# Treatment Protocol: HGT-REP-081

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| **Study Title:** | A Multicenter Open-label Treatment Protocol to Observe the Safety of Replagal® (agalsidase alfa) Enzyme Replacement Therapy in Canadian Patients with Fabry Disease |
| **Study Number:** | HGT-REP-081 |
| **Study Phase:** | Phase 3/4 |
| **Product Name:** | Replagal (agalsidase alfa) |
| **Indication:** | Fabry disease |
| **Investigators:** | Multicenter |
| **Sponsor:** | Shire Human Genetic Therapies, Inc. (Shire) |
| **Sponsor Contact:** | 300 Shire Way<br>Lexington, MA 02421, USA<br>PPD |
| **Medical Monitor:** | PPD, MD, MPH |

| | Date |
|---|---|
| **Original Protocol:** | 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 |

## SYNOPSIS

**Sponsor:**
Shire Human Genetic Therapies, Inc. (Shire)

**Name of Finished Product:** Replagal®

**Name of Active Ingredient:** agalsidase alfa

**Study Title:**
A Multicenter Open-label Treatment Protocol to Observe the Safety of Replagal® (agalsidase alfa) Enzyme Replacement Therapy in Canadian Patients with Fabry Disease

**Study Number:** HGT-REP-081

**Study Phase:** Phase 3/4

**Objective(s):**
The objective of this study is to observe the safety of Replagal in Canadian patients with Fabry disease.

**Study Design:**
A minimum of 60 patients and up to 200 patients are expected to participate in this treatment protocol. Two cohorts are included in this protocol: Cohort 1 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 forms are signed.

All eligible patients may receive Replagal produced by the bioreactor process (Replagal AF) on this treatment plan until Replagal AF is commercially available for the patient, the patient's participation is discontinued, or the study is discontinued, whichever comes first. Safety data will be collected throughout the treatment protocol.

**Population:**
The study population consists of Canadian patients with Fabry disease.

**Test Product, Dose, and Mode of Administration:**
For Cohort 1: Replagal, at a dose of 0.2 mg/kg body weight, administered as an intravenous (IV) infusion over 40 minutes, EOW

For Cohort 2: Replagal, at a dose of 0.2 mg/kg body weight, administered as an IV infusion over 40 minutes, weekly

**Duration of Treatment:**
Dosing will continue until Replagal AF is commercially available to the patient, the patient's participation is discontinued, or the study is discontinued, whichever comes first.

**Efficacy Assessments:**
Not applicable

**Safety Assessments:**
Safety endpoints, including adverse events (AEs), vital signs, blood tests, and antibodies to agalsidase alfa, will be assessed throughout this study.

**Statistical Methods:**
No formal statistical tests will be conducted. Tabular summaries of patient baseline demographic and clinical characteristics, patient disposition, medical history, physical examination, vital signs, AEs, blood tests, anti-agalsidase alfa antibody, and infusion information will be produced for the safety population. The safety population includes all patients who receive at least 1 full or partial infusion of Replagal.

Adverse event tabular summaries will be based on all treatment-emergent AEs recorded; AEs will be coded using the Medical Dictionary for Regulatory Activities coding dictionary.

**Date of Amendment 5 Approval:** 27 March 2015

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# LIST OF IN-TEXT TABLES



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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Term | Definition |
|---|---|
| 2D | 2-dimensional |
| AE | adverse event |
| CFDI | Canadian Fabry Disease Initiative |
| cGMP | current Good Manufacturing Practice |
| CRF/eCRF | case report form/electronic case report form |
| CRO | contract research organization |
| EC | Ethics Committee |
| ECG | electrocardiogram |
| EOS | end of study |
| EOW | every other week |
| ERT | enzyme replacement therapy |
| $Gb_3$ | globotriaosylceramide |
| GCP | good clinical practice |
| GFR | glomerular filtration rate |
| GLA | α-galactosidase A |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IRAE | infusion-related adverse event |
| IRB | Institutional Review Board |
| IV | intravenous |
| LA | left atrium |
| LBBB | left branch bundle block |
| LV | left ventricular |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NDS | New Drug Submission |
| pHEK | primary human embryonic kidney |

| Term | Definition |
|---|---|
| PK | pharmacokinetic |
| PT | preferred term |
| REB | Research Ethics Board |
| Replagal AF | Replagal manufactured using the animal component-free, bioreactor process (agalAF1) |
| Replagal | Replagal roller bottle |
| SAE | serious adverse event |
| Shire | Shire Human Genetic Therapies, Inc. |
| sNDS | Supplemental New Drug Submission |
| SOC | system organ class |
| TIA | transient ischemic attack |
| UK | United Kingdom |
| US/USA | United States/United States of America |

# 1 INTRODUCTION

## 1.1 Overview of Fabry Disease

Fabry disease is a rare, progressive, debilitating, glycosphingolipid storage disorder. It is caused by deficient activity of the lysosomal enzyme α-galactosidase A, which results from a mutation in the α-galactosidase A (GLA) gene, located on chromosome Xq22.1. α-galactosidase A cleaves galactose in the alfa-anomeric configuration from glycosphingolipids, in particular globotriaosylceramide ($Gb_3$).[1] Mutations in the GLA gene lead to decreased or complete absence of enzyme activity that, in turn, result in accumulation of varying amounts of $Gb_3$ in cells in vascular beds, cardiomyocytes, and various other cells, tissues, and organs throughout the body. The clinical manifestations of Fabry disease typically include angiokeratomas, acroparesthesias, anhydrosis, anhedonia, chronic renal insufficiency leading to renal failure, hypertrophic cardiomyopathy with arrhythmias and infarction, and microvascular cerebral events including transient ischemic attacks (TIAs), stroke, and dolychoectasia.[2] In general, patients with complete absence of GLA have a classic phenotype with rapidly progressing renal, cardiac, and cerebrovascular events whereas patients with reduced GLA have an attenuated clinical phenotype.[3]

Clinical onset of Fabry disease typically occurs during childhood or adolescence with recurrent episodes of severe neuropathic pain in the extremities, characteristic cutaneous lesions known as angiokeratomas, and a distinctive but asymptomatic corneal dystrophy termed cornea verticillata. Vital organs, especially the heart, kidneys, and brain, are progressively affected with increasing age.[4]

In contrast to classical X-linked disorders, females may also be affected, presumably from biased X-linked inactivation and lack of cross-cellular correction of lyonized cells by normal cells. Females may inherit an X-linked Fabry mutation from either parent and are not asymptomatic carriers. Females account for twice the number of male patients. Clinically, manifestations in females range from mild to severe phenotypes.[5, 6] The onset of symptoms and age of diagnosis in females occur approximately 10 years later than in males.[7]

Before the availability of dialysis or renal transplantation, renal complications accounted for the mortality of male Fabry patients during the fourth or fifth decade of life.[8] Median age of death in males is 50 to 55 years of age. Death in female patients with Fabry disease is, on average, a decade or more later than in males and occurs primarily as a result of cardiac or cerebrovascular complications.[9, 10]

Data on the true global incidence of Fabry disease are scarce, and estimates vary among 1:117,000, ~1:50,000, and ~1:4,600 live births. Estimates suggest that the ratio of patients with the later-onset disease: Classic phenotypes are 7:1.[11, 12]

The diagnosis of Fabry disease may be made in males based on low levels of plasma or leukocyte GLA activity or by the presence of a gene mutation. In females, a presumptive diagnosis of Fabry disease may be based on the presence of characteristic clinical findings that must be confirmed by genotyping.

Prior to the advent of enzyme replacement therapy (ERT) in 2001, Fabry disease was an underdiagnosed condition that was primarily recognized in males with symptoms of the classical disease severity. Women were rarely diagnosed.[12-14]

## 1.2 Nonclinical Studies

The nonclinical studies have demonstrated that agalsidase alfa is well tolerated in acute toxicology studies in mice and rats and in multiple dosing studies in rats, rabbits, and monkeys. Toxicology studies have included a single-dose intravenous (IV) toxicology study in rats testing doses up to 10.0 mg/kg (a dose that is 50-fold greater than the standard human dose of 0.2 mg/kg every other week (EOW) and 25-fold greater than the maximum human dose of 0.4 mg/kg once weekly tested in clinical studies [TKT027]). Chronic toxicology studies have included 13-week and a 26-week repeated IV dose studies in rats and a 13-week repeated IV dose study in cynomolgus monkeys where doses up to 1 mg/kg/week were tested, which was 10-fold greater than the standard human dose and 2.5-fold greater than the maximum tested human dose. None of these tests showed evidence of significant toxicity associated with agalsidase alfa. In addition, an in vitro tumorigenicity study in cultured primary human embryonic kidney (pHEK) cells was performed, and this study demonstrated that agalsidase alfa did not alter the in vitro tumorigenicity or growth rates of normal pHEK cells (data on file).

Reproductive studies in male and female rats and female rabbits revealed no untoward effects on male or female reproductive function, histopathology of reproductive organs, or embryo-fetal development. The pharmacokinetic (PK) properties and biodistribution of agalsidase alfa in mice, rats, rabbits, and monkeys have been well characterized. Following a single IV administration, serum levels of agalsidase alfa followed a biphasic distribution in several animal species including rats and monkeys. The elimination half-lives were less than 2 hours in all species, and serum levels returned to predose values 24 hours after administration. Both the maximum serum concentration immediately after dosing and the area under the concentration time curve were approximately proportional to the administered dose in rats and monkeys. There were only minor effects on PK parameters following multiple dosing in rats and monkeys.

Biodistribution studies in rats using iodine-125-labeled agalsidase alfa have demonstrated that significant amounts of agalsidase alfa can be found in key organs pathologically affected in Fabry disease after IV administration, in particular the kidneys and heart. Single- and multiple-dose pharmacodynamic studies in knockout mice have demonstrated a significant reduction in $Gb_3$ in the liver, heart, and kidneys.

Further details on the nonclinical studies are provided in the Investigator's Brochure (IB).

## 1.3 Previous Human Experience

Clinical studies of agalsidase alfa have been conducted in the United States (US), United Kingdom (UK), Canada, Australia, Europe, Brazil, and Japan.

The clinical development program has included 3 placebo-controlled clinical studies of 6-month dosing duration in adults (TKT003, TKT005, TKT010) and open-label maintenance studies for patients continuing from these and other studies (TKT006, TKT007, TKT011, TKT013, and TKT015).

Additionally, a study in female patients (TKT014), a study in dialysis and renal transplant patients (TKT019), and a single-center, open-label, compassionate use study (TKT012) have also been performed. Three completed studies have been conducted in children (TKT023, TKT029, and TKT5S001). An additional study (TKT028) was conducted in patients with left ventricular hypertrophy. Other completed studies include REP001a, a Phase 4 study of alternative dosing regimens for Replagal in Canadian patients with Fabry disease; HGT-REP-059, a treatment protocol to provide access to Replagal for patients with Fabry disease in the US; HGT-REP-082, a comparability study between Replagal produced from agalsidase alfa manufactured by 2 different processes in Canada; HGT-REP-060, an open-label extension study for TKT028; and HGT-REP-084, a study of treatment-naïve children using Replagal manufactured using the bioreactor process (Replagal AF).

In total, 514 adults and 67 children have received Replagal in completed Shire-sponsored studies. Long-term safety experience demonstrates that Replagal therapy has been generally well tolerated in clinical studies, as well as in commercial and compassionate use.

Additional details of these clinical studies are available in the Investigator Brochure.

## 1.4 Current Therapies

The current approved treatment for Fabry disease is ERT. There are 2 products in this therapeutic class: agalsidase alfa (marketed under the trade name of Replagal® in countries outside the United States, by Shire) and agalsidase beta (Fabrazyme®; Genzyme). Both are indicated for long-term treatment in patients with a confirmed diagnosis of Fabry disease (GLA deficiency). Replagal is currently approved in 52 countries worldwide and has investigational status in Canada.

### 1.4.1 Replagal (agalsidase alfa)

Replagal is manufactured from agalsidase alfa using an aseptic filling process in a facility in compliance with current Good Manufacturing Practice (cGMP) regulations. Replagal is formulated as a sterile product suitable for parenteral administration. The formulation of Replagal includes sodium phosphate as a buffering agent, polysorbate 20 as a stabilizing agent, and sodium chloride as an isotonic agent.

Replagal is intended for use as ERT for patients with Fabry disease. It is anticipated that replacement of the deficient enzyme may contribute to correction of the enzymatic defect and allow for improved metabolism of the natural substrate for the enzyme. Over time, chronic replacement of the deficient enzyme could theoretically alter the natural history of Fabry disease, with concomitant improvements in renal and cardiac function, metabolism, neuropathic pain, and quality of life.

### 1.4.2 Differences between Replagal and Fabrazyme Enzyme Replacement Therapies

Replagal is produced by a genetically engineered continuous human cell line. Fabrazyme is produced using a Chinese hamster ovary cell line. Other differences include post-translational modification of mannose residues such as glycosylation, sialylation, and phosphorylation, which can potentially influence the tissue uptake and the rate of development of antibodies to the exogenously administered enzymes. Formulation excipients may also contribute to differences in individual patient sensitivities to the treatments.

### 1.4.3 Summary of Known and Potential Risks and Benefits to Human Subjects

A summary of the risks and benefits for Replagal is provided in the IB.

## 1.5 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 New Drug Submission (sNDS) for Replagal bioreactor (agalAF1 or AF) drug substance process by implementing a bioreactor process in place of the previously employed roller bottle process and eliminating animal-sourced raw materials. There are no changes to the Replagal drug product formulation, manufacturing site, manufacturing process, and container closure. A supplemental NDS (SNDS) for the new manufacturing process was submitted to Health Canada in March 2009. Approval of the new manufacturing process was not granted. 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.

As of 01 March 2015, Replagal 1 mg/mL concentrate for solution for infusion has been approved in 52 countries. The approved dose for Replagal in these countries is 0.2 mg/kg EOW administered by intravenous (IV) infusion over 40 minutes. As of 31 August 2014, the estimated cumulative worldwide patient exposure of Replagal RB and AF is 17,222 person-years treatment; the estimated cumulative worldwide patient exposure of Replagal AF is 11,626 person-years. No new safety concerns have been identified upon the change in manufacturing process from Replagal RB to Replagal AF.

## 2 OBJECTIVE

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

# 3 OVERALL DESIGN AND PLAN

A minimum of 60 patients and up to 200 patients are expected to participate in this protocol. Two cohorts are included in this protocol: Cohort 1 is for patients who may also be enrolled in the Canadian Fabry Disease Initiative (CFDI) and provides Replagal treatment on an 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.

All patients may continue to receive Replagal on this treatment plan until Replagal is commercially available for the patient or the patient's participation or the study is discontinued, whichever comes first. Safety data will be collected throughout the treatment protocol.

# 4 POPULATION SELECTION

The population consists of Canadian patients with Fabry disease.

Each patient in Cohort 1 must meet the following criteria to receive treatment (inclusion criteria for Cohort 1 are consistent with the CFDI):

1. The patient has a documented diagnosis of Fabry disease.
2. The patient is sufficiently compliant with study activities to participate in this treatment plan, as judged by the investigator.
3. The patient must meet current Canadian guidelines for ERT for Fabry disease[15] by meeting any of the following criteria:
   a. Age-adjusted glomerular filtration rate (GFR) <80 mL/min or a decline in GFR of >10% that is sustained for 3 months and for which other causes of declining renal function have been excluded by a nephrologist or any 2 of the following:
      - Isolated proteinuria ≥500 mg/day/1.73 $m^2$ without other cause
      - Nephrogenic diabetes insipidus
      - Fanconi syndrome
      - Hypertension
   b. Evidence of cardiac involvement related to Fabry disease including any 2 of the following:
      - Left ventricular (LV) wall thickness >12 mm
      - Left ventricular hypertrophy by electrocardiogram (ECG); Estes ECG score must be >5
      - Left ventricular mass index by 2-dimensional (2D) echocardiogram 20% above normal for age
      - Diastolic filling abnormalities by 2D echocardiogram or other accepted measures of diastolic filling. E/A ratio >2.0 and deceleration time <140 msec
      - Increase of LV mass of at least 5 g/$m^2$/year, with 3 measurements over a minimum of 12 months
      - Increase of left atrium (LA) size on 2D echo at least 10% above normal for age. In parasternal long axis view >33 mm; in 4-chamber view >42 mm
      - Cardiac conduction and rhythm abnormalities: AV block, short PR interval, left branch bundle block (LBBB), ventricular or atrial tachyarrhythmias, sinus bradycardia (in the absence of drugs with negative chronotropic activity)
      - Delayed posterolateral LV wall late enhancement on magnetic resonance imaging as evidence of advanced cardiac disease with fibrosis.
   c. Evidence of neurological involvement related to Fabry disease, including 1 of the following:
      - Stroke or TIA prior to the age of 55 documented by a neurologist
      - Acute onset unilateral hearing loss

- Acute monocular visual loss without other cause

d. Chronic, intractable diarrhea and/or abdominal pain/cramps, refractory to standard management for at least 6 months
e. Chronic, intractable neuropathic pain, refractory to analgesics and standard pain management for at least 6 months

Each patient in Cohort 2 must meet the following criteria to receive treatment:

1. Patient must have participated in REP001a.

Patients who meet any of the following criteria will be excluded from the study:

1. The patient has experienced an anaphylactic or anaphylactoid reaction or other infusion-related reaction which, in the opinion of the investigator, precludes further treatment with Replagal or may interfere with the interpretation of the study.
2. The patient is otherwise unsuitable for the study, in the opinion of the investigator.
3. The patient is enrolled in another clinical study, other than the CFDI.

# 5 STUDY TREATMENT(S)

## 5.1 Description of Treatment(s)

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

Patients in Cohort 2 will continue to receive Replagal at a dose of 0.2 mg/kg body weight administered as an IV infusion over 40 (±10) minutes weekly (±2 days).

Refer to the Infusion and Pharmacy Manuals for detailed instructions on special precautions and handling.

## 5.2 Treatment Administration

Replagal will be provided by Shire in vials as a concentrate for solution for infusion.

Replagal infusions may occur at the clinical site, at home, or at a qualified satellite treatment center at the investigator's discretion. Patients experiencing severe or serious adverse events (AEs) that are also infusion-related AEs (IRAEs) must receive their infusions at the clinical site or qualified treatment center until they have had 2 successive infusions without severe or serious IRAEs. Clinical judgment of the investigator for management of any other IRAEs occurring during home infusions will be used. Patients receiving Replagal as home therapy are required to return to the clinical site for biannual or annual safety visits as indicated in the schedule of events (Appendix 1 and Appendix 2).

The qualified, trained medical personnel will follow the Study Pharmacy and/or Infusion Manuals provided separately from this protocol that outlines all operating procedures to be followed for this treatment protocol, including drug receipt, reconstitution, and the required patient assessments before, during, and after infusion of study drug. Clinical evaluations will remain under the medical supervision of the investigator.

## 5.3 Selection and Timing of Dose for Each Patient

For patients in Cohort 1, Replagal will be administered at a dose of 0.2 mg/kg body weight as an 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 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.

## 5.4 Method of Assigning Patients to Cohorts

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

## 5.5 Blinding

Not applicable.

## 5.6 Packaging and Labeling

Replagal is supplied as a sterile, clear, colorless concentrate for dilution for IV infusion. Replagal will be provided in single-use, 5 mL vials containing 3.5 mL of concentrate at a concentration of 1 mg/mL.

Study drug labels will contain information necessary to meet the applicable regulatory requirements.

## 5.7 Storage

Replagal will be provided by the sponsor (or designee) to the clinical study sites, qualified satellite sites, or patient residences (or other approved location) in a temperature-controlled, monitored container. The vials should be stored in a refrigerator at 2-8°C (36-46°F). A minute amount of fine particulate matter, causing the solution to appear slightly hazy, may be present during storage.

## 5.8 Investigational Product Accountability and Destruction

The final disposition of all investigational product must be recorded on a patient-by-patient basis. The date and time of administration of the study drug will be documented on the appropriate case report form/electronic case report form (CRF/eCRF).

All used, partially used, and unopened study drug vials must be returned to the sponsor-designated pharmacy.

# 6 TREATMENT PROTOCOL PROCEDURES

Complete schedules of events 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.

## 6.1 Eligibility Criteria

Eligibility criteria (provided in Section 4) will be reviewed, and patient eligibility will be determined prior to the patient receiving the first dose of Replagal.

## 6.2 Disease and Treatment History

Documentation of diagnosis with Fabry disease will be collected up to 6 months prior to the patient receiving the first dose of Replagal.

## 6.3 Demographics

Patient demographics, including patient sex, age, and race, will be collected.

## 6.4 Medical History

A review of the patient's medical history will occur up to 6 months prior to the patient receiving the first dose of Replagal. This review will include a review of body systems, documentation of current procedures, and documentation of current concomitant medication usage. In addition, the patient will be queried on the following:

- Relevant intercurrent illness and chronic disease update
- Medication use and dose (particularly those used to treat Fabry disease)
- Site of prior ERT (ie, hospital, infusion center, doctor's office, home, other)
- Disease-specific review of symptoms, including:
  - Head, neck, and thyroid
  - Eyes, ears, nose, and throat
  - Chest and lungs
  - Heart
  - Lymph nodes
  - Abdomen
  - Anorectal
  - Genitourinary
  - Skin
  - Musculoskeletal

- Endocrine
- Neurological
- Other

## 6.5 Physical Examination

Complete physical examinations will occur prior to the first dose of Replagal administration and during the biannual or annual safety visits, as applicable. The physical examinations will include assessments of:

- Head, neck, and thyroid
- Eyes, ears, nose, and throat
- Chest and lungs
- Heart
- Lymph nodes
- Abdomen
- Anorectal
- Genitourinary
- Skin
- Musculoskeletal
- Endocrine
- Neurological
- Height (measured at baseline for all patients, and for patients <18 years at baseline, height will also be measured at biannual or annual safety visits until they are ≥18 years of age)
- Weight (within 1 month prior to the first Replagal infusion)
- Other

Clinically significant findings from the physical examinations are to be reported as AEs.

## 6.6 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).

## 6.7 Blood Tests

Blood will be collected within 6 months prior to the patient receiving the first dose of Replagal and at the biannual or annual safety visits for the following assessments: creatinine, glucose, urea, potassium, sodium, chloride, bicarbonate, and fasting lipids profile.

## 6.8 Antibody Assessments

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 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. Sample collection, processing, and shipping instructions will be detailed in the study laboratory manual. This manual is to be provided by the central laboratory.

## 6.9 Replagal Administration

Patients in Cohort 1 will receive Replagal IV infusions EOW until Replagal is commercially available to the patient or the patient's participation or the study is discontinued.

Patients in Cohort 2 will receive Replagal IV infusions weekly until Replagal is commercially available to the patient or the patient's participation or the study is discontinued.

Replagal administration will occur as described in Section 5.2; home infusions may occur at the discretion of the investigator.

## 6.10 Adverse Events Assessments

### 6.10.1 Definitions of Adverse Events and Serious Adverse Events

#### 6.10.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational product-related. This includes an exacerbation of a pre-existing condition.

Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (This includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important.)
- Clinically significant abnormalities in physical examination, vital signs, and weight

Throughout the study, the investigator must record all AEs on the AE eCRF, regardless of the severity or relationship to investigational product. The investigator should treat patients with

AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or abnormal clinical laboratory values.

In addition, AEs may also include laboratory values that become significantly out of range as determined by the investigator or in the opinion of the investigator. In the event of an out-of-range value, the laboratory test should be repeated until it returns to normal or can be explained and the patient's safety is not at risk.

Additional illnesses present at the time when informed consent is obtained are regarded as concomitant illnesses and will be documented on the appropriate pages of the eCRF. Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as AEs and must be documented as such in the eCRF.

#### 6.10.1.2 Infusion-related Reactions

An infusion-related reaction 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. Adverse events that are considered infusion-related reactions will be noted as such in the appropriate field on the eCRF. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion, will not be defined as infusion-related reactions. All AEs should be recorded, together with causality assessment.

A list of the most common infusion-related reactions that have been reported in patients with Fabry disease during Replagal infusions is included in the current Replagal IB.

#### 6.10.1.3 Serious Adverse Event

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

- Death
- Is life-threatening
- Requires 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 require medical or surgical intervention to prevent one of the outcomes listed in this definition. A life-threatening AE is defined as an AE that placed the patient, in the view of the initial reporter, at immediate risk of death from the AE as it occurred

(ie, it does not include an AE that, had it occurred in a more severe form, might have caused death).

### 6.10.2 Classification of Adverse Events and Serious Adverse Events

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grading scale should be referenced when assessing the severity of an AE. If an AE is not described in the NCI CTCAE, the severity should be recorded based on the scale below. The severity of all AEs/SAEs should be recorded on the appropriate CRF/eCRF page as Grade 1, 2, 3, or 4 corresponding, respectively, to a severity of mild, moderate, severe, or life-threatening (Table 6-1).

**Table 6-1 Adverse Event Severity**

| Severity | Definition |
|---|---|
| Grade 1 (Mild) | No limitation of usual activities. |
| Grade 2 (Moderate) | Some limitation of usual activities. |
| Grade 3 (Severe) | Inability to carry out usual activities. |
| Grade 4 (Life-threatening) | Immediate risk of death. |

#### 6.10.2.1 Clarification between Serious and Severe

The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations.

### 6.10.3 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product is to be determined by the investigator based on the following definitions (Table 6-2).

**Table 6-2 Adverse Event Relatedness**

| Relationship to Product(s) | Definition |
|---|---|
| Not Related | Unrelated to investigational product |
| Possibly Related | A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals. |
| Probably Related | A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds. |

### 6.10.4 Procedures for Recording and Reporting Adverse Events

#### 6.10.4.1 Adverse Event Monitoring and Period of Observation

Adverse events will be monitored continuously throughout the study.

For the purposes of this study, the period of observation extends from the time at which the patient, the patient's parent(s), or the patient's legally authorized representative gives informed consent until the patient's final evaluation of the study. For safety purposes, the final evaluation will be defined as the follow-up evaluation performed approximately 30 days after the last dose for patients who complete the study.

If the investigator considers it necessary to report an AE in a study patient after the end of the safety observation period, he or she should contact the sponsor to determine how the AE should be documented and reported.

#### 6.10.4.2 Reporting Serious Adverse Events

Any SAE, regardless of relationship to investigational product, which occurs in a patient after informed consent, should be recorded by the clinical site on an SAE form. The SAE must be completely described on the patient's eCRF, including the judgment of the investigator as to the relationship of the SAE to the investigational product. The investigator will promptly supply all information identified and requested by the sponsor (or contract research organization [CRO]) regarding the SAE.

The investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the Shire medical monitor on an SAE form. This form must be completed and FAXED or EMAILED within 24 hours of the investigator's learning of the event to:

**Shire Pharmacovigilance and Risk Management Department:**
**International FAX:** PPD **(UK) OR United States and Canada**
**FAX:** PPD
PPD
**AND**
**Shire Medical Monitor:** PPD **, MD, MPH**
PPD
**FAX:** PPD **(USA)**

Any follow-up information must also be completed on an SAE form and faxed or emailed to the same numbers listed above.

In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire medical monitor by telephone; this is in addition to completing and transmitting the SAE form as stated above. The following provides contact information for the Shire medical monitor.

| **If an SAE is assessed as severe and unexpected or life-threatening, contact:** |
|---|
| PPD, MD, MPH<br>PPD<br>**Shire300 Shire Way, Lexington, MA 02421, USA**<br>**Telephone:** PPD **Fax:** PPD **(USA)**<br>**Mobile:** PPD<br>PPD |

The investigator must promptly report all required information to the Institutional Review Board (IRB)/Ethics Committee (EC)/Research Ethics Boards (REB). It is the responsibility of the sponsor to ensure that each investigator receives a copy of any Council for International Organizations of Medical Sciences I/MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The investigator or sponsor must ensure that the IRB/EC/REB receives a copy of the report and that a copy is also filed within their study files.

### 6.11 Management of Infusion-related Adverse Events

If a patient has an IRAE during the infusion of study drug, the investigator or the home infusion nurse should decide, based on his or her clinical judgment, whether the infusion should be slowed or temporarily or permanently discontinued. Mild and transient effects may not require medical treatment or discontinuation of the infusion. Infusion-related AEs that occur post-infusion should be assessed and treated symptomatically as needed. If severe allergic or anaphylactic-type reactions occur, the administration of Replagal should be discontinued immediately and appropriate treatment initiated. The current medical standards for emergency treatment are to be observed.

Patients experiencing a recurrent IRAE may be premedicated. Pretreatment, generally with oral antihistamines and corticosteroids, from 1 to 3 hours prior to infusion has prevented subsequent reactions in those cases where symptomatic treatment was required. If infusions continue without incident, then tapering of medications can be considered.

### 6.12 Pregnancy

The sponsor must be notified in the event of a pregnancy occurring during the course of the study and through 30 days after the patient's last dose of study drug. Pregnancy is not to be reported as an AE; the pregnancy form should be used to report the pregnancy. The pregnancy will be followed through delivery or final outcome.

### 6.13 Removal of Patients from the Study

Patients may withdraw from the treatment protocol at any time. The investigator or sponsor may withdraw a patient from the treatment protocol for the following medical or administrative reasons:

- Adverse event: If a patient experiences an AE that, in the judgment of the investigator, the sponsor, or the Shire medical monitor, presents an unacceptable consequence or risk to the patient, the patient will be withdrawn from the treatment protocol.
- Adverse laboratory experience: If a patient has an adverse laboratory experience that, in the judgment of the investigator, the sponsor, or the Shire medical monitor, presents an unacceptable consequence or risk to the patient, the patient will be withdrawn from the treatment protocol.
- Comorbidity: If a patient develops a comorbidity during the course of the treatment protocol that is not associated with the condition under study, and that requires treatment that is not consistent with protocol requirements, the patient will be withdrawn from the treatment protocol. A patient will be withdrawn from the treatment protocol if, in the judgment of the investigator, he or she develops an intercurrent illness that, in any way, justifies his or her withdrawal.
- Refusal of treatment: If for any reason the patient refuses treatment during the treatment protocol, the patient will be withdrawn from the treatment protocol, and the reason for refusal will be documented on the CRF. Reasonable efforts will be made to monitor the patient for AEs following such discontinuation. Such efforts will be documented in the CRF.
- Withdrawal of informed consent: A patient may withdraw his or her informed consent to participate in the treatment protocol at any time and for any reason.
- Lack of efficacy: The patient will be withdrawn from the treatment protocol if, in the opinion of the CFDI investigator, a lack of efficacy is observed.

At the time of discontinuation or withdrawal, patients will undergo all safety evaluations required for the end-of-study (EOS) visit. The investigator will complete the appropriate eCRF describing the reason for discontinuation.

In addition, patients who withdraw or are discontinued will have a follow-up assessment for safety at the clinical site 30 days after their last infusion of Replagal.

## 6.14 Institutional Review Board/Ethics Committee/Research Ethics Board

Before initiation of the treatment protocol, the investigator must provide the sponsor with a copy of the written IRB/EC/REB approval of the protocol and the ICF. This approval must refer to the ICF and to the study title, study number, and version and date of issue of treatment protocol, as given by the sponsor on the cover page of the protocol. Local IRBs may be given the option to delegate to the central IRB identified for the study.

Status reports must be submitted to the IRB/EC/REB at least once per year. The IRB/EC/REB must be notified of completion of the treatment protocol. Within 3 months of treatment protocol completion or termination, a final report must be provided to the IRB/EC/REB. A copy of these reports shall be sent to the site's study monitor. The investigators must maintain an accurate and complete record of all submissions made to the IRB/EC/REB, including a list of all reports and documents submitted. Adverse events that are reported to Health Canada or other regulatory agencies must be submitted promptly to the IRB/EC/REB.

## 6.15 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigators abide by good clinical practice (GCP) as described in the 21 Code of Federal Regulations Parts 50, 54, 56, and 312 and the International Conference on Harmonisation (ICH) GCP Guidelines Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

## 6.16 Patient Information and Informed Consent

Before enrolling in the treatment protocol, each patient, the patient's parent(s), or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the treatment protocol have been explained in a form understandable to him/her. An ICF that includes information about the treatment protocol will be prepared and given to the patient, the patient's parent(s), or the patient's legally authorized representative. This document will contain all Health Canada- and ICH-required elements.

The ICF must be in a language understandable to the patient, the patient's parent(s), or the patient's legally authorized representative(s) and must specify who informed the patient, the patient's parent(s), or the patient's legally authorized representative(s).

After reading the informed consent document, the patient, the patient's parent(s), or the patient's legally authorized representative must give consent in writing. The patient's consent must be confirmed at the time of consent by the personally dated signature of the patient, the patient's parent(s), or the patient's legally authorized representative and by the personally dated signature of the person conducting the informed consent discussions.

If the patient, the patient's parent(s), or the patient's legally authorized representative is unable to read, oral presentation and explanation of the written ICF and information to be supplied to the patient must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient or by a local legally recognized alternative (eg, the patient's thumbprint or mark) or by the personally dated signature of the patient's parent(s) or the patient's legally authorized representative. The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the patient, the patient's parent(s), or the patient's legally authorized representative. The original signed consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required solely for the treatment protocol until valid consent has been obtained.

A model of the ICF to be used in this treatment protocol will be provided to the sites separately from this protocol.

Where applicable, signed assent(s) to participate in the treatment protocol will be obtained.

## 6.17 Patient Confidentiality

Patient names will not be supplied to the sponsor. Only the patient number and patient initials will be recorded in the eCRF, and if the patient name appears on any other document, it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be told that representatives of the sponsor, a designated CRO, the IRB/EC/REB, or regulatory authorities may inspect their medical records to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

## 6.18 Case Report Form Completion

Case report forms are provided for each patient. All forms must be filled out by authorized study personnel. All corrections to the original CRF entry must indicate the reason for change.

The investigator is required to sign the CRF after all data have been captured for each patient. If corrections are made after review and signature by the investigator, he or she must be made aware of the changes and his or her awareness must be documented by resigning the CRF.

## 6.19 Monitoring

Monitoring procedures that comply with current GCP guidelines will be followed. Review of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the sponsor or its designee, who will review the CRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

## 6.20 Regulatory Administration

Appropriate regulatory documentation will be collected as mandated by Health Canada.

## 6.21 Premature Closure of the Treatment Protocol

### 6.21.1 Treatment Protocol Termination

If the sponsor or an investigator discovers conditions arising during the treatment protocol that indicate that the clinical investigation should be halted due to an unacceptable patient risk, the treatment protocol may be terminated after appropriate consultation between Shire and the investigators.

In addition, a decision on the part of Shire to suspend or discontinue development of the test material may be made at any time.

### 6.21.2 Site Termination

A specific site may be terminated separate from the general treatment protocol for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site
- Insufficient adherence by the investigator to protocol or regulatory requirements

## 6.22 Record Retention

Essential documents should be retained by the site for at least 2 years after the last approval of a marketing application and until there is no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will notify the investigator if these documents must be retained for a longer period of time. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Records will be maintained by the sponsor for a period of 25 years and will be accessible for on-site inspection by Health Canada inspectors.

## 6.23 Publication and Disclosure Policy

All information concerning the study material, such as patent applications, manufacturing processes, basic scientific data, and formulation information supplied by the sponsor and not previously published, are considered confidential and will remain the sole property of the sponsor. The investigator agrees to use this information only in accomplishing this study and will not use it for other purposes.

It is understood by the investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies.

In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the sponsor with complete test results and all data developed in the study in a timely manner.

The investigator and any other clinical personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with Shire, provided Shire a copy of the draft document intended for publication, and obtained Shire's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential. Shire will use the information for registration purposes and for the general development of the drug.

# 7 STATISTICAL METHODS

No formal statistical tests will be conducted. Tabular summaries of patient baseline demographic and clinical characteristics, patient disposition, medical history, physical examination, 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 1 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 all as appropriate, unless otherwise indicated.

## 7.1 Demographic and Clinical Characteristics

Baseline demographics and other patient characteristics, including disease history, physical exam, vital signs, and medical history, will be presented by cohort.

## 7.2 Patient Disposition

The disposition of all enrolled patients will be summarized with frequencies and percentages including patients who completed the study and patient who discontinued study treatment prior to the end of study visit.

## 7.3 Treatment Exposure

Infusion information will be listed by patient and visit. The cumulative dose of study drug taken and the duration of study drug exposure will be summarized descriptively by cohort.

## 7.4 Anti-agalsidase Alfa Antibodies

Antibody data will be listed by patient and visit. The status of antibodies and neutralizing antibody will be summarized descriptively by cohort.

## 7.5 Adverse Events and Other Safety Assessments

Adverse event tabular summaries will be based on all treatment-emergent AEs recorded; AEs will be coded using the Medical Dictionary for Regulatory Activities coding dictionary.

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

The number and percentage of patients reporting SAEs will be presented by cohort, SOC, and PT; in addition, an SAE listing will be presented.

The number and percentage of patients reporting an infusion-related reaction will be presented by cohort, SOC, and PT. An infusion-related reaction is defined as an AE that: (1) begins either during or within 12 hours after the start of the infusion and (2) is judged by the investigator to be possibly or probably related to study drug.

The number and proportion of patients experiencing an AE(s) that led to permanent discontinuation will be summarized by cohort, SOC, and PT. Furthermore, a listing of all patients who permanently discontinued due to an AE(s) will be provided.

Furthermore, safety will be evaluated by assessing vital signs and blood tests. Data for vital signs and blood tests will be listed for each patient and abnormal values will be flagged. Shift tables from baseline to last visit may be presented for vital signs, and a summary table may be presented for blood tests.

## 7.6 Interim Analysis

One or more interim analyses may be performed for purposes of data submissions to regulatory authorities. If the analysis is deemed to be necessary, then a prospective statistical analysis plan will be developed prior to the analysis. The plan will included, at a minimum: (1) rationale to perform the interim analysis; (2) endpoints to be analyzed; and (3) the distribution list for the interim analysis results. The trial will not stop due to the results from the interim analysis. In addition, as this is a single-arm study, no multiplicity adjustment will be made due to the interim analysis.

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# 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[c] and Weight | X[d] | | X | |
| Vital Signs[e] | | X | X | |
| Blood Tests[f] | 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 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 or annual 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] Height is measured at baseline for all patients and for patients <18 years at baseline, height will also be measured at biannual or annual safety visits until they are ≥18 years of age.

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

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

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

# 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[c] and Weight | X[d] | | X | |
| Vital Signs[e] | | X | X | |
| Blood Tests[f] | 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 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 or annual 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] Height is measured at baseline for all patients and for patients <18 years at baseline, height will also be measured at biannual or annual safety visits until they are ≥18 years of age.

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

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

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

## Appendix 3 Investigator's Signature

**Study Title:** A Multicenter Open-label Treatment Protocol to Observe the Safety of Replagal® (agalsidase alfa) Enzyme Replacement Therapy in Canadian Patients with Fabry Disease

**Study Number:** HGT-REP-081

**Final Date Amendment 5:** 27 March 2015

I have read Study HGT-REP-081 and the Replagal Investigator's Brochure, and I agree to conduct the study as outlined herein.

**Signatory**

**Investigator**

_____
**Signature** **Date**

_____
**Print Name** **Institution**

**Shire Medical Monitor**

PPD

PPD

PPD

P

_____
**Signature** **Date**

_____
**Print Name**

## Appendix 4 Justification for Amendment 5 and Summary of Changes

As described in the table below, the protocol was amended primarily for the following reasons:

- To align with the updated CFDI-001 protocol language that allows for biannual or annual site visits
- To update the anti-drug antibody methods section

Other changes were made to update the document with current content where appropriate and these changes are listed in the table below.

The following editorial changes were made throughout the document and are not listed in the table below unless they are needed to help the reader to understand overall changes to a section:

- Changes in grammar, spelling, punctuation, and format
- Minor editorial changes (including changes for consistency and clarity)
- Updates to the abbreviation list and references

### Table A1 HGT-REP-081 Protocol Changes from Amendment 4 to Amendment 5

| Section(s) Affected | Type of Change[a] | Description of Change |
|---|---|---|
| All | Revision | Increased potential patient enrollment from 180 patients to 200 patients |
| Section 1: Introduction | Revision | Made minor updates to ensure content on Fabry disease, Replagal clinical studies, and Replagal approvals are all up to date. |
| Section 1.5: Rationale | Addition; Revision | Text was added to clarify that Replagal is no longer approved in Canada.<br>Text was revised to update the country approvals and commercial experience with Replagal. |
| Section 5.3: Selection and Timing of Dose for Each Patient; Section 6; Treatment Protocol Procedures; Appendix 1: Schedule of Events for Cohort 1 ; Appendix 2: Schedule of Events for Cohort 2 | Addition | Added option for mandatory visits to occur annually or biannually, based on investigator judgment, and in alignment with the CFDI protocol.<br><br>*Prior*: Visits to the site must occur biannually (twice yearly).<br>*New*: Visits to the site may be biannual (twice yearly) or annual. |
| Section 6.8: Antibody Assessments | Deletion; addition | Anti-drug antibody assessment methodologies have been updated to be in line with current regulatory guidance and amenable to sample testing at a CRO. The relevant protocol text is being updated to reflect this change.<br><br>*Prior wording:* Blood samples will be collected for determination of |

## Table A1 HGT-REP-081 Protocol Changes from Amendment 4 to Amendment 5

| Section(s) Affected | Type of Change[a] | Description of Change |
|---|---|---|
| | | anti-agalsidase alfa antibodies within 6 months prior to the patient receiving the first dose of Replagal and at the biannual safety visits. Blood samples collected for anti-agalsidase antibody determination will be evaluated at Shire HGT. Anti-agalsidase alfa serum samples will be analyzed following a tiered approach. First, all samples will be screened using Enzyme-Linked Immunosorbent Assays (ELISAs) for the presence of anti-agalsidase alfa IgG, IgA, IgM and IgE isotype antibodies. If a sample meets the IgG, IgA, IgM, or IgE positive cut point criteria, the appropriate ELISA will be used to confirm the presence of antibodies and to determine titer. Samples that are confirmed positive for the presence of anti-agalsidase alfa IgG, IgA, IgM, or IgE antibodies will be further evaluated for the presence of neutralizing antibodies (NAb) using an enzyme inhibition assay.<br><br>*New wording:* 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 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. Sample collection, processing, and shipping instructions will be provided in the study laboratory manual to be provided by the central laboratory. |
| Appendix 3 | Deletion | Appendix 3 was removed. It contained description information on infusion-related reactions. This appendix was removed since the language is verbatim in the Investigator Brochure Edition 20, currently used at sites, and it was therefore redundant in the protocol. |

[a] Options include revision, addition, or deletion.