pegunigalsidase alfa for Treating Fabry Disease

Clinical Pharmacokinetic and Immunogenicity
Phase 1/2 Study results

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Disclosure Information

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David G. Warnock

- Consultant for Genzyme Corporation, Actelion, Protalix and Amicus
- These activities have been fully disclosed and are managed under a Memorandum of Understanding with the Conflict of Interest Resolution Board of the University of Alabama at Birmingham

I will discuss the investigational use of pegunigalsidase alfa in Fabry disease in my presentation

Fabry disease and currently available ERTs

X-linked disorder

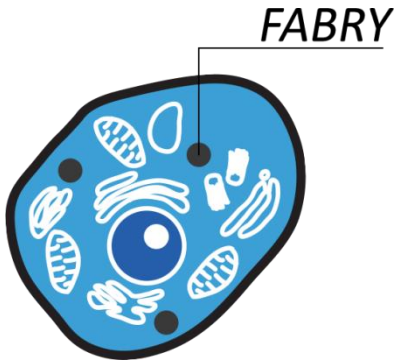
Caused by the loss of function of the lysosomal enzyme α-galactosidase-A (α-gal-A)

Progressive Gb3 accumulation

Occurs in most tissues and cell types

Variable phenotype

This depends on mutation (Classic versus Non-Classic) and gender



Available Treatments

agalsidase beta: Approved in the US & the EU. Administrated IV at 1 mg/kg body weight. *

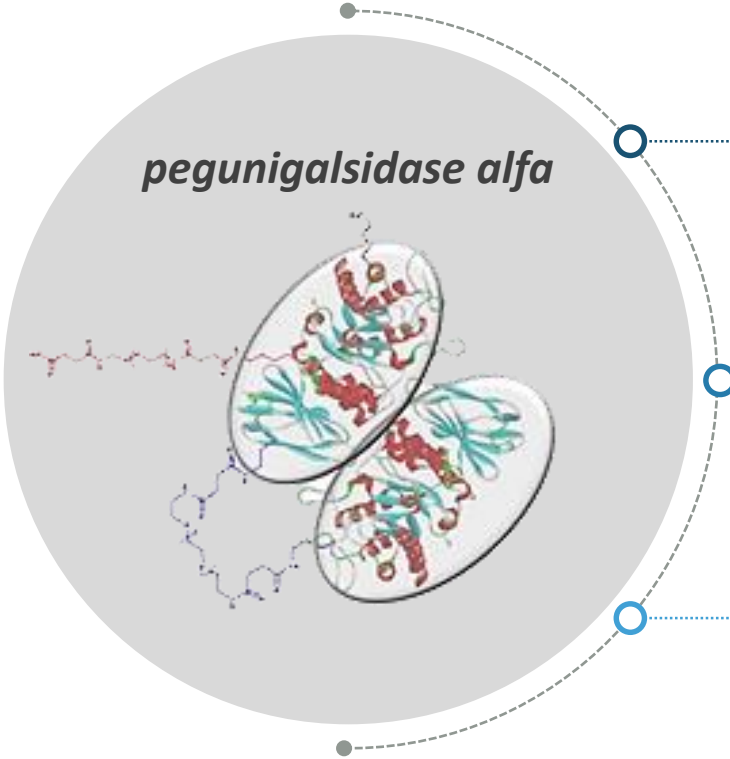
agalsidase alfa: Approved in the EU. Administrated IV at 0.2 mg/kg body weight. **

Unmet clinical need

- Continuous disease progression,
- Immune response: infusion reactions and long-term efficacy
- Safety profile especially in males with Classic Fabry Disease

* agalsidase beta USPI ; ** agalsidase alfa SMPC

pegunigalsidase alfa: A chemically modified α-Gal-A enzyme



PEGylated covalently-linked homodimer composed of two subunits produced in plant cells

Subunits linked together through the 2000Da PEG cross-linker resulting in 114 kDa enzyme

Contains additional PEG moieties bound to only one subunit through a lysine residue

Pharmacokinetics and immunogenicity: Intrinsic and extrinsic factors[1;2]

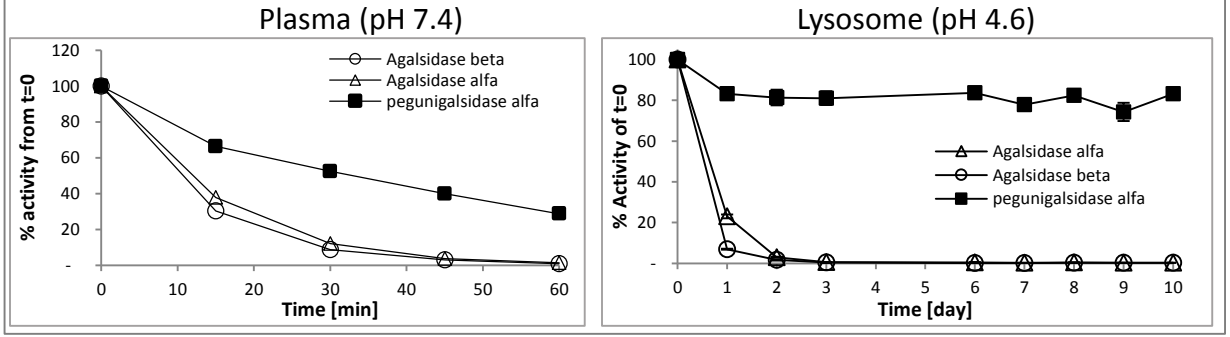
	Pharmacokinetics	Immunogenicity
Intrinsic	▪ Size and charge ▪ Multimer/aggregate state ▪ Molecular stability ▪ Glycosylation and other post-translational modifications	▪ Sequence/structure ▪ Size and charge ▪ Molecular stability ▪ Multimer/aggregate state ▪ Glycosylation and other post-translational modifications
Extrinsic	▪ Route of administration ▪ Dose ▪ Age/gender ▪ Disease or study population ▪ Target frequency and distribution ▪ Clearance mechanism	▪ Route of administration ▪ Dose and exposure ▪ Age/Gender ▪ Immune tolerance status ▪ Disease or study population

1. Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products, **August 2014; FDA CDER/CBER**
2. Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins, **September 2015**, EMEA/CHMP/BMWP/14327/2006 Rev. 1

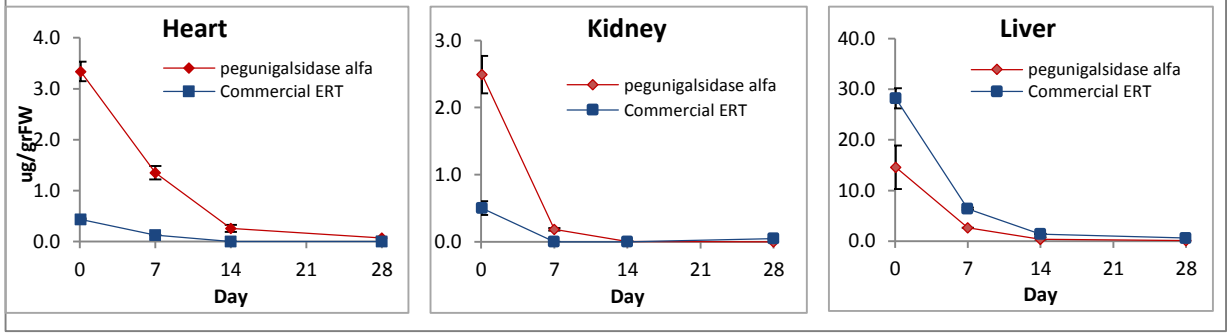
Stability and impact on biodistribution and bioavailability

- Pegylation and cross linking increase drug stability and leads to extended circulation half life
- Greater bioavailability (higher AUC) relative to existing ERTs in Fabry patients*
- Greater uptake into heart and kidney than existing ERTs, but less uptake into liver**

Higher stability in plasma and under acidic lysosomal-like conditions**



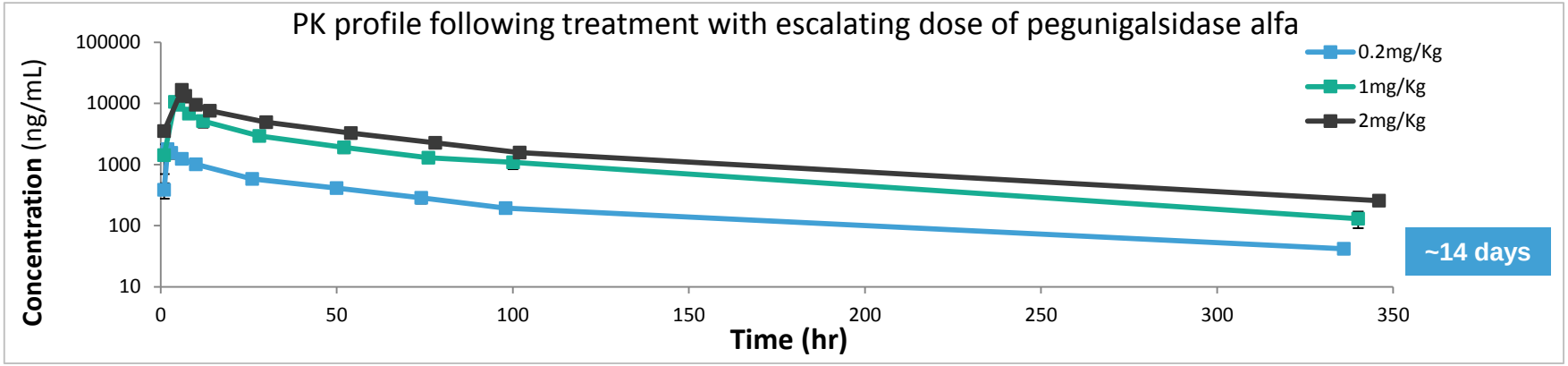
Higher enzyme activity in Fabry mice heart and kidney (µg/g FW)**

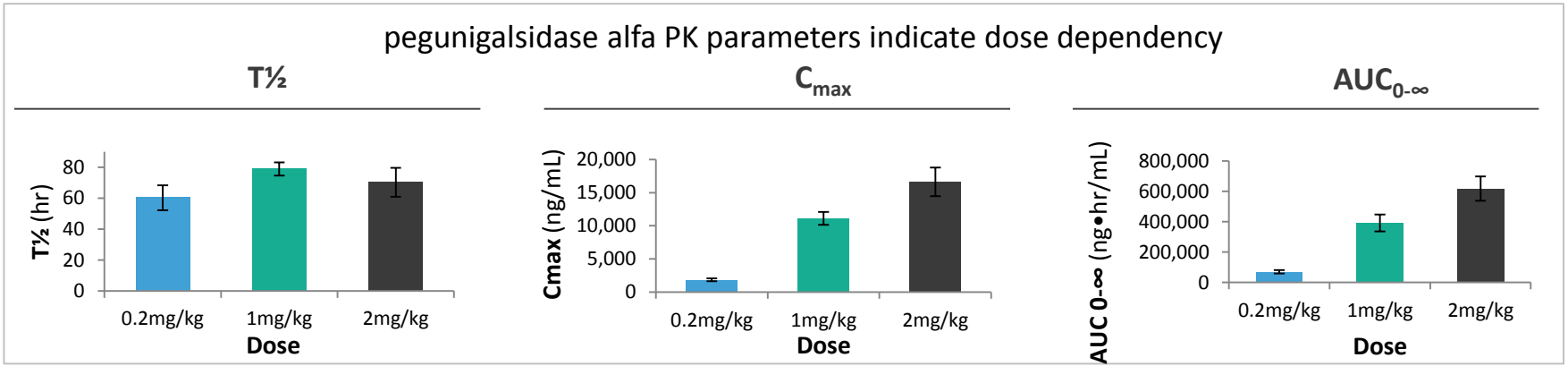


* agalsidase alfa -SMPC; agalsidase beta - USPI **Kizhner T. et al 2015

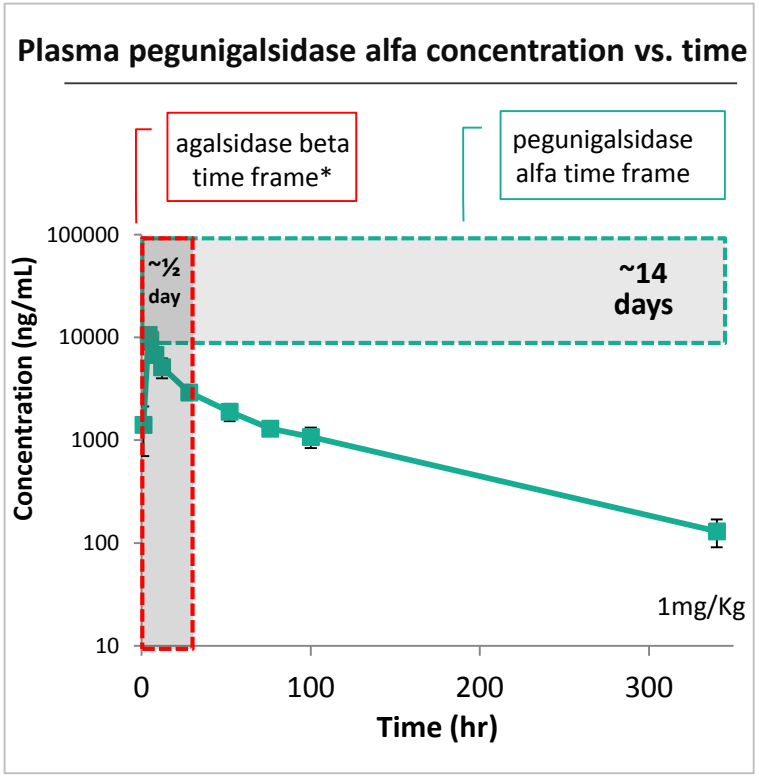
Pharmacokinetics (PK)

Increased stability and extended half life



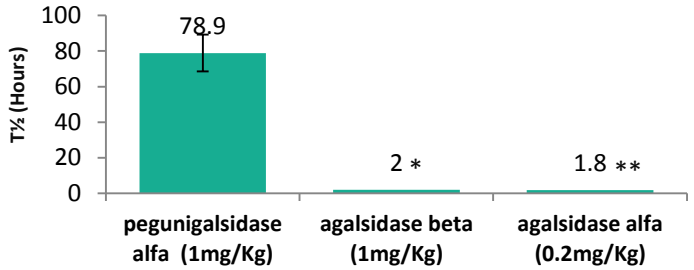


Available enzyme in the circulation throughout the two week intervals between IVs

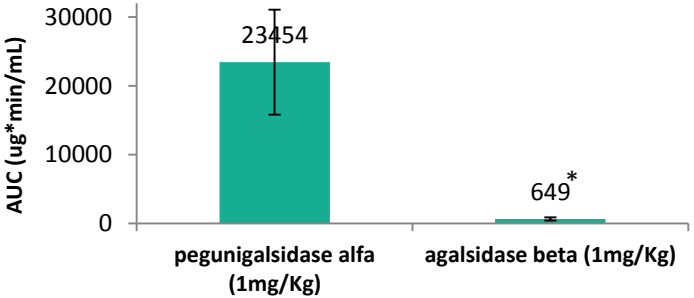


Substantially greater enzyme activity than current ERTs*,**

T½: Approx. 80 hours



AUC (0-∞): >35 fold from current ERTs



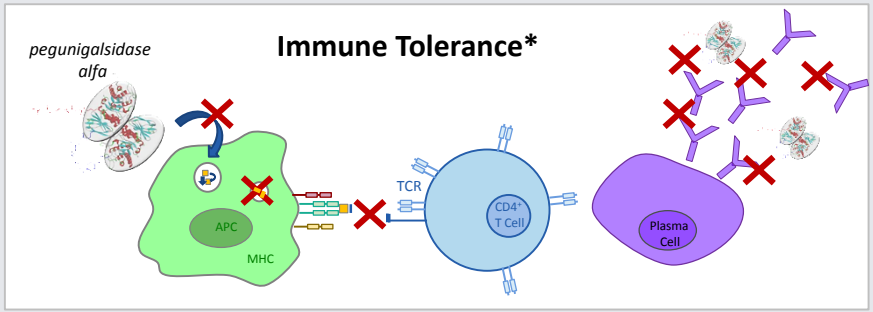
*agalsidase beta – USPI ; ** agalsidase alfa -SMPC

Potential impact on immunogenicity

01 Chemical modification has the potential to hamper the antigen presentation of pegunigalsidase alfa by Antigen Presenting Cells (APC)
- Processing
- Recognition by T-helper cells

02 PEGylation potentially reduces immunogenicity by masking immunogenic epitopes

03 Potential induction of immune tolerance due to improved stability and prolonging/continuous exposure



*Adopted from: M. Ing et al., Cell. Immunol. (2015)

Immunogenicity evaluation – current clinical experience (n=16)

Low incidence of ADA:

3/16 patients→19%

Low titers

Max titer 4633

Neutralizing ADA:

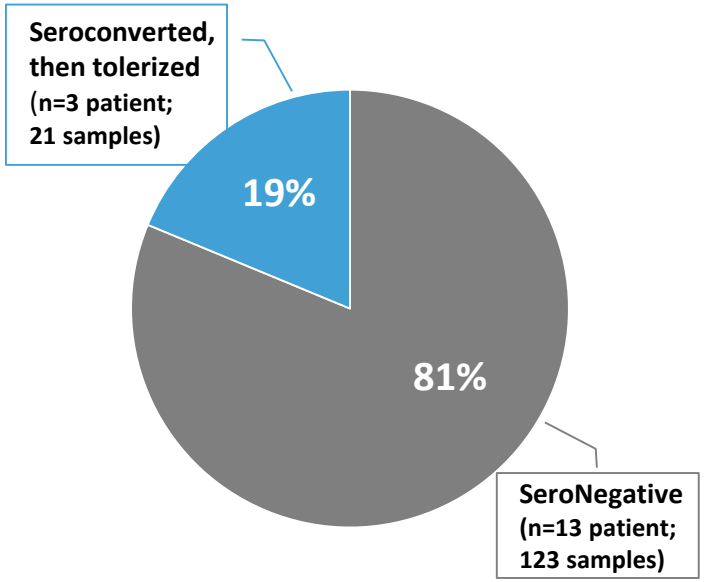
2/3 positive patients had neutralizing activity in some samples

Immune tolerization

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

Low incidence of treatment induced Anti Drug Antibodies (ADA) demonstrate by:

Incidence of treatment induced ADA

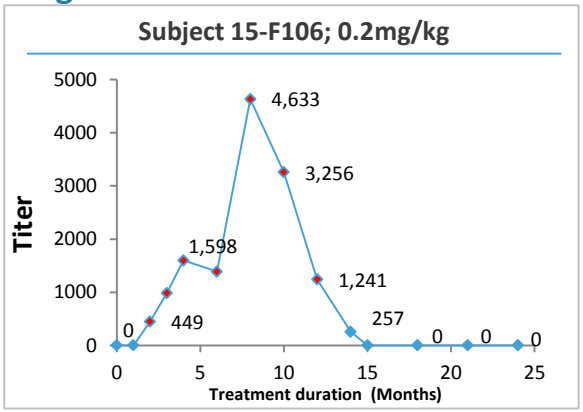


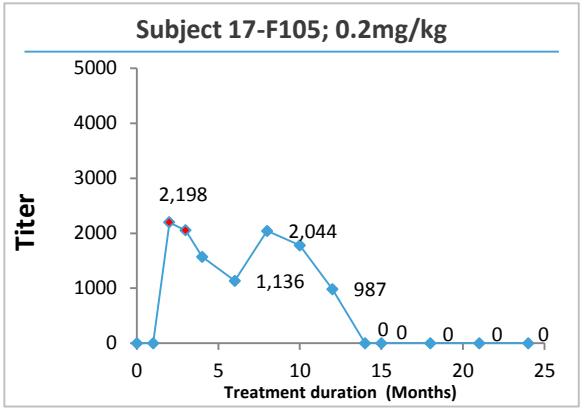
- Serum samples were withdrawn once a month for 4 first months and then once every 2 months
- 144 samples were analyzed* of which 123 were ADA negative
- Confirmed positive samples further characterized* for:
  - Neutralizing activity
  - Anti glycan
  - Anti PEG

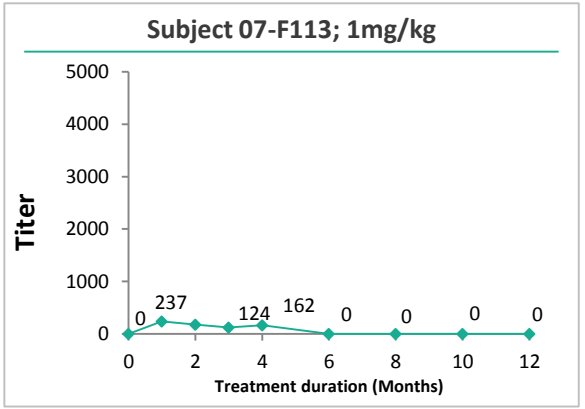
* According to the regulatory guidelines, using sensitive and validated methods

Transient and reversible impact of ADA (n=3) on PK

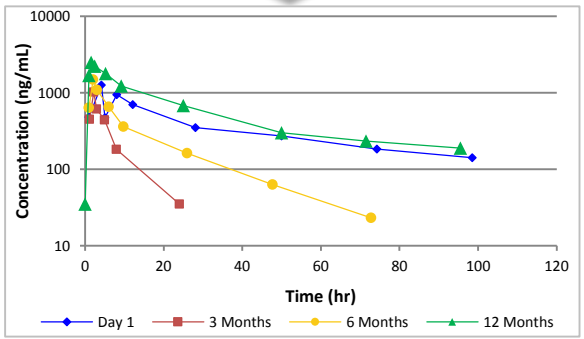
ADA$^+$: IgG Titers

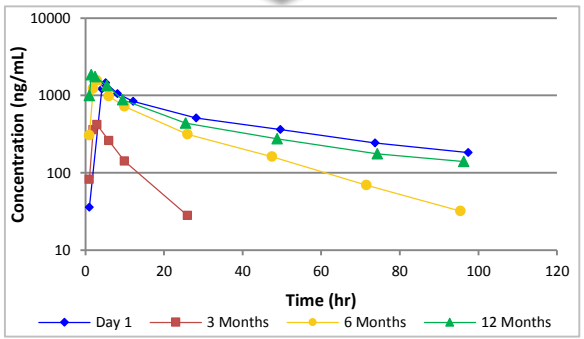


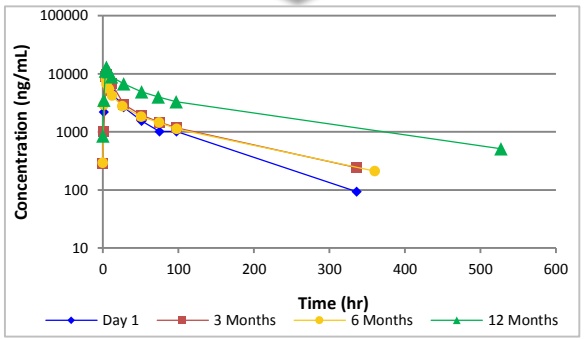




PK profiles







nAb positive samples are indicated in red;

pegunigalsidase alfa: Conclusions from Phase I/II studies

- Markedly extended circulatory half-life compared with other ERTs
- 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

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Thank You