Enhanced Pharmacokinetics Profile of *Pegunigalsidase Alfa* (PRX-102) Supports Once-monthly 2mg/Kg Dosing For the Treatment of Fabry Disease

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INTRODUCTION

Abstract:

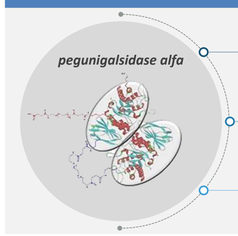
Pegunigalsidase alfa, a novel PEGylated Enzyme Replacement Therapy (ERT) for Fabry disease (FD), was administrated intravenously (IV) every other week (EOW) in three escalating doses (0.2, 1.0 and 2.0 mg/kg) to FD patients in a Phase 1/2 study. *Pegunigalsidase alfa* was found to be safe and well tolerated and demonstrated effectiveness in various disease parameters.

The pharmacokinetic (PK) parameters of *pegunigalsidase alfa* were markedly improved compared to the two currently marketed ERTs. The half-life of *pegunigalsidase alfa* was about 80 hours Vs. about 2 hours of *agalsidase alfa* and *beta*, with C_{max} of the 2mg/kg cohort approximately 10-fold higher than those published for *agalsidase beta*.

This study presents a PK modelling of 4 weeks infusion intervals with *pegunigalsidase alfa* 2mg/kg. A PK projection was performed, based on the parameters of the 2mg/kg dosed EOW cohort, in order to estimate *pegunigalsidase alfa* PK profile if given once every 4 weeks (E4W). This PK projection showed that over a 4 week time frame, a single IV of 2mg/kg *pegunigalsidase alfa* was estimated to have a greater area under the curve (AUC, ~45 fold) than 2 infusions of *agalsidase beta* EOW. The weekly projected average concentration (C_{ave}) indicated that measurable levels of *pegunigalsidase alfa* at the 3rd and 4th weeks post infusion were expected, within the same order of magnitude as *agalsidase beta* in the 1st week post infusion and much higher than the negligible *agalsidase beta* levels in the 2nd week post infusion.

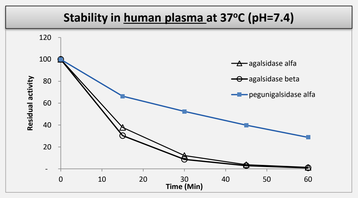
As a conclusion, the unique characteristics of *pegunigalsidase alfa*, together with the results of the PK projection modelling, serve as the rationale for initiating an on-going phase 3 study that will assess the safety, efficacy and PK of 2mg/kg *pegunigalsidase alfa* administered IV E4W in FD patients. Treating patients E4W is expected to improve the patients' quality of life and may address the clinical needs of early or younger diagnosed patients.

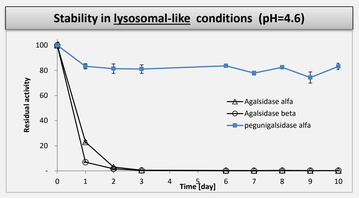
Pegunigalsidase Alfa:
A Chemically Modified α-Gal-A Enzyme



- PEGylated covalently-linked homodimer composed of two subunits produced in plant cells
- 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
- Enzyme maintains its catalytic activity and translocation to the lysosome of target cells

Prolonged Stability in Biological Matrices
Compared to the other ERTs



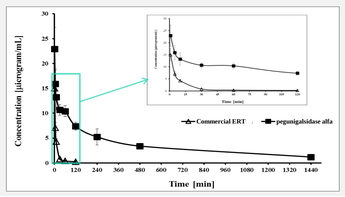


In-vitro studies indicated that the *pegunigalsidase alfa* has improved stability in biological matrices, which could improve pharmacokinetics and pharmacodynamics properties. [1]Kizhner et al., 2015.

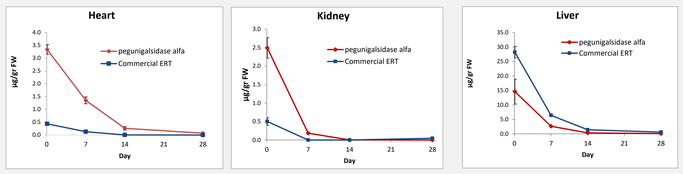
Extended Pharmacokinetics & Prolonged Activity
in Target Organs of Fabry Mice *In-Vivo*

Pegunigalsidase alfa Plasma Pharmacokinetics (PK) in Fabry Mice[1]

Extended Pharmacokinetics in Fabry mice model
(quantified by activity assay)



Pegunigalsidase alfa Exhibits Prolonged Activity in Target Organs of Fabry Mice[1]



Increased delivery of the active enzyme to the target organs

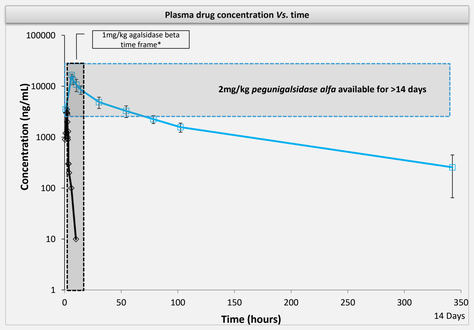
Reduced clearance by the liver

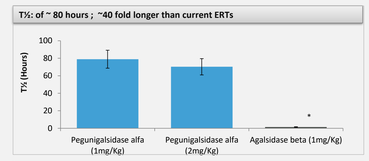
µg/gr FW = amount of enzyme [µg] per gr of tissue fresh weight [FW]

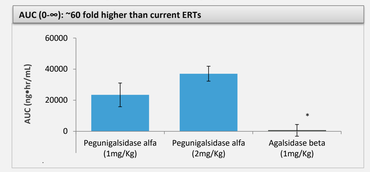
[1]Kizhner et al., 2015.

Phase 1/2 Pharmacokinetics (PK) Results
Available enzyme in the circulation throughout the 2-week interval between infusions

Substantially Greater Enzyme Exposure Than Current ERTs*







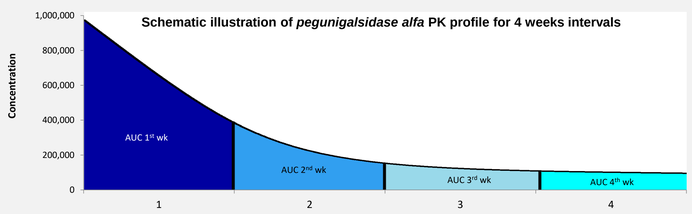
*agalsidase beta – USPI ; AUC units: ng•hr/mL; 1ng•hr/mL = 0.06 µg•min/mL

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 the *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.

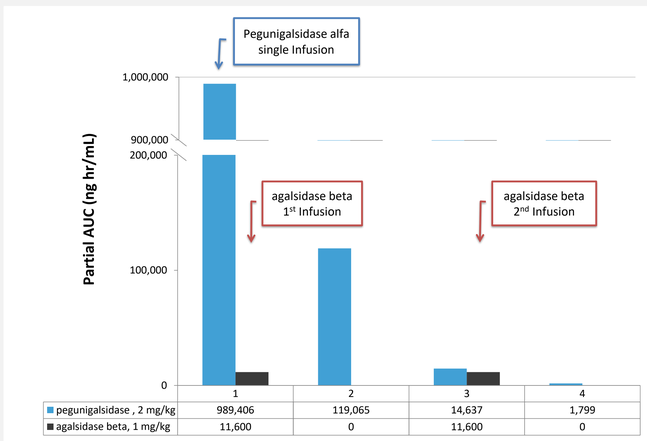
PROJECTION MODELING APPROACH

Analysis Process and Projection Modeling Approach

- PK data obtained from the Phase 1/2 study
- Information on the PK characteristics of *agalsidase beta* (Fabrazyme®) is available in the package insert ([2]*agalsidase beta* USPI) and in [2]Eng et al, 2001
- Projection modeling was done using Phoenix WinNonlin Software
- Weekly Partial AUC and average concentration (C_{ave}) calculations enabled the comparison and estimation of the drug availability on weeks 1, 2, 3 and 4 of pegunigalsidase alfa and compared it to agalsidase beta every 2 weeks



COMPARATIVE PK PROJECTION MODELLING RESULTS



PK modeling
Repeat administration every 2 or 4 weeks

	pegunigalsidase alfa, 2 mg/kg		*agalsidase beta**, 1 mg/kg	
	4 weeks interval		2 weeks interval	
Time (week)	Partial AUC (ng•hr/mL)	C_{ave} for week (ng/mL)	Partial AUC (ng•hr/mL)	C_{ave} for week (ng/mL)
1	989,406	5,889	11,600	70
2	119,065	709	nil	nil
3	14,637	87	11,600	70
4	1,799	11	nil	nil
5	989,627	5,891	11,600	70
6	119,092	709	nil	nil
7	14,640	87	11,600	70
8	1,800	11	nil	nil
9	989,627	5,891	11,600	70
10	119,092	709	nil	nil
11	14,640	87	11,600	70
12	1,800	11	nil	nil

Partial AUC = Area Under the Curve calculated per week

*based on agalsidase beta - USPI

Comparative PK Projection Modeling suggest that greater AUC in a single IV infusion of 2 mg/kg *pegunigalsidase alfa*, compared to 2 infusions of 1 mg/kg *agalsidase beta* over a 4 week time frame:

- Measurable levels of pegunigalsidase alfa in the 3rd and 4th week after single infusion.
- 3rd week after a single 2mg/kg *pegunigalsidase alfa* IV- has the same order of magnitude as *agalsidase beta* after the 2nd infusion.
- 4th week after 2mg/kg *pegunigalsidase alfa* IV – higher levels than the negligible agalsidase beta levels in the 2nd week after 2nd infusion.

CONCLUSIONS

- The unique characteristics of *pegunigalsidase alfa*, as well as the safety and efficacy results from the phase I/II and the PK projection modelling, provide the rationale for initiating a phase 3 study that will assess the safety, efficacy and PK of 2 mg/kg *pegunigalsidase alfa* administered IV every 4 weeks in adult patients with Fabry disease.
- Treating patients every 4 weeks is expected to improve the quality of life and treatment compliance with lower treatment burden while maintaining clinical stability with half the infusions comparted to currently approved ERT.
- This dose and once-monthly regimen have the potential to result in a comparable efficacy and safety profile with a reduced immunogenicity compared to current ERTs.
- This has the potential to delay the risk of developing disease complications in mild to moderate patients by slowing disease progression.

ON-GOING CLINICAL STUDY – BRIGHT

BRIGHT Study Objectives & Design

bright — A Fabry clinical study of once-monthly ERT

- Open label switch over study to evaluate the safety and efficacy of **2.0 mg/kg** pegunigalsidase alfa every **4 weeks**
- Patients with Fabry disease currently treated with *agalsidase alfa or agalsidase beta* switched to *pegunigalsidase alfa*
- Treated with ERT for at least 3 years, and on the same dose (>80% labelled dose/kg) for at least 6 months before the switch to *pegunigalsidase alfa*.
- **Study Duration:** 12 months treatment on *pegunigalsidase alfa* 2 mg/kg every 4 weeks
- **30 patients**, 15±3 from each enzyme
- After completion, patients will be offered enrollment in a open label extension study under pegunigalsidase alfa

[1]Kizhner T., Azulay Y., Hainrichson M., et al. (2014). Characterization of a chemically modified plant cell culture expressed human α-Galactosidase-A enzyme for treatment of Fabry disease. *Mol. Genet. Metab.* 114 259–267
[2]Eng C.M., Banikazemi M., Gordon R.E., et al. (2001). A phase 1/2 clinical trial of enzyme replacement in Fabry disease: pharmacokinetic, substrate clearance, and safety studies. *Am J Hum Genet* 68: 711–722

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