Pegunigalsidase alfa, a novel PEGylated Enzyme Replacement Therapie , evaluated in Fabry patients with progressing kidney disease - RCT study design

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ABSTRACT

Fabry disease is an X-linked multisystem lysosomal storage disorder, affecting males and females caused by the deficient of α-galactosidase-A (α-Gal-A) activity. Long-term disease manifestations include progressive renal failure, hypertrophic cardiomyopathy, cardiac rhythm disturbances, stroke and death(1). Two enzyme replacement therapies (ERT) and an oral chaperon therapy are commercially available. The clinical benefit of available treatments may not be as robust as anticipated, especially in the subset of males with 'classic' Fabry disease. In the context of ERT, a combination of factors including dose, dosing interval, presence of anti-drug antibodies, estimated glomerular filtration rate (eGFR) may lead to proteinuria at the time of ERT could explain the less than optimal responses achieved by the currently available ERT(2). Pegunigalsidase alfa is a novel PEGylated homo-dimer ERT which is more stable(3), has a favorable safety profile, potential less development of anti-drug antibodies, and enhanced pharmacokinetic profile (~80 hours half-life and higher AUC) compared to other available ERT(4). Adult Fabry disease patients (males and females) deteriorating in kidney function with annualized eGFR ≤-2 mL/min/1·73 m^2/year while on agalsidase beta have been enrolled into BALANCE, a phase-III double-blind, active control study (NCT02795676), and were randomized (2:1 ratio) to pegunigalsidase alfa or continue agalsidase beta for 2 years at 1 mg/kg every other week. The primary outcome is the difference in mean annualized slope of eGFR during the study between the two groups. The current work describes the design and methods of the study protocol and the baseline characteristics for approximately 75 patients enrolled at 29 US and European study sites by: age, sex, enzymatic activity, genetic mutations, Fabry disease symptoms, previous Fabry disease treatment length, kidney function (eGFR, eGFR slope, UPCR, Lyso-Gb_3 and anti-drug antibodies pre-treatment status).

PREVIOUS RESULTS FROM PEGUNIGALSIDASE ALFA PHASE I/II STUDY(4)

PHARMACOKINETICS:

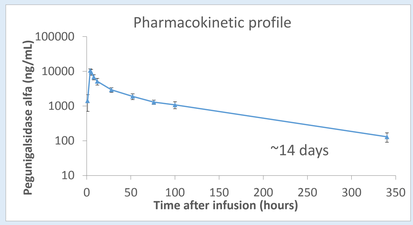
- Prolonged half-life (≈80 hours)
- Two weeks infusion intervals coverage

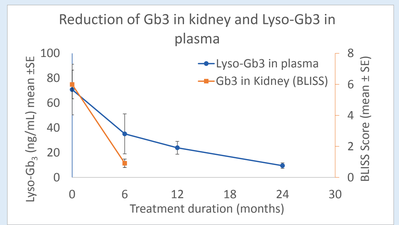
PHARMACODYNAMICS:

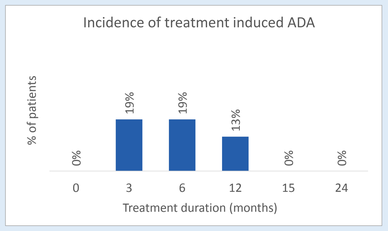
- Correlation between the reduction of Gb_3 in the kidney and the reduction of Lyso-Gb3 in plasma

IMMUNOGENICITY:

- PEG moieties may mask immunogenic epitopes
- Potentially reduces the immune response and cross-reactivity to pre-existing ADA and enabling tolerization in ERT-naïve patients







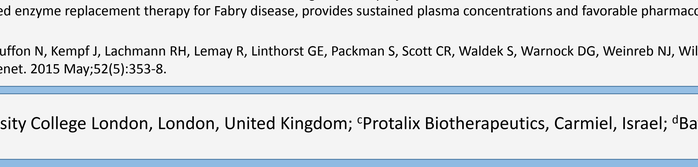
STUDY DESIGN

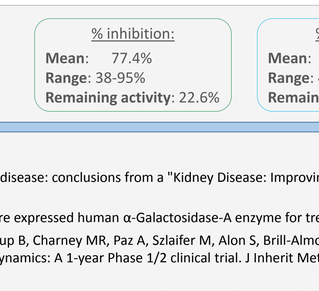
Unmet Clinical Needs (2,5)

- Continuous disease progression (e.g. kidney deterioration)
- Development of immune response to the ERT
- Infusion reactions
- Limited long-term efficacy of the ERT

A randomized, double-blind, active control study evaluating the safety and efficacy of pegunigalsidase alfa compared to agalsidase beta on renal function in patients with Fabry disease previously treated with agalsidase beta.

- Study duration: 24 months
- Study population: 78 adult patients (no more than 50% females)
- Randomization to pegunigalsidase alfa or agalsidase beta with 1 mg/kg EOW:
  - Ratio 2:1 pegunigalsidase alfa to agalsidase beta
  - Stratified by Urine protein to creatinine ratio (UPCR) of < or ≥1 g/g (1000 mg/g) by spot urine sample
- The final analysis at 24 months aims to demonstrating superiority of pegunigalsidase alfa vs. agalsidase beta on renal function





pegunigalsidase alfa:
A novel PEGylated homo-dimer ERT

Main Inclusion Criteria

- Symptomatic Fabry Patients:
  - Males: plasma and/or leucocyte alpha galactosidase activity (normal lab levels) less than 30% mean normal levels and one or more of the characteristic features of Fabry disease (neuropathic pain, cornea verticillata, clustered angiokeratoma)
  - Females: historical genetic test results consistent with Fabry pathogenic mutation and one or more of the described characteristic features of Fabry disease
- Screening eGFR by CKD-EPI equation 40 to 120 mL/min/1.73 m^2
- Linear negative slope of eGFR of ≥ 2 mL/min/1.73 m^2/year based on at least 3 previous serum creatinine values over approximately one year

Main Exclusion Criteria

- History of anaphylaxis or Type 1 hypersensitivity reaction to agalsidase beta
- History of renal dialysis or transplantation
- History of acute kidney injury in the 12 months prior to screening
- Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated or dose changed in the 4 weeks prior to screening
- UPCR > 0.5 g/g (0.5 mg/mg or 500 mg/g) and not treated with an ACE inhibitor or ARB
- Cardiovascular event and/or cerebrovascular event (myocardial infarction, unstable angina) in the 6 month period before randomization
- Congestive heart failure NYHA Class IV

METHODS & RESULTS

Baseline Kidney Function:

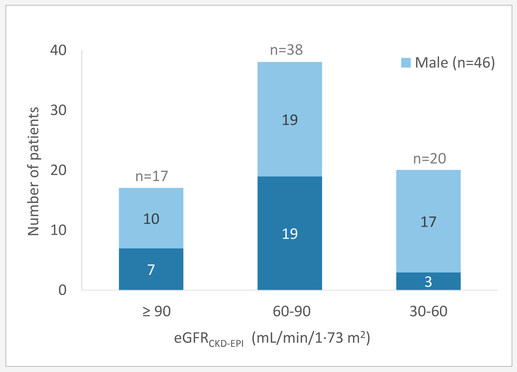
eGFR is an established indicator of CKD and CKD progression and is used as a marker of kidney function and therapeutic efficacy in Fabry disease, change in eGFR is considered a clinically significant endpoint to predict loss of kidney function.

eGFR was calculated from the patient's serum creatinine values using the CKD-EPI formula. About 50% of the patients had eGFR values between 60-90 mL/min/1.73m^2 and the remaining patients were equally distributed between eGFR below 60 and eGFR above 90 (**Panel A**).

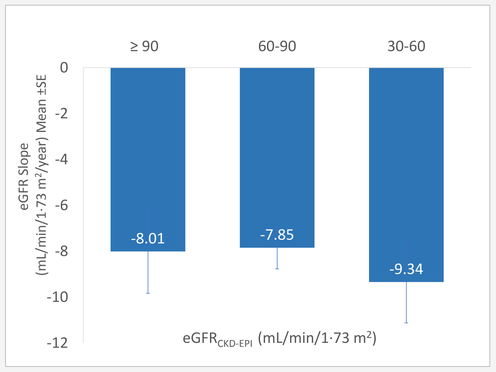
The annualized eGFR slope was determined on at least 3 previous serum creatinine values over approximately one year before screening (**Panel B**).

eGFR and eGFR slope is being evaluated monthly over the study period of 24 month.

A. Number of patients by $eGFR_{CKD-EPI}$ level



B. Annualized slope at screening by $eGFR_{CKD-EPI}$ level



Baseline Characteristics

Parameter		ALL	Female	Male
Number of patients	N	78	30	48
Age started ERT (years)	**mean** ± SE	**37.0** ± 10.2	**39.2** ± 9.8	**35.7** ± 10.3
Age at screening (years)	mean ± SE	**44.8** ± 9.9	**45.2** ± 9.8	**45** ± 10.1
Fabry Disease Biomarkers				
Plasma Lyso-Gb3* (nM)	N	48	16	32
	mean ± SE	**32.7** ± 4.8	**8.5** ± 0.9	**44.7** ± 6.2
	range	(0.8, 143.9)	(2.8,16.2)	(0.8,143.9)
Kidney function - eGFR				
Baseline $eGFR_{CKD-EPI}$ (mL/min/1.73m2)	N	75	29	46
	mean ± SE	**73.3** ± 2.3	**78.2** ± 4.9	**70.9** ± 3.3
	range	(30.0, 125.8)	(47.2, 107.2)	(30.0, 125.8)
eGFR Slope at Screening (mL/min/1.73m2/year)	N	78	30	48
	mean ± SE	**-8.1** ± 0.7	**-8.1** ± 1.2	**-8.1** ± 0.8
	range	(-32.6,-2.1)	(-32.6,-2.3)	(-29.7,-2.1)
Kidney function- UPCR				
Number of patients with UPCR ≥500 mg/gr	N	74	28	46
	n (%)	**21** (28.3%)	**3** (10.7%)	**18** (39.1%)

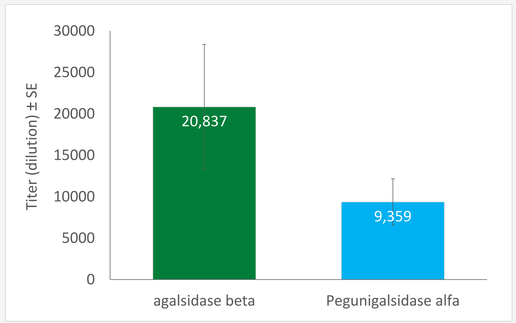
Baseline ADA Status:

In total, as part of the current analysis, 47 available samples from the enrolled patients were tested for anti-drug antibodies (ADA) for both agalsidase beta and pegunigalsidase alfa at screening:

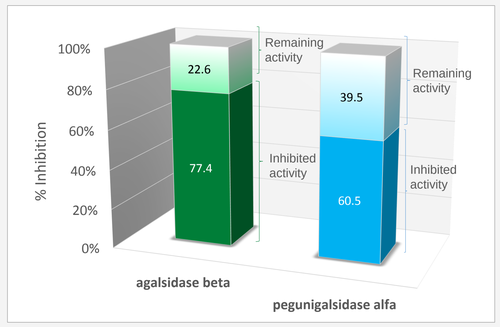
- Females: 1/13 sample tested positive for ADA (7.7%)
- Males: 14/34 sample tested positive for ADA (41%)

These baseline immunogenicity data indicate higher reactivity (titer, **Panel C**) and higher relative (%) inhibition (**Panel D**) toward agalsidase beta compared to pegunigalsidase alfa, potentially leaving higher levels of active enzyme available to reach target organs when treating with pegunigalsidase alfa.

C. ADA titers to agalsidase beta and pegunigalsidase alfa



D. Neutralizing activity of ADA positive samples



% inhibition:
Mean: 77.4%
Range: 38-95%
Remaining activity: 22.6%

% inhibition:
Mean: 60.5%
Range: 41-85%
Remaining activity: 39.5%

CONCLUSIONS

- Pegunigalsidase alfa is a novel PEGylated stable homo-dimer ERT(3), with prolonged half-life, which has shown to reduce both Gb_3 burden in kidney and Lyso-Gb_3 in the plasma(4).
- BALANCE Study (NCT02795676), is a randomized, double blind, active control, multicenter study, fully enrolled, aiming at demonstrating pegunigalsidase alfa superiority in kidney function (eGFR) at 24 months versus agalsidase beta.
- BALANCE enrolled adult Fabry patients previously treated with agalsidase beta with deteriorating kidney function to be treated with either pegunigalsidase alfa or agalsidase beta (2:1) for 24 months.
- The baseline characteristics of the patients enrolled into the BALANCE study includes:
  - Approximately 50% of the patients had eGFR values between 60-90 mL/min/1.73 m^2 where the remaining patients were equally distributed to have eGFR below 60 and eGFR above 90.
  - The mean annualized slope at screening was -8.01 ± 1.8(SE) with lowest mean slope shown for patients with low $eGFR_{CKD-EPI}$ 30-60 mL/min/1.73 m^2.
  - The presence of ADA was not an exclusion criteria for the study. ADA reactivity was evaluated at screening for both agalsidase beta and pegunigalsidase alfa, indicating higher reactivity (titer) and higher % inhibition for agalsidase beta compared to pegunigalsidase alfa, potentially leaving higher levels of active enzyme available when treating with pegunigalsidase alfa.

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