STATISTICAL ANALYSIS PLAN

Study Sponsor:	Shire Human Genetic Therapies, Inc. (Shire) 300 Shire Way Lexington, MA USA 02421
Protocol Title:	A Multicenter Open-label Treatment Protocol to Observe the Safety of Replagal® (agalsidase alfa) Enzyme Replacement Therapy in Canadian Patients with Fabry Disease
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SAP Author:	PPD
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AF	animal component free bioreactor manufacturing process
agalAF1	agalsidase alfa animal component-free bioreactor manufacturing process
BUN	blood urea nitrogen
CFDI	Canadian Fabry Disease Initiative
CRF	case report form
CSR	clinical study report
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EOW	every other week
ERT	enzyme replacement therapy
EU	European Union
FDA	Food and Drug Administration
HC	Health Canada
ICH	International Conference on Harmonisation
IgA	Immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IRR	Infusion-related reactions
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
Max	maximum

NA	not applicable
NAb	neutralizing antibody
NDS	new drug submission
PT	preferred term
RB	roller bottle manufacturing process
Replagal AF	Replagal manufactured using bioreactor method with animal-free components
Replagal RB	Replagal manufactured using a roller bottle method
SAE	serious adverse event
SAP	statistical analysis plan
sNDS	supplemental new drug submission
SOC	system organ class
SOE	schedule of events
SD	standard deviation
TEAE	treatment-emergent adverse event

1 INTRODUCTION

1.1 Background

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Shire Protocol HGT-REP-081.

This phase IIII/IV study is being completed to provide analysis of the safety of Replagal® (agalsidase alfa) in Canadian patients with Fabry disease.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by Heath Canada (HC), and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The following documents were reviewed in preparation of this SAP:

- The original HGT-REP-081 protocol issued on 30 September 2010, Amendment 1 issued on 23 November 2010, Amendment 2 issued on 06 December 2010, Amendment 3 issued on 15 September 2011, Amendment 4 issued on 28 March 2013, and Amendment 5 issued on 27 March 2015 [1]

- Case Report Forms (CRFs) Specification for Protocol HGT-REP-081

- ICH Guidance on Structure and Content of Clinical Study Reports (E3) [2]

- ICH Guidance on Statistical Principles for Clinical Trials (E9) [3]

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study.

This SAP outlines the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

1.2 Study Rationale

The original Replagal New Drug Submission (NDS) was approved in Canada in 2004, indicated for long-term treatment in patients with Fabry disease. In March 2009, Shire submitted a Supplemental NDS (sNDS) for Replagal bioreactor (agalAF1 or AF) drug substance process by implementing a bioreactor process in place of the previously employed roller bottle (RB) process and eliminating animal-sourced raw materials. There are no changes to the Replagal drug product formulation, manufacturing site, manufacturing process, and container closure. Supplies of the roller bottle Replagal (Replagal RB) are no longer manufactured, and this protocol provides a mechanism to maintain uninterrupted supply of Replagal (Replagal AF) to Canadian patients.

The purpose of this SAP is to outline the planned analyses to be completed to support the CSR for Protocol HGT-REP-081, and to document technical and detailed specifications for the final analysis of the data collected for protocol HGT-REP-081. The statistical methods and analyses described here are based on those presented in the study protocol (original: 30 September 2010; amendment 1: 23 November 2010; amendment 2: 06 December 2010; amendment 3: 15 September 2011; amendment 4: 28 March 2013; amendment 5: 27 March 2015). The analyses identified in this SAP will be included in regulatory submissions. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR or addendum to CSR as needed, and would be to further explore for known or new safety signals, or answer specific regulatory concerns.

2 STUDY OBJECTIVES

The objective of this protocol is to observe the safety of Replagal in Canadian patients with Fabry disease.

3 STUDY DESIGN

3.1 General Description

This is an open-label, single-arm, multicenter, Phase III/IV safety study and is designed to evaluate the safety of Replagal in Canadian patients with Fabry disease. All patients may continue to receive Replagal in this treatment plan until Replagal AF is commercially available for the patient, the patient's participation or the study is discontinued, whichever comes first. Safety data will be collected throughout the treatment protocol.

A minimum of 60 patients with Fabry disease and up to 200 patients are expected to participate in this protocol. Two cohorts are included in the protocol; Cohort 1 is for patients from the Canadian Fabry Disease Initiative (CFDI) and provides Replagal treatment on an every other week (EOW) regimen and cohort 2 is only for patients who participated in REP001a and provides Replagal treatment on a weekly regimen. Patients may begin to enroll in the treatment protocol as soon as the eligibility criteria are fulfilled and informed consent is obtained.

3.2 Discussion of Study Design, Including the Choice of Control Groups

This protocol is intended to follow the same schedule and assessments as the CFDI protocol, and the safety visits in this protocol are intended to coincide with the twice annual or annual visits recommended by the CFDI. This includes the collection of screening data which will be obtained up to 6 months prior to the patient's initiation of treatment with Replagal, to align with the patients' current biannual assessment schedule in the CFDI.

For patients in Cohort 1, Replagal will be administered at a dose of 0.2 mg/kg body weight as an intravenous (IV) infusion over 40 (± 10) minutes EOW (± 5 days).

For patients in Cohort 2, Replagal will be administered at a dose of 0.2 mg/kg body weight as an IV infusion over 40 (± 10) minutes weekly (± 2 days).

Based on the weights obtained at the biannual visits, or annual visits, as applicable, the dose should be updated if the weight change is ± 5% from the initial weight or from the previous visit, or at the discretion of the investigator.

3.3 Method of Assigning Patients to Treatment Groups

This is a single-arm study, thus all patients will be assigned to one treatment group.

3.4 Method of Assigning Patients to Cohorts

Only patients who have participated in REP001a will be enrolled in Cohort 2 to receive weekly dosing with Replagal. All other patients will be enrolled in Cohort 1 to receive EOW dosing with Replagal.

3.5 Randomization and Blinding

This is an open-label study, thus neither randomization nor blinding will occur.

3.6 Determination of Sample Size

Health Canada requested that a minimum number of patients be specified in order to obtain meaningful safety data from this safety clinical trial. With a minimum of 60 subjects, there will be at least a 95% chance of observing at least one adverse event (AE) of a given type, if the event has a frequency of 5%.

4 EFFICACY AND SAFETY VARIABLES

4.1 Schedule of Evaluations

Complete schedules of events (SOE) for Cohort 1 and Cohort 2 are provided in Appendix 1 and Appendix 2. This protocol is intended to follow the same schedule and assessments as the CFDI protocol, and the safety visits in this protocol are intended to coincide with the biannual or annual visits recommended by the CFDI.

Patients enrolled in this study must be treated in accordance with current Canadian guidelines for the treatment of Fabry disease.

4.2 Primary Efficacy Endpoint

There is no primary efficacy endpoint in this study. The primary endpoint is safety as described in section 5.4.

4.3 Secondary Efficacy Endpoint

Not applicable

4.4 Safety Assessments

Safety and tolerability will be assessed by AE reporting, changes in vital signs (from immediately before to immediately after every infusion), and changes from screening assessments to biannual visits in physical examination, blood tests, and anti-agalsidase alfa antibodies (in serum).

4.5 Drug Concentration Measurements

Not applicable

5 STATISTICAL ANALYSIS

5.1 General Methodology

All analysis will be performed by the Biometrics Department, Shire HGT using SAS® Software version 9.3 or higher (SAS institute, Cary, NC, USA). All study data will be presented in by-patient data listings.

No formal statistical tests will be conducted. Tabular summaries of patient baseline demographic and clinical characteristics, patient disposition, medical history, vital signs, AEs, anti-agalsidase alfa antibody, and infusion information will be produced for the safety population. The safety population includes all patients who receive at least one full or partial infusion of Replagal. Continuous data collected prior to receiving study drug and at subsequent visits will be summarized using descriptive statistics (n, mean, median, minimum, maximum, and standard deviation). Categorical data will be summarized as frequencies and percentages. All data summaries will be presented for each cohort and overall, as appropriate, unless otherwise indicated

Cohort:
Cohort is defined as:

- Cohort 1: Patients from CFDI and receiving Replagal on EOW regimen
- Cohort 2: Patients who participated in REP001a and receiving Replagal on weekly regimen

Data Derivations:
The following key derived and computed variables have been initially identified. It is expected that additional variables may be required. The SAP will not be amended for additional variables. All derived and computed variables, including additional variables later identified, will be documented in the "Define Document," and also in the SAS analysis dataset creation programs. The following are anticipated data derivations:

- *Screening period*: Within 6 months prior to first dose
- *Pre-treatment period*: Prior to first study drug infusion
- *Day 1*: Day of first study drug infusion
- *Date of Enrollment (entry)*: Date informed consent is signed
- *Baseline:* Last valid non-missing assessment made prior to the first study drug infusion.
- *Change from Baseline:* Post-baseline value – Baseline Value

- *% Change from Baseline:* {(Change from Baseline / Baseline) * 100}
- *Change from Pre-infusion:* Value immediately after infusion – value immediately before infusion.
- *% Change from Pre-infusion:* {(Change from pre-infusion / pre-infusion) * 100}
- *Age:* integer of {(date of informed consent – date of birth) / 365.25}
- *Duration of study drug exposure*: (Date of last infusion – date of first infusion)+1
- *Descriptive statistics*: n, mean, standard deviation (SD), median, minimum (min), and maximum (max)

Handling of Outliers:
For analysis purposes an outlier is defined to be an observed value which is known to be the result of an obvious error, or an observed value beyond medical reasoning. No outliers will be excluded from any analyses. The analysis may be repeated, however, by excluding any potential outliers (i.e. a sensitivity analysis performed).

Missing Dates for Adverse Events:
For partial AE dates, the non-missing parts of the partial dates will be used to determine if an AE occurred prior to the first dose of Replagal. Unless the non-missing parts are *unambiguously* before or after the first Replagal, it will always be assumed that the AE occurred after the first Replagal dose.

5.2 Analysis Populations

The safety population is defined as all patients who receive at least one full or partial infusion of Replagal. All safety analyses will utilize the safety population.

5.3 Patient Disposition

Patient disposition, including the number of patients who signed informed consent, were included in the safety populations, completed or discontinued the study, and the primary reason for discontinuation will be tabulated by cohort, previous Enzyme Replacement Therapy (ERT) status, and overall, along with percentages. Percentages will be based upon the total number of patients in the safety population.

A patient listing will be presented for the safety population, showing study completion/termination status. Additionally, a patient listing will be presented for any consented patients with any inclusion, exclusion and eligibility violation showing whether the patient met eligibility criteria, along with the results of each inclusion and exclusion criteria, and whether any exemptions were granted.

5.4 Protocol Deviations

Shire defines a protocol deviation as an incident involving noncompliance with the protocol, but one which typically does not have significant effects on the patient's rights, safety, welfare, or the integrity of the resultant data. Patient records will be examined on a case-by-case basis prior to database lock to determine if they have violated conditions set forth in the study protocol. Protocol violations are defined as more serious deviations that may affect the subject's rights, safety, or welfare, or the integrity of the resultant data or any serious deviation that affects the collection of data for a primary endpoint.

Patients in the safety population having protocol deviations will be presented in data listings.

5.5 Demographics and Other Baseline Characteristics

5.5.1 Demographics

Demographics and baseline characteristics will be summarized by cohort, age group, previous ERT status and overall based on the safety population. Descriptive statistics will be summarized for age at informed consent, baseline height (cm), baseline weight (kg), and duration of Fabry disease (years). Frequencies and percentages will be tabulated for sex, race, ethnicity, and age group.

5.5.2 Medical/Surgical History

Medical/Surgical history will be summarized by cohort, previous ERT status and overall based on safety population. The number and percentage of patients with medical history in any and each body system will be tabulated.

5.5.3 Fabry Disease Treatment History

Fabry disease treatment history will be summarized by cohort and overall based on safety population. The method of Fabry confirmation, the number and percentage of patients with previous treatment with Fabrazyme, and with previous treatment with Replagal will be tabulated, along with descriptive statistics on the duration (in months) and dose of the previous treatment.

5.6 Treatment Compliance and Extent of Exposure

Treatment compliance and extend of exposure will be summarized by cohort, previous ERT status and overall based on the safety population. The number of infusions initiated, missed (uninitiated), partial, and complete, average infusion time (in minutes) initiated and completed, duration of exposure to Replagal AF both in days and weeks, and cumulative dose of study drug taken will be summarized using descriptive statistics.

5.6.1 Primary Endpoint

Not applicable

5.6.2 Secondary Endpoints

Not applicable

5.6.3 Subset Analyses

Although no subgroup analysis is explicitly indicated in the study protocol, subgroup analyses by sex group, age group, previous ERT status, anti-drug antibody (ADA) status and neutralizing antibody (NAb) status will be performed, as applicable. Subgroups of age group, previous ERT status, ADA status and NAb status are defined as:

Age group (years) is defined as:

- <18
- ≥18

Previous ERT status is defined as:

- Previously on Fabrazyme (switched)
- Previously on RB Replagal
- Treatment-Naïve
- Other (including the patients who were previously on Fabrazyme and Replagal, on Replagal RB and Replagal AF, and whose ERT status is unknown)

ADA status is defined as:

- Positive: At least one positive test for ADA during the study evaluation period
- Negative: No positive test for ADA during the study evaluation period

NAb status is defined as:

- Positive: At least one positive test for NAb during the study evaluation period
- Negative: No positive test for NAb during the study evaluation period

5.6.4 Exploratory Analyses

Not applicable

5.7 Analysis of Safety

5.7.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version 13.1 or higher, and will be tabulated by cohort, previous SRT status, age group and overall based on the safety population. .

Pre-treatment AEs are any AEs that occur from the time the patient has signed informed consent until prior to the first study drug infusion.

Treatment-emergent adverse events (TEAEs) will be defined as those events that occurred or worsened in severity after first treatment with Replagal AF until 30 days after the last dose.

Infusion-related reactions (IRRs) will be defined as an AE that 1) begins either during or within 12 hours after the start of the infusion and 2) is judged as possibly or probably

related to study drug. AEs that are considered IRRs will be noted as such in the appropriate field on the CRF.

A serious AE (SAE) is any AE occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening
- Require hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

TEAEs will be summarized by system organ class (SOC) and preferred term (PT). The total number of TEAEs by SOC and PT, as well as the number and proportion of patients experiencing a TEAE will be tabulated; a patient will be counted only once within each SOC and PT. TEAEs by SOC and PT will be tabulated by severity. In the case of multiple occurrences of the same TEAE (at the PT level) in an individual patient, the TEAE that is classified as the most severe (i.e., maximum severity) will be identified for the analysis by severity. In addition, TEAEs by SOC and PT will be tabulated by relationship to study drug by reporting the episode with the closest relationship to study drug.

The number and percentage of patients reporting IRRs will be tabulated for any IRR, and by SOC and PT by cohort, previous SRT status, age group, sex and overall based on the safety population. IRRs by SOC and PT will be tabulated by severity and cohort, by serious and cohort, and by closest relationship. In addition, the number and percentage of patients with at least one, and no IRRs will be tabulated by anti-drug antibody (ADA) status and neutralizing antibody (NAb) status status.

The number and percentage of patients reporting SAEs will be tabulated for any SAE, and by SOC and PT by cohort, previous SRT status, age group, sex and overall based on the safety population. In addition, SAEs by SOC and PT will be tabulated by severity and relationship by cohort, separately.

The number and percentage of patients reporting TEAEs that led to permanent discontinuation will be tabulated for any TEAE, and by SOC and PT by cohort, previous ERT status, age groups and overall.

Separate data listings will be presented showing all SAEs, deaths, and TEAEs leading to treatment discontinuation.

All AEs will be listed by patient for the safety population and those AEs considered to be treatment-emergent, as well as IRRs will be flagged as such.

5.7.2 Clinical Laboratory Evaluations

Blood will be collected within 6 months prior to the patient receiving the first dose of Replagal and at the biannual/annual safety visits for the following assessments: creatinine, glucose, blood urea nitrogen (BUN), potassium, sodium, chloride, bicarbonate, and fasting lipids profile (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides).

The observed values and change from baseline will be summarized by biannual visit for laboratory data using descriptive statistics. Shift tables will also be presented comparing the baseline values to those at each biannual visit. Shifts over time will be presented by low, normal, and high. The numbers (and percentages) of patients within each category will be tabulated. Lab assessments will be summarized by cohort, previous ERT status and overall based on the safety population.

Any patient, who had a clinically significant abnormal value, as determined by the investigator, will be listed.

All laboratory data from both scheduled and unscheduled (i.e., unexpected) visits will be presented in the data listings for the safety population. However, for the summary tables only laboratory data associated with scheduled visits will be summarized.

If there are repeated or retest laboratory measurements associated with a given study visit then, in general, the second set of measurements with respect to date/time order, will be used for the statistical analysis unless the values are invalid or missing. In this instance a value from the first set of measurements will be used provided it is valid and non-missing.

5.7.3 Vital Signs

Vital signs, including blood pressure, pulse, respiratory rate, and temperature, will be measured immediately prior to each infusion and immediately following each infusion (± 10 minutes). Vital signs will be summarized by cohort, previous ERT status and overall based on the safety population.

The observed values immediately prior to first infusion at baseline and immediately after infusion at the end of study (EOS) visit, and changes from these values baseline to EOS will be summarized using descriptive statistics for temperature, pulse, respiration rate, systolic and diastolic blood pressure, and weight. Additionally, height at baseline will also be summarized.

Within each visit the observed values immediately prior to infusion and after infusion will be summarized using descriptive statistics. Changes from immediately prior to infusion to and after infusion will also be summarized.

5.7.4 Physical Findings

Not applicable since physical examinations data are not collected in CRF.

5.7.5 Anti-agalsidase alfa Antibody Results

Serum samples will be collected for evaluation of anti-agalsidase alfa antibodies within 6 months prior to the patient receiving the first dose of Replagal and at the biannual or annual safety visits, as applicable. Analysis of anti-agalsidase alfa antibodies will be performed using a validated electrochemiluminescent (ECL) immunoassay following a tiered approach (screening, confirmatory, and titer). Samples that are confirmed positive for the presence of anti-agalsidase alfa antibodies will be further evaluated for the presence of neutralizing antibodies using an enzyme inhibition assay.

Anti-agalsidase alfa antibody data are obtained from 2 different testing schemes. Anti-agalsidase alfa antibody samples collected were initially tested (prior to Nov 2014) following a tiered approach at Shire and results were reported by isotype. First, all samples were screened using enzyme linked immunosorbent assays (ELISAs) for the presence of anti-agalsidase alfa Immunoglobulin G (IgG), Immunoglobulin A (IgA), Immunoglobulin M (IgM), and Immunoglobulin E (IgE) isotype antibodies. When a sample met the IgG, IgA, IgM, or IgE positive cut-point criteria, the appropriate ELISA was used to confirm the presence of antibodies and to determine titer. Samples confirmed with the presence of anti-agalsidase alfa IgG, IgA, IgM, or IgE antibodies were further evaluated for presence of Nab using an enzyme activity based neutralization assay. During 2014, a new test method was developed and validated at a contract research organization. The later time point samples were first screened using an ECL bridge assay. Samples screened “positive” are then confirmed by competition with agalsidase alfa in the ECL bridge format. The titer of confirmed positive samples is then determined using the same ECL bridge assay, and all confirmed positive samples are further characterized using the enzyme activity based neutralization assay.

The number and percentage of patients who become positive for any antibody isotype, each isotype, and NAb will be tabulated at baseline, at each biannual visit and overall. Shift tables of status of any antibody isotype and Nab from baseline to each biannual visit will be presented based on a classification of observations as Positive, Negative, and Not Available (NA). Both IgG and ADA data will be referred to as ADA data for the convenience of presentation. For ADA, the change in titer forantibody positive patients from baseline to each biannual visit will be summarized. These analyses will be done for the safety population overall, by cohort, and by previous ERT status.

All anti-agalsidase alfa antibody data will be listed, a listing of patients who became ADA, NAb, and IgE positive will be provided.

5.7.6 Patient Follow-up

The 30-day follow-up of patient data will be presented in data listings for the safety population.

6 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

6.1 Analysis of Pharmacokinetic Data

Not applicable

6.1.1 Drug-drug and Drug-disease Interactions

There will be no analyses of drug-drug or drug-disease interactions.

6.2 Changes in the Conduct of the Study

Any changes in the conduct of the study after approval of this analysis plan, which may impact analyses performed, will require a revision of this analysis plan prior to database lock.

6.3 Changes from the Analyses Planned in the Protocol

Any changes from the analyses planned in the protocol and not discussed in the analysis plan will be presented in the clinical study report.

7 STATISTICAL/ANALYTIC ISSUES

7.1 Adjustments for Covariates

There will be no adjustments for covariates.

7.2 Handling of Dropouts or Missing data

Missing values will not be imputed with the exception of analyses involving partial dates and the data obtained at early termination visits.

7.3 Interim Analyses and Data Monitoring

All final planned analyses per protocol and this SAP will be performed only after the last patient has completed the study and the database has been locked. Several data review meetings will be held prior to database lock to allow ongoing safety review and clinical data cleaning and completion of final analyses.

One interim analyses were performed in 2015 for the purposes of evaluating the safety of Replagal AF in Canadian patients with Fabry disease, in order to support the safety profile of Replagal AF. Patients who enrolled and received at least 1 dose (full or partial) of Replagal on or before 04 November 2012, and have been in the study for 24 months or withdrew prematurely from the study as of 03 November 2014, were included in this interim analysis. This interim analysis was for safety purposes; the primary analysis endpoints were safety endpoints, including adverse event (AE), treatment emergent AE (TEAE), serious AE (SAE), AE leading to discontinuation of the study, infusion-related AE, and antibody status. The safety interim results were distributed to the Shire clinical trial team.

7.4 Multicenter Studies

Although this is a multi-center study, patient enrollment varies greatly among the sites so that grouping at the site level is impractical. Therefore, the statistically analysis will not be performed at the site level. However, selected data might be summarized by site or geographical region if deemed necessary.

7.5 Multiple Comparisons and Multiplicity

As there is only one group of patients in the study, no multiplicity adjustment is needed.

7.6 Examination of Subgroups and Interactions

All analyses will be performed overall and by cohort. Additionally, as specified above, selected analyses will also be performed by previous ERT status, and/or age group.

There are no planned analyses involving interactions.

7.7 Sensitivity Analysis

For analysis purposes, an outlier is defined to be an observed value which is known to be the result of an obvious error, or an observed value beyond medical reasoning. No outliers will be excluded from the main analysis. A sensitivity analysis may be performed by excluding any potential outliers.

8 REFERENCES

1. A Multicenter Open-Label Treatment Protocol to Observed the Safety of Replagal® (agalsidase alfa) Enzyme Replacement Therapy in Canadian patients with Fabry Disease. Clinical Trial Protocol: HGT-REP-081. Shire 28 March 2013

2. ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports, 30 November 1995.

3. ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials, 5 February 1998.

Appendix 1 Schedule of Events for Cohort 1 (EOW Replagal Dosing Regimen)

Evaluation	Within 6 Months Prior to First Dose	Treatment Period		End of Study (30 days after last dose)
		Dosing Every Other Week (±5 days)	Biannual/Annual Visits to Site[a]	
Informed Consent	X			
Treatment Protocol Entry Criteria	X			
Medical History	X			
Demographics	X			
Disease and Treatment History	X			
Physical Examination[b]	X		X	
Height[f] and Weight	X[e]		X	
Vital Signs[c]		X	X	
Blood Tests[d]	X		X	
Serum Anti-agalsidase alfa Antibody	X		X	
Drug Administration		X	X	
AE Assessment		X	X	X

Abbreviations: AE = adverse event; CFDI = Canadian Fabry Disease Initiative; EOW=every other week

[a] Biannual or annual visits, as applicable, are intended to coincide with visits in the Canadian Fabry Disease Initiative (CFDI) protocol. Procedures and study assessments during these visits will be performed at the clinical site. For patients receiving home infusions, the infusions given at the biannual visits may be administered at the clinical site.

[b] Physical examination includes assessments of head, neck, and thyroid; eyes, ears, nose, and throat; chest and lungs; heart; lymph nodes; abdomen; anorectal; genitourinary; skin; musculoskeletal; endocrine; neurological; and other.

[c] Include blood pressure, pulse, respiratory rate, and temperature. Vitals signs are taken immediately before and immediately after every infusion (±10 minutes).

[d] Includes creatinine, glucose, urea, potassium, sodium, chloride, bicarbonate and fasting lipids profile.

[e] Subject weight should be obtained within 1 month prior to the first infusion

[f] Height measured at baseline for all patients, and for patients <18 years at baseline height will also be measured at biannual safety visits until they are ≥18 years of age.

Appendix 2 Schedule of Events for Cohort 2 (Weekly Replagal Dosing Regimen for Patients who Participated in REP001a)

Evaluation	Within 6 Months Prior to First Dose	Treatment Period		End of Study (30 days after last dose)
		Dosing Every Week (±2 days)	Biannual/Annual Visits to Site[a]	
Informed Consent	X			
Treatment Protocol Entry Criteria	X			
Medical History	X			
Demographics	X			
Disease and Treatment History	X			
Physical Examination[b]	X		X	
Height[f] and Weight	X[e]		X	
Vital Signs[c]		X	X	
Blood Tests[d]	X		X	
Serum Anti-agalsidase alfa Antibody	X		X	
Drug Administration		X	X	
AE Assessment		X	X	X

Abbreviations: AE = adverse event; CFDI = Canadian Fabry Disease Initiative

[a] Biannual or annual visits, as applicable, are intended to coincide with visits in the Canadian Fabry Disease Initiative (CFDI) protocol. Procedures and study assessments during these visits will be performed at the clinical site. For patients receiving home infusions, the infusions given at the biannual visits may be administered at the clinical site.

[b] Physical examination includes assessments of head, neck, and thyroid; eyes, ears, nose, and throat; chest and lungs; heart; lymph nodes; abdomen; anorectal; genitourinary; skin; musculoskeletal; endocrine; neurological; and other.

[c] Include blood pressure, pulse, respiratory rate, and temperature. Vitals signs are taken immediately before and immediately after every infusion (±10 minutes).

[d] Includes creatinine, glucose, urea, potassium, sodium, chloride, bicarbonate and fasting lipids profile.

[e] Subject weight should be obtained within 1 month prior to the first infusion.

[f] Height measured at baseline for all patients, and for patients <18 years at baseline height will also be measured at biannual safety visits until they are ≥18 years of age.