This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

SPONSOR is committed to publicly disclosing all medical research results that are significant to patients, health care providers or payers—whether favorable or unfavorable to the SPONSOR product—in an accurate, objective and balanced manner in order for our customers to make more informed decisions about our products.
Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

SYNOPSIS

Sponsor: Shire	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Replagal® (agalsidase alfa)	**Volume:**	
Name of Active Ingredient: Replagal® (agalsidase alfa)	**Page:**	

Study Title:
A Phase II Comparability Study between Replagal Produced from Agalsidase Alfa Manufactured by 2 Different Processes in Adult Male Patients with Fabry Disease

Investigators and Study Centers: Multicenter (see Appendix 12.1.4)

Publication (reference): Not Applicable

Studied Period:

06 December 2011 (first patient enrolled) to
28 December 2012 (last patient completed)

Study Phase: II

Objectives: The primary objective of this study was to compare the pharmacodynamic (PD) profile, as assessed by urine sediment globotriaosylceramide (Gb_3) levels before and after the transition from Replagal RB (manufactured by the roller bottle process) to Replagal AF (manufactured by the bioreactor process).

The secondary objectives of this study were:

- To compare the pharmacodynamic (PD) profile as assessed by plasma Gb_3 levels, before and after the transition from Replagal RB to Replagal AF
- To compare the pharmacokinetic (PK) profiles and exposure before and after the transition from Replagal RB to Replagal AF
- To evaluate the safety and tolerability of Replagal before and after the transition from Replagal RB to Replagal AF

Methodology: This was an open-label, single-arm, multicenter, phase II study to compare the PD and PK parameters of Replagal (agalsidase alfa) produced using 2 different manufacturing processes (Replagal RB and Replagal AF). Approximately 30 adult male patients with Fabry disease between 18 and 65 years of age were planned to be enrolled to ensure that at least 20 evaluable patients were obtained.

The study was open to patients with any of the following ERT history: (1) naïve to ERT; (2) at the time of enrollment had received Replagal RB for at least 26 weeks; (3) at the time of enrollment had received Replagal RB, but for fewer than 26 weeks. The actual enrolled study population included only patients who had received Replagal RB for at least 26 weeks of at the time of enrollment.

After informed consent was obtained, a retrospective chart review (if available) was performed for all patients prior to Screening. The chart review included the following: medical history, ERT history (eg, Fabrazyme and Replagal), genetic mutation analysis or other documentation of Fabry disease, plasma and urine Gb_3 measurements (if available) and concomitant medication data (as available).

The study duration was approximately 18 weeks, comprising a screening period of approximately 14 days, a treatment period of 15 weeks during which all patients received 1 infusion of 0.2 mg/kg Replagal RB (Week 0), followed by 7 EOW infusions of Replagal AF (beginning at Week 2), and an End-of-Study (EOS) visit (Week 16).

Fasting blood specimens and an 8-hour urine specimen collection for PD assessments were obtained prior to the EOW dosing from Week 2 to Week 14 and at the End-of-Study visit at Week 16. Blood specimens for PK were obtained at Week 0, 2, and 14. The safety and tolerability endpoints were assessed throughout the study through the reporting of adverse events, laboratory tests, vital signs, ECGs, the use of concomitant medications, physical examinations, and anti-agalsidase alfa antibodies.

Number of Patients (Planned and Analyzed):
Approximately 30 patients were planned; 17 patients met eligibility criteria and received treatment in the study; all of these patients were analyzed for PD, PK, and safety.

Diagnosis and Main Criteria for Inclusion:
Eligible patients were adult male patients diagnosed with Fabry disease. Patients currently on dialysis, expected to begin dialysis during the study, who had received a kidney transplant, or on the renal transplant waiting list were excluded from the study. Patients were to test negative for anti-agalsidase alfa antibodies at screening.

Test Product, Dose and Mode of Administration, Lot Number:
Replagal RB 0.2 mg/kg IV EOW, Lot number: [redacted]

Replagal AF 0.2 mg/kg IV EOW, Lot numbers: [redacted]

Duration of Treatment: Patients who had received Replagal RB for at least 26 weeks prior to entering the study received 1 dose of Replagal RB at baseline before switching to Replagal AF. They then received 14 weeks of treatment with Replagal AF.

Reference Therapy, Dose and Mode of Administration, Lot Number:
Not applicable

Criteria for Evaluation:

Pharmacodynamics:
At time points throughout the study, 8-hour urine and fasting plasma specimens were collected for assessment of urine and plasma Gb_3 levels. Change from baseline to the end of study was assessed for urine and plasma Gb_3 levels.

Pharmacokinetics:
At time points throughout the study, serum specimens were collected to derive PK parameters including:

- maximum observed serum enzyme activity (C_{max})

- C_{max} normalized for dose ([C_{max}]/[mU/kg])
- time of C_{max} (T_{max})
- area under the serum enzyme activity-time curve from time zero to the last sampling time at which serum enzyme activities were measurable ($AUC_{0\text{-}last}$)
- $AUC_{0\text{-}last}$ normalized for dose ([$AUC_{0\text{-}last}$]/[mU/kg])
- area under the serum enzyme activity-time curve extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- $AUC_{0\text{-}\infty}$ normalized for dose ([$AUC_{0\text{-}\infty}$)/[mU/kg])
- terminal rate constant (λ_Z) derived from the slope of the log-linear regression of the terminal portion of the serum enzyme-activity-time curve
- terminal half-life ($t_{½}$) calculated as 0.693/ λ_Z
- mean residence time extrapolated to infinity (MRT_{inf}), calculated as $AUMC_{0\text{-}\infty}/AUC_{0\text{-}\infty}$
- total clearance (CL) calculated as dose/ $AUC_{0\text{-}\infty}$
- volume of distribution at steady-state (V_{ss}) calculated as MRT_{inf}·CL
- distribution of volume (V_z) derived from the elimination phase

Pharmacokinetic parameters were computed from individual α-galactosidase A activity-time data and summarized at each of these time points for the following PK parameters:

- Dose-normalized area under the enzyme activity-time curve from time 0 to the time of the last quantifiable sample ($AUC_{0\text{-}last}$/Dose)
- Dose-normalized area under the enzyme activity-time curve (AUC) extrapolated to infinity ($AUC_{0\text{-}\infty}$/Dose)
- Dose-normalized maximum serum enzyme activity (C_{max}/Dose)

Safety:
Safety assessments included adverse events, clinical laboratory evaluations, electrocardiograms (ECGs), vital signs, physical examinations, anti-agalsidase alfa antibody, and concomitant medications/surgical procedures.

Statistical Methods:
This study was intended to be descriptive and was not powered to conduct a comparison of Replagal RB and AF. Therefore, no formal statistical tests were performed for PD or PK parameters.

For exploratory purposes, analyses of changes over time from baseline to follow-up PD

assessments were performed.

Continuous PK data were summarized by the following: number of observations, mean, standard deviation (SD), geometric mean, coefficient of variation (CV), median, minimum, and maximum value. Categorical PK data were summarized with frequencies and/or percentages. For reporting of the serum activity sample, tabulation was presented by product and scheduled PK time point.

For continuous variables other than PK, summary statistics consisted of the sample size, mean, standard deviation (SD), minimum, median, and maximum. For continuous PD endpoints, 90% confidence intervals (CI) of the mean or median, as appropriate, were also provided. Categorical discrete data were summarized using frequency and percentages of patients.

Summary of Results

Pharmacodynamics:

The mean urine Gb3 at Baseline was 919.27 nmol/g creatinine (90% confidence interval (CI) of the mean: 500.0 0, 1338.54). At EOS the mean was 890.59 nmol/g creatinine (90% CI of the mean: 467.69, 1313.49); this was an average mean decrease of -28.68 nmol/g creatinine (90% CI: -110.26, 52.90). After adjusting for the baseline value, there was an average percent increase of 1.65% (90% CI: -13.07, 16.38). The 90% CIs of the change and percent change from baseline both contain the value of zero, therefore there was no difference between urine Gb3 from the Replagal RB period and urine Gb3 14 weeks after the switch to Replagal AF.

The mean plasma Gb3 at baseline was 5.276 nmol/mL (90% CI: 4.614, 5.937). At EOS the mean plasma Gb3 was 5.446 nmol/mL (90% CI 4.764, 6.128); this was an average mean increase of 0.170 nmol/mL (90% CI -0.042, 0.383) and an average percent increase of 3.29% (90% CI -0.73, 7.30). Based on the 90% CIs of the change and percent change from baseline there was no difference in plasma Gb3 between the Replagal RB treatment period and the end of the Replagal AF treatment period.

There were no observed differences between Replagal RB and Replagal AF for urine and plasma Gb3 levels, respectively, with sensitivity analyses using a least squared mean model for mean change over time as well as a random coefficient model for rate of change.

Pharmacokinetics:

The PK profiles and primary PK exposure parameters (ie, AUC and C_{max}) of Replagal RB and Replagal AF indicate that Replagal AF exhibited lower systemic exposure and a more rapid clearance rate, compared to Replagal RB.

Safety:

There were no deaths or patient discontinuations due to TEAEs or for any other reasons.

The analysis of safety parameters (AEs, concomitant medications, IRRs, serum chemistry laboratory assessments, and ECGs) did not indicate differences in the safety profile between Replagal AF and RB.

There were no clinically meaningful changes in serum chemistry values.

There were no reported clinically significant abnormal changes in physical examination findings

or vital signs

There were no clinically meaningful differences in ECG results.

The development of anti agalsidase alfa antibodies did not correlate with IRR occurrence.

CONCLUSIONS

This section contained Summary and Conclusion information which could be considered promotional in nature. This section has been removed to allow the reader to draw their own conclusions.

Final Date: 27 June 2013