PRX-102 α -Galactosidase-A

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

Derralynn Hughes,

LSDU, Institute of Immunity and Transplantation, Royal Free London NHS Foundation Trust, London, UK,

Disclosure

- Support for research Genzyme Sanofi, Shire
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- Honoraria for speaking Shire, Genzyme, Amicus
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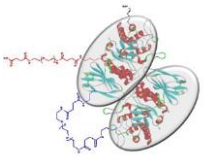
- Investigator for clinical trials and registries
- Shire, Genzyme, Protalix, Biomarin, Actelion, Amicus

PRX-102

Human α-galactosidase-A Enzyme



- Novel ERT intended for treating adult and paediatric patients with confirmed diagnosis of Fabry disease.
- PRX-102 – plant cell expressed recombinant human alpha-GAL-A enzyme, covalently-linked, stable homo-dimer.
- Comprised of two subunits, covalently-linked via a 2 kDa PEG moiety resulting in a stable homo-dimer
  - Anticipated to have longer half-life and higher AUC in plasma and under acidic lysosomal-like conditions
  - Anticipated to have different immunogenicity profile
  - Maintaining enzyme activity post modification
- Intended dosing regimen: 1mg/kg every 2 weeks.
- Translocated to the lysosome of target cells and hydrolyses accumulated Gb3 substrate.

Phase I/II

Interim Clinical Report

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
- Naïve or patients who are off ERT in the last 6 months; negative to 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

Three year study design

PRX-102: Phase I/II Interim Report. ~15 Patient Years.

Cut off Date July 30, 2015

Total number of infusions: 410

	0.2mg/kg (225 infusions)	1mg/kg (129 infusions)	2mg/kg (56 infusions)
Pharmacokinetics	All patients	All patients	All patients
Safety & Immunogenicity up to 24M	All patients	All patients	All patients
Exploratory Efficacy	**12M treatment** of 0.2mg/kg dose cohort (n=6)	**6M treatment** of 1mg/kg dose cohort (n=6)	**3M treatment** of 2mg/kg dose cohort (n=4)

Demographics & Baseline Enzymatic Activity

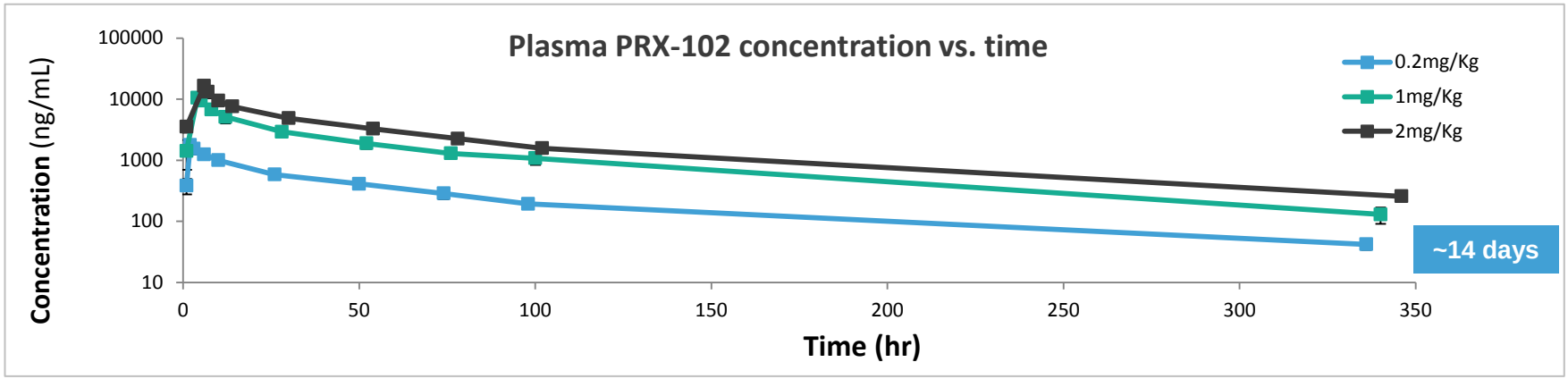
	0.2 mg/kg (n=6)	1 mg/kg (n=8)*	2 mg/kg (n=4)
Mean age (years) ± SD (range)	30.0 ± 10.8 (21-50)	34 ± 9.7 (17.5-52.5)	40.6 ± 9.5 (21-54)
Male : Female	4:2	6:2	1:3
Ethnicity			
Caucasian	4	4	4
African American	1	2	0
Asian	0	0	0
Other	1	0	0

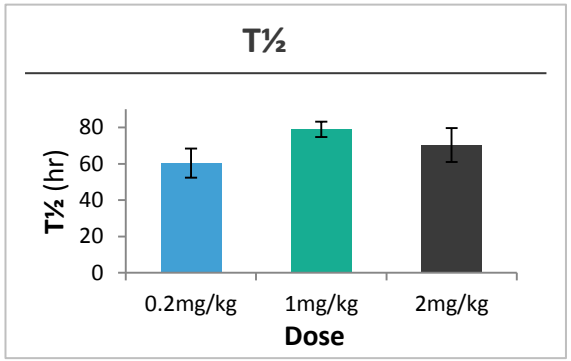
Mean Enzymatic Activity	**0.2 mg/kg (males=4, females=2)**	**1 mg/kg (males*=6, females=2)**	**2 mg/kg (males=1, females=3)**
In leucocytes (range) (normal 33-134 nmol/hr/mg prt.)	Males: 3.15 (1.6-5)	Males: 2.67 (0-7.8)	Male 0.56
	Females: 27.5 (15-40)	Females: 69.5 (67-72)	Females: 42.66 (33-53)
In 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)

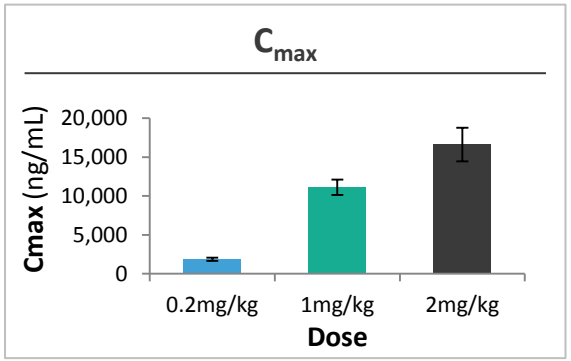
* one subject discontinued due to AE; one subject discontinued due to non compliance

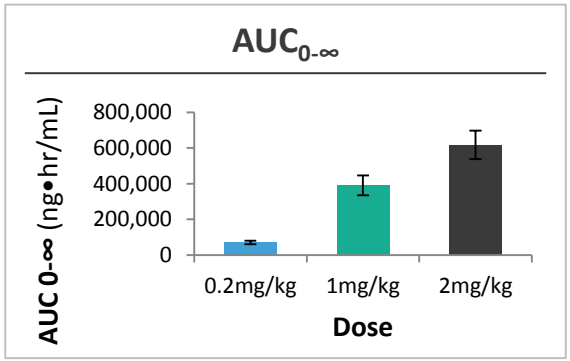
Pharmacokinetics

Available Enzyme Throughout 2-Week Interval





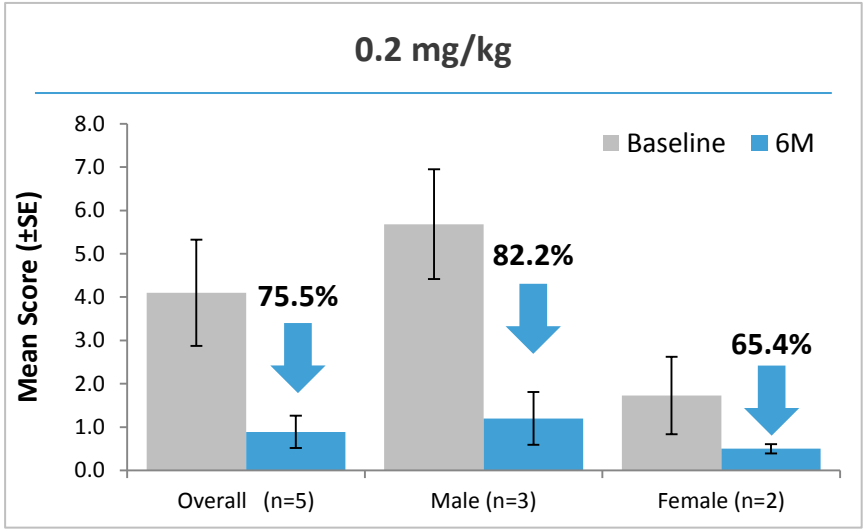


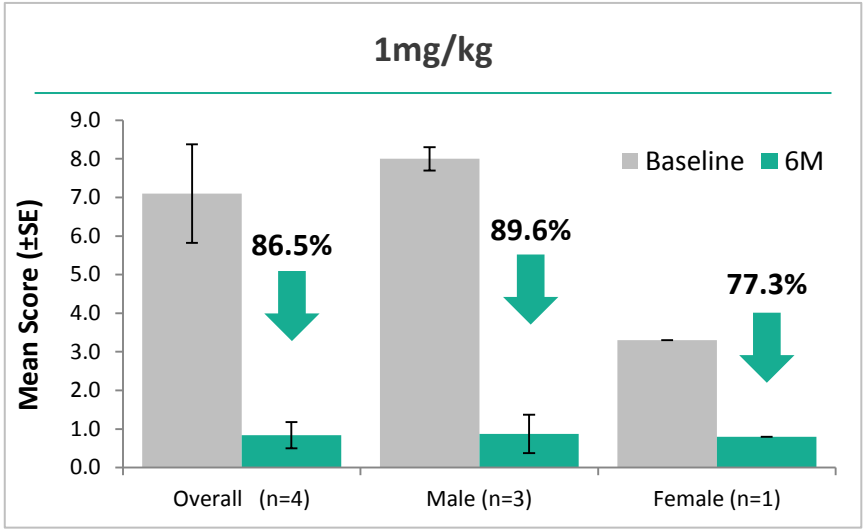


Efficacy

Reduction of Gb3 in Kidney Peritubular Capillaries

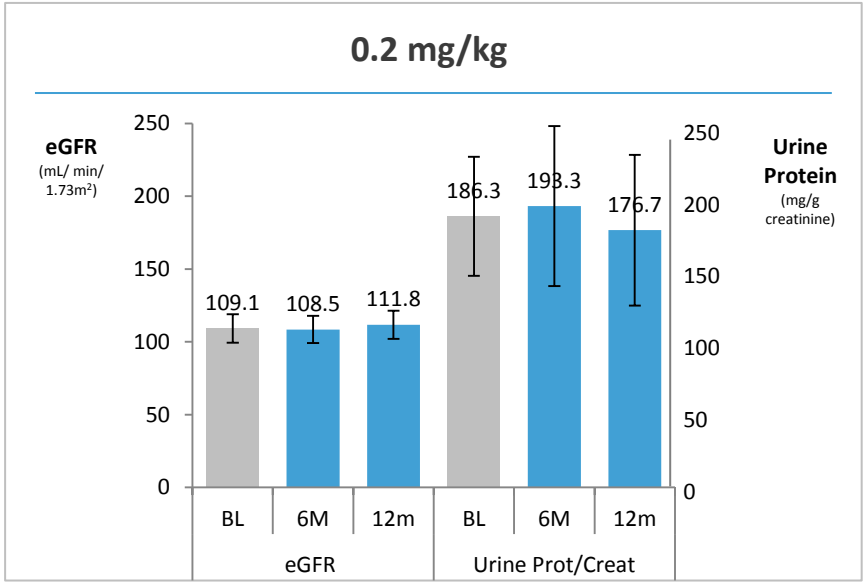
Quantitative BLISS Score

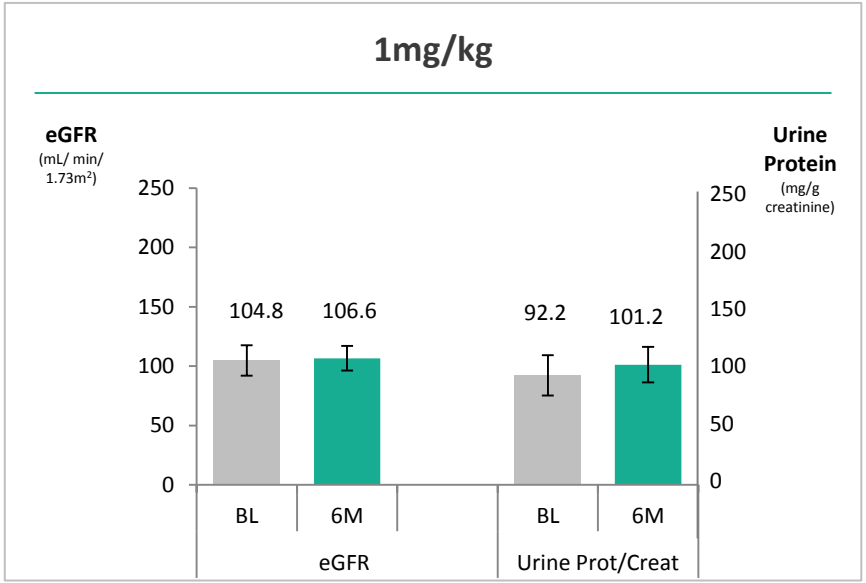




- >300 PTCs were scored for Gb3 inclusions in each biopsy
- Slides underwent digital imaging before scoring
- Images were distributed in a random and blinded manner for annotation by 1 pathologist, and subsequent scoring by 2 other pathologists

Stable/Positive Kidney Functions



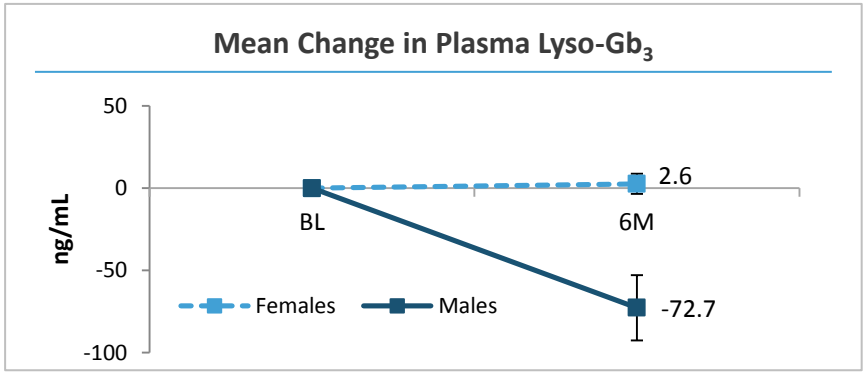


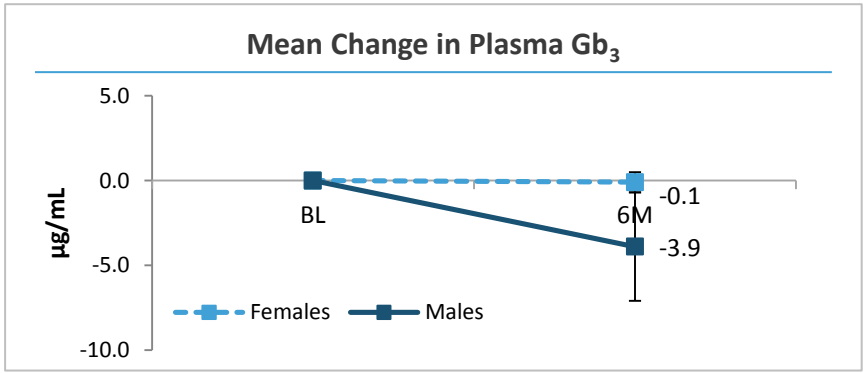
Dose	Gender	Pat ID	Annualized eGFR Slope	AVG eGFR Slope
0.2 mg/kg	M	12-F103	0	0.16
	M	04-F104	0.2	
	M	17-F105	0.6	
	M	15-F106	-0.18	

Dose	Gender	Pat ID	Annualized eGFR Slope	AVG eGFR Slope
1 mg/kg	M	09-F108	0.49	0.72
	M	03-F112	3.08	
	M	07-F113	-0.94	
	M	12-F114	0.24	

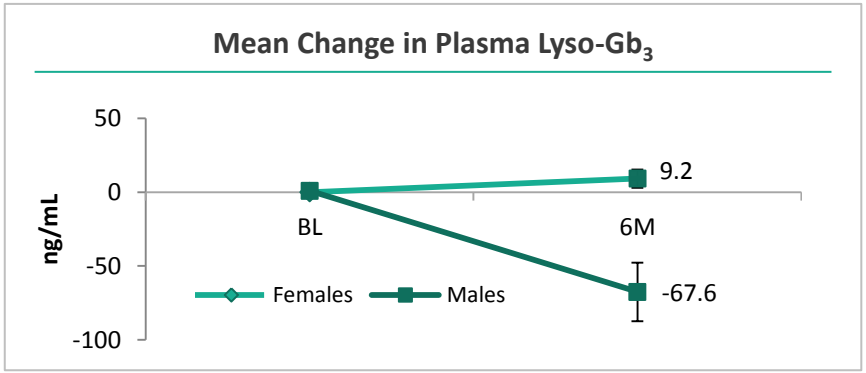
Reduction of Plasma Gb3 and Lyso-Gb3 Concentration

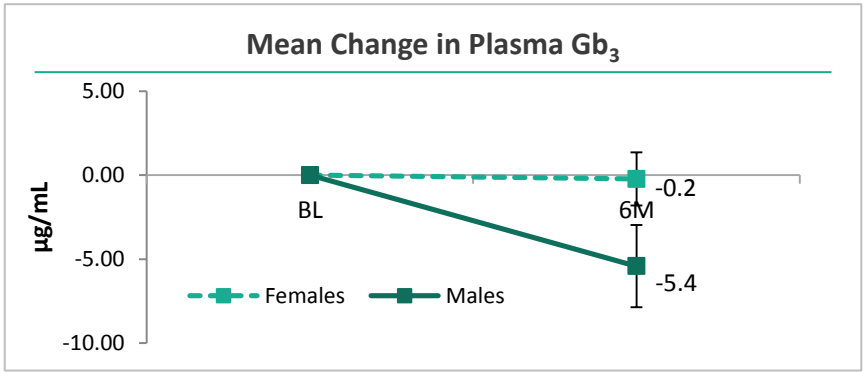
0.2 mg/kg





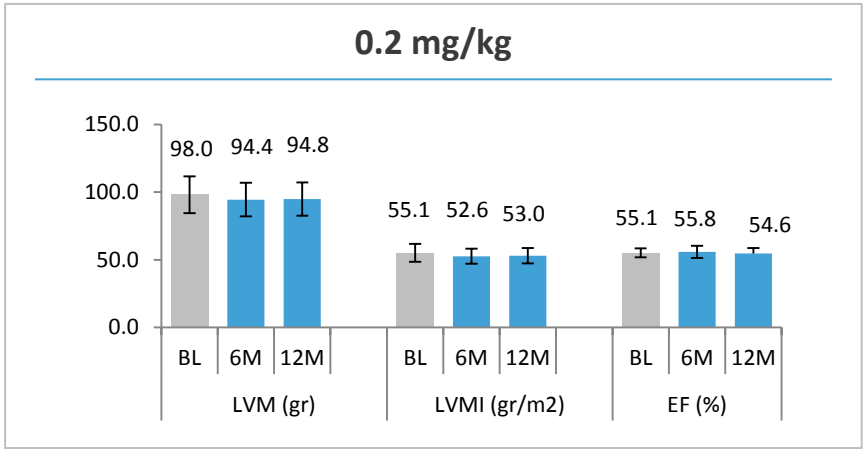
1mg/kg

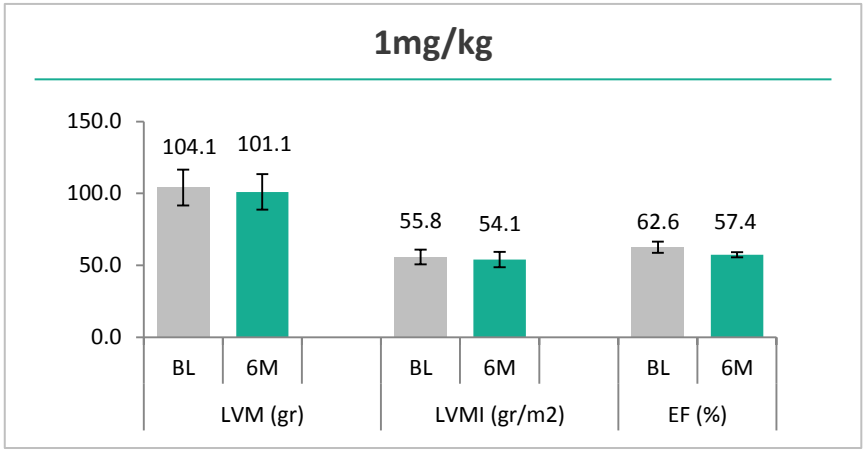


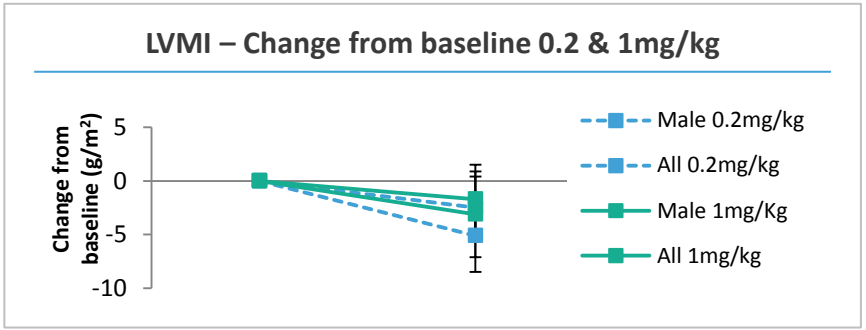


Stable Cardiac Parameters (by MRI)

Mean LVM, LVMI and EF

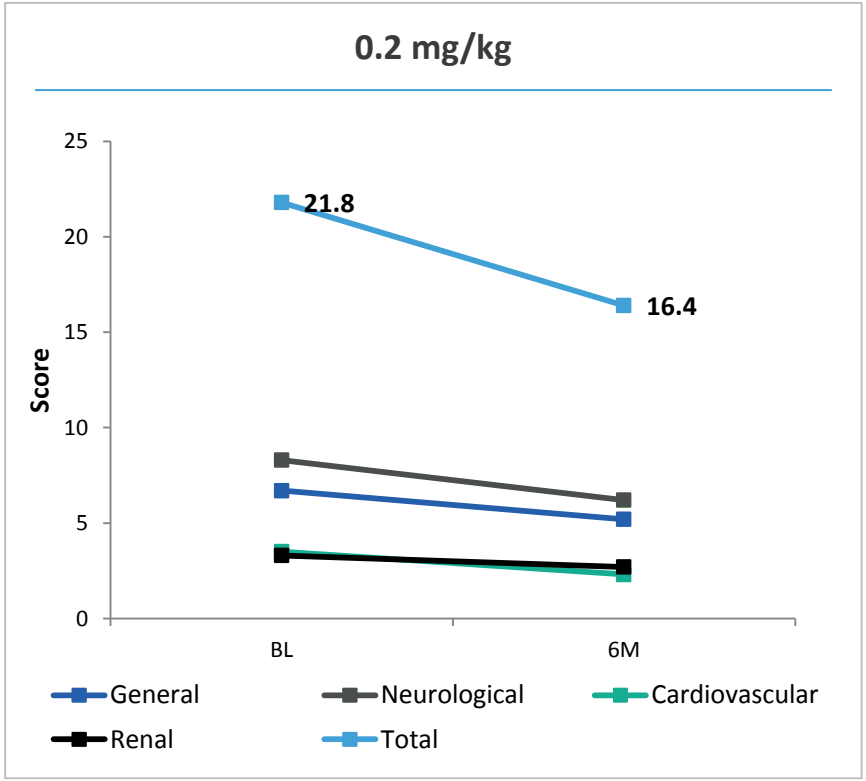


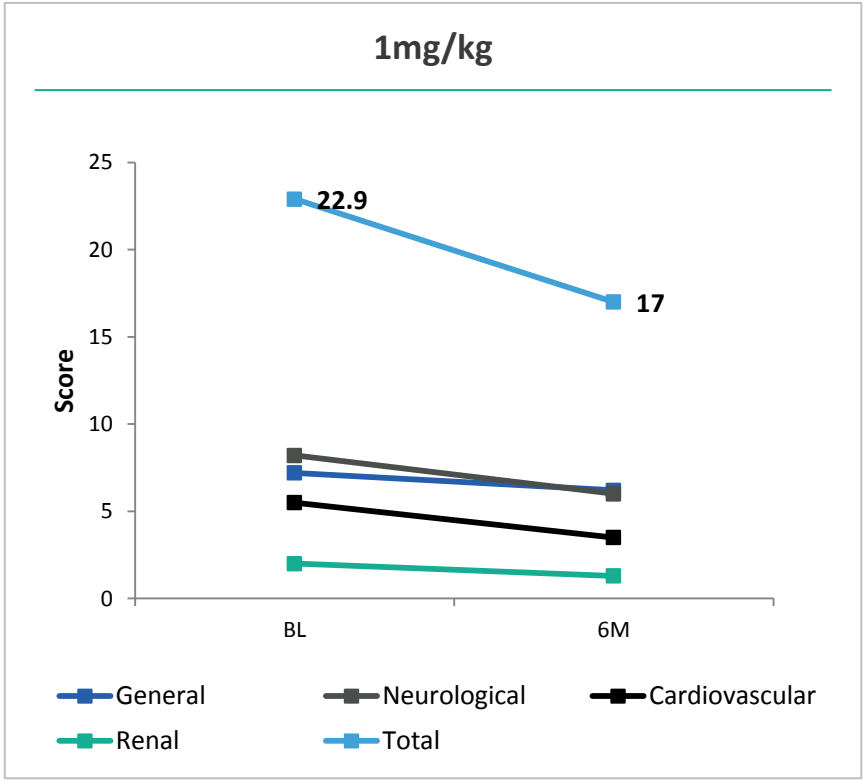




Normal ranges:
LVM(g): 85-181(M); 66-115(F)
LVMI(g/m2): 46-84(M); 37-67(F)
EF(%): 55-74(M); 54-74(F)

Reduction of Mainz Severity Score Index (MSSI)





Safety

Safety in 410 infusions, ~15 patient years

192 (100%)

Total AEs in 17/18 subjects

188 (97.9%)
AEs mild and moderate

4 (2.1%)
Severe

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

2 (1%)
Serious AEs

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

51 (26.6%)
Related, possibly related

141 (73.4%)
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.

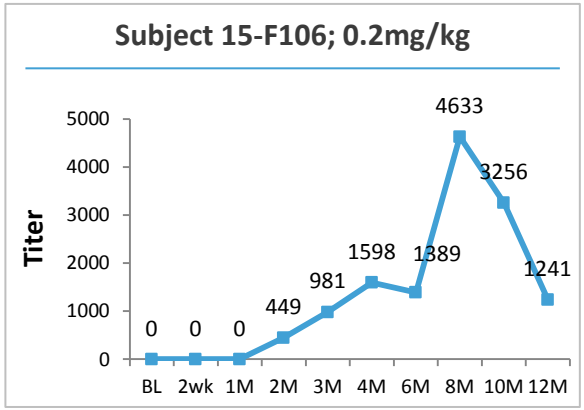
8 Patients Experienced 30 AEs*

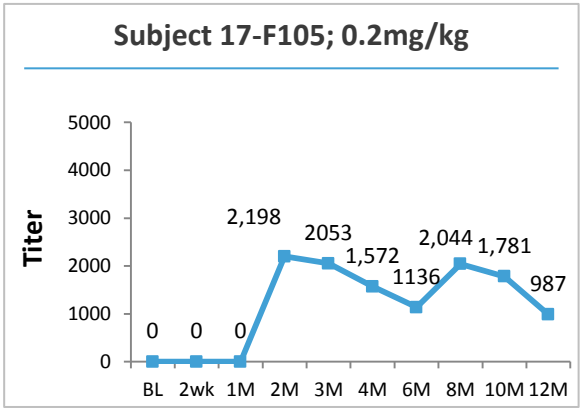
ID	Visit	Adverse Events (CRF term / MedDRA Preferred term)	Treatment Relationship
		0.2 mg/kg	
01-F101	1	Headaches / Headache	**Unrelated**
12-F103	3	Generalized itching / Pruritus generalized	**Unlikely**
51-F102	1, 3	Chest tightening / Chest discomfort	**Possibly**
	1	Sneezing / Sneezing	**Possibly**
	3	Nausea / Nausea	**Possibly**
	6	Sweating / Hyperhidrosis	**Unlikely**
	27	Sneezing and sinus drainage / Paranasal sinus hypersecretion	**Possibly**
		1.0 mg/kg	
04-F107	2, 15	Hypotension / Hypotension	**Probably**
	3	Lightheadedness / Dizziness	**Possibly**
	9	Short of breath / Dyspnea	**Possibly**
	13	Maculo-papular erythematous / Rash maculo-papular	**Probably**
09-F108	6, 8	Infusion reaction / Infusion related reaction	**Possibly**
	15	Pain at left chest / Chest pain	**Possibly**
	17	Itching / Pruritus	**Possibly**
	17	Rash /Rash	**Unlikely**
	18	Rash at tape site / Dermatitis contact	**Unrelated**
	20	Nausea / Nausea	**Possibly**
	20	Dizziness / Dizziness	**Possibly**
10-F111	1	Bronchospasm / Bronchospasm	**Definitely**
		2.0 mg/kg	
15-F117	1-7	Abdominal cramping / Abdominal pain	**Possibly**
17-F118	3	Epigastric pain / Abdominal pain upper	**Unrelated**

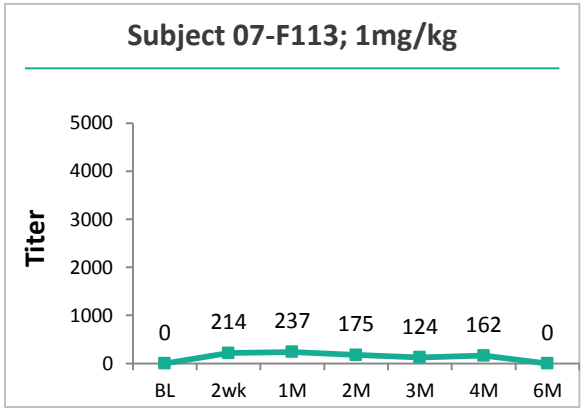
*During or within 2 hours of PRX-102 Infusion

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

- Low incidence of antibody formation with low titers which are reduced by 1 year of treatment
  - Three (3) patients had treatment induced ADA in at least one visit (19%).
  - Two (2) of these 3 patients had neutralizing antibodies (nAb), one of which was nAb positive only in 2/8 samples
  - At the time of the report, no patient in the 2.0 mg/kg cohort developed treatment induced antibodies
- 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)



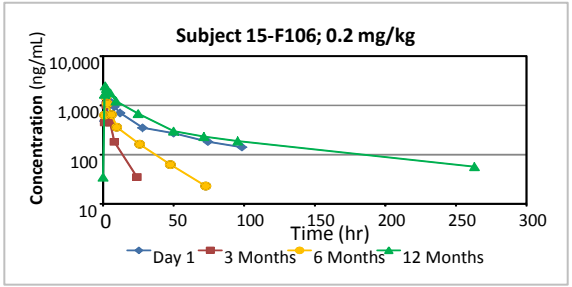


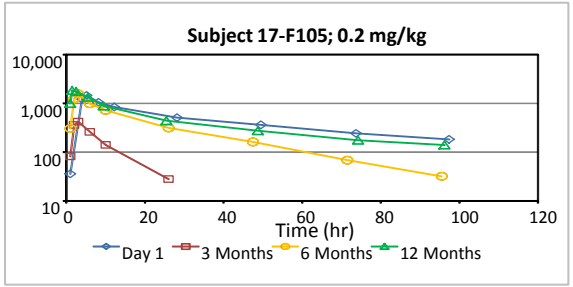


Reversible & Transient Effect on PK in ADA Positive Patients

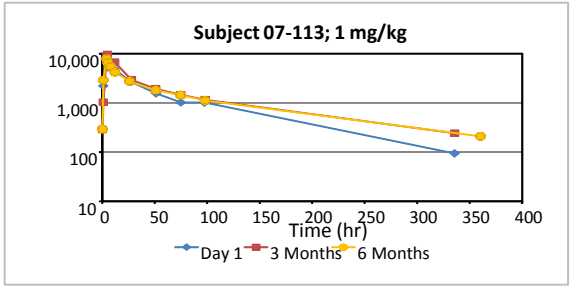
PK of ADA positive patients

0.2mg/kg ➔Transient impact of ADA on PK



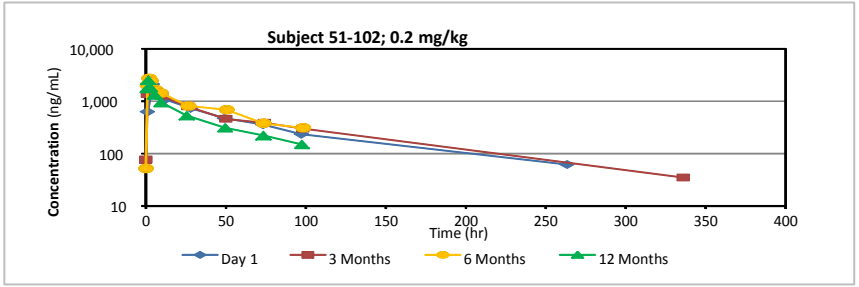


1mg/kg ➔No impact of ADA on PK

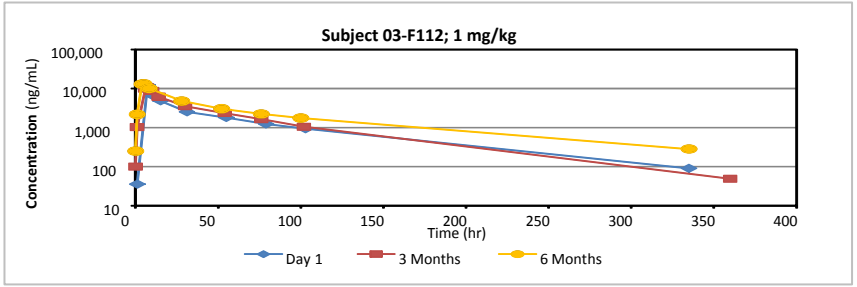


Example of PK of ADA negative patients

0.2 mg/kg



1 mg/kg



Overall Conclusions

PK:

PRX-102 has a longer half-life and a substantially higher AUC [1]

- PRX-102 has unique PK properties
- Available enzyme throughout 2-week infusion intervals offers optimal opportunity for attenuating disease progression

Safety:

PRX-102 is well tolerated

- The majority of adverse events are mild and moderate in severity
- Limited formation of antibodies - Only 19% treatment induced antibody formation – Indication for immune tolerance observed in long-term data

Efficacy:

Demonstrate effectiveness, in various disease endpoints including:

- Non deterioration in kidney function
- Reduction of Gb3 inclusions in kidney peritubular capillaries
- Reduction of plasma Gb3 and Lyso-Gb3
- Stable cardiac function
- Reduction in MSSI score

[1.] Eng et al Am.J.Hu.Genetics 2001; Schiffmann et al PNAS 2000

Acknowledgements

- Simeon Boyd[2], Pilar Giraldo[3], Derlis Gonzales[4], Myrl Holida[5], Ozlem Goker- Alpan[6], Gustavo Maegawa[7] Mohamed Atta[8], Kathy Nicholls[9], Raphael Schiffmann[10], Ahmad Tuffaha[11], Jeannie Visootsak[12] , Laura Barisoni[13], Robert Colvin[14], J.Charles Jannette[15] Sari Alon[16], Jenny Krupko[16], Mali Szlaifer[16], Einat Brill-Almon[16], Raul Chertkoff[16]

- [2]Department of Pediatrics, Section of Genetics, MIND Institute, UC Davis Medical Center, Sacramento, USA, [3] Hospital de Dia Quiron, Zaragoza, Spain, [4]Instituto Privado De Hematologia Investigacion Clinica, Asunción, Paraguay, [5]University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA, [6]O&O Alpan LLC, Fairfax, Virginia, USA, [7]Mckusick Nathans Institute of genetic Medicine, Department of pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [8]Department of Medicine, division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA [9]Nephrology Department, the Royal Melbourne Hospital, Melbourne, Australia, [10]Baylor Institute of Metabolic Diseases, Baylor University Medical Center, Dallas, Texas, USA, [11]Kansas University Medical Center, Kansas City, Kansas, USA, [12]Emory Genetics, Emory University Hospital, Atlanta, Georgia, USA, [13]University of Miami, Department of Pathology, Miami Florida, USA, [14]Massachusetts General Hospital ,Harvard Medical School, Department of Pathology Boston, Massachusetts, USA, [15]University of North Carolina, Department of Pathology, Chapel Hill, North Carolina, USA, [16]Protalix Biotherapeutics

Thank You