pegunigalsidase alfa α-Galactosidase-A

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

Derralynn Hughes

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

Disclosure Information

WORLD*Symposium*™ 2017

Derralynn Hughes

- Consultant for: Shire, Genzyme, Amicus, Actelion, Biomarin, Protalix
- Research support from: Genzyme Sanofi, Shire
- Honoraria for speaking: Shire, Genzyme, Amicus
- Investigator for clinical trials and registries: Shire, Genzyme, Protalix, Biomarin, Actelion, Amicus

I will discuss the use of pegunigalsidase alfa in my presentation

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 *pegunigalsidase alfa* 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

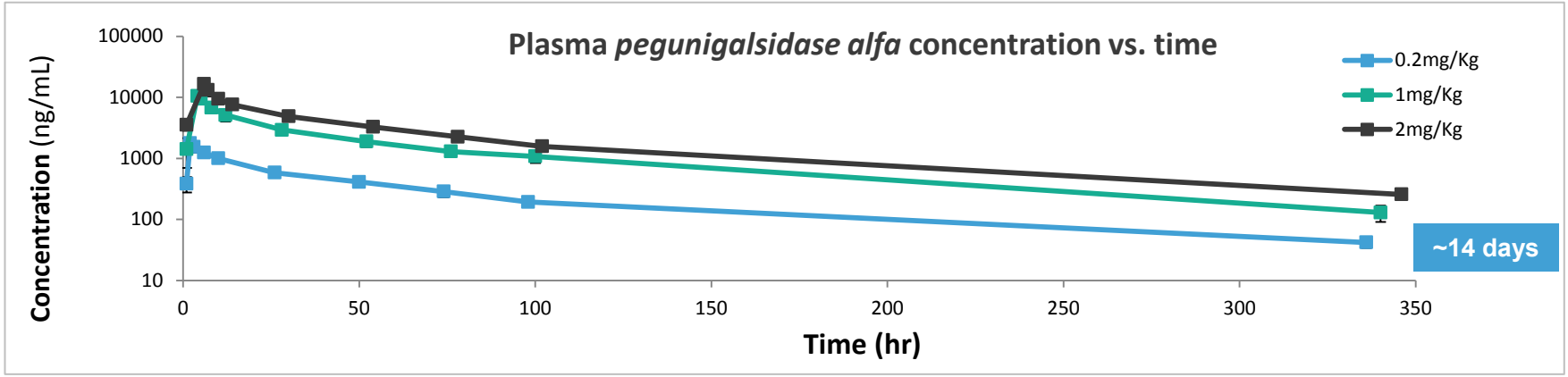
	0.2 mg/kg (n=6)	1 mg/kg (n=8)*	2 mg/kg (n=4)
Mean age (years) ± SD (range)	30.0 ± 10.8 (21-50)	34 ± 9.7 (17.5-52.5)	40.6 ± 9.5 (21-54)
Male : Female	4:2	6:2	1:3
Ethnicity			
Caucasian	4	4	4
African American	1	2	0
Asian	0	0	0
Other	1	0	0

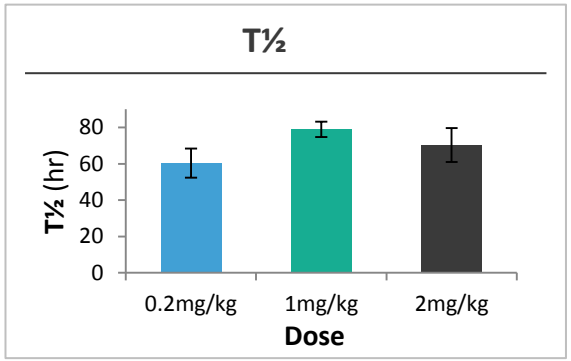
Mean Enzymatic Activity	**0.2 mg/kg (males=4, females=2)**	**1 mg/kg (males*=6, females=2)**	**2 mg/kg (males=1, females=3)**
In leucocytes (range) (normal 33-134 nmol/hr/mg prt.)	Males: 3.15 (1.6-5) Females: 27.5 (15-40)	Males: 2.67 (0-7.8) Females: 69.5 (67-72)	Male 0.56 Females: 42.66 (33-53)
In plasma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

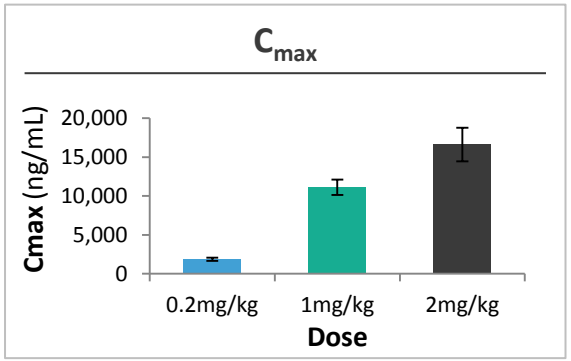
* one subject discontinued due to AE; one subject discontinued due to non compliance

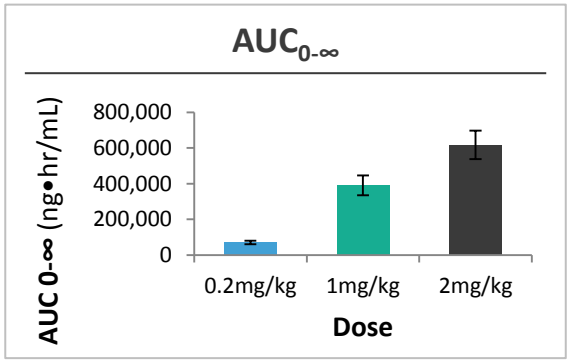
Pharmacokinetics

Available Enzyme Throughout 2-Week Interval









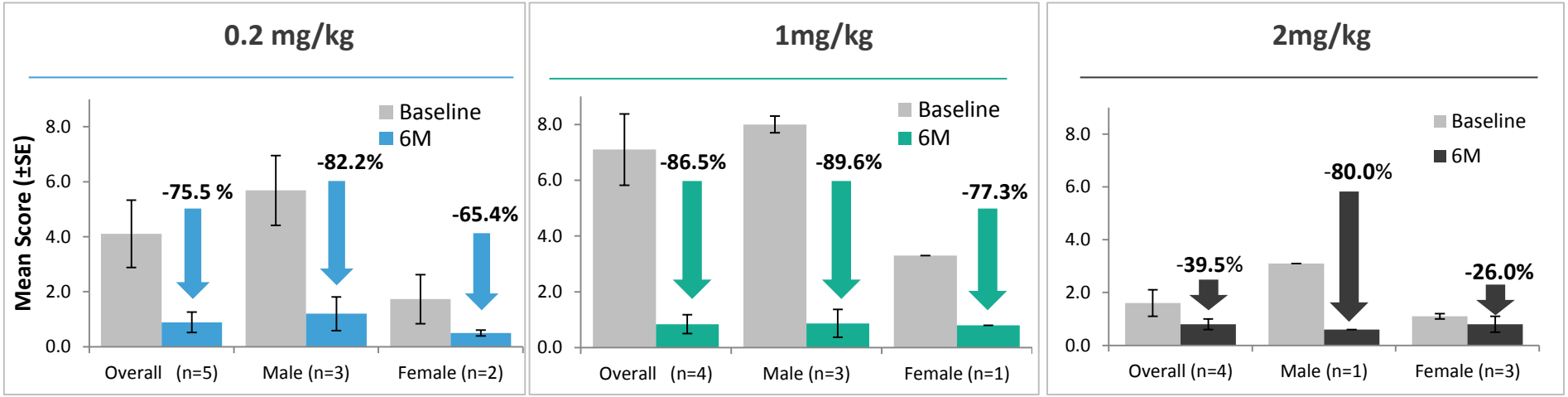
Efficacy

Efficacy analysis presented for:

- All patients (n=16)
- Classic Fabry Disease (FD) patients (n=10 ; 9M:1F)
  - Symptomatic adult FD patients
  - Plasma and/or leucocyte alpha galactosidase activity less than 30% mean normal levels
  - And one or more of the described characteristic features of FD:
    - Characteristic Facies
    - Neuropathic pain
    - Cornea verticillata
    - Clustered angiokeratoma
    - Diaphoresis
    - Abdominal pain
    - Diarrhea/constipation

Reduction of Gb3 in Kidney Peritubular Capillaries

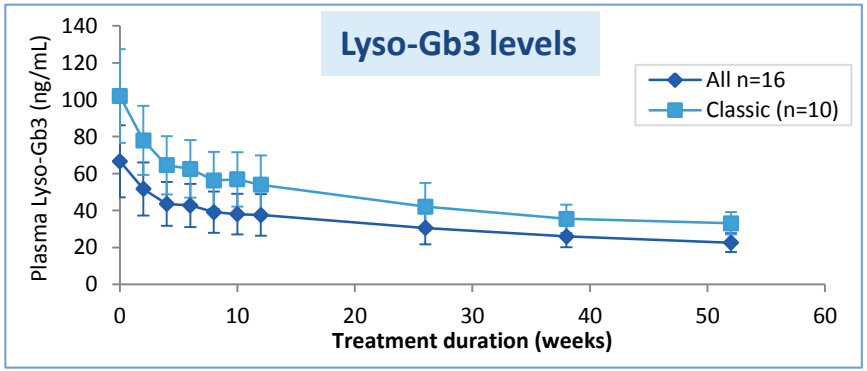
Quantitative BLISS Score

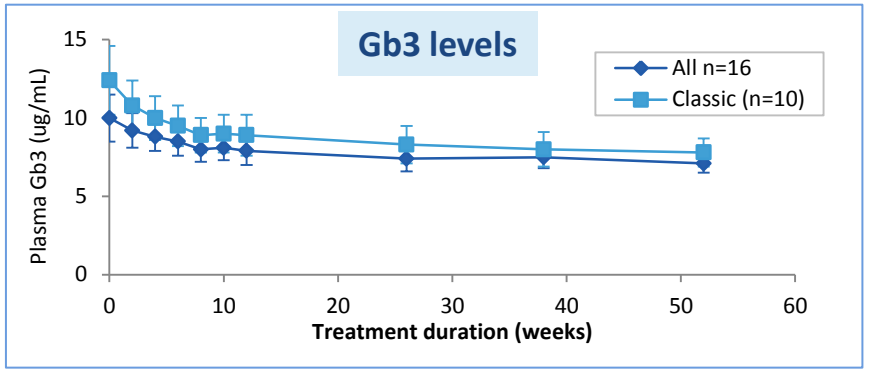


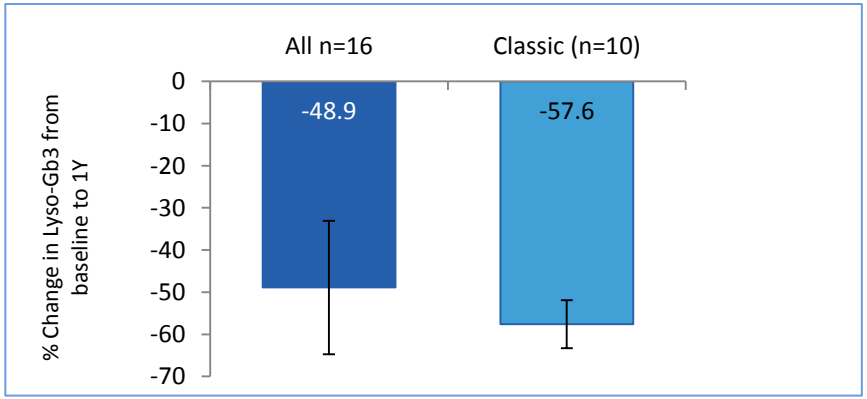
	% change ±SE
All Patients (n=13)	**-67.8±8.9**
Classic Patients (n=8)	**-84.1±3.3**

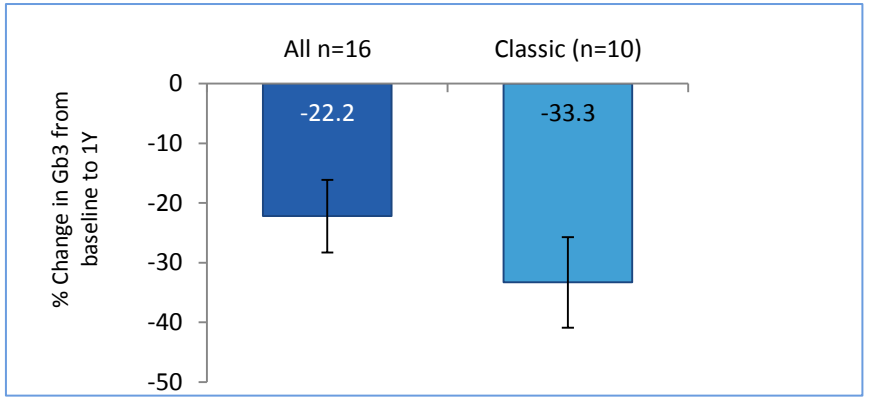
- >300 PTCs were scored for Gb3 inclusions in each biopsy
- Slides underwent digital imaging before scoring
- Images were distributed in a random and blinded manner for annotation by 1 pathologist, and subsequent scoring by 2 other pathologists

Biomarkers -Plasma Gb3/Lyso-Gb3



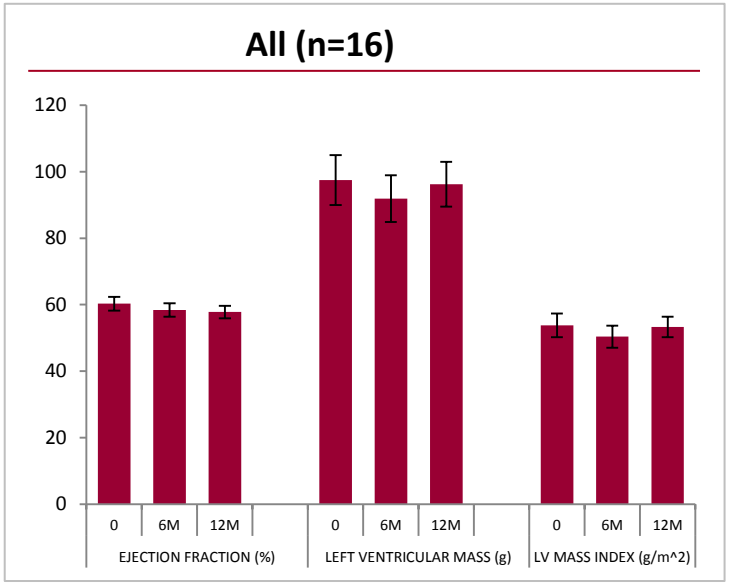


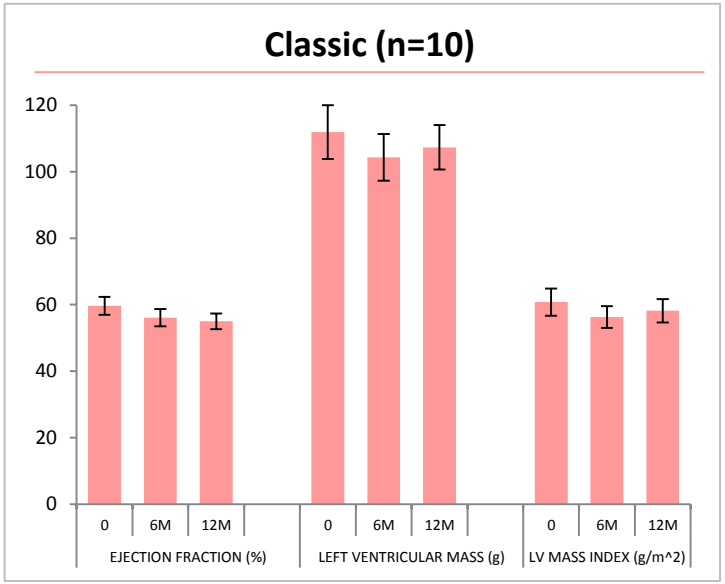




Stable Cardiac Parameters (by MRI)

Mean LVM, LVMI and EF

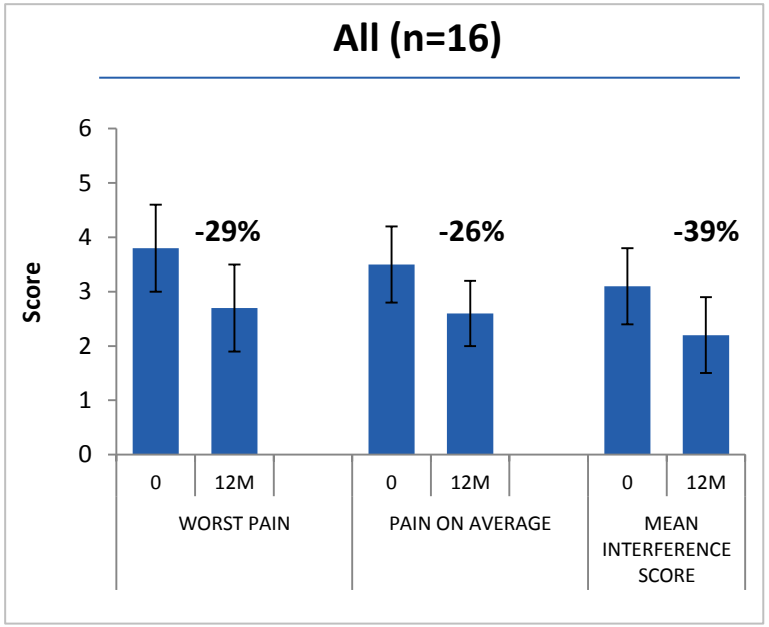


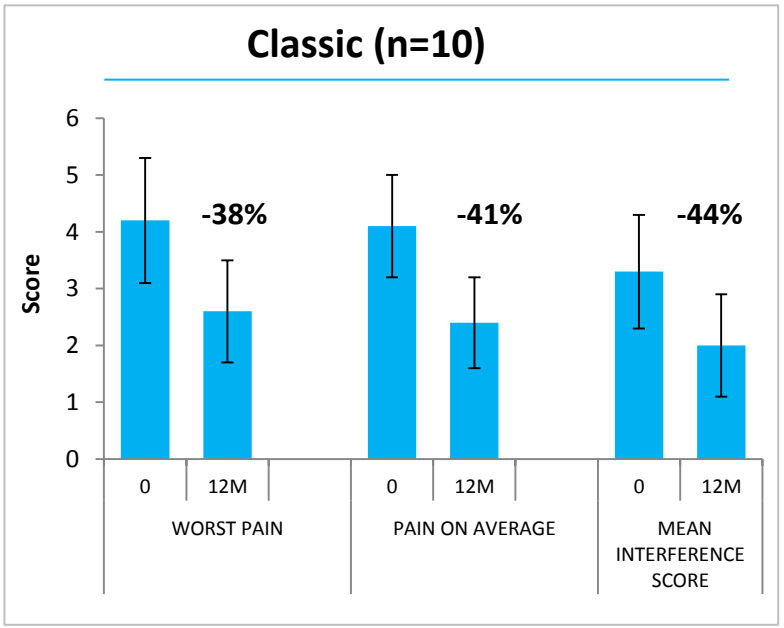


- No cardiac fibrosis observed throughout the year of treatment

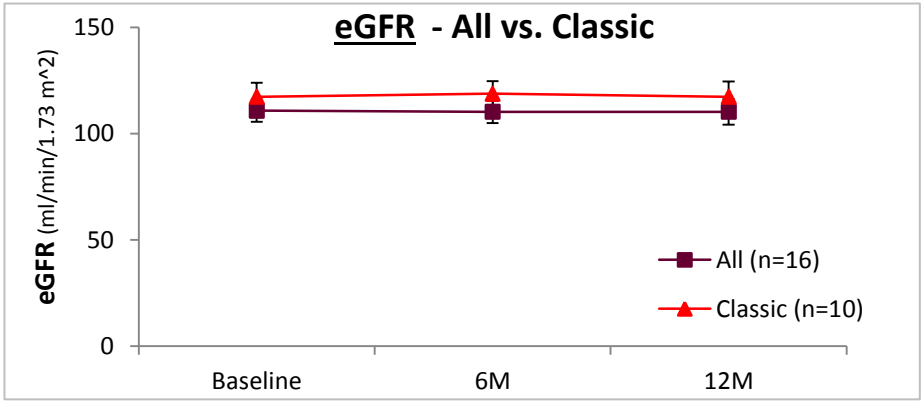
Normal Ranges (MRI)	Male	Female
LVM(g)	85-181	66-115
LVMI (g/m^2)	46-84	37-67
EF (%)	55-74	54-74

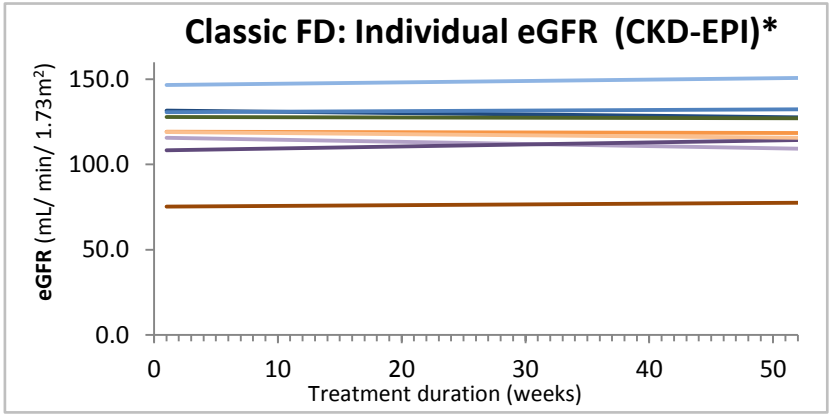
Brief Pain Inventory (BPI)

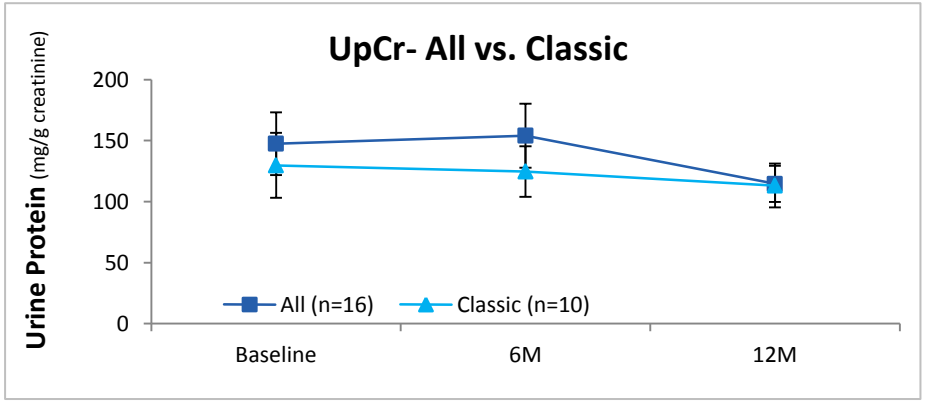




Stable Kidney Functions







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

Safety

Safety in 416 Infusions

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 pegunigalsidase alfa IgG was negative and anti pegunigalsidase alfa IgE was positive at baseline. **28 year old male, pre treatment renal hematoma post kidney biopsy- Not related.

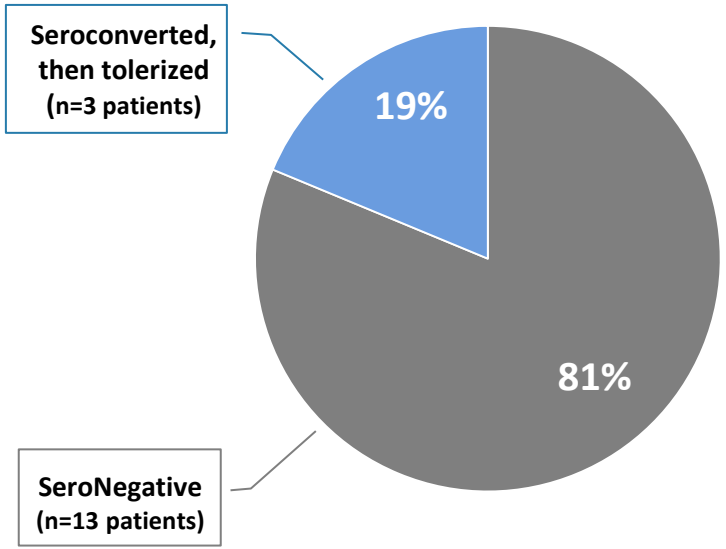
8 Patients Experienced 30 AEs*

ID	IR AEs	Description (MeDRA Preferred Term)	Treatment-induced ADA
0.2 mg/kg			
01-F101	(+)	Headache	(-)
51-F102	(+)	Chest discomfort, Sneezing, Nausea, Hyperhidrosis	(-)
12-F103	(+)	Pruritus generalized	(-)
26-F104	(-)		(-)
17-F105	(-)		(+)
15-F106	(-)		(+)
1.0 mg/kg			
04-F107	(+)	Hypotension, Dizziness, Dyspnea, Rash maculo-papular	(-)
09-F108	(+)	Infusion related reaction, Chest pain, Pruritus, Rash, Dermatitis contact, Nausea, Dizziness	(-)
10-F111	(+)	Bronchospasm	(-)
03-F112	(-)		(-)
07-F113	(-)		(+)
12-F114	(-)		(-)
12-F115	(-)		(-)
2.0 mg/kg			
15-F116	(-)		(-)
15-F117	(+)	Abdominal pain	(-)
17-F118	(+)	Abdominal pain upper	(-)
09-F119	(-)		(-)

*During or within 2 hours of pegunigalsidase alfa Infusion

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

Incidence of Treatment Induced ADA



123/144 samples (16 patients) tested negative for ADA*

Low incidence of ADA with low titers -
3/16 patients→19%

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

Reversible and transient effect on PK

* According to the regulatory guidelines, using sensitive and validated methods

Overall Conclusions

pegunigalsidase alfa **–**
PEGylated covalently-linked recombinant alpha-GAL-A enzyme, stable homodimer, produced in plant cells

PK:
pegunigalsidase alfa **has a longer half-life and a substantially higher AUC**

- Available enzyme throughout 2-week infusion intervals

Safety:
pegunigalsidase alfa **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
- Improvement in pain parameters

Following FDA and EMA discussions Phase 3 Program initiated

Next Phase 3 studies

Balance Study

- 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
- Classic FD patients
- 2 years treatment duration
- Extension study will be offered to patients at the end of the study

Bridge Study

- An open label switch over study
- 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

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[2]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 , Iowa City, Iowa, USA, [6]O&O Alpan LLC, Fairfax, Virginia, USA, [7]University of Florida, Gainesville, Florida, USA, [8]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [9]The Royal Melbourne Hospital, Melbourne, Australia, [10]Baylor University Medical Center, Dallas, Texas, USA, [11]Kansas University Medical Center, Kansas City, Kansas, USA, [12]University of Miami, Miami Florida, USA, [13]Massachusetts General Hospital ,Harvard Medical School, Boston, Massachusetts, USA, [14]University of North Carolina, Chapel Hill, North Carolina, USA, [15]Protalix Biotherapeutics, Carmiel, Israel

Thank You