Pegunigalsidase alfa for the Treatment of Fabry Disease - Phase III Open Label, Switch-Over Study from agalsidase alfa – Preliminary Results

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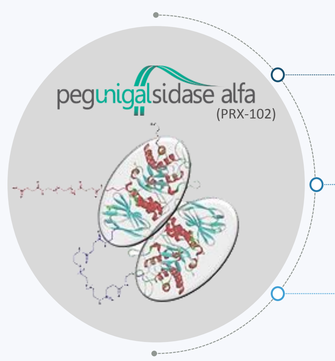
Abstract

Pegunigalsidase alfa is a novel, PEGylated, covalently-linked recombinant α-Galactosidase-A enzyme homodimer, for the treatment of Fabry disease.
The "BRIDGE" study (PB-102-F30; NCT03018730) is an on-going Phase III, open label, switch-over study, assessing the safety and efficacy of *pegunigalsidase alfa* in Fabry disease patients previously treated with *agalsidase alfa* for at least 2 years. The study enrolled 22 adult patients to be treated with 1mg/kg *pegunigalsidase alfa* every other week for 12 months. The kidney function related inclusion criteria are estimated glomerular filtration rate (eGFR) ≥ 40 ml/min/1.73m^2 and no or treated proteinuria.
The baseline characteristics of the first 16 patients (9 males and 7 females) enrolled: age 27-60 years of age; kidney function: 8/16 patients are treated with ACEi or ARBs, of which 3/16 have proteinuria, mean eGFR of 75.4 and 86.0 mL/min/1.73m^2 for males and females, respectively; with a mean annualized eGFR slope of -8.0 and -5.1 mL/min/1.73m^2/year for males and females, respectively; mean residual leucocytes enzymatic activities of 5.9% of normal for males and 27.9% of normal for females, and plasma lyso-Gb3 of 53.6 for males and 13.8 nM for females, respectively.
Preliminary results of the first 16 patients treated for 6 months with *pegunigalsidase alfa* show improvement in the mean annualized eGFR slope, from -6.8 mL/min/1.73m^2/year while on *agalsidase alfa*, to +3.7 mL/min/1.73m^2/year after switching and treatment with *pegunigalsidase alfa*.
These results suggest the potential benefit of *pegunigalsidase alfa* for improving renal function of Fabry disease patients currently treated with the available enzyme replacement therapies. To date 11 patients who successfully completed the bridge study were already enrolled to the extension study (PB-102-F60 "BRILLIANCE")

Pegunigalsidase alfa: PEGylated, Chemically Modified α-Gal-A Enzyme



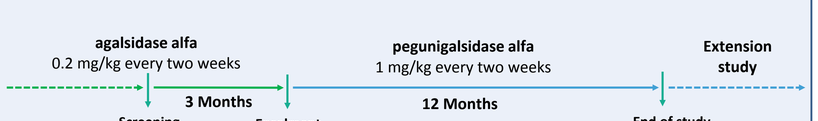
Subunits linked through a **2KDa PEG cross-linker** resulting in 114 kDa enzyme. Contains additional **PEG moieties** bound to only one subunit through a lysine residue

Shown extended half-life and stability in plasma as well as lysosomal-like conditions, while reaching target organs and subcellular lysosomes

PEG moieties are masking some enzyme epitope which could be recognized by the immune system → Potentially reducing the immune response to the enzyme plus reduced cross reactivity to pre-existing ADA

Study Objective and Design

- Multicenter, open label switch-over study to evaluate the safety and efficacy of switching from *agalsidase alfa* to *pegunigalsidase alfa*
  - 22 adult Fabry disease patients (male and female)
  - Previously treated with *agalsidase alfa* for at least 2 years



Main Inclusion/Exclusion Criteria

Main inclusion criteria

- Age: 18-60 years
- A documented diagnosis of Fabry disease
- Treatment with *agalsidase alfa* for at least 2 years
- eGFR$_{CKD-EPI}$ ≥ 40 ml/min/1.73 m^2
- At least 2 historical serum creatinine evaluations since starting *agalsidase alfa* treatment

Main exclusion criteria

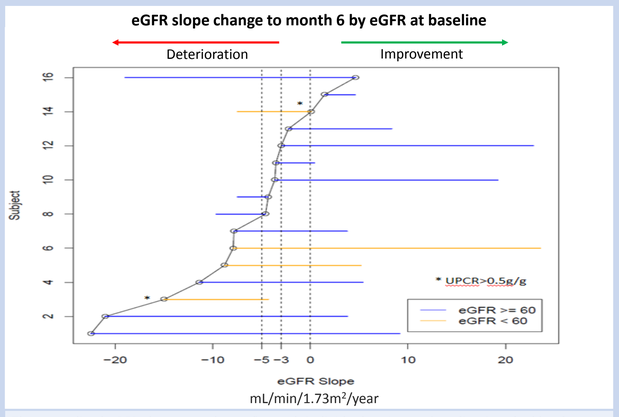
- History of anaphylaxis or Type 1 hypersensitivity reaction to *agalsidase alfa/beta*
- History of renal dialysis or transplantation and/or acute kidney injury in the 12 months prior to screening
- Start or change in dose of ACEi or ARB in the 4 weeks prior to screening
- UPCR > 0.5 g/g and not treated with ACEi or ARB
- Cardiovascular and/or Cerebrovascular event in the 6 months before randomization

Baseline Characteristics of First 16 Patients Enrolled

Parameter	ALL Mean	ALL SD	Female Mean	Female SD	Male Mean	Male SD
Number of patients	n=16		n=7		n=9	
Age at screening years	**46.3**	± 10.1	**47.1**	± 12.4	**45.7**	± 8.6
Age started ERT years	**37.9**	± 10.9	**39.9**	± 11.5	**36.4**	± 10.9
Residual enzyme activity – leucocytes %	**15.5**	± 13.1	**27.9**	± 10.2	**5.9**	± 2.6
Residual enzyme activity – plasma %	**14.1**	± 15.6	**28.5**	± 12.7	**2.9**	± 3.9
Number of patients with proteinuria UPCR≥500 mg/gr	**3**		**1**		**2**	
Number of patients treated with ACEi/ARB	**8**		**4**		**4**	
Plasma Lyso-Gb$_3$ nM; (normal ≤ 2.4 nM)	**36.18**	± 47.16	**13.81**	± 6.11	**53.57**	± 58.01
Plasma Gb$_3$ nM; (normal ≤ 4961 nM)	**6049**	± 2219	**5468**	± 1875	**6501**	± 2464
Urine Lyso-Gb$_3$ pM/mM creatinine; (normal-0 pM/mM)	**47.29**	± 40.99	**45.48**	± 31.11	**49.11**	± 51.63
eGFR$_{CKD-EPI}$ at Baseline (V1) mL/min/1.73m^2	**80.0**	± 21.8	**86.0**	± 17.8	**75.4**	± 24.5
Annualized Slope on *agalsidase alfa* (~2Y, including V1) mL/min/1.73m^2/year	**-6.8**	± 7.4	**-5.1**	± 4.4	**-8.0**	± 9.2

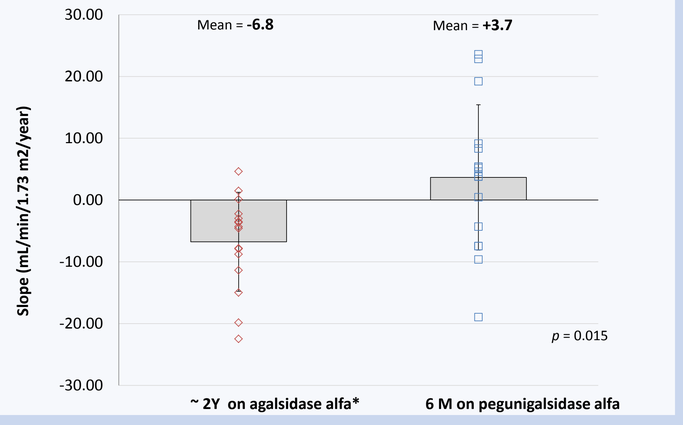
Study Results

Mean and Individual Annualized eGFR Slopes Pre- and Post- Treatment with *pegunigalsidase alfa* (6 M; n=16): Preliminary Results



The annualized eGFR slopes are shown for each individual patient at baseline (marked by the open circle (○)) and at 6 months "Post" switch to *pegunigalsidase alfa* (shown by the end of each subject's line). The figure is distinguishing, by color, between eGFR ≥ 60 baseline (orange) or <60 at baseline (blue). Patients with UPCR >0.5 g/g at baseline are indicated by asterisk. The vertical lines at -5 and -3 eGFR slopes indicating the rate of progression of renal disease as described in the "European expert consensus statement on therapeutic goals in Fabry disease" (Wanner at al., 2018), i.e. -3 indicating progression and -5 indicating fast progression of kidney disease.

- In the current analysis 12 out of 16 patients had negative eGFR slope (<-3 mL/min/1.73m^2/year) prior to enrolment
- The majority of the patients, 75%, show improvement after 6 month of treatment with *pegunigalsidase alfa*
- Preliminary results indicate a mean change of annualized eGFR slope of 10.5 mL/min/1.73m^2/year , i.e. from -6.8 mL/min/1.73m^2/year while on *agalsidase alfa*, to +3.7 mL/min/1.73m^2/year after switching to *pegunigalsidase alfa*.
- All 7 patients with fast progressing kidney disease, who started with a mean annualized slope below -5 mL/min/1.73m^2/year, improved following 6 months of treatment with *pegunigalsidase alfa*:
  - 2 patients stated with a slope of below -20 mL/min/1.73m^2/year
  - 2 patient stated with a slope of below -10 mL/min/1.73m^2/year
  - 3 patients stated with a slope of below -5 mL/min/1.73m^2/year



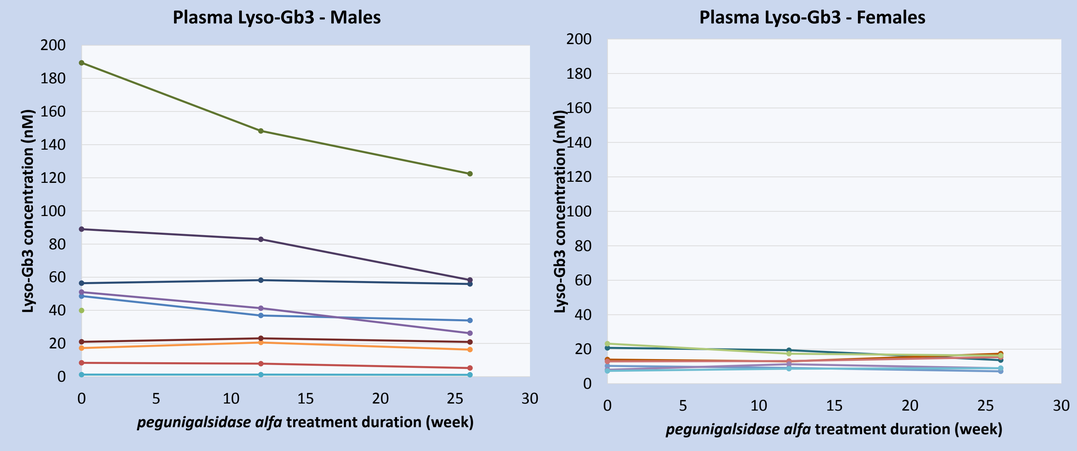
* Based on available historical serum creatinine for approximately 2 years and study 3 month screening period values

eGFR mL/min/1.73m^2 is calculated using CKD-EPI formula

eGFR Slope = mL/min/1.73m^2/year

	Males (n=9)	Females (n=7)
eGFR$_{CKD-EPI}$ Mean Baseline (range)	**75** (49-114)	**86** (55-109)
Mean annualized eGFR slope on *agalsidase alfa*	**-8.04**	**-5.13**
Mean annualized eGFR slope 6 months on *pegunigalsidase alfa*	**1.29**	**6.71**

Plasma Lyso-Gb3: Improvement (reduced levels) or Stability Throughout Treatment Period



Safety

8.6 patient years – cutoff date August 2018, N=18 (11M, 7F)

100% (69)
Total AEs in 15/18 patients (83.3%)

97.1% (67) AEs mild and moderate	2.9% (2) Severe	2.9% (2) Serious AEs	13.0% (9) Related, possibly related	87.0% (60) Not related, unlikely related
14 patients	2 patients	2 patients	3 patients	14 patients

Most common related AEs (# of AEs):
- Itching (2)
- Pruritus (2)
- Type 1 Hypersensitivity (1)
- Nausea, nasal congestion, sneezing, erythema (1 each)

Summary and conclusions

- Preliminary results from BRIDGE study indicate:
  - Improvement in kidney function following 6 months of treatment with *pegunigalsidase alfa* in patients switched from *agalsidase alfa,* as shown by annualized eGFR slope
  - Stability or improvement in plasma Lyso-Gb3
- Preliminary study results show that switching from *agalsidase alfa* to *pegunigalsidase alfa* is safe and well tolerated
- Currently, 11 patient rolled over to a long-term extension study (PB-102-F60 "BRILLIANCE")

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