Pegunigalsidase alfa for treating Fabry disease

Clinical Pharmacokinetic and Immunogenicity Phase 1/2 Study Results

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Abstract

pegunigalsidase alfa (PRX-102) is a novel, PEGylated, chemically modified, α-galactosidase A for the treatment of Fabry disease (FD).

Immune responses to therapeutic protein could potentially impact its efficacy and/or safety. In FD, an X-linked disorder caused by the loss of function of the lysosomal enzyme α-galactosidase-A, anti-drug antibody (ADA) formation toward the enzyme has been shown to occur in a high percentage of male patients, especially with nonsense mutations. Immunogenicity and its impact on plasma pegunigalsidase alfa pharmacokinetics (PK) was evaluated in 16 FD patients participating in a Phase I/II study of PRX-102 administered IV every other week in three cohorts (Cohort 1, 2 and 3 received 0.2, 1.0 and 2.0 mg/kg PRX-102, respectively).

Results: Immunogenicity: Three male patients developed treatment-induced IgG antibodies to pegunigalsidase alfa (ADA+); this comprised two patients from Cohort 1, one from Cohort 2 and zero ADA+ patients in Cohort 3. All three ADA+ patients became negative in the second year of treatment, consistent with reduced immunogenicity and induced tolerance during pegunigalsidase alfa treatment.

Impact on PK: pegunigalsidase alfa has a favorable PK profile [maximum concentration (Cmax) and overall enzyme amount (AUC)] with a higher amount of active enzyme available throughout the 2-week treatment intervals. The two ADA+ patients in Cohort 1 exhibited a distinct and reversible effect on PK profile resulting in decreased Cmax and AUC at 3 and 6 months compared to Day 1. PK profile parameters improved and returned to the baseline profile after 12 months of treatment, suggesting that the ADA impact on pegunigalsidase alfa PK was transient and reversible. The ADA+ patient in Cohort 2 had a low ADA titer and had stable PK parameters throughout the study.

In summary: pegunigalsidase alfa has an extended circulatory half-life and higher AUC, additionally there is a low immune response toward pegunigalsidase alfa. The reduced immunogenicity of pegunigalsidase alfa is associated with improved PK profiles that may reflect long-term induction of tolerance in previously seroconverted patients and has the potential for clinical benefit in treating FD patients.

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)

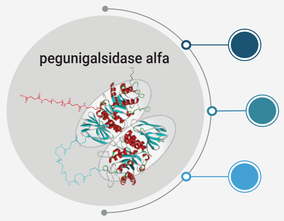
Progressive Gb3 accumulation
Occurs in most tissues and cell types

Variable phenotype
Classic versus Non-Classic; Depends on genotype (mutation) and gender

Available Treatments
agalsidase beta: Approved in the US & the EU. Administrated IV at 1 mg/kg body weight (USPI).
agalsidase alfa: Approved in the EU. Administrated IV at 0.2 mg/kg body weight (SMPC).

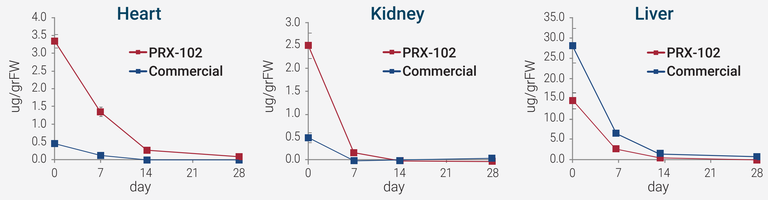
Unmet clinical need
- Continuous disease progression Immune response: Infusion reaction and long-term efficacy
- Safety profile especially in males with classic Fabry disease

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

Prolonged activity in target organs of Fabry mice*



- pegunigalsidase alfa (PRX-102) show increased delivery of the active enzyme to the target organs, heart and kidney, in Fabry mice than existing ERTs.
- pegunigalsidase alfa show reduced clearance by the liver.

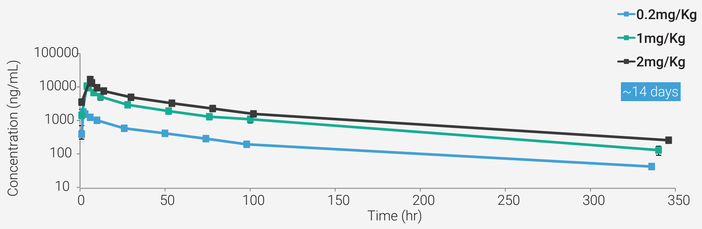
*Kizhner et al 2015

Results

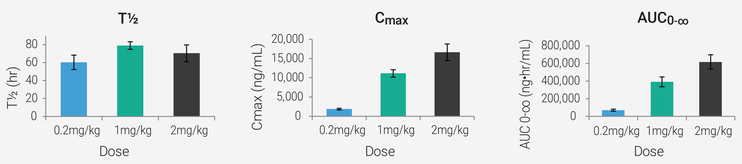
Pharmacokinetics (PK)

Increased stability and extended half-life

PK profile following treatment with escalating dose of pegunigalsidase alfa

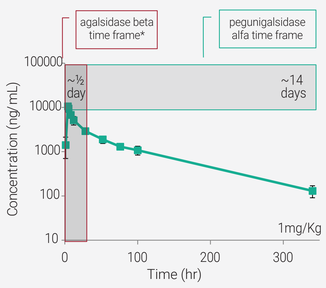


pegunigalsidase alfa PK parameters indicate dose dependency



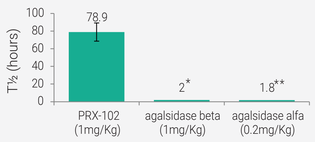
Available enzyme in the circulation throughout the two-week intervals between IVs

Plasma PRX-102 concentration vs. time

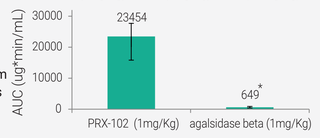


Substantially greater enzyme activity than current ERTs*,**

T½: Approx. 80 hours



AUC (0-∞): >35 fold from current ERTs



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

Pharmacokinetics data of pegunigalsidase alfa (PRX-102): Phase I/II studies show that the PEGylation and cross-linking of the alpha-Gal-A enzyme resulted in a substantially longer plasma half-life, higher Cmax, 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 over the two-week intervals between the infusions, which may indicate a significantly greater target organ availability of the enzyme.

Immunogenicity

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

Immune Tolerance*

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

The PEGylation and cross-linking of alpha-Gal-A enzyme generate a long-lasting enzyme presence, which offers potential protection against the formation of anti-drug antibodies (ADA). This protection is possibly due to the inhibition of antigen processing and presentation by APC and further recognition by T-helper cells, thus preventing T-cell activation, limiting the activation of antigen-specific B cells, and as a result, reducing the risk for the generation of treatment-induced ADA (Ing et al 2016).
Furthermore, the PEG moieties bound only at one end have the potential for a masking effect of exposed epitopes by PEG molecules (Turecek et al 2016). pegunigalsidase alfa thus also has the potential to induce immune tolerance due to improved stability and continuous exposure.

Immunogenicity evaluation – current clinical experience (n=16)

Low incidence of ADA:
3/16 patients -> 19%

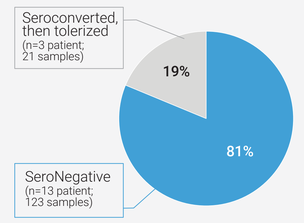
Low titers
Max titer 4633

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



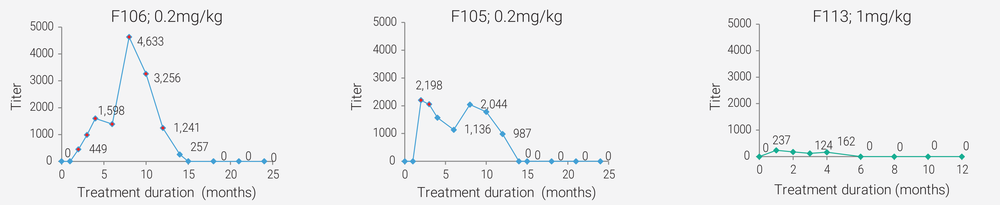
- Serum samples were withdrawn once a month for 4 first months and then once every 2 months
- 144 samples were analyzed* of which 123 were ADA negative
- Confirmed positive samples further characterized* for:
  - Neutralizing activity
  - Anti glycan
  - Anti PEG

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

Immunogenicity of pegunigalsidase alfa: A rigorous evaluation of ADA was conducted in the Phase I/II studies of ERT naïve Fabry patients treated with pegunigalsidase alfa. Samples for immunogenicity evaluation were collected at the baseline visit, weeks 4, 8, and 12 and months 4, 6, 8, 10, and 12, as well as two months after the last infusion. The assays for ADA evaluation are all validated, precise, robust and sensitive in accordance with the current US and EU guidelines. **As shown above, the immunogenicity clinical data of phase I/II studies showed a low incidence of treatment-induced ADA with low titers. Furthermore, all three ADA-positive patients turned to be negative for ADA after 12M of treatment, indicating induction of immune tolerance.**

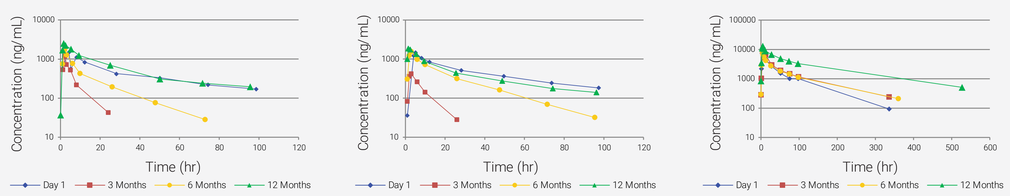
Transient and reversible impact of ADA (n=3) on PK

ADA+ : IgG Titers



nAb positive samples are indicated in red

PK profiles



Following treatment with pegunigalsidase alfa, only three patients developed treatment induced anti-drug IgG antibody. Different titer levels and pattern, and a different impact on PK were shown. For one (1mg/kg) patient, the anti-drug antibody had no effect on PK profiles; for the other two patients (0.2mg/kg), the anti-drug antibody had transient and revisable effect on PK profile throughout the course of treatment. All three patients turned to be seronegative after the first year of treatment.

pegunigalsidase alfa: Pharmacokinetic and immunogenicity conclusions from Phase I/II studies

01 Markedly extended circulatory half-life and higher AUC compared with other ERTs

02 Low incidence of treatment-induced ADA with reversible & transient effect on PK

03 ADA response was transient, and tolerization was observed

04 ADA positivity had no observed impact on safety and efficacy

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