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

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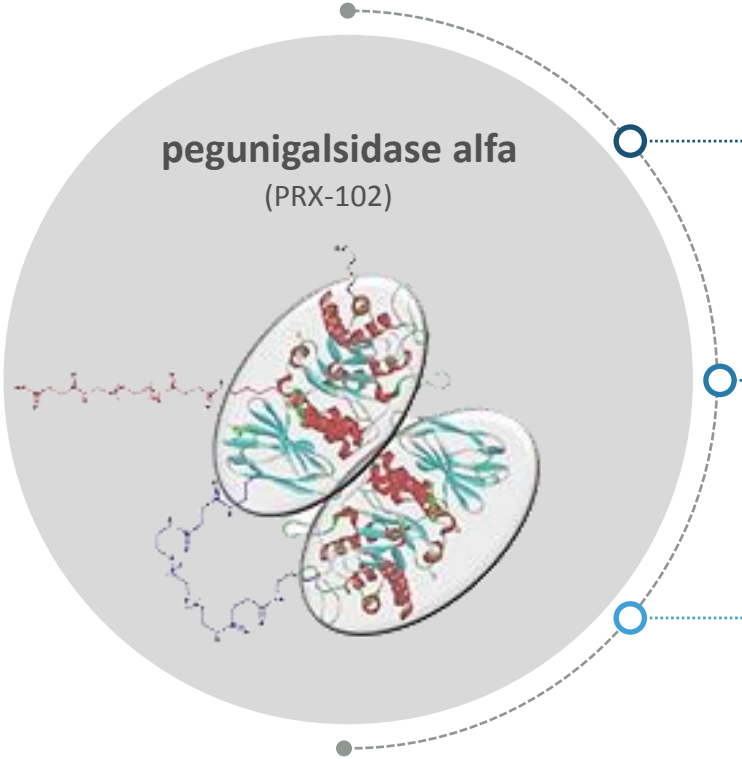
pegunigalsidase alfa: PEGylated, Chemically Modified α-Gal-A Enzyme



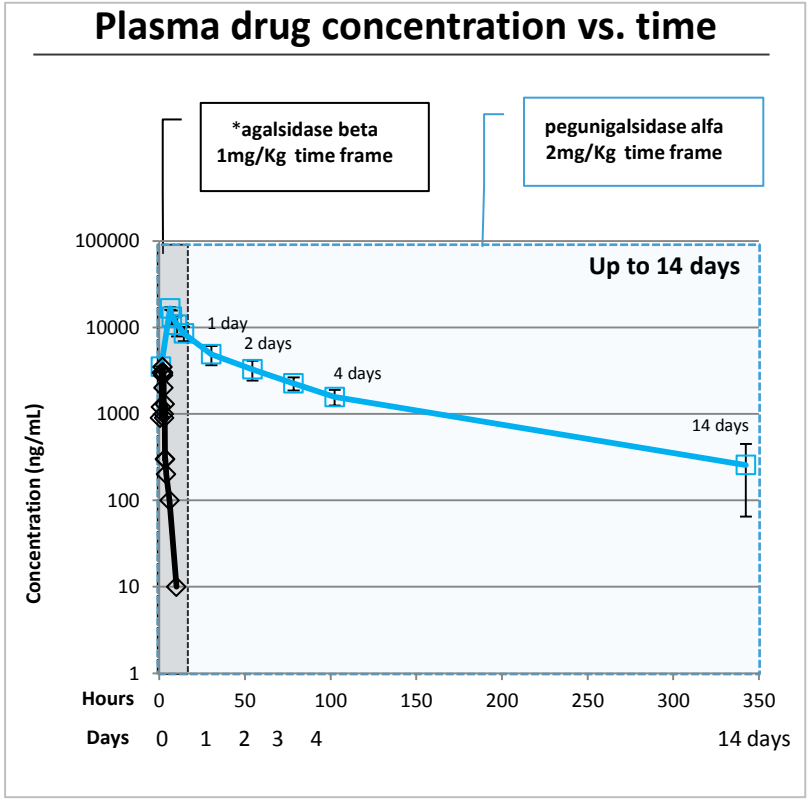
Subunits linked through a **2KDa PEG cross-linker** resulting in 114 kDa enzyme. Contains additional **PEG moieties** bound to only one subunit through a lysine residue

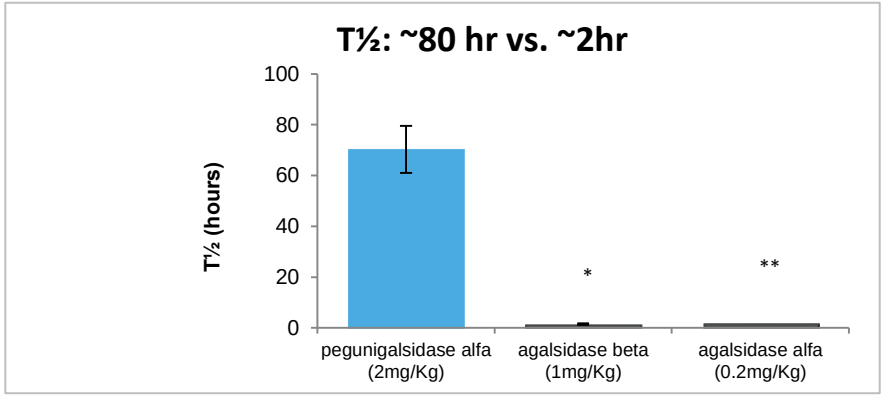
Shown extended half-life and stability in plasma as well as lysosomal-like conditions, while reaching target organs and subcellular lysosomes

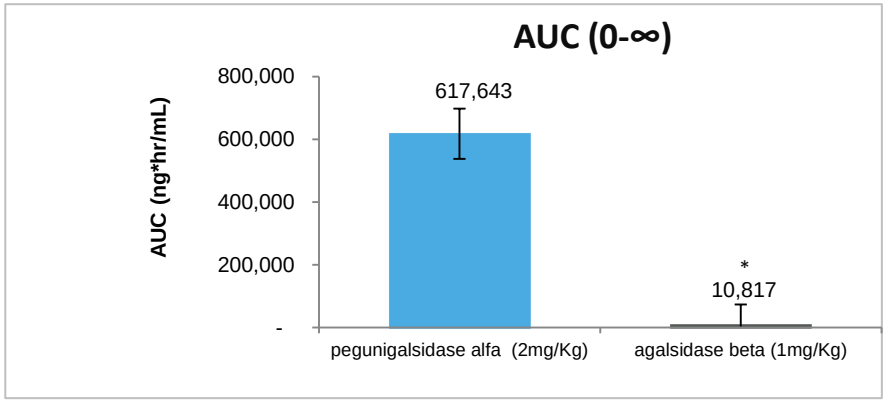
PEG moieties are masking some enzyme epitopes which could be recognized by the immune system → Potentially reducing the immune response to the enzyme plus reduced cross reactivity to pre-existing ADA

Pharmacokinetics: pegunigalsidase alfa

Longer half life and higher exposure compared to other ERTs





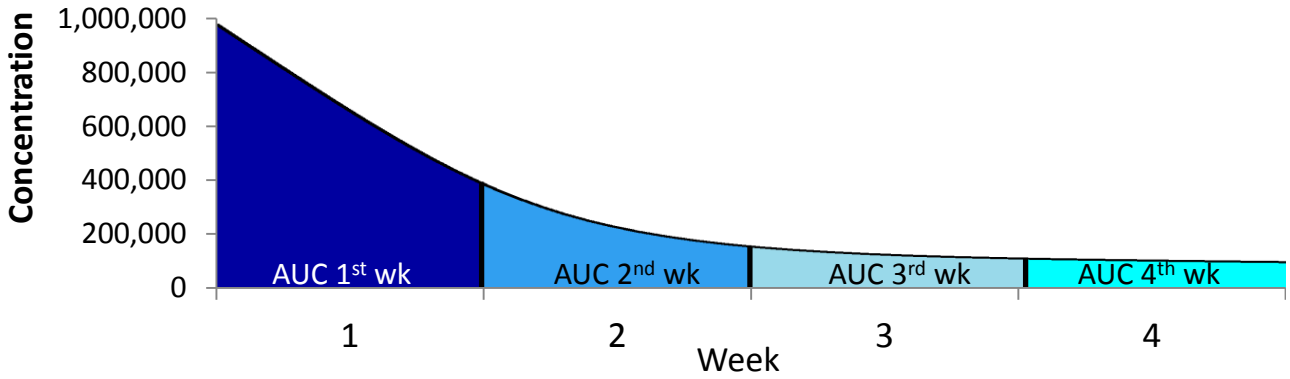


*agalsidase beta – USPI ; ** agalsidase alfa –SMPC; AUC units: ng•hr/mL; 1ng•hr/mL = 0.06 µg•min/mL

Pre-study Design Projection Modeling Approach

- 2 mg/Kg PK data obtained from the Phase I/II study were the bases for the 4 weeks regimen modeling
- Weekly Partial AUC and weekly Average Concentration (C_{ave}) enabled the estimation of the drug availability on weeks 1, 2, 3 and 4 of pegunigalsidase alfa

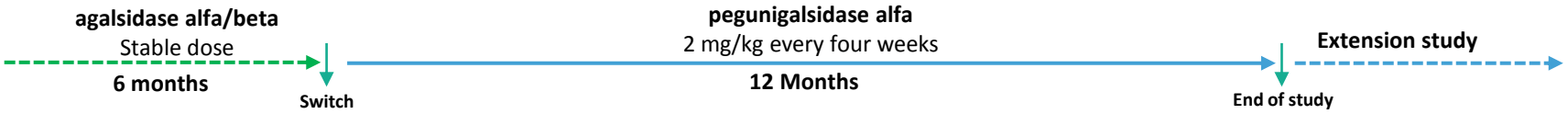
Schematic illustration of pegunigalsidase alfa PK profile for 4 weeks intervals



BRIGHT- Study Objective and Design

PB-102-F50 NCT03018730

- Open label switch over study to evaluate the safety and efficacy and pharmacokinetics of **2.0 mg/kg** pegunigalsidase alfa **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 (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:**
    alpha galactosidase activity less than lower limit of normal
  - **Females:**
    historical genetic test results consistent with Fabry mutations
- **eGFR CKD-EPI ≥ 30 ml/min/1.73 m^2 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/1.73m^2**
- 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

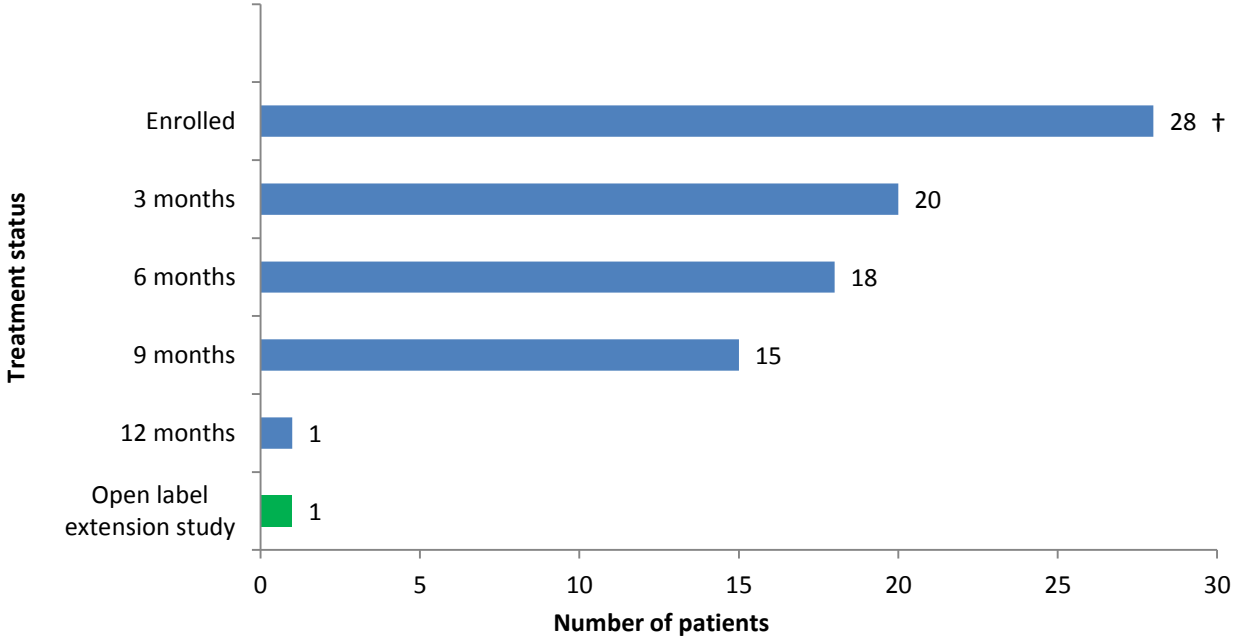
Baseline Characteristics of 25 Patients

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

Preliminary Results

Patients Treatment Duration Up To December 23rd 2018



- Currently samples from 15 patients underwent PK and ADA 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

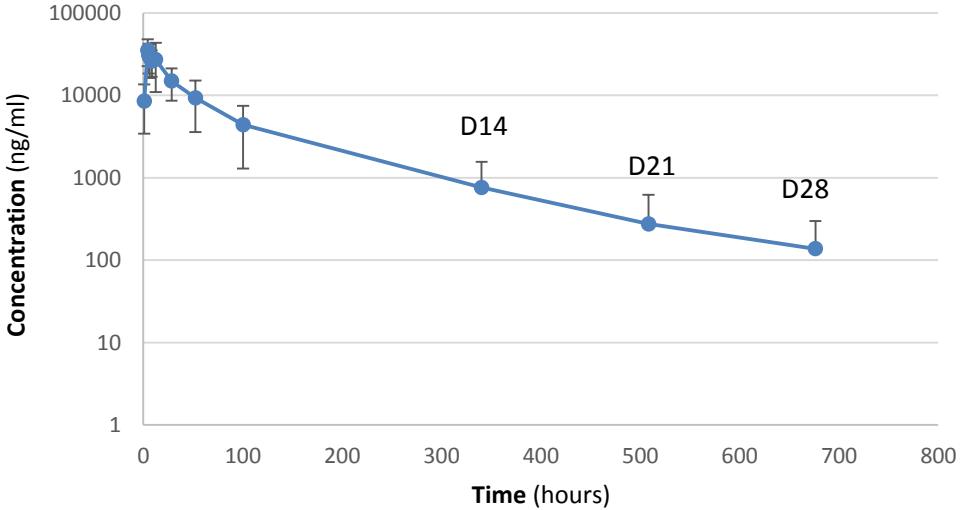
Pharmacokinetics (PK) Data

pegunigalsidase alfa PK profile

Method

- Blood samples were taken for PK analysis 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

Mean plasma pegunigalsidase alfa levels (n=15)



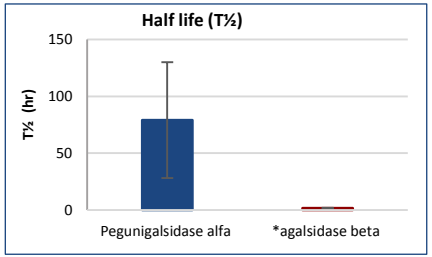
Results

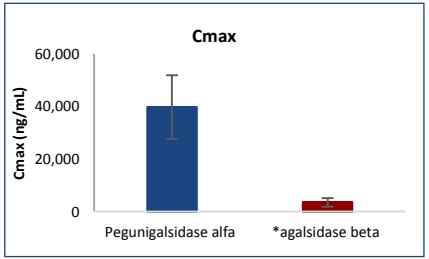
- **pegunigalsidase alfa was found to be present in the plasma throughout the 4 week infusion interval**
- **Activity results indicated that pegunigalsidase alfa remained active over the 4 weeks**

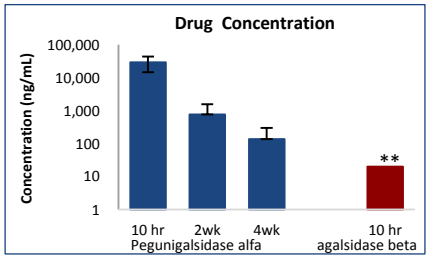
Preliminary Pharmacokinetics (PK) Data - Confirming Study Assumptions

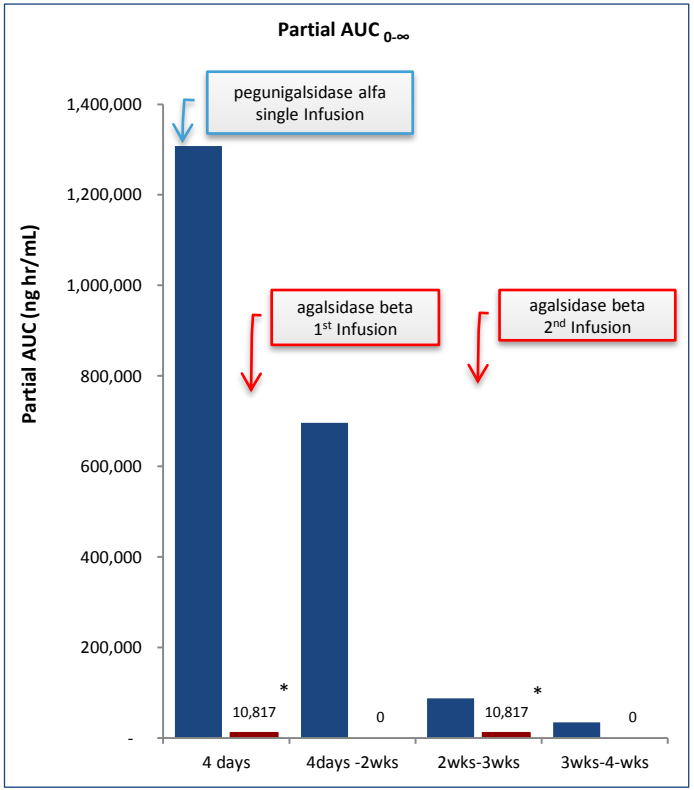
pegunigalsidase alfa (2mg/kg E4W) *vs.* published agalsidase beta data (1mg/kg E2W)

- 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 weeks 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

Preliminary Pharmacokinetics (PK) Data

Pre-existing anti-drug antibodies (ADA) effect

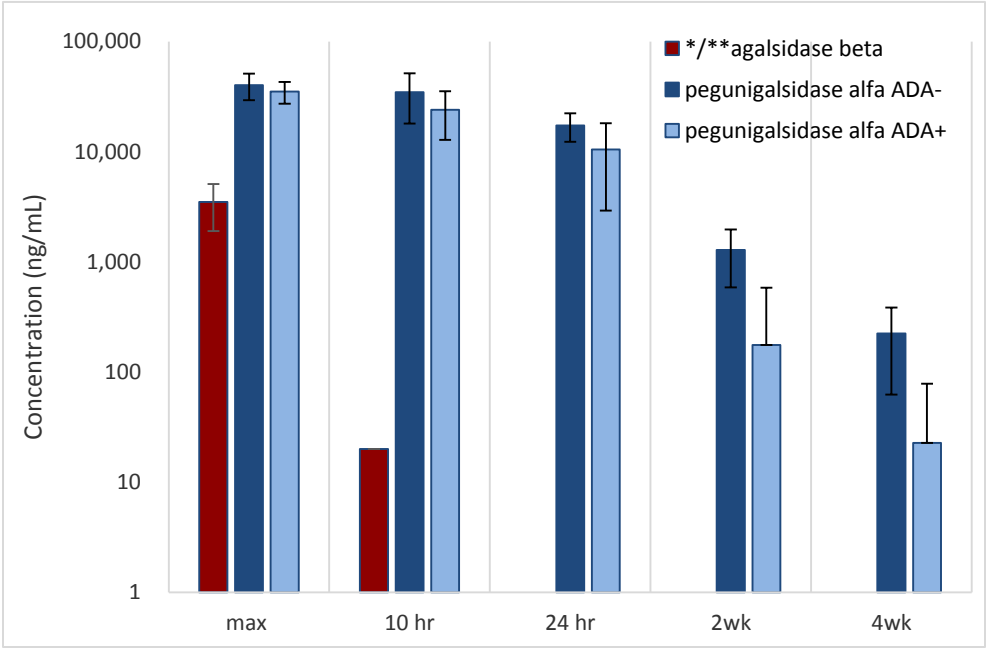
Method

- Serum samples for pre-dosing ADA status were tested using validated assays
- N=15, all previously treated with agalsidase beta

Results

- Single infusion of 2mg/Kg pegunigalsidase alfa remains in circulation for up to 4 weeks regardless of pre-existing ADA that were generated prior to the switch
- pegunigalsidase alfa concentration in the circulation was higher than agalsidase beta, based on published information, even in the presence of anti drug antibodies

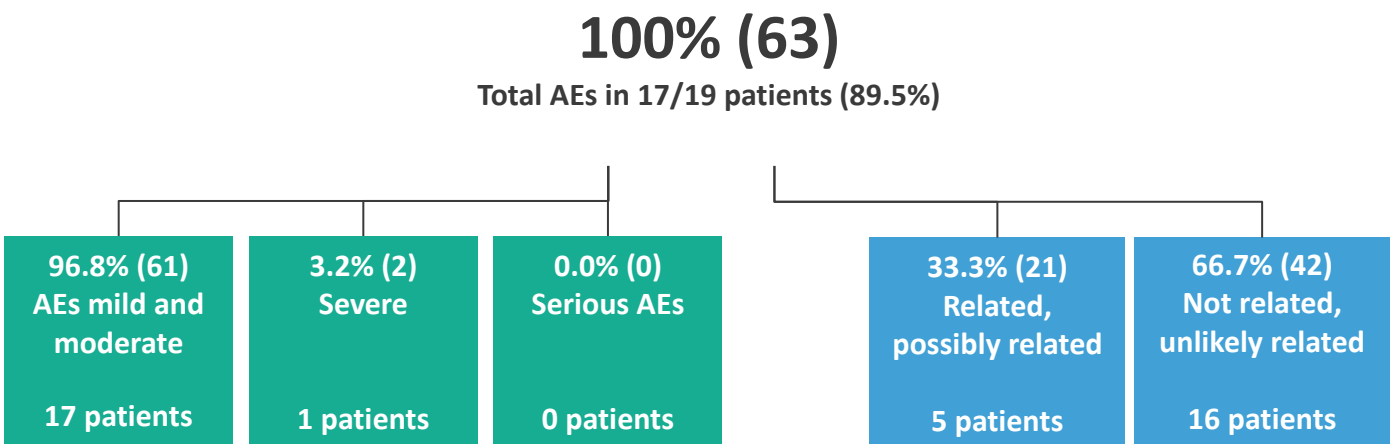
ERT concentrations over 4 weeks post infusion



* Fabrazyme USPI; **Eng et al 2001

Safety (8.6 patient years – cutoff date August 2018)

N=19 (16M, 3F)



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

- 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 and regimen of 2.0 mg/kg pegunigalsidase alfa every 4 weeks
- Patients treated with either agalsidase alfa or agalsidase beta were switched to receive pegunigalsidase alfa 2mg/kg E4W
- Preliminary PK study 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
- pegunigalsidase alfa remains in the circulation for up to 4 weeks including in patients with pre-existing ADA+
- Preliminary study results show that the treatment is well tolerated
- First patients are rolling over to a long term Extension study

Acknowledgements

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- **Patients and their families**
- **Study site clinical teams**
- **Co-authors:** *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]*

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