Pegunigalsidase alfa, a Novel PEGylated ERT for Fabry Disease – Two Years Safety and Efficacy Follow Up

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ABSTRACT

The current report is a two years follow-up of 11 Fabry Disease (FD) patients treated with pegunigalsidase alfa as part of Phase I/II sequential clinical studies (NCT01678898 (3 months) and its extensions NCT01769001 (12 months) and NCT01981720 (up to 60 months)). These studies evaluate the safety, pharmacokinetics and efficacy parameters of naïve symptomatic male and female FD patients (>18 y.o.) treated with pegunigalsidase alfa administered intravenously (IV) every other week.

Fabry Disease is an X-linked disorder caused by the loss of function of the lysosomal enzyme α-Galactosidase-A. Pegunigalsidase alfa, is a novel, PEGylated, crosslinked α-galactosidase A enzyme, which has a more stable homo-dimeric structure and enhanced pharmacokinetic properties including prolonged half-life of approximately 80 hours, and a substantially higher AUC result compared with the other commercial enzyme replacement therapies.

Results: Pegunigalsidase alfa was well tolerated by all patients treated. Efficacy evaluation following two years of treatment with pegunigalsidase alfa showed continuous stabilization in cardiac and renal parameters. Furthermore, continuous improvement in the disease symptoms as shown by gastrointestinal (GI) questioner, MSSI (Mainz Severity Score Index) and biomarkers **was also demonstrated**.

Conclusions and looking forward: These observations of either stability or improvement in disease parameters are consistent with the one year treatment results previously reported. This pegunigalsidase alfa study (NCT01981720), is ongoing and planned to continue for a total of up to 60 months treatment duration.

Additionally, three phase III switchover studies, including a study with an alternative dose and regimen, are currently ongoing to further evaluate the safety and efficacy of pegunigalsidase alfa.

STUDY 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

	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 Enzyme Activity: • 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

Safety Results

Eleven (11) pegunigalsidase alfa treated patients experienced a total of 295 AEs during 2 years of treatment (a total of 906 infusions). All AEs were mild or moderate in intensity except for 4 severe AEs (i.e. pain in extremity, renal hematoma, migraine and headache). Two of these, migraine and headache were considered by the investigator to be possibly and definitely related to treatment. One SAE was reported - renal hematoma. Nine(9) of the 11 treated patients experienced 70 adverse events during or within 2 hours of the infusion; 22/70 (31.4%) were considered by the investigator to be probably, possibly or definitely related to treatment (abdominal pain, nausea, chest discomfort, infusion related reaction, chest pain, diarrhea, edema, dizziness, nervousness, paranasal sinus hypersecretion, sneezing and pruritus) all recovered without sequelae

Safety in 906 Infusions (=34.8 patient years)
100% (295 AEs)

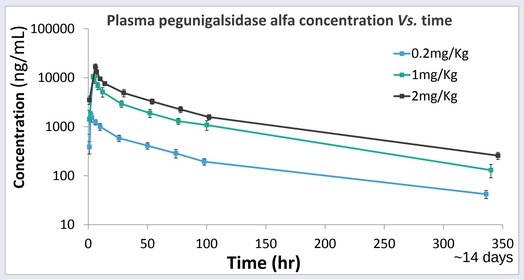
Total AEs in 11 patients completing 2 years of treatment

- **98.6% (291)** AEs mild and moderate
- **1.4% (4)** Severe
  - 2 Severe treatment related, 1 pt.. (Migraine, Headache)
  - 2 Severe not treatment related in 2 other pts. (Renal Hematoma, Pain in Extremity)
- **0.3% (1)** Serious AEs
  - Kidney hemorrhage post biopsy, not treatment related*
- **14.6% (43)** Related, possibly related 6 patients
- **85.4% (252)** Not related, unlikely related 11 patients

*28 year old male, pre treatment renal hematoma post kidney biopsy- Not related.

PHARMACOKINETICS & IMMUNOGENICITY RESULTS

Pharmacokinetics

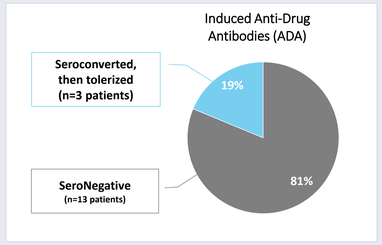


Dose	T1/2 (hr)	Cmax (ng/mL)	$AUC_{0-\infty}$ (ng•hr/mL)
0.2	**60.3** ± 19.6	**1,858** ± 531	**70,070** ± 26,044
1	**78.9** ± 10.3	**11,123** ± 2,409	**390,896** ± 136,476
2	**70.7** ± 18.0	**16,625** ± 4,299	**619,393** ± 158,562

PK Summary:

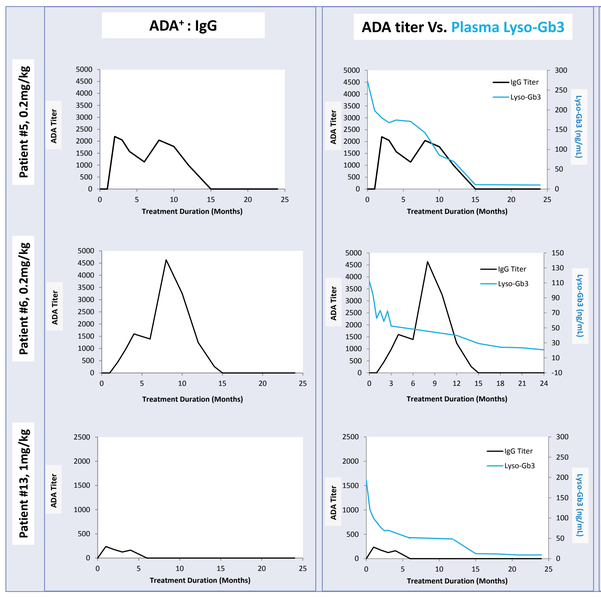
- Pegunigalsidase alfa PK parameters and profile indicate dose dependency
- Available Enzyme Throughout 2-Week Interval

Immunogenicity



Summary of Immunogenicity observations:

- **Low incidence** (19%) **of ADA with low titers** (Max titer 4633)
- **Neutralizing Antibodies:** 2/3 ADA positive patients had neutralizing activity in some samples
- **Immune Tolerization:** All 3 ADA positive patients turned to be negative for ADA after 12M of treatment



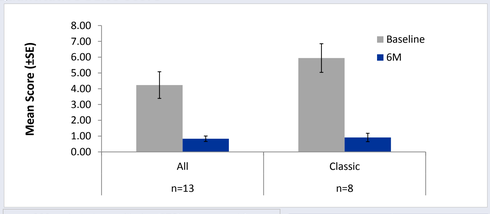
Presence of anti-drug antibodies had a transient and reversible effect on PK and no effect on the continuous reduction of plasma biomarkers (PD):

The impact of ADA presence on PD and PK is shown for each of the 3 ADA positive patients.
As shown, ADA did not interfere with the continues reduction of Fabry disease biomarkers, presented by plasma Lyso-Gb3.
Yet, the presence of ADA in 2 of the 3 ADA positive patients had a transient and reversible effect on the plasma PK characteristics. The impact on PK is presented as the change (increase) in drug clearance rate. Clearance rate was reduced and reverted back to the initial level following 12M of peguniogalsidase alfa treatment (in the patient with low ADA titer, low clearance rates are shown throughout the 12 M).

EFFICACY RESULTS

Reduction of Gb3 in Kidney Peritubular Capillaries

Quantitative BLISS Score



- >300 peritubular capillaries (PTC) 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

	% change ±SE
All patients	**-67.8** ± 8.9
Classic patients	**-84.1** ± 3.3

The enzyme presence and activity in the kidney cells is evidently shown by the reduction of Gb3 inclusions in the kidney peritubular capillaries.

BLISS score of individual treated patients was reduced to or remained at a low level. The mean score reduction was 84.1 % in the classic FD patients and 67.8% in the entire cohort.

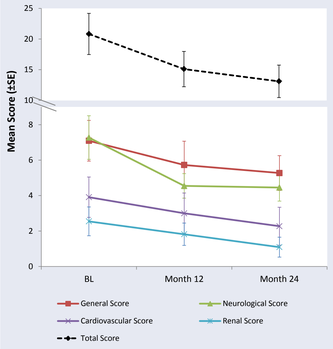
Stable Cardiac Parameters (by MRI)

Mean LVM, LVMI and EF

To estimate left ventricular mass (LVM), LVM index, ejection fraction (EF), and the presence of cardiac fibrosis were assessed every 6 months of pegunigalsidase alfa treatment. MRI read was done centrally in a blinded manner.

Cardiac MRI results showed that the majority of patients maintained cardiac parameters within the normal ranges throughout the 24-month study and thatno new fibrosis was observed.

Improvement in Mainz Severity Score Index (MSSI)



The Mainz Severity Score Index (MSSI) was used to assess the overall burden of Fabry disease symptoms.

Improvements in each subscale of the MSSI was observed during the study.

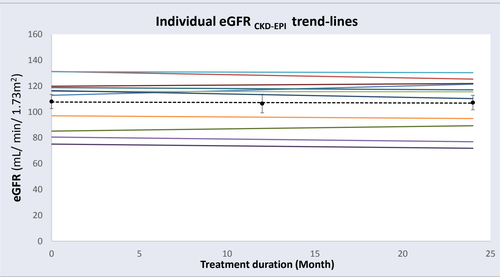
Continuous Stability of Renal Function

Renal failure is the most common cause of death in male Fabry disease patients (Germain, 2010). Increased proteinuria together with kidney failure is one of the dominant clinical manifestation of the disease.

All patients treated with pegunigalsidase alfa for 2 years show stable eGFR levels.

The figure presents the individual and mean (dashed line) eGFR trend lines for 2 years on pegunigalsidase alfa.

$eGFR_{CKD-EPI}$	eGFR at Baseline	eGFR at 24M
Mean (±SD)	108.02 ± 18.10	107.20 ± 18.63

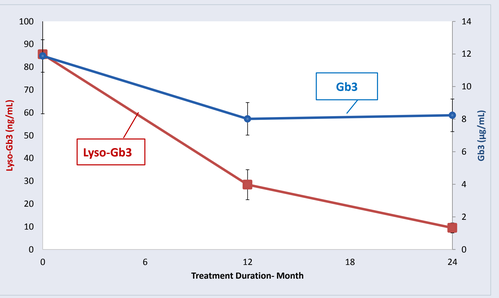


Biomarkers Reduction - plasma Gb3/Lyso-Gb3

Fabry disease biomarkers (Plasma Gb3 and lyso-Gb3) concentration was assayed throughout the study.

A continues reductions in plasma levels of both Gb3 and lyso-Gb3 levels were observed following 2 years of pegunigalsidase alfa treatment.

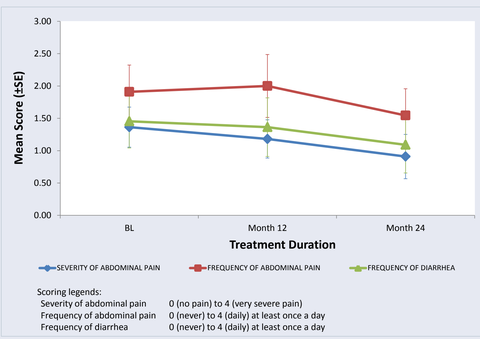
Change from baseline to 24M	Absolute change	% change
Gb3	-76.12 µg/mL	-88.94 %
Lyso-Gb3	-3.64 ng/mL	-30.65 %



Improvement in Gastrointestinal Symptoms

Assessment of Gastrointestinal symptoms was carried out using the Gastrointestinal Symptoms Assessment (GSA) questionnaire for severity of abdominal pain, frequency of abdominal pain, and frequency of diarrhea, at baseline and after every three months of treatment (Dehout et al. 2004).

The majority of patient responses to the GSA questionnaire showed a stable or favorable trend in the severity of abdominal pain, frequency of abdominal pain, and frequency of diarrhea after 12 and 24 months of treatment.



Scoring legends:

Severity of abdominal pain	0 (no pain) to 4 (very severe pain)
Frequency of abdominal pain	0 (never) to 4 (daily) at least once a day
Frequency of diarrhea	0 (never) to 4 (daily) at least once a day

Overall Conclusions

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

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

- Available enzyme throughout 2-week infusion intervals
- Markedly extended circulatory half-life compared with other ERTs

Safety:
pegunigalsidase is well tolerated

- Majority of adverse events – mild and moderate in severity
- Low incidence of treatment induced ADA with reversible & transient effect on PK
- ADA response was transient and tolerization was observed
- ADA positivity had no observed impact on safety and efficacy

Efficacy:
Demonstrated effectiveness, in various disease endpoints including:

- Stable kidney and cardiac function
- Reduction of Gb3 inclusions in kidney peritubular endothelial cells
- Continuous reduction of plasma Gb3 and Lyso-Gb3
- Improvement in Gastrointestinal Symptoms

Ongoing Phase III Studies

balance (a Fabry clinical 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
- 2 years treatment duration
- Extension study will be offered to patients at the end of the study

ClinicalTrials.gov Identifier:NCT02795676

bridge (a Fabry clinical study)

- An Ex-US open label switch over study from agalsidase alfa
- 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

ClinicalTrials.gov Identifier:NCT03018730

bright (A Fabry clinical study of once-monthly ERT)

- An open label, switch over study from agalsidase alfa and beta
- Assess the safety, efficacy and PK of pegunigalsidase alfa 2 mg/kg IV administrated every 4 Weeks in FD patients currently treated with ERT
- 1 year treatment duration
- Extension study will be offered to patients at the end of the study

ClinicalTrials.gov Identifier:NCT03180840

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