Novel Treatment for Fabry Disease

IV Administration of Plant Derived α-galactosidase-A Enzyme, Phase 1/2 Safety and Efficacy Study

Interim Report

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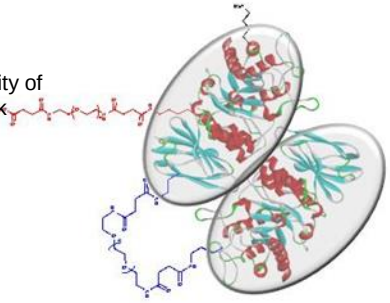


Disclosure Information

WORLD Symposium, Orlando, 2015

Ozlem Goker- Alpan, MD

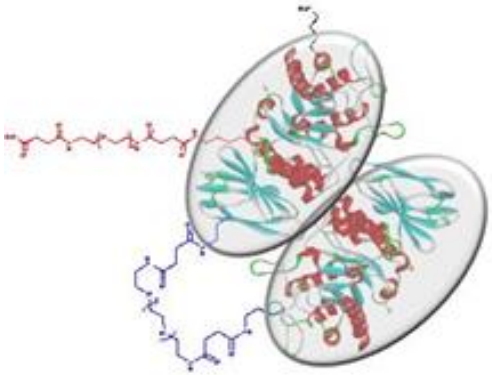
I have the following financial relationships to disclose:

- Consulting for: Genzyme, Shire, Amicus, Biomarin, Pfizer, Actelion
- Fees for non-CME/CE services received directly from a commercial Interest or their agents from: Genzyme, Shire, Pfizer
- Contracted Research: Genzyme, Amicus, Shire, Protalix, Alexion
- Grant support, Speaker Bureau : Genzyme, Pfizer, Shire

In my presentation

- I will discuss preliminary results of investigational use of PRX-102 in patients with Fabry disease.
- This study was sponsored by Protalix Biotherapeutics

PRX-102 - Chemically Modified Plant Derived Human α-galactosidase-A Enzyme



Product Characteristics

- PEGylated, cross-linked, covalently bound, stable homo-dimer
- Longer circulatory half-life, higher AUC

Scope of Interim analysis - Cutoff Date November 30, 2014

- Total number of infusions - 6.3 patient years
- 0.2mg/kg: 6 pts, 139 infusions
- 1mg/kg: 6 pts, 25 infusions

End points:

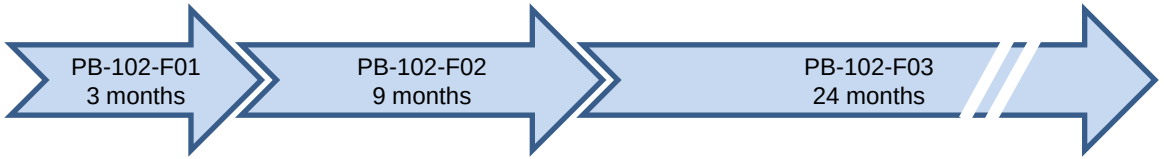
- Pharmacokinetics 0.2mg/Kg (n=6), 1mg/Kg (n=4)
- Exploratory Efficacy: 6M treatment of 0.2mg/kg dose cohort (n=6)
- Safety : all enrolled patients, 0.2mg/kg, 1mg/kg (n=12)

Phase 1/2, Open Label, Dose Ranging
General Design

- Adult male and female Fabry patients
- PRX-102 dose groups: 0.2, 1 or 2 mg/kg
- Intravenously, every 2 weeks

- Main Inclusion Criteria:
  - Symptomatic Fabry patients
  - Naïve or patients who have not received ERT in the last 6 months and have a negative anti PRX-102 antibody test
  - eGFR ≥ 60 mL/min/1.73m^2

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

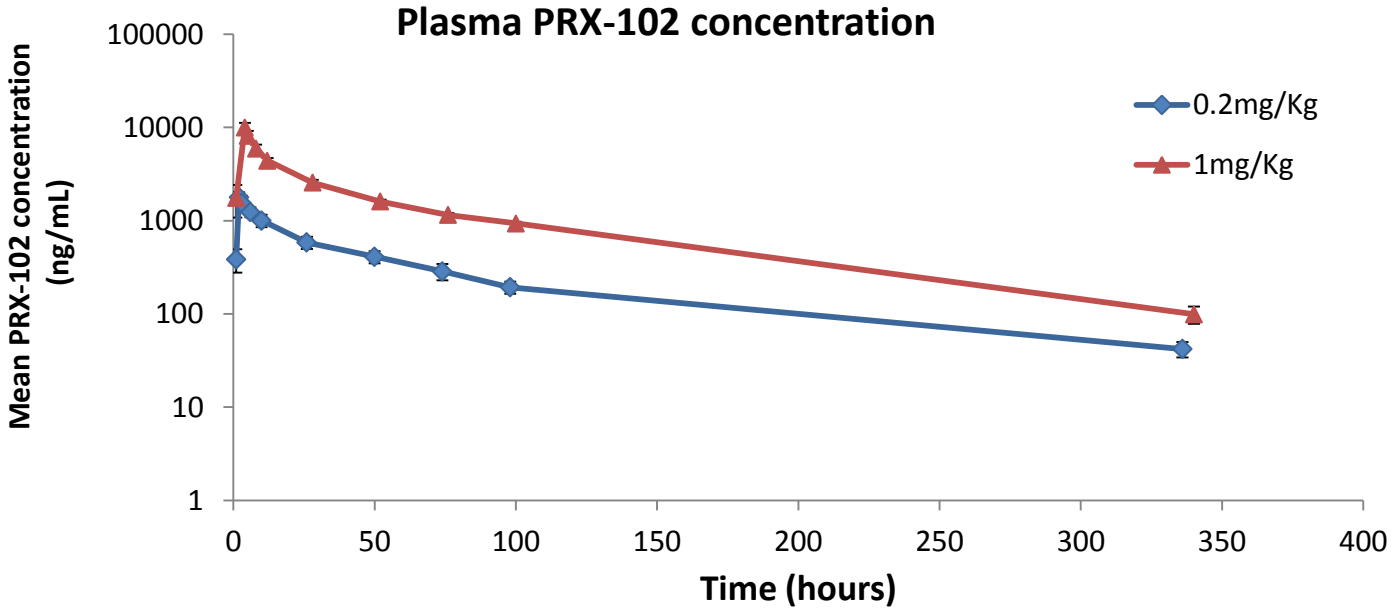


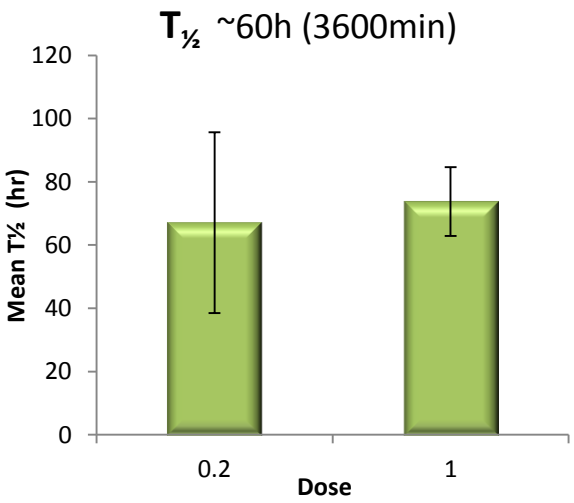
Demographics & Baseline Enzymatic Activity

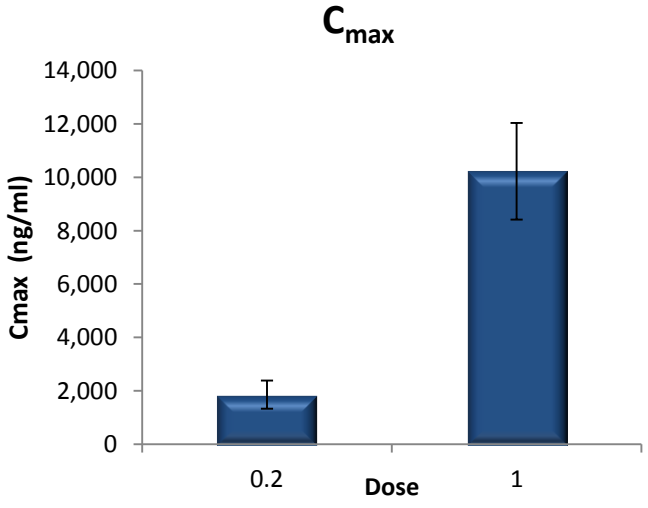
	0.2 mg/kg (n=6)	1 mg/kg (n=6)
Mean age (years) ± SD (range)	30.0 ± 10.8 (21-50)	33.7 ± 9.5 (27-52)
Male : Female	4:2	5:1
Caucasian	4	6
African American	1	0
Asian	0	0
Other	1	0

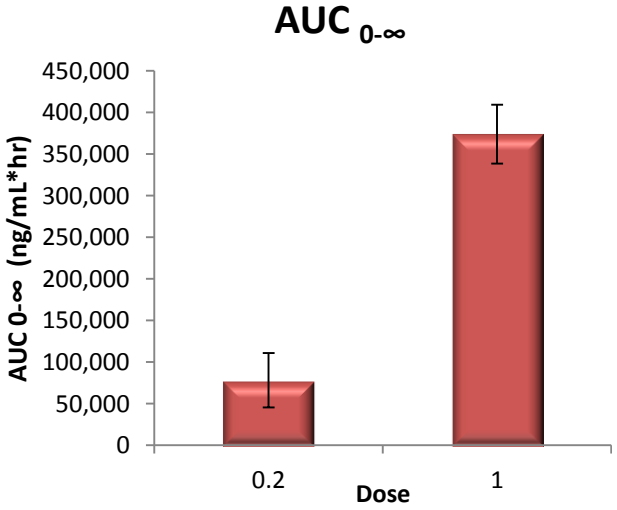
Mean Enzymatic Activity	0.2 mg/kg (males=4, females=2)	1 mg/kg (males=5, females=1)
In leucocytes (range) (normal 33-134 nmol/hr/mg prt.)	Males: 3.15 (1.6-5)	Males: 3.2 (0.61-7.8)
	Females: 27.5 (15-40)	Female: 72
In plasma (range) (normal 4-21.9 nmol/hr/ml)	Males: 0.22 (0-0.4)	Males: 0.3 (0.05-0.44)
	Females: 3.15 (2-4.3)	Female: 5.8

Pharmacokinetics



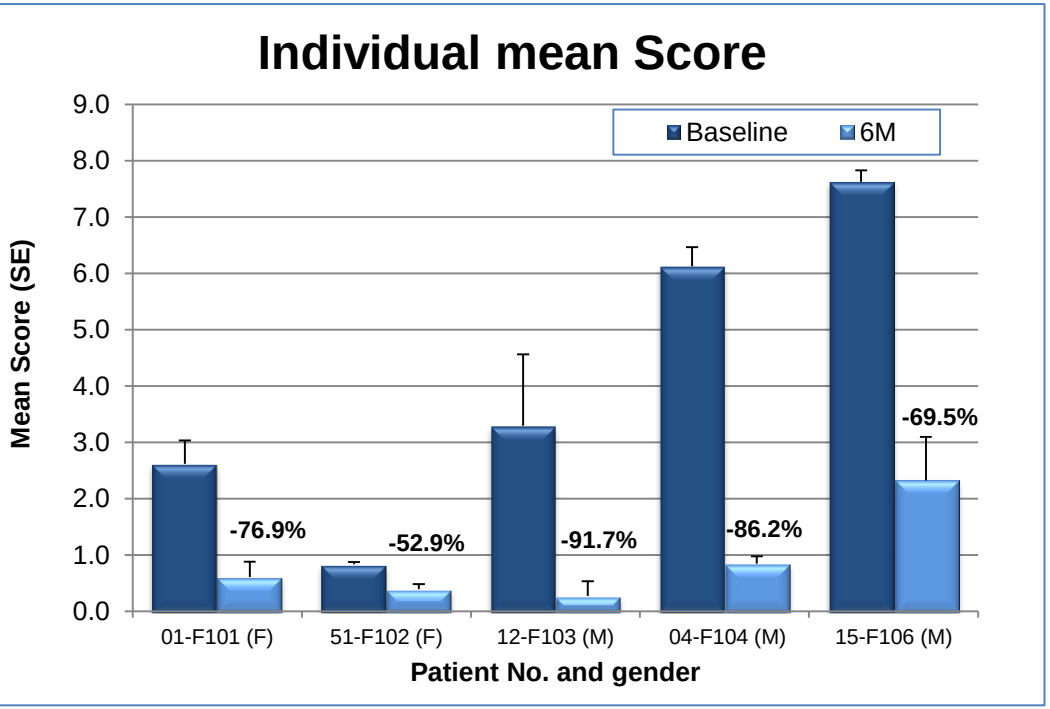


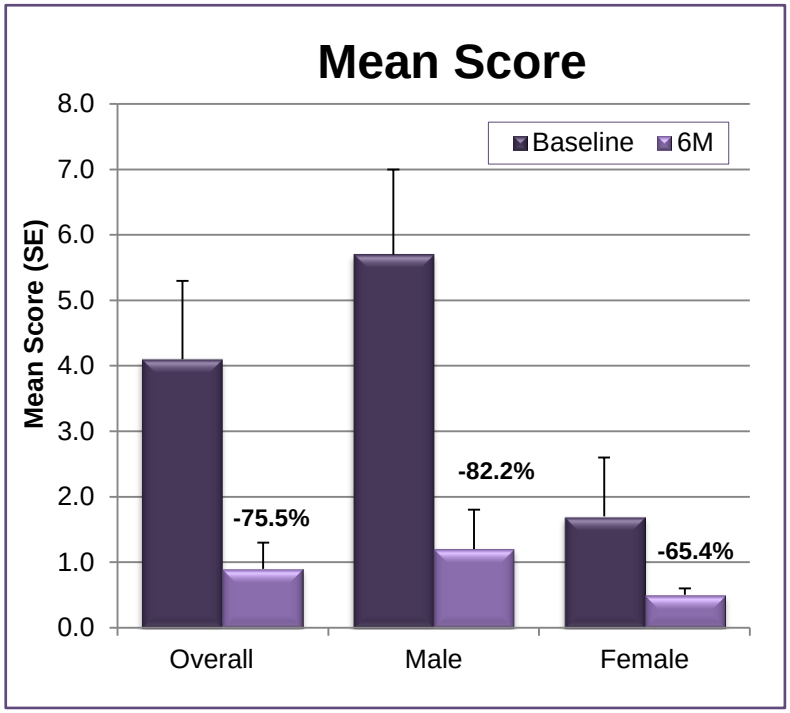




Exploratory Efficacy Results

6M Reduction of Gb3 in Kidney Peritubular Capillaries
Quantitative BLISS Score

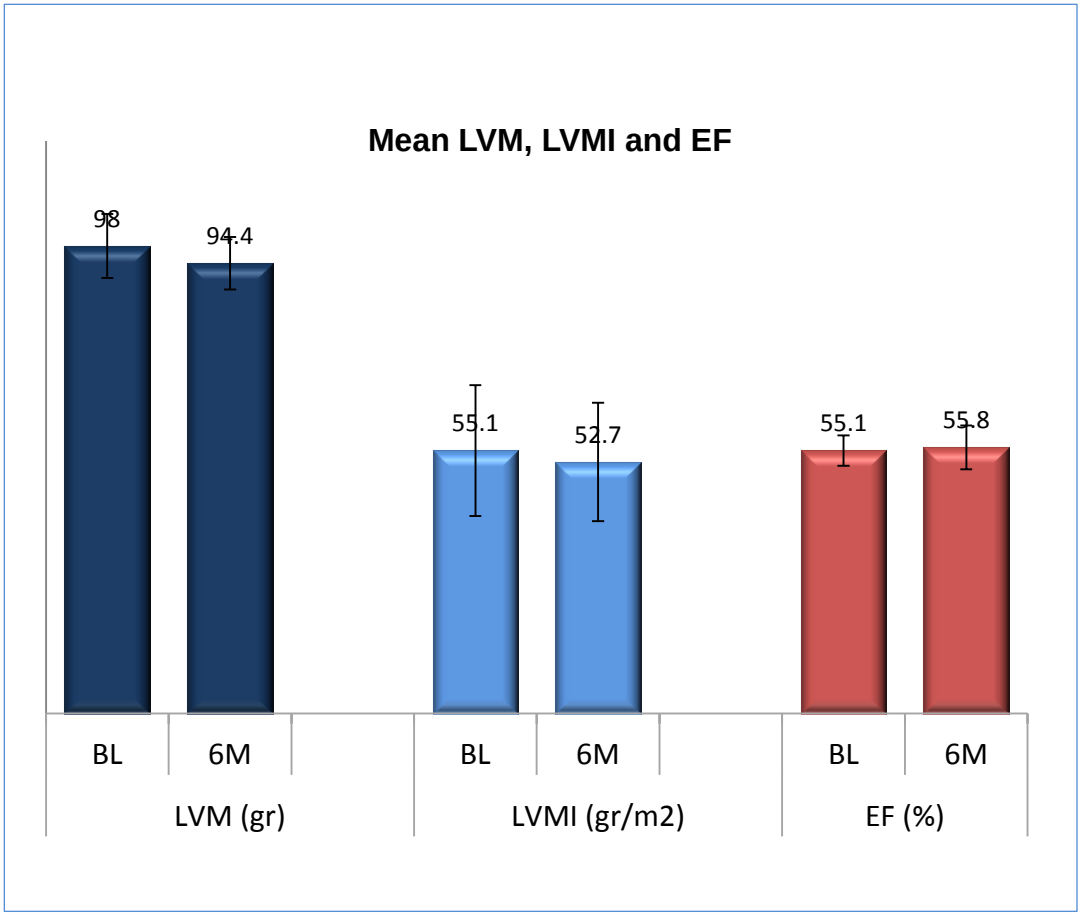




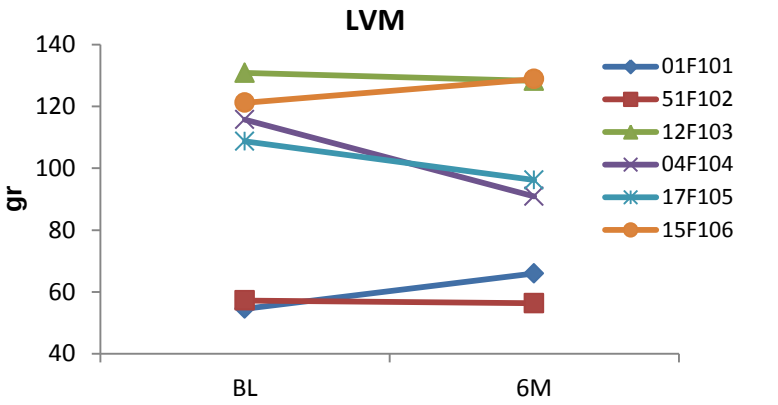
Patient No. and gender	Absolute Change from Baseline	% Change from Baseline
01-F101 (F)	-2.0	-76.9
51-F102 (F)	-0.4	-52.9
12-F103 (M)	-3.0	-91.7
04-F104 (M)	-5.3	-86.2
15-F106 (M)	-5.3	-69.5
All Mean (SE)	**-3.2**	**-75.5 (6.8)**
Male Mean (SE)	**-4.5**	**-82.2 (6.9)**
Female Mean (SE)	**-1.2**	**-65.4 (12.5)**

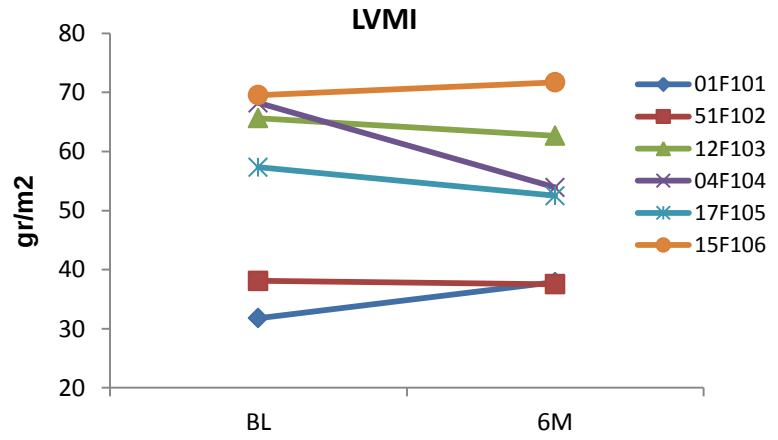
- Slides underwent digital imaging before scoring
- Images were distributed in a random and blinded manner for annotation by 1 pathologist, and subsequent scoring by 2 other pathologists
- >300 PTCs were scored for Gb3 inclusions in each biopsy

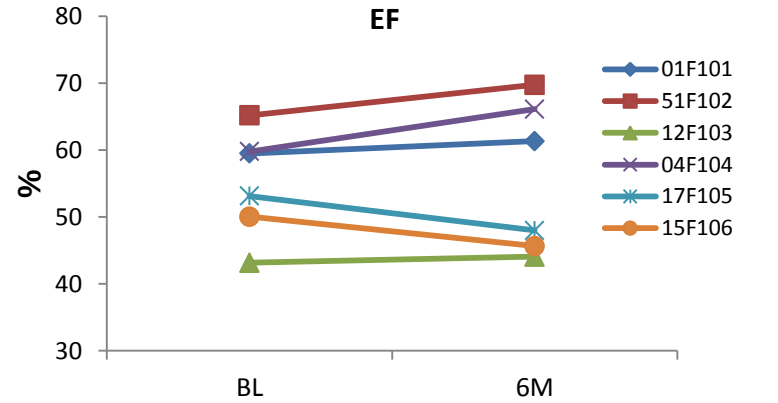
Stability of Cardiac Parameters by MRI



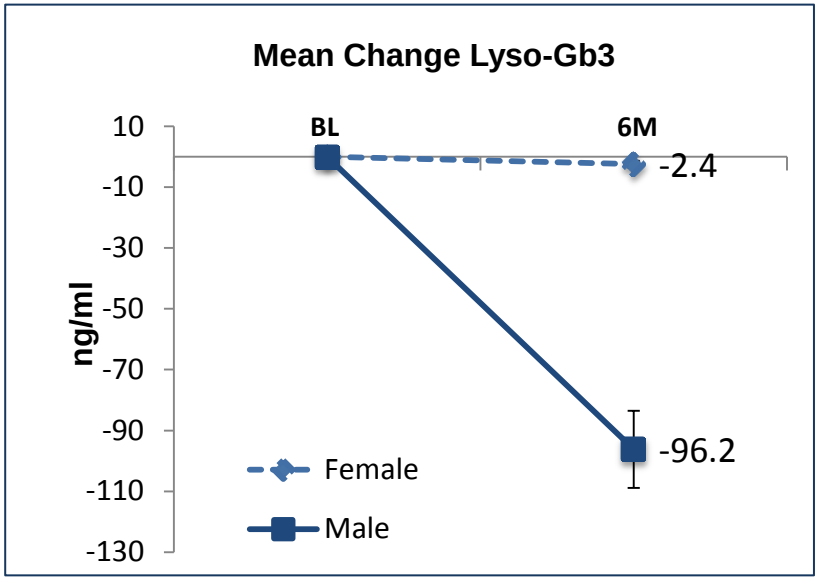
Normal ranges (MRI)	Male	Female
LVM (g)	85-181	66-115
LVMI (g/m2)	46-84	37-67
EF (%)	55-74	54-74

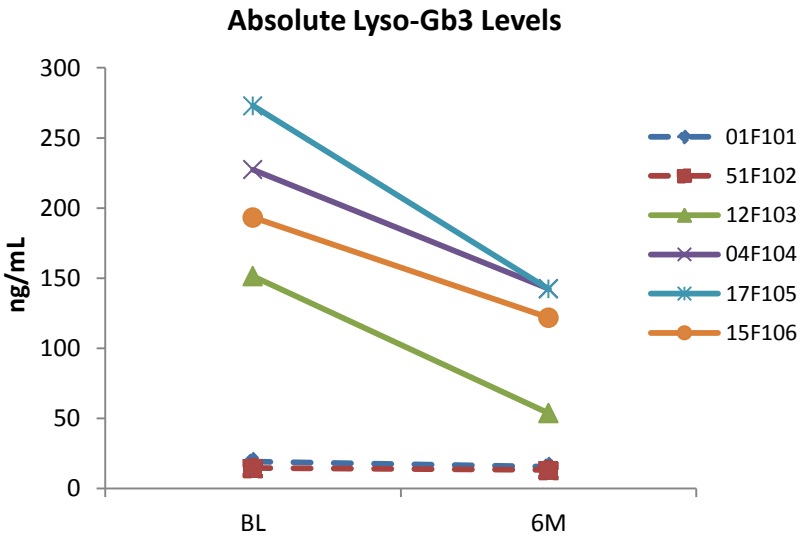


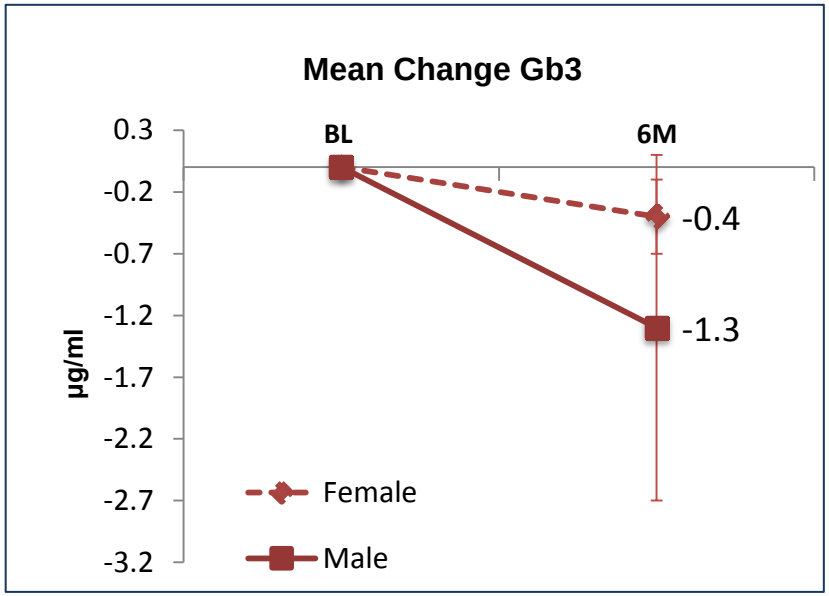


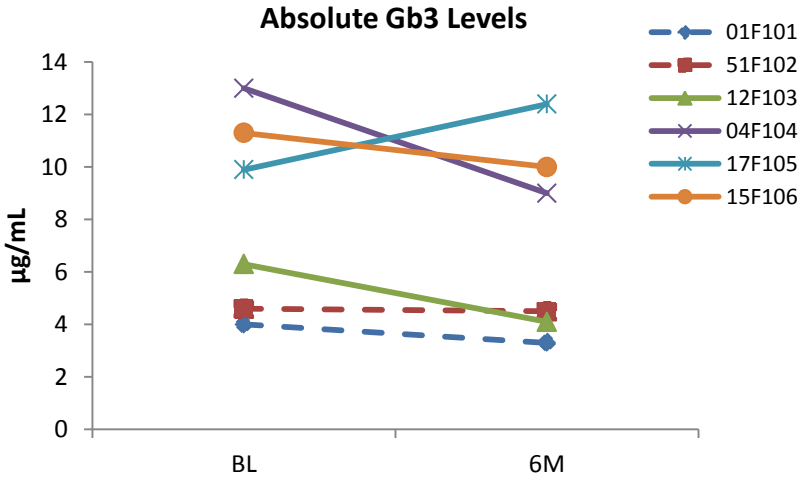


Reduction of Plasma Gb3 and Lyso-Gb3 Concentration

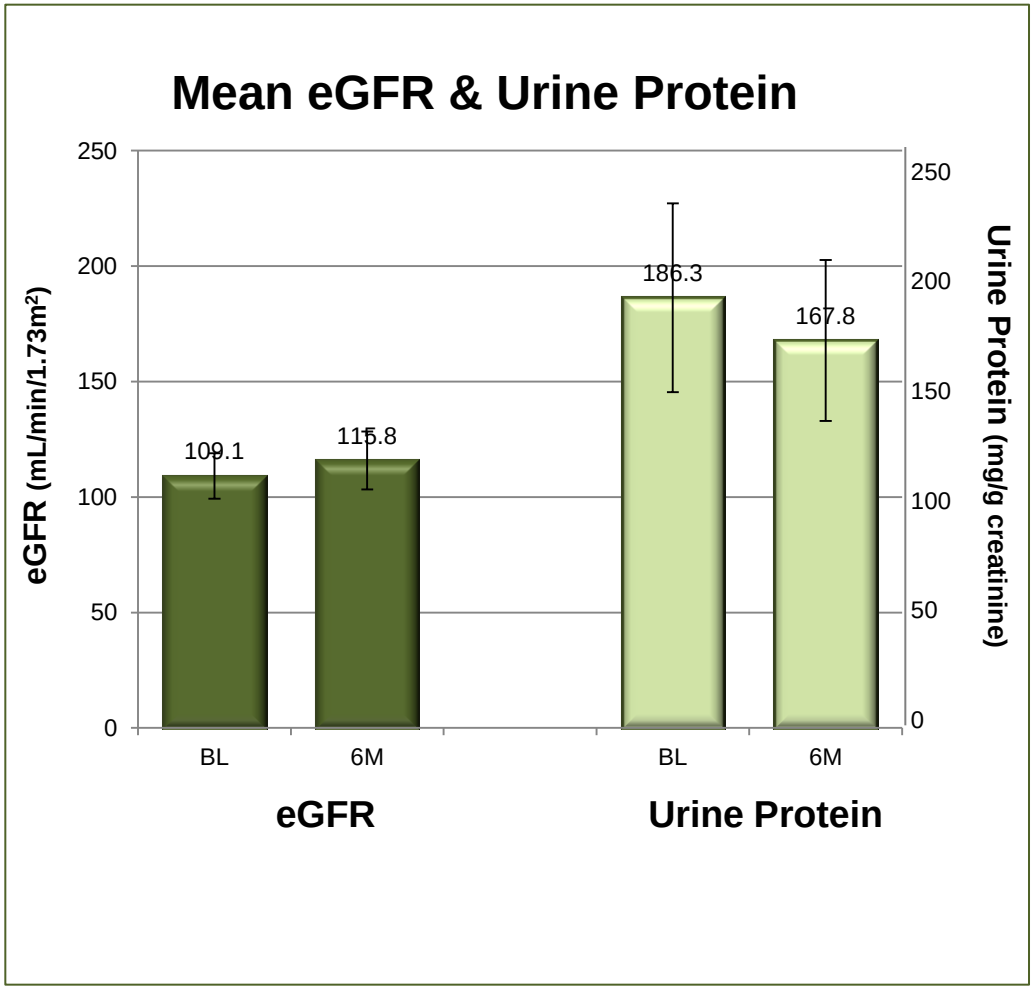


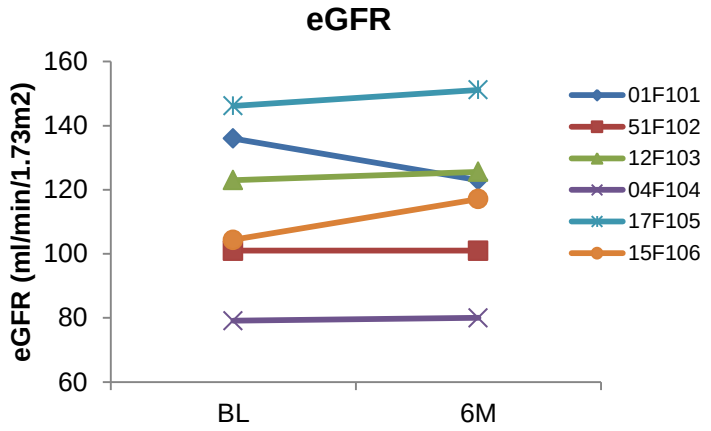


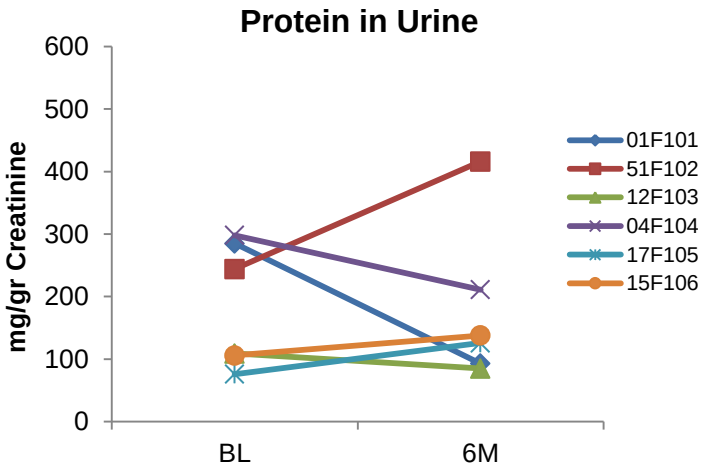




Stable Kidney Functions







Normal ranges:
eGFR: 90-135mL/min/1.73m^2
Urine protein: <200 mg/gr creatinine

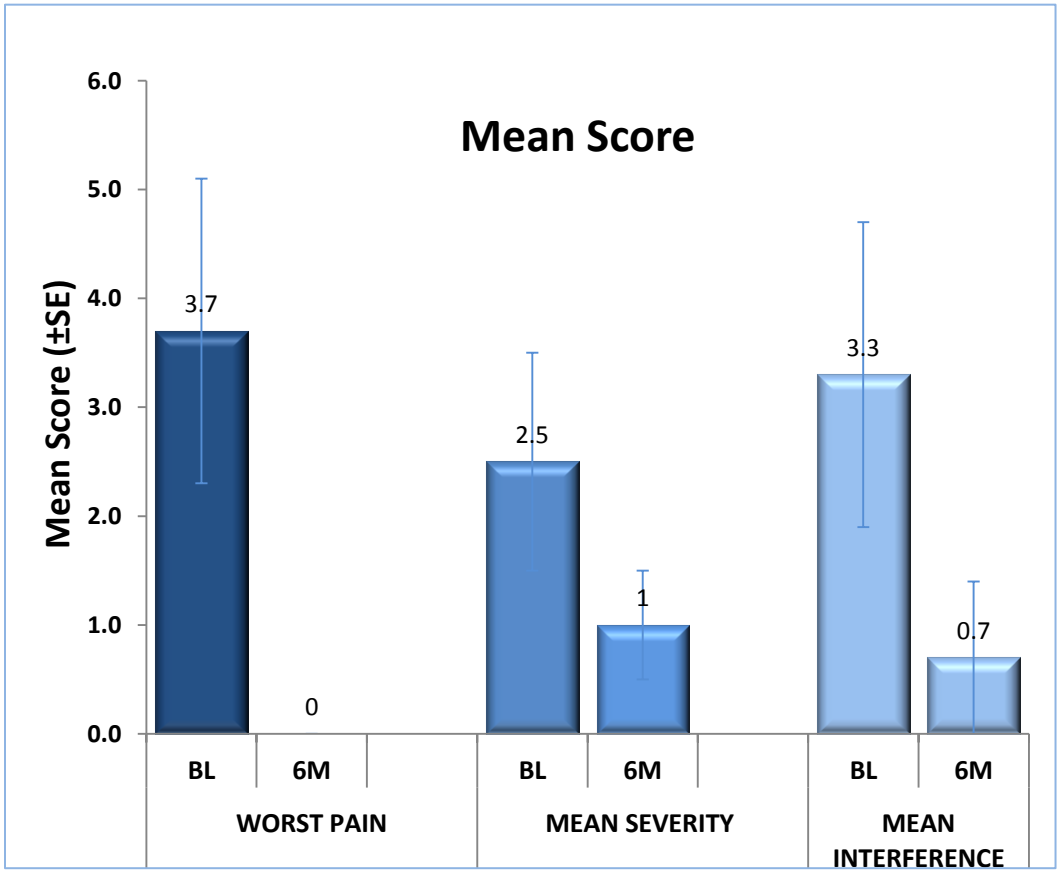
Improvement in Brief Pain Inventory (BPI)

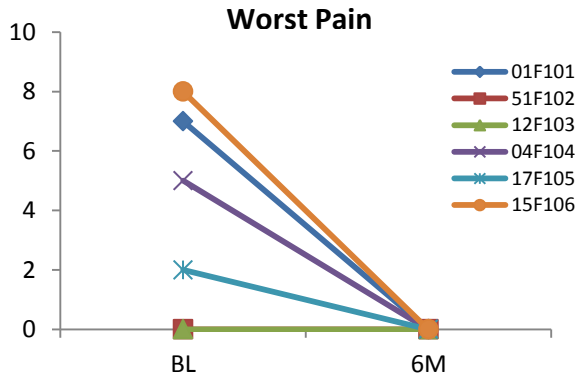
Pain Intensity (Severity)

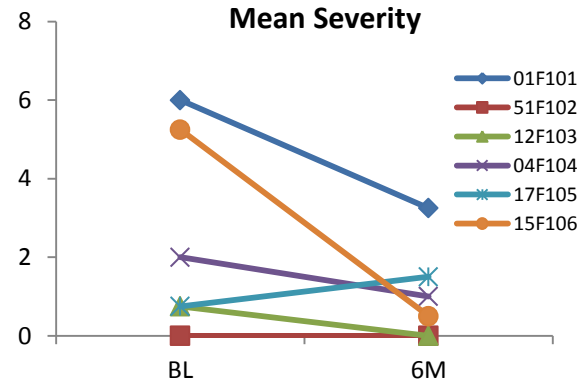
- Pain at its Worst
- Mean Severity: Worst, Least, Average, Now

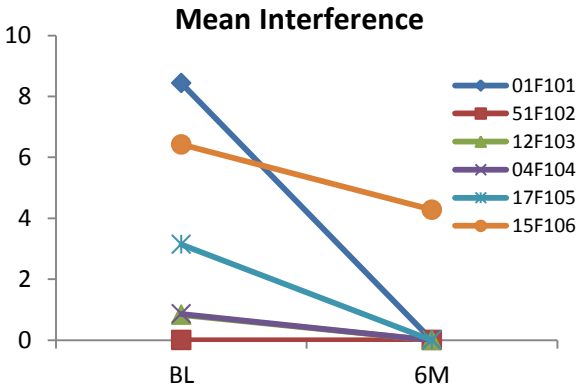
Impact on functioning (Interference)

- Mean Interference: Walking, Work, Mood, Enjoyment of life, Relations with others, Sleep

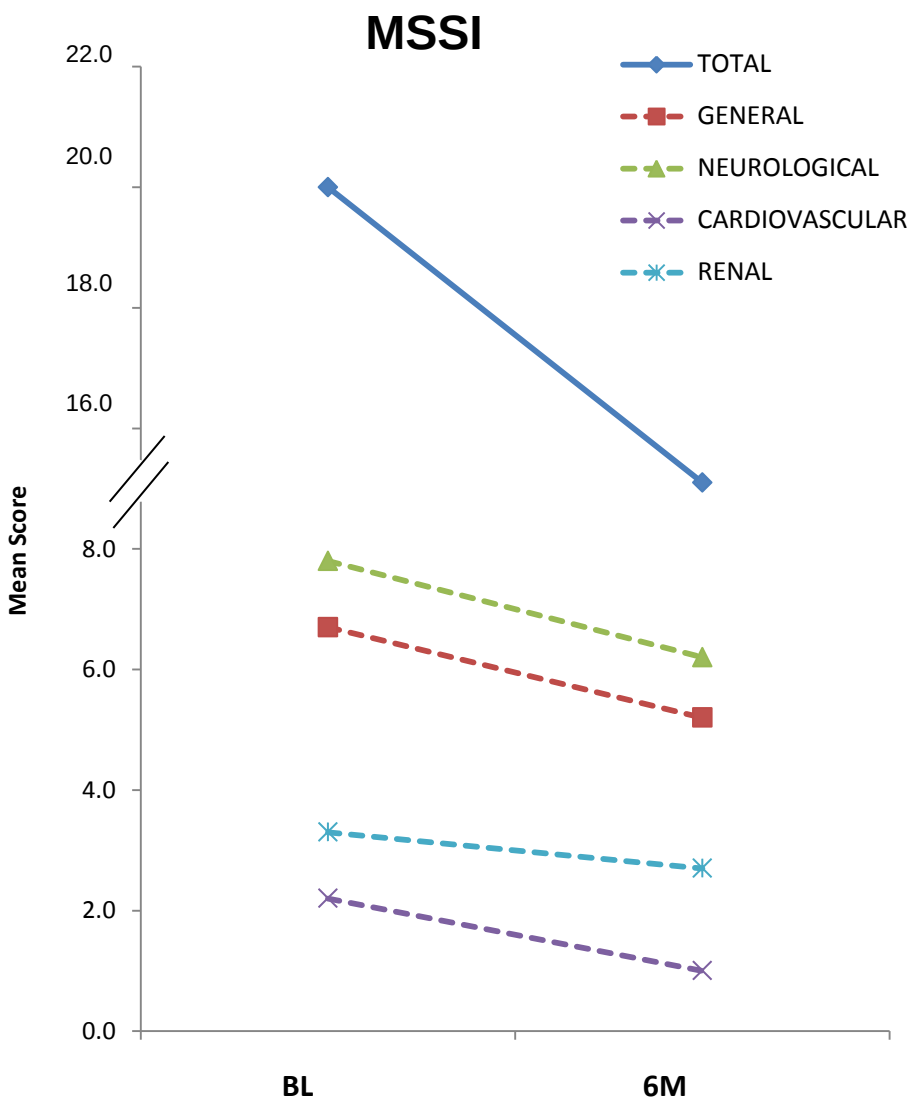


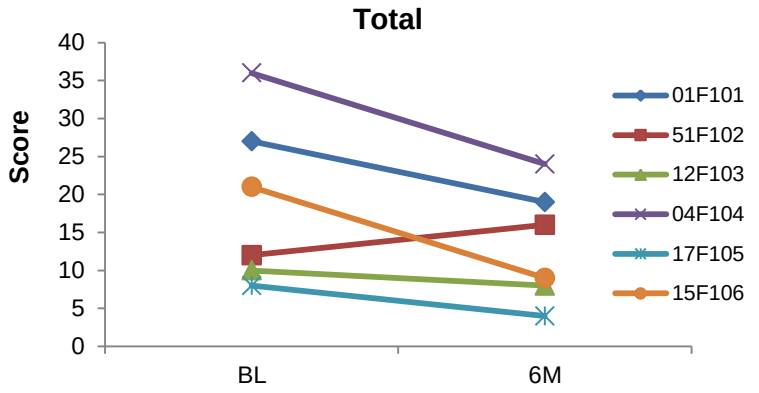


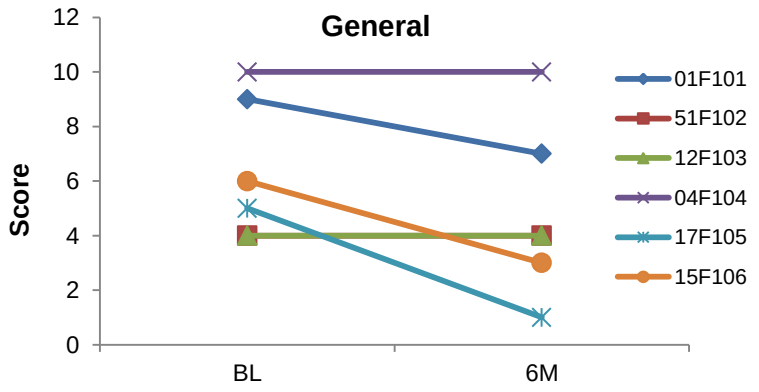


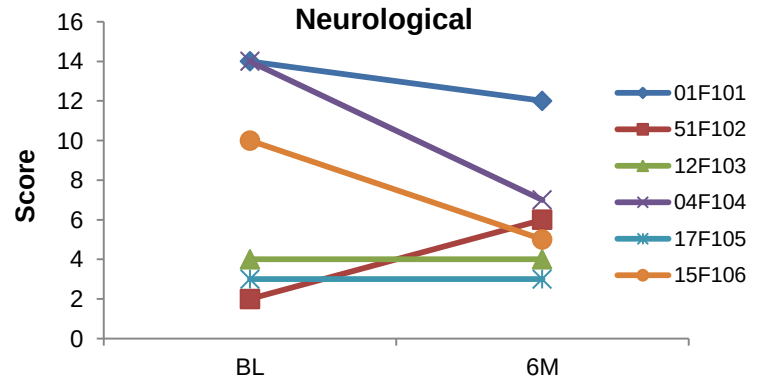


Reduction of Mainz Severity Score Index (MSSI)









Safety

Safety

	0.2 mg/kg N=6 (4M;2F)	1 mg/kg N=6 (5M;1F)	Overall
Adverse events (All causalities)	50	22	72
Mild or moderate	50 (100%) (n=6)	21 (95%) (n=4)	71 (99%) (n=10)
Severe or very severe	0	1[a] (n=1)	1 (n=1)
Serious Adverse Events	0	2[a;b] (n=2)	2

[a] 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.

[b] 28 year old male, pre treatment renal hematoma post kidney biopsy- Not related

Overall, the drug was well tolerated with most AEs being mild and moderate

Safety

	0.2 mg/kg N=6 (4M;2F)	1 mg/kg N=6 (5M;1F)	Overall
Non related events # patients	41 (82%) n=6	8 (36%) n=3	49 (68%) n=9
Related events # patients	9 (18%) n=2	14 (64%) n=4	23 (32%) n=6

Related Adverse Events:

0.2 mg/kg:

Partial right conjunctiva/corneal edema, chest tightening, nausea, subconjuctival hemorrhage, hoarseness of voice, sneezing, loose bowels

1mg/kg:

Rash maculo-papular, lightheadedness, asymptomatic hypotension, pain increased in hands, tightness in feet and lower legs, shaky legs, infusion reaction (vomiting), chest tightness intermittent, shortness of breath, bronchospasm, mild nausea, facial flushing

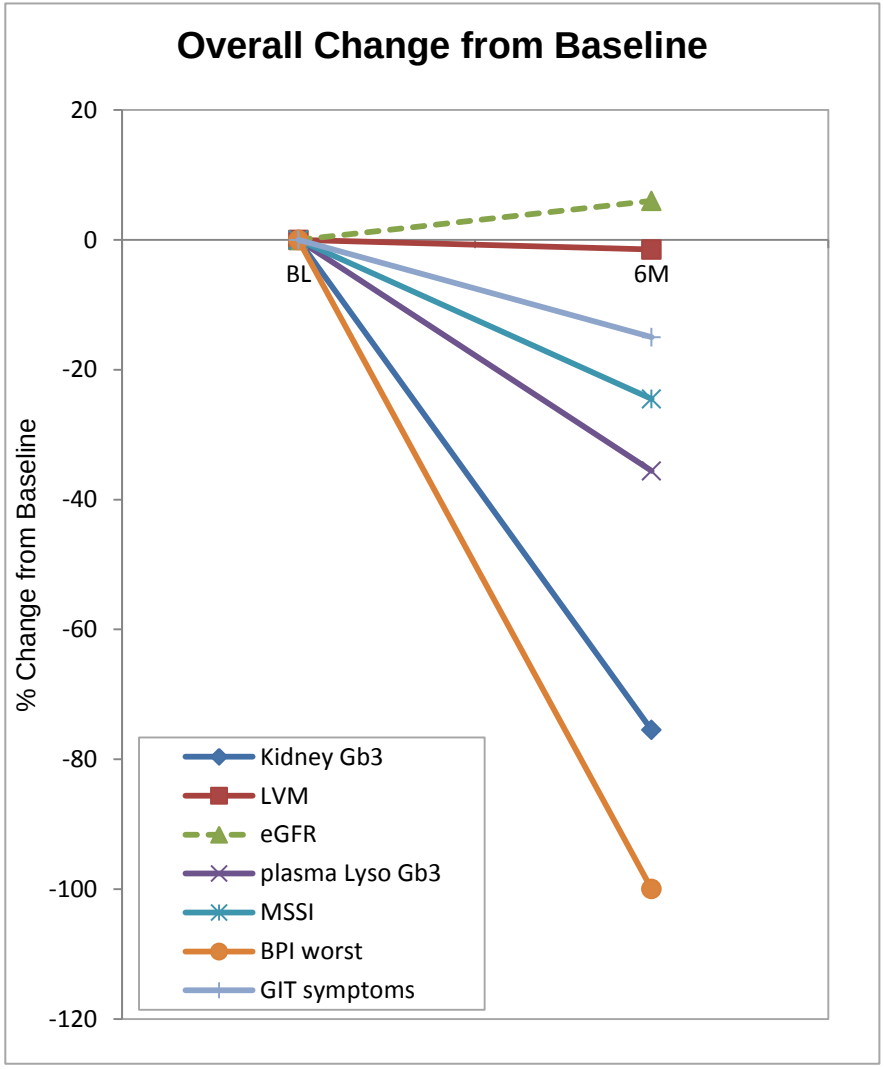
Anti-Drug Antibodies

Dose	ADA positive
0.2mg/kg n=6	2/6
1mg/kg n=2	0/2
All	2/8

- 2 male patients developed ADA within the first 3M of ERT, one of which with inhibitory antibodies; titers < 2000
- All adverse events of these two patients were considered mild and not related by the investigators: (gastroenteritis between infusions, respiratory infections, dry mouth)

Summary

- This interim report shows that PRX-102 is a potential safe and effective therapeutic agent for Fabry disease
- Treatment with 0.2mg/kg for 6M, demonstrated meaningful improvement or stability in main Fabry disease parameters
  - Mean reduction in renal PTC Gb3
  - Improvement in pain parameters
  - Stability of cardiac parameters
  - Stability of renal functions
  - Improvement in disease scoring index (MSSI)
- PRX-102 is well tolerated and most adverse events were mild or moderate in intensity
  - One related SAE (hypersensitivity;1mg/kg)
  - 2 pts developed ADA, one of which with inhibitory antibodies



THANK YOU!