Once every 4 weeks 2 mg/kg of *pegunigalsidase alfa* for treating Fabry disease - preliminary results of a phase 3 study

Holida Myrl*[1]**, *Bernat John[1,] Longo Nicola[2], Goker-Alpan Ozlem[3], Wallace Eric[4], Schiffmann Raphael[5], Deegan Patrick[6], Nedd Khan[7], Tøndel Camilla[8], Eyskens Francois[9], Derralynn Hughes[10], Michael West[11], Pilar Giraldo[12], Fatih Ezgu[13], Almon Einat[14], Alon Sari[14], Amit-Cohen Bat-chen[14], Mali Szlaifer[14], Chertkoff Raul[14], Wilcox William[15]

Abstract

Pegunigalsidase alfa, a novel α-galactosidase-A enzyme for the treatment of Fabry disease (FD) is a stable, homo-dimeric PEGylated protein, previously demonstrated (Hughes et al, LDN-2016) to have substantially improved pharmacokinetics (PK) parameters compared to the two currently available enzyme replacement therapies (ERTs).

The ongoing phase 3 trial "BRIGHT" (PB-102-F50, NCT03180840) is an open-label switch-over study assessing safety, PK, and efficacy of *pegunigalsidase alfa* (2mg/kg) given every 4 weeks for 52 weeks to FD patients previously treated with either *agalsidase alfa* or *agalsidase beta*. The aim of the study is to explore a more convenient dosing regimen exploiting the improved PK characteristics of *pegunigalsidase alfa*, as shown by PK modelling from the Phase 1-2 study results (Warnock et al, LDN-2018). The trial enrolls up to 30 patients without severe clinical symptoms and relatively slow disease progression, as evaluated by the investigator.

In PB-102-F50 (BRIGHT) study, *pegunigalsidase alfa* plasma levels are measured at multiple time points before, during, and up to 28±3 days post-infusion for PK evaluation.

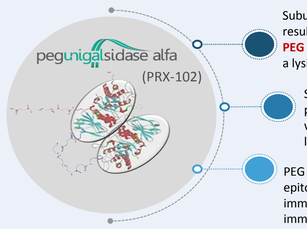
Preliminary PK results, from the first 15 patients, show a half-life of ~80 hours and persistent plasma levels over the entire 4-week dosing interval, with a mean concentration of 138 ± 42 ng/mL on day 28 post-infusion . The Area Under the Curve (AUC) for 0-28 days was found to be 2,126,091 ng*h/mL, of which the mean partial AUC during the 4th week was ~30,000 ng*h/mL confirming the study assumptions.

The AUC for 0-28 days is significantly greater than that of *agalsidase beta* ($AUC_{0-\infty}$ <11,000 ng*h/mL based on package insert).

This interim analysis of the ongoing BRIGHT study, provides evidences of how *pegunigalsidase alfa's* unique biochemical characteristics translate into prolonged systemic exposure potentially supporting a monthly infusion option. This feature is expected to ease treatment-related burden for FD patients, potentially impacting quality of life and offering an alternative regimen compared to existing treatments.

Background

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

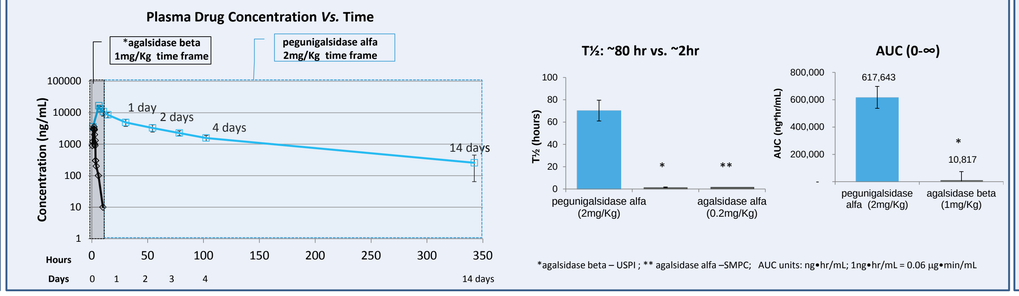


Subunits linked through a **2KDa PEG cross-linker** resulting in 114 kDa enzyme. Contains additional **PEG moieties** bound to only one subunit through a lysine residue

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

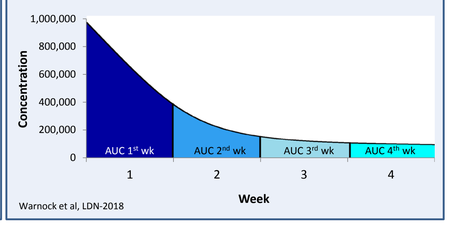
PEG moieties are masking some enzyme epitope which could be recognized by the immune system → Potentially reducing the immune response to the enzyme plus reduced cross reactivity to pre-existing ADA

Phase 1/2 PK Results (Hughes et al.-LDN 2017)



*agalsidase beta – USPI ; ** agalsidase alfa –SMPC; AUC units: ng•hr/mL; 1ng•hr/mL = 0.06 µg•min/mL

Modeling illustration



Warnock et al, LDN-2018

PK data of *pegunigalsidase alfa* in Phase 1/2 studies show that the PEGylation and cross-linking of the α-Gal-A enzyme resulted in a substantially longer plasma half-life, higher C_{max}, and higher AUC compared to the published data of the commercial ERTs, without interfering with the enzymatic activity.

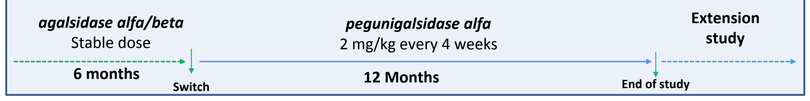
Data show that substantial levels of *pegunigalsidase alfa* enzyme are available in the circulation throughout the two-week intervals between the infusions, which may indicate a significantly greater availability of the enzyme to the target organs.

This data served as the basis for the on-going Phase 3 study of a new regimen with longer intervals between infusions (2mg/kg every 4 weeks).

Bright Study

Study Objective and Design

- Open label switch over study to evaluate the safety, efficacy and pharmacokinetics of **2.0 mg/kg** *pegunigalsidase alfa* given **every 4 weeks**
- Patients previously treated with *agalsidase alfa* or *agalsidase beta* for at least 3 years, and on a stable dose for at least 6 months
- **Study Duration:** 12 months
- **Study patients population:** Up to 30
- After completion, patients will be offered enrollment in an open label extension study with *pegunigalsidase alfa* at the same regimen (study PB-102-F51)



Main Inclusion/Exclusion Criteria

Inclusion Criteria

- Adult Fabry disease patients (18-60 years)
  - One or more: Neuropathic pain, Cornea verticillata , Clustered angiokeratoma
  - **Males:** α–galactosidase activity less than lower limit of normal
  - **Females:** historical genetic test results consistent with Fabry mutations
- **$eGFR_{CKD-EPI}$ ≥ 30 ml/min/1.73m² at screening visit**
- Treatment with *agalsidase alfa* or *beta* for at least 3 years and on a stable dose
- Patients whose clinical condition, in the opinion of the investigator, is suitable for treatment with ERT every 4 weeks

Exclusion Criteria

- Anaphylaxis or Type 1 hypersensitivity reaction to *agalsidase alfa* or *beta*
- Renal dialysis or transplantation
- **Slope of eGFR more negative than -2 mL/min/1.73m²**
- ACEi or ARB therapy initiated or dose changed in the 4 weeks prior to screening
- UPCR > 0.5 g/g and not treated with an ACEi or ARB
- Cardiovascular event and/or cerebrovascular event in the 6 month before screening

Baseline Characteristics (n=25)

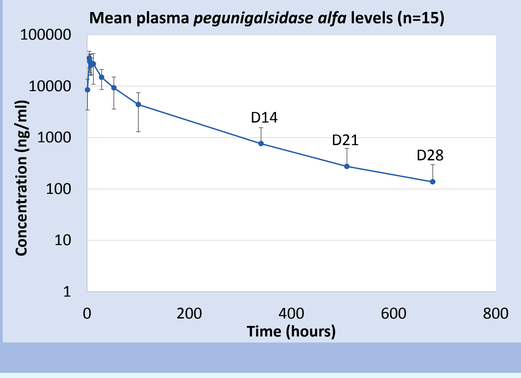
Parameter	ALL (Mean±SD)	Female (Mean±SD)	Male (Mean±SD)
Number of patients	**25**	**5**	**20**
Age at screening years	**39**±11	**47**±4	**37**±11
Age started ERT years	**29**±12	**40**±3	**27**±12
Number of patients previously treated with *agalsidase beta*	**21**	**4**	**17**
Number of patients previously treated with *agalsidase alfa*	**4**	**1**	**3**
Residual enzyme activity in leukocytes %[1]	**11.61**±15.54	**45.67**±18.66	**6.50**±5.67
Number of patients with proteinuria UPCR≥500 mg/gr	**2**	**0**	**2**
Number of patients treated with ACEi/ ARB	**9**	**1**	**8**
Number of patients treated with pre-medication	**9**	**2**	**7**
Plasma Lyso-Gb_3 nM; (normal ≤ 2.4 nM)[2]	**23.93**±23.7	**4.53**±1.49	**30.39**±24.16
Plasma Gb_3 uM; (normal ≤ 4.961 uM)[2]	**4.6**±1.1	**3.9**±0.5	**4.9**±1.1
$eGFR_{CKD-EPI}$ slopes at screening- mL/min/1.73m²/year	**-0.04**±1.97	**-1.48**±2.1	**0.33**±1.8
$eGFR_{CKD-EPI}$ at screening mL/min/1.73m²	**104**±21	**92**±14	**107**±22

[1] n=23, [2]n=13

Pegunigalsidase alfa PK Profile

Method

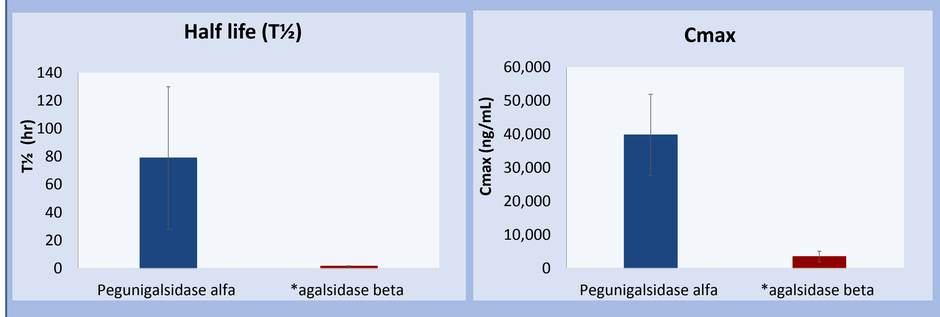
- Blood samples were taken for PK analysis after a single dose of *pegunigalsidase alfa* at the following time points:
  - pre-infusion, 1 hour after the beginning of the infusion
  - at 1, 2, 4, 8, 24, 48, and 96 hours post-infusion
  - at 14, 21 and 28 days post-infusion
- Blood samples were tested for the concentration of *pegunigalsidase alfa* using a validated Sandwich ELISA assay and confirmed by an activity assay



Results

- *Pegunigalsidase alfa* was found to be present in the plasma throughout the 4 week infusion interval
- Activity results indicated that *pegunigalsidase alfa* remained active over the 4 weeks

Comparison of *pegunigalsidase alfa* (2mg/kg E4W) to Published *agalsidase beta* Data (1mg/kg E2W)



- *Pegunigalsidase alfa* demonstrated persistent plasma levels over the entire 4-week dosing interval
- 28 days $AUC_{0-\infty}$ of *pegunigalsidase alfa* (~2,000,000 ng·hr/mL) is significantly greater than *agalsidase beta* (~10,000 ng·hr/mL)
- Mean partial AUC of *pegunigalsidase alfa* at the 4th week is higher than *agalsidase beta* for the entire 2 week interval
- Mean concentration on day 28 post-infusion of *pegunigalsidase alfa* is ~7-fold higher than *agalsidase beta* 10 hours (138 ± 42 vs. 20 ng/mL)

* Fabrazyme USPI Study AGAL-1-002-98: Phase 3 Study in Adult Patients with Fabry Disease; **Eng et al 2001

Safety

(8.6 patient years – cutoff date August 2018) N=19 (16M, 3F)

100% (63)

Total AEs in 17/19 patients (89.5%)

96.8% (61) AEs mild and moderate	3.2% (2) Severe	0.0% (0) Serious AEs	33.3% (21) Related, possibly related	66.7% (42) Not related, unlikely related
17 patients	1 patients	0 patients	5 patients	16 patients

Most common related AEs (# of subjects):

- Infusion related reaction* (2)
- Paresthesia (2)
- Headache, tachycardia, nausea, vomiting, asthenia, pain, pyrexia, back pain, myalgia, pain in extremity, erythema (1 patient each)

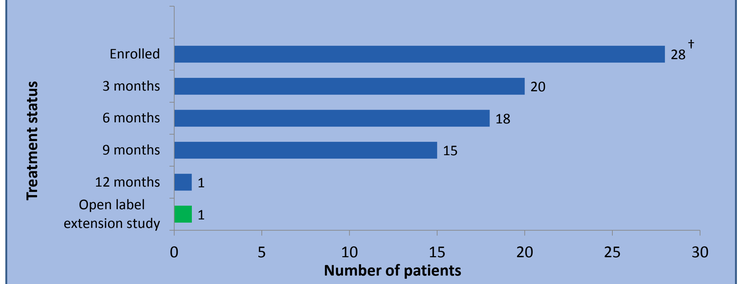
**Infusion related reaction: Nasal congestion, stuffy nose, flank pain, back pain, vomiting, facial flushing, worsening of fever*

Summary and Conclusions

- The unique characteristics of *pegunigalsidase alfa*, including the improved PK profile with longer half life and higher exposure compared to other ERTs, led to the development of a new dosing regimen of 2.0 mg/kg *pegunigalsidase alfa* once every 4 weeks
- Patients treated with either *agalsidase alfa* or *agalsidase beta* were switched to receive *pegunigalsidase alfa* 2mg/kg E4W
- Preliminary PK data show that *pegunigalsidase alfa*, given at 2mg/kg E4W, results in a continuous presence of an active enzyme throughout the 4 weeks infusion interval
- Preliminary study results show that the treatment is well tolerated
- First patients are rolling over to a long term extension study (PB-102-F51)

Patients Treatment Duration

(Up To January 2019)



- Currently samples from 15 patients underwent PK evaluation
- 8 patients are receiving treatment as part of a homecare set up

† One patient received first infusion only, the patient was involved in a car accident after which discontinued from the study

[1]University of Iowa , Iowa City, Iowa, USA, [2]University of Utah,Salt Lake City , USA, [3]O&O Alpan LLC, Fairfax, Virginia, USA, [4]University of Alabama, Birmingham USA, [5]Baylor University Medical Center, Dallas, Texas, USA, [6] Lysosomal Disorders Unit, Cambridge University,Cambridge, UK, [7] Infusion Associates,Michigan, USA, [8] Haukeland University Hospital, Bergen, Norway, [9] Antwerp University Hospital UZA, Edegem, Belgium [10]LSDU, Institute of Immunity and Transplantation, Royal Free London NHS Foundation Trust, London, UK, [11] Dalhousie University , Halifax, Nova Scotia, Canada, [12]Hospital de Dia Quiron, Zaragoza, Spain, [13] Gazi Universitesi, Ankara, Turkey, [14]Protalix Biotherapeutics, Carmiel, Israel, [15] Emory University School of Medicine,Atlanta , USA