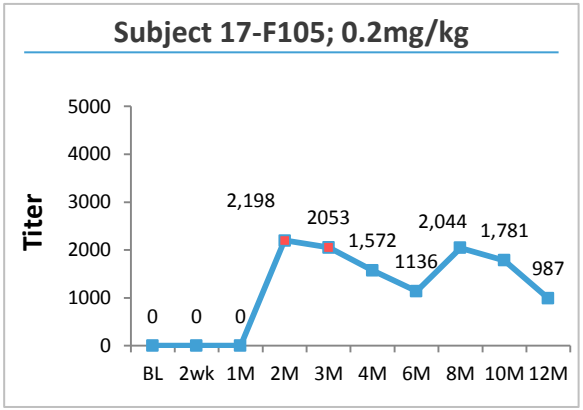
169 (75.8%)
Not related, unlikely related

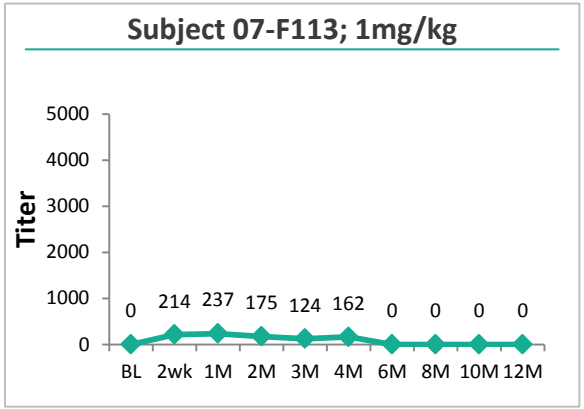
*52 year old male experienced a Grade 3 serious adverse event of bronchospasm related to the study drug 40 minutes following the first infusion initiation, received a total of 115mg investigational drug. Was treated with inhalations, adrenalin and steroids, and discharged the following day. Discontinued Per Protocol. Anti PRX-102 IgG was negative and anti PRX-102 IgE was positive at baseline. **28 year old male, pre treatment renal hematoma post kidney biopsy- Not related.

Low Incidence of Treatment Induced Anti-Drug Antibodies (ADA)

- Low incidence of ADA formation with low titers reduced by 1 year of treatment
- Three male patients had treatment induced ADA in at least one visit (19%).
- 2 of these 3 patients had neutralizing antibodies (nAb), one of which was nAb positive only in 2/8 samples
- No treatment induced ADA in the 2.0 mg/kg cohort
- One of these 3 patients turned to be negative after 12M
- One (1) patient who received partial dose and had hypersensitivity reaction was withdrawn, per protocol, from the study. This patient was found to have detectable ADA pre-dosing with PRX-102, immediately after infusion and in the follow up visits (1M & 3M)



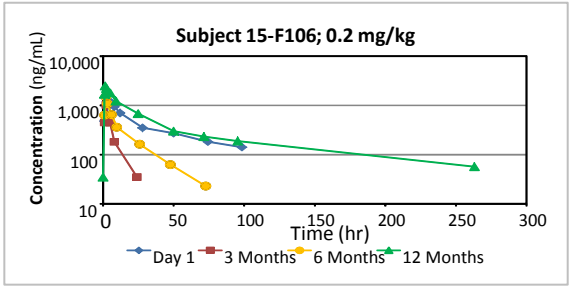


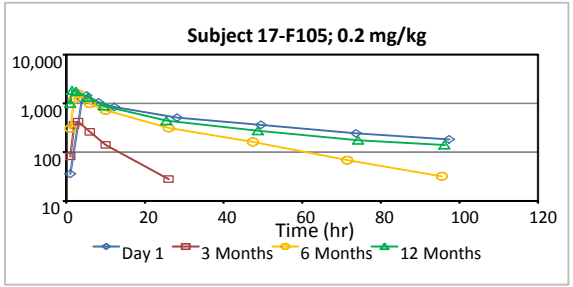


Reversible & Transient Effect on PK in ADA Positive Patients

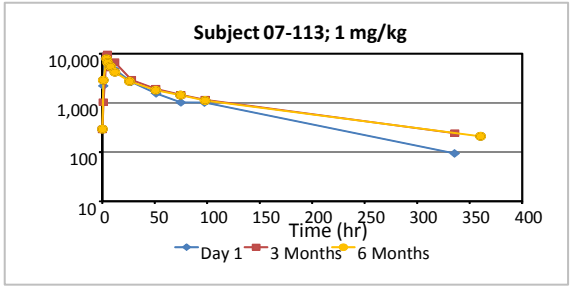
PK of ADA positive patients

0.2mg/kg ➔Transient impact of ADA on PK



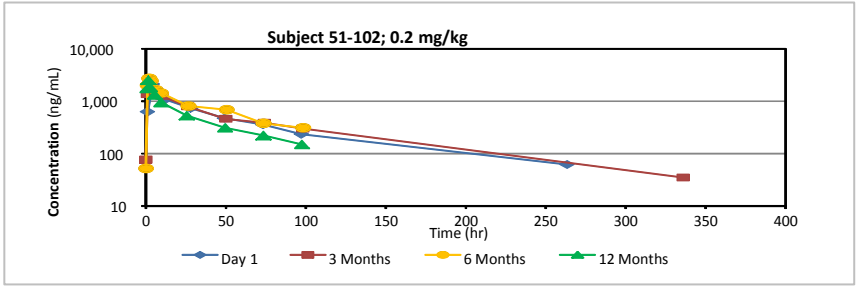


1mg/kg ➔No impact of ADA on PK

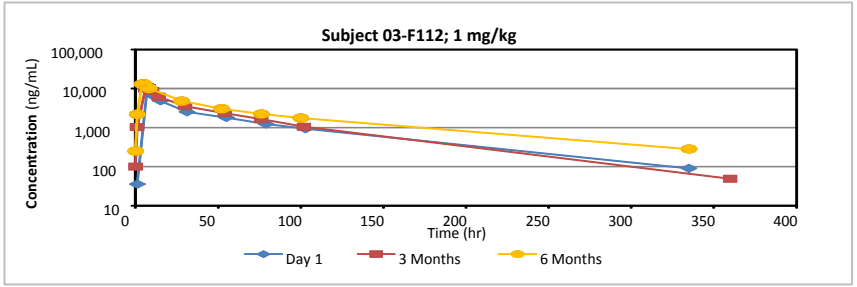


Example of PK of ADA negative patients

0.2 mg/kg



1 mg/kg



Overall Conclusions

PRX-102 – plant cell expressed recombinant human alpha-GAL-A enzyme, PEGylated, covalently-linked, stable homo-dimer

PK:

PRX-102 has a longer half-life and a substantially higher AUC

- Available enzyme throughout 2-week infusion intervals

Safety:

PRX-102 is well tolerated

- Majority of adverse events - mild and moderate in severity
- Limited formation of antibodies

Efficacy:

Demonstrated effectiveness, in various disease endpoints including:

- Stable kidney and cardiac function
- Reduction of Gb3 inclusions in kidney peritubular endothelial cells
- Reduction of plasma Gb3 and Lyso-Gb3
- Reduction in MSSI score
- Improvement in Pain parameters

Following FDA and EMA discussions
Phase 3 Program initiated

Next Phase 3 studies

balance a Fabry clinical study

- A randomized, double blind, active control study
- Evaluate the safety and efficacy of PRX-102 compared to agalsidase beta in patients with FD previously treated with agalsidase beta with rapidly declining renal function
- Classic FD patients
- 2 years treatment duration
- Extension study will be offered to patients at the end of the study

bridge a Fabry clinical study

- An open label switch over study
- Assess the safety and efficacy of PRX-102
- 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

Thank You