Clinical Study Protocol

NCT Number: NCT04974749

Title: An Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of REPLAGAL® in Treatment-naïve Chinese Subjects With Fabry Disease

Study Number: TAK-675-3001

Document Version and Date: Amendment 2.0, 23 May 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

Protocol:	TAK-675-3001
Title:	An Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of REPLAGAL® in Treatment-naïve Chinese Subjects with Fabry Disease
Short Title:	REPLAGAL® Study in Treatment-naïve Chinese Subjects
Study Phase:	Phase 3
Drug:	REPLAGAL® (agalsidase alfa)
IND Number:	Non-IND
EUDRACT Number:	2022-004246-35
Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Ave, Lexington, MA 02421, USA
Principal / Coordinating Investigator:	[redacted] MD, PhD [redacted]
Protocol History:	Amendment 2.0: 23 May 2023 Amendment 1.0: 07 Feb 2022 Original Protocol: 17 Mar 2021 (Final)

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

DocuSigned by:

Signature: [redacted] *Date:* 24-May-2023 | 11:15:14 JST

[redacted], MD, PhD

Investigator's Acknowledgement

I have read this protocol for Study TAK-675-3001.

Title: An Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of REPLAGAL® in Treatment-naïve Chinese Subjects with Fabry Disease

I have fully discussed the objectives of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: _____

_____

Signature: _____ *Date:* _____

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

The table below provides an overview of the changes from the previous version (Amendment 1.0, dated 07 Feb 2022) to the current version of the protocol (Amendment 2.0, dated 23 May 2023).

The primary reasons for the amendment are to:

- Modify the ITT definition to include all subjects enrolled in the study.
- Add re-consent for pediatric subjects expected to reach legal age of 18 years old in China during the study.

Grammatical, typographical, or minor edits for clarity, administrative, and general formatting revisions are not identified.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number 2.0	**Amendment Date 23 May 2023**	**China**
Section(s) Affected by Change	**Description of Each Change**	**Rationale for Change**
Cover Page	Added EUDRACT Number 2022-004246-35.	Since this study includes pediatric patients, it falls under Article 46 of the EU pediatric regulation and therefore results will need to be posted on EUDRACT, even though the study is conducted in China only.
Protocol Signature Page	Updated the responsible personnel authorized to sign for Sponsor's (Takeda) Approval.	Changes to the study personnel.
CONTACTS	Added contact detail of Takeda Clinical Research Physician for protocol- or safety-related questions or concerns.	In addition to IQVIA medical monitor, added another option for Investigator to contact for protocol- or safety-related questions or concerns.
Section 1.1 Synopsis; Section 5.1 Inclusion Criteria	Inclusion Criterion #1; text revised as follows: For the subjects <18 years old, subjects will give assent AND their parent(s)/legally authorized representative should sign the ICF accordingly.	Only one parent's signature is required for ICF. Corrected typo to read "parent(s)."

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number 2.0	**Amendment Date 23 May 2023**	**China**
Section(s) Affected by Change	**Description of Each Change**	**Rationale for Change**
Section 1.1 Synopsis; Section 5.1 Inclusion Criteria	Inclusion Criterion #8: Added 'inclusive' for the eGFR range (45 to 120 mL/min/1.73 m^2)	To clarify to include the two cutoff border numbers of eGFR.
Section 1.1 Synopsis; Section 9.4 Statistical Analysis Set	Definition of ITT set revised to clarify ITT set will include all subjects who sign the ICF, are enrolled in the study, and have received at least 1 study drug infusion (full or partial).	Modified the ITT definition to include all subjects enrolled in the study.
Section 1.2 Schedule of Activities Footnote b; Section 8.1.2 Baseline Visit Period (Week -1)	Added text 'serum chemistry, hematology, urinalysis, and ECG performed at screening within 7 days prior to baseline visit may be used as the baseline.'	Screening assessment for serum chemistry, hematology, urinalysis, and ECG may be used as baseline if assessment is performed within 7 days prior to baseline.
Section 1.2 Schedule of Activities footnote s; Section 5.4.1 Female Contraception; Section 8.2.3.5 Pregnancy Test	Clarified that female subjects of childbearing potential must have a negative pregnancy test (ie., a urine pregnancy test, or a negative serum β-hCG test when a urine test is positive) to be eligible for the study.	For clarity and consistency.
Section 2.1 Indication and Current Treatment; Section 2.2 Product Background and Clinical Information; Section 4.2 Justification for Dose	Updated worldwide REPLAGAL approval status for treatment of Fabry disease as of 31 Jan 2023. Updated clinical information according to the latest edition of the IB.	Revised to be consistent with the latest edition of the IB.
Section 4.1 Overall Design; Section 6.7 Protocol Considerations for Unavoidable Circumstances Such as the COVID-19 Pandemic	Described the COVID-19 pandemic as an example of "unavoidable circumstances".	Added flexibility in wordings to not limit the unavoidable circumstances to COVID-19 pandemic.
Section 6.7 Protocol Considerations for Unavoidable Circumstances Such as the COVID-19 Pandemic	Text revised as, "Any protocol deviations, missing visits, or missing assessments related to COVID-19 restrictions will be recorded and reported in the clinical study report."	For clarity.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number 2.0	**Amendment Date 23 May 2023**	**China**
Section(s) Affected by Change	**Description of Each Change**	**Rationale for Change**
Section 7.3 Withdrawal from the Study	Added text, "Subjects who discontinue or withdraw will not be replaced."	For clarity.
Section 7.4 Subjects "Lost to Follow-up" Prior to the Last Scheduled Contact/Visit	Clarified that contact attempts to subjects or their legally authorized representative can be made in person, or by phone or video. Added that the contact attempts should be documented in the medical record.	To clarify the methods and documentation process of attempts to contact subjects.
Section 8.1.3.2 Evaluation Visits at Week 8, 16, 28, 40, and 52	Added text, "Unscheduled visit(s) will be recorded in the eCRF."	To add the record of unscheduled visit.
Section 8.2.1.1 Height and Weight	Added text, "BMI should be calculated by the investigator using the weight and height measured during the baseline visit."	Added description of BMI calculation.
Section 8.2.3.1 Physical Examination	Added text to clarify assessment of clinically significant changes from baseline physical examination.	Corrected the safety assessment of physical examination finding.
Appendix 1.5 Ethical Considerations, Informed Consent	Text added to clarify that when pediatric subjects reach legal age of 18 years old in China during the study, they should re-consent using the adult ICF.	According to ICH E11 "Clinical Investigation of Medicinal Products in the Pediatric Population", Section 2.6 on Ethical Considerations, when the minor reaches the legal age re-consent is required.
Appendix 3.1 Adverse Event Definitions, Clinical Laboratory and Other Safety Assessment	Added 'physical examination finding' to the list of clinical assessments.	Abnormal physical examination findings can also be considered an adverse event.

BMI: body mass index; β-hCG: beta human chorionic gonadotropin; COVID-19: coronavirus disease 2019; ECG: electrocardiogram; eCRF: electronic case report form; eGFR: estimated glomerular filtration rate; EUDRACT: European Union Drug Regulating Authorities Clinical Trials database; ICF: informed consent form; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ITT: intent-to-treat.

See Appendix 7 for protocol history, including all previous amendments.

CONTACTS

SAE Reporting

In the event of a serious adverse event (SAE), the investigator should complete an SAE electronic Case Report Form (eCRF) in English or report via the paper safety report form (as back-up) within 24 hours of becoming aware of any SAE. The fax number and email address are provided in the Form Completion Instruction.

Protocol and Safety-Related Questions or Concerns

For protocol- or safety-related questions or concerns, the investigator must contact Takeda Clinical Research Physician or IQVIA medical monitor:

[redacted], **M.D., Ph.D.**
Takeda Clinical Research Physician
Mobile: [redacted]
Email: [redacted]

[redacted], **M.D., Ph.D.**
IQVIA [redacted]
Mobile: [redacted]
Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Takeda within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Takeda licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that the product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	• Capsule fill empty or overage • Bottle/vial fill shortage or overage • Capsule/tablet damaged/broken • Syringe/vial cracked/broken	• Syringe leakage • Missing components • Product discoloration • Device malfunction
Labeling	• Label missing • Leaflet or Instructions for Use missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing
Packaging	• Damaged packaging (eg, secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottle/vial • Particulate in packaging	

Please report the product quality complaint using Clinical Trial Material Compliant Form via the email address:

ctmcomplaint@takeda.com

For instructions on reporting adverse events related to product complaints, see Appendix 3.4.

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: TAK-675-3001	**Drug:** REPLAGAL (agalsidase alfa)
Title of the study: An Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of REPLAGAL® in Treatment-naïve Chinese Subjects with Fabry Disease	
Short title: REPLAGAL® Study in Treatment-naïve Chinese Subjects	
Study phase: 3	
Number of subjects (total and per treatment arm): 20 safety evaluable subjects in total (at least 25% are ≥7 to <18 years old)	
Principal/Coordinating Investigator: [redacted]	
Sites and Regions: 4 to 6 sites in China	
Study period (planned): 2021-2024	**Clinical phase:** 3

Objectives:

Primary: The primary objective of this study is to assess the safety of REPLAGAL (0.2 mg/kg every other week [EOW] up to 52 weeks), by evaluating the incidence of serious treatment-emergent adverse events (TEAEs) over the study period, in treatment-naïve Chinese subjects with Fabry disease.

Secondary: The secondary objectives are as follows:

- To evaluate other safety parameters of REPLAGAL
- To evaluate the efficacy of REPLAGAL on the renal parameter (ie, estimated glomerular filtration rate [eGFR])
- To assess the efficacy of REPLAGAL on left ventricular mass index (LVMI) and left ventricular ejection fraction (LVEF)
- To evaluate the efficacy of REPLAGAL on other renal variables, pain, and pharmacodynamic markers (plasma globotriaosylsphingosine [lyso-Gb3])
- To evaluate the change in hearing for subjects <18 years old
- To evaluate the pharmacokinetics (PK) of REPLAGAL in treatment-naïve Chinese subjects with Fabry disease.

Rationale: On 28 Aug 2020, REPLAGAL received approval of its New Drug Application from China's National Medical Products Administration for the treatment of Fabry disease. As part of the approval requirements and post-authorization commitment, the China Health authority has requested that further efficacy and safety data be collected from Chinese patients with Fabry disease. For that, a Phase 3 interventional study was proposed. This study is intended to evaluate the safety, efficacy, and PK of REPLAGAL in treatment-naïve Chinese subjects with Fabry disease.

Investigational product, dose, and mode of administration:

The investigational product is REPLAGAL (agalsidase alfa), which will be supplied as a sterile, clear, colorless concentrate for dilution for intravenous (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.

REPLAGAL infusions will occur at the clinical site. Subjects will receive REPLAGAL at a dose of 0.2 mg/kg body weight administered as an IV infusion over 40 minutes (±10 minutes) EOW (±4 days), except on Day 1 (Week 0) and Week 28 visits where the length of infusion must be exactly 40 minutes to support the PK sampling.

Methodology:

This is a China-only, Phase 3, multicenter, nonrandomized, open-label, single-arm study to evaluate the safety, efficacy, and PK of REPLAGAL in treatment-naïve Chinese subjects with Fabry disease. The study will consist of EOW treatment with 0.2 mg/kg IV infusion of REPLAGAL for up to 52 weeks. A total of 20 safety evaluable subjects aged ≥7 to ≤65 years are planned to be enrolled with at least 25% of the total eligible subjects in the age range of ≥7 to <18 years old.

The study will include a screening period, a baseline visit period, a treatment period, and a safety follow-up period. Screening assessments will occur from Week -7 through Week -2. Baseline visit period will be at Week -1. After completion of baseline procedures and assessments, eligible subjects will receive 0.2 mg/kg IV infusions of REPLAGAL EOW (±4 days) from Day 1 (Week 0) up to Week 52 (end of treatment visit) during the treatment period. Evaluation visits will be performed at clinical site at Week 8 (±4 days), Week 16 (±4 days), Week 28 (±4 days), Week 40 (±7 days), and Week 52 (±7 days). Additionally, PK assessments will occur at Day 1 (Week 0) and Week 28 (±4 days). In order to ensure subjects' safety, subjects will undergo a follow-up period of approximately 14 days (+7 days), after the completion of the treatment infusion (or the last infusion for early treatment discontinued subjects).

Safety assessments include monitoring of adverse events (AEs), use of concomitant medication, clinical laboratory values, antibody formation, vital signs, physical examination, and electrocardiogram results.

Efficacy assessments include measurements of eGFR, urine protein/creatinine ratio, LVMI, LVEF, and Brief Pain Inventory (BPI).

For pediatric subjects (<18 years old at screening), additional assessment for hearing will be performed.

Pharmacodynamic assessment includes plasma lyso-Gb3.

Pharmacokinetic assessments will be completed by obtaining blood samples at pre-specified time points in the study. Ten subjects (5 adult subjects and 5 pediatric subjects) will provide intensive PK samples and other subjects will provide sparse PK samples.

Inclusion and Exclusion Criteria:

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

Inclusion Criteria:

The subject will not be considered eligible for the study without meeting all of the criteria below.

1. Subject and/or legally authorized representative must voluntarily sign an Institutional Review Board/Independent Ethics Committee approved written informed consent form (ICF) after all relevant aspects of the study have been explained and discussed with the subject. For the subjects <18 years old, subjects will give assent AND their parent(s)/legally authorized representative should sign the ICF accordingly.
2. The subject has confirmed diagnosis of Fabry disease as determined by the investigator, according to medical record including:
   - For male subject, Fabry disease is confirmed by a deficiency of α-galactosidase A (GLA) activity and a mutation in the GLA gene
   - For female subject, Fabry disease is confirmed by a mutation in the GLA gene.
3. The subject is 7 to 65 years of age, inclusive, at screening.
4. Female subjects of childbearing potential must have a negative pregnancy test at screening.
5. Female subjects of childbearing potential must agree to use a medically acceptable method of contraception at all times during the study and for at least 14 days after the final investigational product infusion; the methods of acceptable contraception are listed in the protocol.
6. The subject is deemed, as determined by the investigator, to have adequate general health to undergo the specified protocol-related procedures and to have no safety or medical contraindications for participation.
7. The subject has not received any treatment (approved or investigational) specific to Fabry disease, such as enzyme replacement therapy, chaperone therapy, or substrate reduction therapy.

8. The adult subject (≥18 years old) must have an eGFR of 45 to 120 mL/min/1.73 m^2 (inclusive). Serum creatinine is tested and the eGFR is calculated by central laboratory using the Chronic Kidney Disease Epidemiology equation.

Exclusion Criteria:

The subject will be excluded from the study if any of the following exclusion criteria are met.

1. In the opinion of the investigator, the subject's life expectancy is ≤5 years.
2. The subject has undergone or is scheduled to undergo kidney transplantation or is currently on dialysis or has any signs or symptoms of end stage renal disease.
3. The subject has a urine protein/creatinine ratio of >500 mg/g.
4. The subject has a clinically relevant history of allergy or signs or symptoms of severe hypersensitivity, which in the investigator's judgment, will substantially increase the subject's risk if he or she participates in the study.
5. In the opinion of the investigator, the subject has non-Fabry disease-related cause of end organ (renal, cardiovascular, central nervous system) dysfunction/failure or is receiving medications that may affect the rate of disease progression, as assessed by renal measures.
6. The subject has a positive test result at screening for hepatitis B surface antigen with detectable hepatitis B viral DNA load, hepatitis C virus (HCV) antibody with confirmation by HCV ribonucleic acid polymerase chain reaction testing, or human immunodeficiency virus antibody.
7. The subject has received prior treatment with any of the following medications, with the exception of non-systemic use:
   - Chloroquine
   - Amiodarone
   - Monobenzone
   - Gentamicin
8. The subject is pregnant or lactating.
9. The subject has a body mass index >35 kg/m^2.
10. The subject is treated or has been treated with any investigational drug for indication other than Fabry disease within 30 days prior to study start.
11. The subject and/or the subject's parent(s)/legal guardian is unable to understand the nature, scope, and possible consequences of the study.
12. The subject is unable to comply with the protocol, eg, uncooperative with protocol schedule, refusal to agree to all of the study procedures, inability to return for evaluations, or is otherwise unlikely to complete the study, as determined by the investigator.

Maximum duration of subject participation in the study:

The subject's maximum duration of participation from screening to safety follow-up period is expected to be approximately 61 weeks (or 14.2 months).

- Screening period: up to 6 weeks (42 days)
- Baseline visit period: up to 1 week (7 days)
- Treatment period: up to 52 weeks
- Safety follow-up period: 2 weeks (14 days)

Statistical analysis:

Analysis Set

The statistical analysis will include the following analysis sets:

- The **intent-to-treat (ITT) set** will include all subjects who sign the ICF, are enrolled in the study, and have received at least 1 study drug infusion (full or partial).

- The **modified intent-to-treat (mITT)** set will include all enrolled subjects (all subjects from the ITT set) who have received at least 1 dose of investigational product and completed at least 1 post-baseline efficacy assessment of the endpoints. The mITT set will be used for efficacy analyses.
- The **safety set** will include all subjects in the ITT set who receive at least 1 dose of REPLAGAL. The safety set will be used for the analysis of safety endpoints.
- The **per-protocol (PP) set** will include all subjects in the mITT set excluding subjects with major protocol deviations. The PP set will be identified by a team consisting of, at a minimum, a physician and a statistician from Takeda. The PP set will be used for an efficacy sensitivity analysis.
- The **pharmacokinetic (PK) set** will include all subjects in the ITT who receive at least 1 dose of investigational product and provide intensive or sparse PK samples. The **intensive PK set** will include subjects in the PK set who provide intensive sampling. Five adult subjects and 5 pediatric subjects will be included in this set. Pharmacokinetic parameters will be derived from the intensive PK set.

Study Endpoints

Primary Endpoint:

- Serious TEAEs

Secondary Endpoints:

- TEAEs
- Infusion-related reactions (IRRs)
- Anti-drug antibody against agalsidase alfa assessment, including neutralizing antibody (NAb) status
- Laboratory assessments
- Vital signs
- Electrocardiogram results
- Change from baseline at Week 52 in renal function, assessed by eGFR
- Change over time in eGFR
- Change over time in LVMI and LVEF as measured by echocardiography
- Change over time in urine protein/creatinine ratio
- Change over time in pain as assessed by BPI-Short Form
- Change over time in plasma lyso-Gb3 level
- Change in hearing (audiology testing for subjects <18 years old at screening)
- PK parameters

Sample Size

A sample size of 20 safety evaluable subjects is planned to be enrolled in this study to descriptively provide an estimate of the serious TEAE rate. No formal sample size calculations have been done and the sample size is based on feasibility.

Efficacy Analyses

Continuous variables will be summarized with descriptive statistics including the mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized with the frequency and percentage of subjects falling within each category. Subsequently, longitudinal data will be analyzed using mixed-effects model for repeated measures, using both the mITT and PP sets (using the PP set will serve as a sensitivity analysis).

The observed values, the change from baseline, the change over time, and the percentage change from baseline for the efficacy measurements (eGFR, urine protein/creatinine ratio, plasma lyso-Gb3, LVMI, and LVEF) will be summarized by sex and visit. Subject listings will be provided for clinical outcomes from the BPI-Short Form measurement.

Audiology results will be produced at baseline and (if applicable) for each post-baseline evaluation visit. Audiology data will also be presented in the form of individual subject listings.

Efficacy analyses will be based on the mITT set, with the PP set as a sensitivity analysis.

Safety Analyses

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Treatment-emergent AEs will be summarized for overall and by system organ class (SOC) and preferred term (PT). Analysis of AEs will be performed at both subject level and AE level. Similar displays will be provided for IRRs. The AEs will be summarized by severity, seriousness, and relationship to investigational product.

Subjects will be counted once per SOC and once per PT. Multiple events of the same type will be combined for each subject and, when doing this, the worst severity or outcome for each event type will be presented for the analysis. When calculating event rates, the denominator will be the total population size, irrespective of dropouts over the course of follow-up.

Tabular summaries of other safety endpoints (eg, vital signs, blood tests, concomitant medications [coded using the World Health Organization Drug Dictionary], anti-agalsidase alfa antibody status, and infusion information) will be produced at baseline and, if applicable, for each post-baseline evaluation visit.

Changes in the results of physical examination from the baseline will be presented by visit and body system in the form of a shift table.

The observed values and the change from baseline for electrocardiogram (ECG) parameters (PR, QRS, QT, QTc, and heart rate) will be summarized by visit. The number of subjects with normal and abnormal ECG results during the study period will be summarized by visit in the form of a shift table.

Laboratory data will be listed by subject. Subjects with newly occurring abnormalities outside the normal range will be flagged, listed separately, and summarized. The mean change from baseline in laboratory values or a shift table also will be provided at each visit. Change from baseline will be calculated by subtracting the baseline value from the post-baseline value.

Vital sign data will be listed by subject, and any newly occurring changes outside the reference range from baseline will be flagged. Mean changes from baseline for vital sign data will be summarized. Subjects with notable abnormal values will be identified and listed separately along with their values.

The number and percentage of subjects reporting at least one use of concomitant medication during the study will be reported. Subject listings will be provided describing the reason(s) for study discontinuation.

Antibody data, including NAbs, will also be presented in the form of individual subject listings.

Safety data will be analyzed using the safety set.

Pharmacokinetic Analyses

Statistical analysis of PK data will be based on the PK set as well as the intensive PK set.

For the PK set, individual concentrations will be listed and summarized by scheduled time points for all subjects and by age (eg, ≥18 years vs <18 years). For the intensive PK set, individual concentration will be summarized for all subjects and by age. Individual PK parameters of REPLAGAL will be listed and summarized by treatment for all subjects as well as by age with descriptive statistics (number, arithmetic mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, and CV of geometric mean). Pharmacokinetic parameter estimates will be computed, where appropriate, from individual serum-concentration time data using noncompartmental methods and actual times. Figures of individual and mean (±SD) concentration-time profiles of REPLAGAL will be generated based on nominal time points for all subjects and by age.

1.2 Schedule of Activities

Table 1. Schedule of Activities

Study Assessments and Procedures	Screening Period[a]	Baseline Visit Period[b]	Treatment Period[c]						Safety Follow-up Period (End of Study)
			EOW REPLAGAL Infusion (±4 days; Week 0 through Week 52)[d]	Evaluation Visit[e]					Telephone Contact/Visit[f]
	Week -7 through Week -2	(Week -1)		Week 8 (±4 days)	Week 16 (±4 days)	Week 28 (±4 days)	Week 40 (±7 days)	Week 52 (±7 days) EOT or Early Discontinuation[g]	14 days (+7 days) from EOT or Last Infusion for Discontinued Subjects
Informed consent[h]	•								
Inclusion/exclusion criteria review	•	•							
Confirmation of Fabry disease[i]	•								
Demography	•								
Medical history	•								
Physical examination	•				•			•	
Vital signs[j]	•	•	•	•	•	•	•	•	
Height[k]	•	•		•	•	•	•	•	
Weight[l]	•	•	•	•	•	•	•	•	
Audiology testing[m]		•		•	•	•	•	•	
Pain (BPI-Short Form)		•		•	•	•	•	•	
Dose calculation[n]			•	•	•	•	•	•[g]	
REPLAGAL infusion[o]			•	•	•	•	•	•[g]	
PK sampling[p]			•			•			
12-Lead ECG	•	•			•			•	
Echocardiography[q]		•			•			•	
eGFR calculation[r]	•	•		•	•	•	•	•	
Pregnancy test[s]	•	•		•	•	•	•	•	
Serum chemistry[t]	•	•		•	•	•	•	•	
Hematology[u]	•	•		•	•	•	•	•	
Serum ADA and neutralizing antibodies[v]		•		•	•	•	•	•	
Plasma lyso-Gb3[w]		•		•	•	•	•	•	
Urinalysis[x]	•	•		•	•	•	•	•	
Urine protein/creatinine ratio[x]	•	•		•	•	•	•	•	
Viral testing[y]	•								
Review of AEs	•	•	•	•	•	•	•	•	•
Prior/concomitant medications, and medical/surgical interventions	•	•	•	•	•	•	•	•	•

ADA=anti-drug antibody; AE=adverse event; β-hCG=beta-human chorionic gonadotropin; BPI=Brief Pain Inventory; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EOT=end of treatment; EOW=every other week; HCV=hepatitis C virus; IRR=infusion-related reaction; lyso-Gb3=globotriaosylsphingosine; PK=pharmacokinetic; SAE=serious adverse event

[a] Screening procedures can be performed over multiple days within a period of up to 42 days following the subject's (or the subject's parent(s)/legally authorized representative) signature of the informed consent form.

[b] All baseline procedures and evaluations must be completed prior to the first REPLAGAL infusion and will be performed at the clinical site. Serum chemistry, hematology, urinalysis, and ECG performed at screening within 7 days prior to baseline visit may be used as the baseline.

[c] During the treatment period, all study assessments and procedures should be completed on the day(s) of the scheduled visit.

[d] The REPLAGAL infusions are to be administered at the clinical site.

[e] Procedures and evaluations to be performed at site visits will occur at the clinical site.

[f] The safety follow-up period (end of study) is 14 days (+7 days) following EOT infusion (or the last infusion for discontinued subjects). During this period, there will be a telephone call/scheduled visit to query for AEs, SAEs, and concomitant medications. Subjects who experienced SAEs, or mild, moderate, or severe AEs may be requested to visit the clinical site for further examination. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure.

[g] For subjects who discontinue the study early, all EOT assessments and procedures should be completed except for dose calculation and REPLAGAL infusion.

[h] Informed consent must be obtained prior to performing any study-related procedures.

[i] Fabry disease diagnosis will be confirmed at screening by medical record.

[j] The following vital signs will be collected at all study visits (screening and infusion visits): pulse, blood pressure, respiratory rate, and temperature. On infusion visits (EOW and evaluation visits), vital signs should be obtained as follows: 1) within 10 minutes prior to starting the infusion; 2) 20 minutes (±5 minutes) after the start of the infusion; 3) 10 minutes (±5 minutes) after completing the infusion; and 4) 30 minutes (±5 minutes) after completing the infusion. In the event that a scheduled infusion does not occur on an evaluation visit, the vital signs should still be collected. The vital signs that were taken within 10 minutes prior to the start of the expected infusion should be documented in the electronic case report form. If no IRRs are observed during the first 3 infusions, the observation and vital signs after infusion can be omitted at the discretion of the investigator.

[k] For subjects <18 years of age, height should be measured at screening, baseline, and every evaluation visit during the treatment period. For subjects ≥18 years of age at screening, height should be measured only at the baseline visit.

[l] Weight will be measured at screening, baseline, and every visit during the treatment period, with any dosing adjustments completed prior to the dose administration.

[m] Audiology testing is only applicable to subjects <18 years old.

[n] The first dose of REPLAGAL will be based on the subject's weight at baseline. A change of at least 5% in subject weight from baseline or the last weight used to calculate the dose will require a dose recalculation at the clinical site.

[o] REPLAGAL (at a dose of 0.2 mg/kg body weight) will be administered as an intravenous infusion over 40 minutes (±10 minutes) EOW (±4 days) at the clinical site, except on Day 1 (Week 0) and at the Week 28 visit where the length of infusion must be exactly 40 minutes to support the PK sampling. All study procedures, assessments (except for post-infusion vital signs), and sample collections (except for post-infusion PK sample collection) should be completed prior to administering an infusion, except on Week 40 and 52 visits where REPLAGAL infusion should maintain the ±4 days window period while the evaluation procedures can be done within the ±7 days window period. If at all possible, missed infusions should be avoided. If a subject is not dosed within

21 days from the previous dose, the subject should receive the missed infusion as soon as possible. It may be acceptable to give the next infusion as early as 7 days after the previous infusion. Subsequent infusions will return to the original schedule.

[p] Sampling for PK assessments will be performed only at Week 0 and Week 28 and the PK assessments will be conducted in the Takeda-designated central laboratory. See Table 2 and Table 3 for PK sampling time points.

[q] An echocardiogram performed within 14 days prior to baseline visit may be used as the baseline echocardiogram. Echocardiography will be read locally at the clinical site by the investigator or a qualified designee.

[r] eGFR will be calculated using the Counahan–Barratt equation for subjects <18 years old and the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation for subjects aged 18 years and older and will be conducted in the Takeda-designated central laboratory.

[s] Female subjects of childbearing potential will have a pregnancy test administered at screening, baseline visit, and evaluation visits. Pregnancy testing will be performed using a urine test, and if needed, a serum β-hCG test. If the urine pregnancy test is negative, procedures will be completed; serum β-hCG testing is no longer required. If the urine test is positive, a blood sample will be collected for serum β-hCG testing and sent to either local laboratory or the central laboratory for analysis; no additional procedures should be completed until the result of the serum pregnancy test is available. Female subjects of childbearing potential must have a negative urine pregnancy test, or a negative serum β-hCG test when a urine test is positive to be eligible for the study. A positive serum β-hCG test would result in the subject being a screen failure or discontinued from the study.

[t] Serum chemistry laboratory tests (see Appendix 2 for details) will be performed in the local laboratory unless otherwise specified.

[u] Hematology laboratory tests include complete blood count (see Appendix 2 for details) will be performed in the local laboratory.

[v] ADA samples will be collected at baseline visit and evaluation visits prior to infusion; any samples that are confirmed positive for ADA will also be tested for neutralizing antibodies. The test will be performed in the Takeda-designated central laboratory.

[w] Plasma lyso-Gb3 will be assessed in the Takeda-designated central laboratory.

[x] An early morning spot urine sample will be obtained to measure protein and creatinine levels. Measurement of urine protein/creatinine ratio will be performed as part of urinalysis (see Appendix 2 for details on urinalysis).

[y] Tests for hepatitis B surface antigen with confirmation by hepatitis B viral DNA load, HCV antibody with confirmation by HCV ribonucleic acid polymerase chain reaction testing, and human immunodeficiency virus antibody will be performed in the local laboratory.

Table 2. Intensive Pharmacokinetic Sampling Time Points

Sampling time points[a] *(from start of infusion)*	Pre-infusion	During infusion	End of Infusion	Post-infusion					
	0 min	20 mins	40 mins	50 mins	60 mins	90 mins	120 mins	240 mins	360 mins
Window		±1 min	±1 min	±2 mins	±2 mins	±2 mins	±2 mins	±2 mins	±3 mins
≥18 years old	•	•	•	•	•	•	•	•	•
<18 years old	•		•	•	•	•	•	•	•

[a] Intensive serial PK should be collected in 5 pediatric subjects and 5 adult subjects to allow for accurate estimation of PK parameters including AUC_{0-t} and C_{max}.

Table 3. Sparse Pharmacokinetic Sampling Time Points

Sampling time points[a] *(from start of infusion)*	Pre-infusion	End of Infusion	Post-infusion
	0 min	40 mins	120 mins
Window		±1 min	±2 min
≥18 years old	•	•	•
<18 years old	•	•	•

[a] A reduced/sparse PK sampling schedule will be allowed for subjects not providing intensive PK samples.

2. INTRODUCTION

2.1 Indication and Current Treatment Options

Indication

Fabry disease is a rare, lifelong, slowly progressive, X-linked glycosphingolipid storage disorder with a global incidence estimated at 1:50,000 male live births (Spada et al., 2006). There are an estimated 18,860 patients with Fabry disease in China mainland (Blue book of "Improve the availability of drug for rare disease in China", 2019).

Fabry disease results from a mutation in the α-galactosidase A (GLA) gene located on chromosome Xq22.1, which leads to a partial or full loss of the activity of the lysosomal enzyme GLA (Garman and Garboczi, 2004). More than 400 mutations have been identified in the GLA gene. These consist mainly of missense mutations, but nonsense mutations in addition to single amino acid deletions and insertions were also reported (Mehta et al., 2010). Most of these mutations are "private", having been identified only in individual families (Mehta et al., 2010). As an X-linked disorder, females may inherit an X-linked Fabry mutation from either parent accounting for twice the number of carriers (heterozygotes) as males (hemizygotes). Female carriers are not necessarily asymptomatic (Eng et al., 2007).

Alpha-galactosidase A is a lysosomal hydrolase enzyme that catalyzes the removal of terminal alpha-galactosyl moieties during the catabolism of glycolipids and glycoproteins. Partially active or deficient GLA results in abnormal accumulation of glycolipids (globotriaosylceramide [Gb3]) in cells throughout the body, including capillary endothelial, renal (podocytes, tubular cells, glomerular endothelial, mesangial, and interstitial cells), cardiac (cardiomyocytes and fibroblasts) and nerve cells. Abnormal Gb3 concentrations in membranous structures may impair intracellular trafficking processes, cellular activation, intercellular communication, and cellular homeostasis. This results in inflammatory changes and cytokine release, ultimately leading to apoptosis and eventual organ dysfunction and/or failure (Brady, 1967; Kahn, 1973; Kaye et al., 1988; Desnick, 1995; deVeber et al., 1992; Schaefer et al., 2009).

Fabry disease is characterized by a range of phenotypes that generally correlates with the degree of residual enzymatic activity. The threshold level of alpha-Gal A activity below which clinically significant Fabry disease occurs is thought to be 30 to 35 percent of the mean normal control (Schiffmann et al., 2016). Phenotype presentation becomes more evident during childhood and young adulthood (Eng et al., 2007), and as the patient advances in age organ function deterioration intensifies ultimately leading to organ failure and early death. Most patients display multiple clinical manifestations of the disease, many of which may occur before 10 years of age in males (Deegan et al., 2006). In females, GLA activity is most often higher than males (Arends

et al, 2017) and the onset of symptoms and time of diagnosis can be variable, occurring approximately 10 years later compared with males (Eng et al., 2007; Kruger et al., 2010). The clinical presentation of the disease varies widely among patients, but neuropathic pain and acroparesthesia are typically the first and most frequent symptoms to manifest. Other clinical manifestations of Fabry disease include angiokeratomas, gastrointestinal problems, proteinuria, progressive renal impairment leading to renal failure, hypertrophic cardiomyopathy with arrhythmias, corneal dystrophy, hypohydrosis, and microvascular cerebral events including transient ischemic attacks, stroke, and dolychoectasia (Schiffmann and Ries, 2005; Deegan et al., 2006). Vital organs, especially the heart, kidneys, and brain, are progressively affected with advancing age (Ries and Schiffmann, 2005). As a consequence, physical and functional well-being and quality of life (QoL) are significantly reduced in patients with Fabry disease compared with the general population and patients with other chronic non-genetic disorders (Gold et al., 2002; Miners et al., 2002).

Patients with Fabry disease have a shortened life expectancy with men and women affected by the disorder living 20 years (MacDermot et al., 2001b) and 15 years (MacDermot et al., 2001a; Barbey et al., 2004; Mehta et al., 2004) less than those in the general population, respectively. Prior to the introduction of enzyme replacement therapy (ERT) in 2001, the leading cause of death in patients with Fabry disease was renal disease (Mehta et al., 2009). Since then, significant improvements have been made in supportive care of renal function and cardiac disease is now the primary cause of death (Mehta et al., 2009; Waldek et al., 2009).

Current Treatment Options

Two ERT products have been approved for patients with a confirmed diagnosis of Fabry disease: agalsidase alfa (marketed under the trade name of REPLAGAL® in countries outside the United States [US] by Shire [now part of Takeda]) and agalsidase beta (FABRAZYME®; Sanofi Genzyme).

The first approval of REPLAGAL as treatment for Fabry disease occurred in August 2001 in the European Union. As of 31 Jan 2023, REPLAGAL has been approved as treatment for Fabry disease in 70 countries.

Migalastat (GALAFOLD) was granted approval in Europe in May 2016 and in the US in 2018 as the first chaperone therapy for the long-term treatment of Fabry disease in adults and adolescents aged 16 or older with an amenable mutation in GLA.

2.2 Product Background and Clinical Information

Product Background

Alpha-galactosidase A is a homodimer comprising 2 approximately 50 kDa subunits; GLA is targeted to its lysosomal site of action by mannose-6-phosphate (M6P) moieties, which bind to their cognate receptors in the Golgi directing the enzyme to the prelysosomal compartments. Any enzyme that escapes this routing system is secreted by the cell via the constitutive secretory pathway and is often recaptured by cell surface M6P receptors to be rerouted to the lysosome by the endocytic pathway (Kornfeld and Mellman, 1989). The M6P mediated lysosomal targeting is the key mechanism that made ERT a feasible treatment strategy for lysosomal storage diseases as it enables the targeting of exogenously administered lysosomal enzymes to the appropriate subcellular compartment for their optimal activity.

REPLAGAL (agalsidase alfa) is human GLA produced by genetic engineering technology in a human cell line. REPLAGAL is manufactured using an aseptic filling process in a facility in compliance with current Good Manufacturing Practice and 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 an ERT for patients with Fabry disease. Replacement of the absent or deficient enzyme contributes to the correction of the deficient enzymatic activity and allows for improved metabolism of the natural substrate of 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 QoL.

Clinical Information

Clinical studies of REPLAGAL have been conducted in Australia, Brazil, Canada, Europe, Japan, Paraguay, and the US. The clinical development program was designed to evaluate the safety and efficacy of REPLAGAL in subjects with Fabry disease and includes early phase safety studies, placebo-controlled safety and efficacy studies, and open-label extension studies. Additionally, studies in special populations have been conducted: pediatric subjects, female subjects, dialysis and renal-transplant subjects, and 1 compassionate-use study. A manufacturing change led to additional studies, such as bioequivalence pharmacokinetic (PK)/pharmacodynamic (PD) studies. One open-label, treatment protocol study (HGT-REP-081) evaluating the long-term safety of

REPLAGAL in subjects with Fabry disease following a manufacturing change from roller bottle to bioreactor, animal-free process has been recently completed in Canada (2018).

REPLAGAL has a well-established safety profile. The population exposed to REPLAGAL in clinical studies is considerable relative to the rarity of this genetic disease and represents an extensive clinical database to assess REPLAGAL in the treatment of Fabry disease. As of 31 Jan 2023, the population exposed to REPLAGAL in clinical studies included 779 subjects (641 subjects with Fabry disease and 138 healthy volunteers). The 641 subjects with Fabry disease included 567 adult subjects and 74 pediatric subjects. The estimated cumulative worldwide exposure to REPLAGAL, based on commercial sales data from launch in 2001 through 03 Aug 2022, is approximately 46,233 person-years.

REPLAGAL is generally safe and well-tolerated in the adult and pediatric Fabry populations, as evidenced by over 10 years of clinical and commercial data. In the integrated clinical study datasets (November 2009), REPLAGAL was administered to 153 adult patients for a median of 1.3 years and to 24 pediatric patients (6 to ≤18 years of age) for a median of 1.8 years. Twenty (20) adult patients (13.1%) and 11 pediatric patients (45.8%) were treated for at least 4 years. Given the extent of exposure, most adult patients (151 patients; 98.7%) and all pediatric patients (100.0%) reported at least 1 adverse event (AE), and 56 (36.6%) adult patients and 5 (20.8%) pediatric patients reported at least 1 serious adverse event (SAE). Only 5 (3.3%) adult patients discontinued due to an AE; no pediatric patient discontinued due to an AE. For a more detailed safety profile of REPLAGAL, please refer the Investigator's Brochure (IB).

Data collected in clinical trials to-date indicate that REPLAGAL remains safe and well-tolerated during long-term use. As with other intravenously (IV) administered protein therapeutics, the identified and potential risks of treatment with REPLAGAL include occurrence of infusion-related reactions (IRRs), cardiac ischemic events and arrhythmias triggered by IRRs, and potential development of neutralizing antibodies (NAbs) that may compromise efficacy. Of these, IRRs are idiosyncratic and allergic-type hypersensitivity reactions which may be defined as any new signs or symptoms experienced by subjects during the infusion or any new events occurring on the first day of administration of pharmacologic or biologic agents. Infusion-related reactions are the most commonly observed adverse drug reactions associated with REPLAGAL and generally occur within the first 2 to 4 months after initiation of treatment with REPLAGAL. The clinical experience has indicated that IRRs can be mitigated with a combination of infusion-rate control and medications such as antihistamines, antipyretics or low-dose corticosteroids. Cardiac ischemic events and arrhythmias triggered by IRRs have been also reported as risks associated with REPLAGAL treatment in patients with pre-existing cardiac manifestations of Fabry disease. The majority of these events were mild in severity, nonserious, and resolved. Cardiac events triggered by IRRs are possibly due to the hemodynamic stress caused by infusion. Additionally,

there is no apparent evidence to date for a loss of efficacy due to NAbs against agalsidase alfa. Borderline immunoglobulin E antibody positivity not associated with anaphylaxis has been reported in clinical studies.

The efficacy profile of REPLAGAL was evaluated in clinical studies and REPLAGAL received initial regulatory approval based on reduction of pain in patients with Fabry disease; additionally, the registration studies evaluated important clinical outcome benefits such as QoL, renal function, cardiac structure, and PD (Gb3) measures.

In aggregate, data from randomized double-blind placebo-controlled trials, long-term treatment data from open-label extensions, open-label experiences in special populations, and post-marketing experience demonstrate that treatment with REPLAGAL is an effective treatment that stabilizes and decreases the progression of renal and cardiac disease, demonstrates clinically meaningful results in measures of pain and QoL, and produces a sustained improvement in PD measures in patients with Fabry disease.

2.3 Study Rationale

On 28 Aug 2020, REPLAGAL received approval of its New Drug Application from China's National Medical Products Administration for the treatment of Fabry disease. As part of the approval requirements and post-authorization commitment, the China Health authority has requested that further efficacy and safety data be collected from Chinese patients with Fabry disease. For that, a Phase 3 interventional study was proposed. This study is intended to evaluate the safety, efficacy, and PK of REPLAGAL in treatment-naïve Chinese subjects with Fabry disease.

2.4 Benefit/Risk Assessment

The cumulative clinical and post-marketing experience indicates that the benefit-risk profile of agalsidase alfa for the treatment of Fabry disease remains favorable and supported by the following:

- A high disease burden with life-threatening/debilitating complications
- Alternative treatments are limited and are also associated with significant adverse reactions
- Demonstrated benefit in pain reduction, improvement or stabilization of cardiac and renal function, and reduction in accumulation of Gb3

- Well established safety profile with the main identified risks of IRRs, cardiac events triggered by IRRs, and immunogenicity.

Always refer to the latest version of the REPLAGAL IB for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, PK, efficacy, and safety of REPLAGAL.

2.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; ICH E6 R2, 2016), and applicable national and local regulatory requirements.

The responsibilities of the study sponsor and investigator(s) are described fully in Appendix 1.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of this study is to assess the safety of REPLAGAL (0.2 mg/kg every other week [EOW] up to 52 weeks), by evaluating the incidence of serious treatment-emergent adverse events (TEAEs) over the study period, in treatment-naïve Chinese subjects with Fabry disease.

3.1.2 Secondary Objectives

The secondary objectives are as follows:

- To evaluate other safety parameters of REPLAGAL
- To evaluate the efficacy of REPLAGAL on the renal parameter (ie. estimated glomerular filtration rate [eGFR])
- To assess the efficacy of REPLAGAL on left ventricular mass index (LVMI) and left ventricular ejection fraction (LVEF)
- To evaluate the efficacy of REPLAGAL on other renal variables, pain, and PD markers (plasma globotriaosylsphingosine [lyso-Gb3])
- To evaluate the change in hearing for subjects <18 years old
- To evaluate the PK of REPLAGAL in treatment-naïve Chinese subjects with Fabry disease.

3.2 Study Endpoints

Table 4. Objectives and Endpoints

Objective	Endpoints
Primary	
• To assess the safety of REPLAGAL, by evaluating the incidence of serious TEAEs over the study period, in treatment-naïve Chinese subjects with Fabry disease	• Serious TEAEs
Secondary	
• To evaluate other safety parameters of REPLAGAL	• TEAEs • Infusion-related reactions • Anti-drug antibody against agalsidase alpha assessment, including neutralizing antibody status • Laboratory assessments • Vital signs • Electrocardiogram results
• To evaluate the efficacy of REPLAGAL on the renal parameter (ie, eGFR)	• Change from baseline at Week 52 in renal function, assessed by eGFR using the CKD-EPI equation for subjects ≥18 years old and Counahan–Barratt equation for subjects <18 years old • Change over time in eGFR
• To assess the efficacy of REPLAGAL on LVMI and LVEF	• Change over time in LVMI and LVEF as measured by echocardiography.
• To evaluate the efficacy of REPLAGAL on other renal variables, pain, and PD markers (plasma lyso-Gb3)	• Change over time in urine protein/creatinine ratio • Change over time in pain as assessed by BPI-Short Form • Change over time in plasma lyso-Gb3 level
• To evaluate the change in hearing for subjects <18 years old	• Change in hearing (audiology testing for subjects <18 years old at screening)
• To evaluate the PK of REPLAGAL in treatment-naïve Chinese subjects with Fabry disease	PK parameters include, but are not limited to, the following: • $AUC_{0\text{-last}}$ (min*U/mL): Area under the concentration-time curve from the time of dosing to the last measurable concentration • $AUC_{0\text{-}\infty}$ (min*U/mL): Area under the concentration-time curve from time zero extrapolated to infinity • CL (mL/min): Serum clearance of administered dose (Dose/AUC)

Table 4. Objectives and Endpoints

Objective	Endpoints
	• CL (mL/min/kg): Serum clearance of administered dose normalized for body weight • C_{max}: Maximum concentration observed • $t_{1/2}$ (min): Terminal elimination half-life, defined as the natural log of 2 divided by the terminal rate constant (λz) • t_{max} (min): Time of maximum observed concentration sampled post-dose • V_{ss} (mL): Volume of distribution at steady state • V_{ss} (%BW): Estimate of volume of distribution at steady state normalized for body weight • AUC_{last}/dose (AUC_{last}/[U/kg]): Area under the concentration-time curve at the last sample (AUC_{last}) normalized for the dose of enzyme activity • $AUC_{0-\infty}$/dose ($AUC_{0-\infty}$/[U/kg]): Area under the concentration-time curve at infinity ($AUC_{0-\infty}$) normalized for the dose of enzyme activity • C_{max}/dose (C_{max}/[U/kg]): Maximum serum concentration (C_{max}) normalized for the dose of enzyme activity

AUC=area under the curve; BPI=Brief Pain Inventory; CKD-EPI=Chronic Kidney Disease Epidemiology; CL=serum clearance; C_{max}=maximum concentration observed; eGFR= estimated glomerular filtration rate; LVEF=left ventricular ejection fraction; LVMI=left ventricular mass index; lyso-Gb3=globotriaosylsphingosine; PD=pharmacodynamic; PK=pharmacokinetic; $t_{1/2}$=terminal elimination half-life; TEAE=treatment-emergent adverse event; t_{max}=time of maximum observed concentration; V_{ss}=volume of distribution at steady state

4. STUDY DESIGN

4.1 Overall Design

This is a China-only, Phase 3, multicenter, nonrandomized, open-label, single-arm study to evaluate the safety, efficacy, and PK of REPLAGAL in treatment-naïve Chinese subjects with Fabry disease. The study will consist of EOW treatment with 0.2 mg/kg IV infusion of REPLAGAL for up to 52 weeks. A total of 20 safety evaluable subjects aged ≥7 to ≤65 years are planned to be enrolled with at least 25% of the total eligible subjects in the age range of ≥7 to <18 years old.

The study will include a screening period, a baseline visit period, a treatment period, and a safety follow-up period. Screening assessments will occur from Week -7 through Week -2. Baseline visit period will be at Week -1. After completion of baseline procedures and assessments, eligible subjects will receive 0.2 mg/kg IV infusions of REPLAGAL EOW (±4 days) from Day 1 (Week 0) up to Week 52 (end of treatment [EOT] visit) during the treatment period. Evaluation visits will be performed at clinical site at Week 8 (±4 days), Week 16 (±4 days), Week 28 (±4 days), Week 40 (±7 days), and Week 52 (±7 days). Additionally, PK assessments will occur at Day 1 (Week 0) and Week 28 (±4 days). In order to ensure subjects' safety, subjects will undergo a follow-up period of approximately 14 days (+7 days) after the completion of the treatment infusion (or the last infusion for early treatment discontinued subjects). The complete list of study procedures is presented in Table 1.

In the event a monitor cannot visit the site in a timely manner due to unavoidable circumstances, such as the coronavirus disease (COVID-19) pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain subject safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and permitted by the institutional review board (IRB)/ethics committee (EC), if applicable.

Safety assessments include monitoring of AEs, use of concomitant medication, clinical laboratory values, vital signs, antibody formation, physical examination, and electrocardiogram (ECG) results (Section 8.2.3).

Efficacy assessments include measurements of eGFR, urine protein/creatinine ratio, LVMI, LVEF, and Brief Pain Inventory (BPI). For pediatric subjects (<18 years old at screening), additional assessment for hearing will be performed (Section 8.2.2).

Pharmacodynamic assessment includes plasma lyso-Gb3 (Section 8.2.4.1). Pharmacokinetic assessments will be completed by obtaining blood samples at pre-specified time points in the

study (Section 8.2.4.2). Ten subjects (5 adult subjects and 5 pediatric subjects) will provide intensive PK samples and other subjects will provide sparse PK samples.

4.2 Justification for Dose

REPLAGAL (agalsidase alfa) 1 mg/mL concentrate solution for infusion is approved in 70 countries worldwide as of 31 Jan 2023. REPLAGAL will be administered at the globally approved dose of 0.2 mg/kg EOW by IV infusion over 40 minutes (±10 minutes). This regimen of REPLAGAL has been approved and marketed in Europe and multiple other countries worldwide for the treatment of Fabry disease.

4.3 Duration of Subject Participation and Study Completion Definition

The subject's maximum duration of participation from screening to safety follow-up period is expected to be approximately 61 weeks (or 14.2 months).

- Screening period: up to 6 weeks (42 days)
- Baseline visit period: up to 1 week (7 days)
- Treatment period: up to 52 weeks
- Safety follow-up period: 2 weeks (14 days)

The study completion is defined as when the last subject in the study completes the final protocol-defined assessment(s). This includes the safety follow-up visit or contact, whichever is later (see Section 8.1.4 for the defined safety follow-up period for this protocol).

The study is expected to be completed in approximately 28 months.

4.4 Sites and Regions

The study is planned to be conducted in 4 to 6 sites in China.

5. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

5.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

1. Subject and/or legally authorized representative must voluntarily sign an Institutional Review Board/Independent Ethics Committee approved written informed consent form (ICF) after all relevant aspects of the study have been explained and discussed with the subject. For the subjects <18 years old, subjects will give assent AND their parent(s)/legally authorized representative should sign the ICF accordingly.
2. The subject has confirmed diagnosis of Fabry disease as determined by the investigator, according to medical record including:
   - For male subject, Fabry disease is confirmed by a deficiency of GLA activity and a mutation in the GLA gene
   - For female subject, Fabry disease is confirmed by a mutation in the GLA gene.
3. The subject is 7 to 65 years of age, inclusive, at screening.
4. Female subjects of childbearing potential must have a negative pregnancy test at screening.
5. Female subjects of childbearing potential must agree to use a medically acceptable method of contraception at all times during the study and for at least 14 days after the final investigational product infusion; the methods of acceptable contraception are listed in the protocol (Section 5.4.1).
6. The subject is deemed, as determined by the investigator, to have adequate general health to undergo the specified protocol-related procedures and to have no safety or medical contraindications for participation.
7. The subject has not received any treatment (approved or investigational) specific to Fabry disease, such as ERT, chaperone therapy, or substrate reduction therapy.
8. The adult subject (≥18 years old) must have an eGFR of 45 to 120 mL/min/1.73 m^2 (inclusive). Serum creatinine is tested and the eGFR is calculated by central laboratory using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation.

5.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met.

1. In the opinion of the investigator, the subject's life expectancy is ≤5 years.
2. The subject has undergone or is scheduled to undergo kidney transplantation or is currently on dialysis or has any signs or symptoms of end stage renal disease.
3. The subject has a urine protein/creatinine ratio of >500 mg/g.
4. The subject has a clinically relevant history of allergy or signs or symptoms of severe hypersensitivity, which in the investigator's judgment, will substantially increase the subject's risk if he or she participates in the study.
5. In the opinion of the investigator, the subject has non-Fabry disease-related cause of end organ (renal, cardiovascular, central nervous system) dysfunction/failure or is receiving medications that may affect the rate of disease progression, as assessed by renal measures.
6. The subject has a positive test result at screening for hepatitis B surface antigen with detectable hepatitis B viral DNA load, hepatitis C virus (HCV) antibody with confirmation by HCV ribonucleic acid polymerase chain reaction testing, or human immunodeficiency virus antibody.
7. The subject has received prior treatment with any of the following medications, with the exception of non-systemic use:
   - Chloroquine
   - Amiodarone
   - Monobenzone
   - Gentamicin
8. The subject is pregnant or lactating.
9. The subject has a body mass index >35 kg/m^2.
10. The subject is treated or has been treated with any investigational drug for indication other than Fabry disease within 30 days prior to study start.
11. The subject and/or the subject's parent(s)/legal guardian is unable to understand the nature, scope, and possible consequences of the study.
12. The subject is unable to comply with the protocol, eg, uncooperative with protocol schedule, refusal to agree to all of the study procedures, inability to return for

evaluations, or is otherwise unlikely to complete the study, as determined by the investigator.

5.3 Restrictions

Not applicable.

5.4 Reproductive Potential

5.4.1 Female Contraception

Sexually active females of childbearing potential should use an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 14 days following the last infusion of investigational product. If used, hormonal contraceptives should be administered according to the package insert. Any female of childbearing potential who is not currently sexually active must agree to use acceptable contraception, as defined below, if she becomes sexually active during the study and for 14 days following the last infusion of investigational product.

Female children and adolescent subjects should be either:

- Premenarchal and either Tanner stage 1 or less than age 9 years, or
- Of childbearing potential with a negative pregnancy test at the screening visit (see Section 8.2.3.5). Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Female adult subjects should be either:

- Post-menopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years),
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Of childbearing potential with a negative pregnancy test at the screening visit (see Section 8.2.3.5). Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception with signature in ICF.

Acceptable methods of contraception include the following:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the screening visit, plus condoms. Note: If the subject becomes sexually active during the study, she should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

5.4.2 Male Contraception

Not applicable.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The investigational product is REPLAGAL, which will be 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.

Additional information is provided in the current REPLAGAL IB.

6.1.2 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

REPLAGAL infusions will occur at the clinical site. Subjects will receive REPLAGAL at a dose of 0.2 mg/kg body weight administered as an IV infusion over 40 minutes (±10 minutes) EOW (±4 days), except on Day 1 (Week 0) and Week 28 visits where the length of infusion must be exactly 40 minutes to support the PK sampling. Refer to the instruction manual provided separately from this protocol that outlines all operating procedures to be followed for this study including drug reconstitution and the required subject assessments before, during, and after infusion of investigational product.

6.2.1 Management of Infusion-related Reactions

For guidance on the management of IRRs, see Appendix 3.1.

6.2.2 Interactive Response Technology for Investigational Product Management

An interactive response technology (IRT) will be used for investigational product management tasks including investigational product supply management, inventory management and supply ordering, investigational product expiration tracking, destruction at site tracking, and return of investigational product. Please refer to the instruction manual provided separately from this protocol that outlines the operating procedures regarding the IRT.

6.2.3 Allocation of Subjects to Treatment

This is an open-label, non-randomized study where all subjects will be enrolled to receive REPLAGAL at 0.2 mg/kg EOW. Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned according to the sequence of subject presentation for study participation.

6.2.4 Dosing

REPLAGAL will be administered at a dose of 0.2 mg/kg body weight as an IV infusion over 40 minutes (±10 minutes) EOW (±4 days), except on Day 1 (Week 0) and Week 28 visits where the length of infusion must be exactly 40 minutes to support the PK sampling. The first dose of REPLAGAL will be based on the subject's weight at baseline.

The appropriate dose calculation is obtained as follows: multiply the subject's weight in kilograms by 0.2 mg/kg. (Round up or down to the 1/10th decimal place from the 1/100th decimal place using >0.05 to round up). This will give the number of milliliters of drug required since the concentration is 1 mg/mL. A change in subject weight of ≥5% from baseline or the last weight used to recalculate the dose will require a recalculation of the dose by the clinical site.

REPLAGAL will be provided in single-use, 5 mL vials containing 3.5 mL of concentrate at a concentration of 1 mg/mL. To determine the number of vials required, divide number of milliliters determined above by 3.5 mL. Round up to the whole number and this is the number of vials required to withdraw the number of milliliters needed.

DOSE CALCULATION EXAMPLE for a subject weighing 68 kg:

- 68 kg × 0.2 mg/kg = 13.6 mg of REPLAGAL
  (subject weight × 0.2 mg/kg required per protocol = subject total dose of REPLAGAL)

  Since the concentration is 1 mg per mL, 13.6 mg = 13.6 mL

- 13.6 mL ÷ 3.5 mL = 3.9 vials
  (subject dose ÷ total volume per vial = number of vials required)

  The subject would need 3 full vials and a partial amount of the fourth vial.

All study procedures, assessments (except for post-infusion vital signs), and sample collection (except for post-infusion PK sample collection) should be completed prior to administering an infusion, except on Week 40 and 52 visits where REPLAGAL infusion should maintain the ±4 days window period while the evaluation procedures can be done within the ±7 days window period.

Ideally, investigational product infusions should occur on the same day of the week, EOW (ie, every 14 days), but may occur every 14 days (±4 days) of the target day in order to facilitate subject scheduling. If at all possible, missed infusions should be avoided. If a subject is not dosed within 21 days from the previous dose, the subject should receive the missed infusion as soon as possible. It may be acceptable to give the next infusion as early as 7 days after the previous infusion. Subsequent infusions will return to the original schedule.

6.2.5 Dose Modification

The first dose of REPLAGAL will be based on the subject's weight at baseline. A change of at least 5% in subject weight from baseline or the last weight used to recalculate the dose will require a dose recalculation at the clinical site. Weight will be measured at every infusion visit, as specified in the Schedule of Activities (Table 1), with any dosing adjustments completed prior to the dose administration.

6.3 Labeling, Packaging, Storage, and Handling of Investigational Product

6.3.1 Labeling

Investigational product labels will contain information necessary to meet the applicable regulatory requirements.

6.3.2 Packaging

Investigational product will be packaged in the following labeled containers: single-use, 5 mL vials containing 3.5 mL of concentrate at a concentration of 1 mg/mL.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

REPLAGAL will be provided by the sponsor (or designee) to the clinical sites 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.

Investigational product must be stored in a locked refrigerator, or in a refrigerator in a locked room, with access limited to authorized study personnel.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within the established temperature range. The sponsor, or designee, must be notified of any temperature that fall out of the accepted range. Detailed guidance on storage requirements and issue reporting will be outlined in the Infusion and Pharmacy Manuals.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3.4 Handling

REPLAGAL should be handled as follows:

- REPLAGAL 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.
- REPLAGAL is intended for IV use only.
- REPLAGAL for subject administration should be prepared by slowly mixing the appropriate amount of REPLAGAL into 100 mL of normal saline (0.9% sodium chloride) suitable for IV administration.
- Once diluted into normal saline, the solution should be rocked gently, but not shaken.
- Investigational product should be prepared on the day of infusion. As the product does not contain preservatives, REPLAGAL should be used as soon as possible after diluting with normal saline. Do not store above 25°C (77°F). It is recommended that infusion of the product be initiated within 24 hours of dilution.
- The diluted REPLAGAL must be administered via an IV line that contains a standard filter.
- Do not mix with or administer in conjunction with other drug solutions.
- REPLAGAL vials are intended for one time use only (3.5 mL maximum). Remaining drug product (overfill or unused drug) left in a vial after withdrawing the subject's assigned dose is NOT to be used for subsequent doses.

6.4 Drug Accountability

Investigators, or designee, will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product received, dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section. The investigator has overall responsibility for administering/dispensing the investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol.

No investigational product stock or returned inventory from a Takeda-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

With the written agreement of the sponsor, at the end of the study all unused stock and empty/used investigational product packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of investigational products must be in accordance with local, state, and national laws.

In the event that a site is not allowed to destroy investigational product, all unused stock and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational product being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated contract research organization [CRO]). Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

For this study, REPLAGAL is administered under controlled conditions at a clinical site; therefore, subject compliance with investigational product is anticipated to be high assuming 10% to 20% drop-out rate based on previous REPLAGAL trials.

6.6 Premedication and Prohibited Treatment

6.6.1 Premedications

Subjects experiencing a mild IRR may be premedicated with an antipyretic (eg, acetaminophen) and/or an antihistamine (eg, diphenhydramine) for subsequent infusions. Subjects experiencing a moderate or severe IRR may be premedicated with both an antihistamine and a corticosteroid (eg, diphenhydramine and hydrocortisone) in addition to acetaminophen for subsequent infusions. Premedication with ranitidine as a protective agent for the intestinal mucosa (in conjunction with hydrocortisone) may also be considered. If subsequent infusions continue without incident, then tapering of premedications may also be considered. If the subject experiences 3 additional IRRs of any severity despite premedication, blood should be drawn for anti-agalsidase alfa antibody testing just prior to the next infusion.

6.6.2 Prohibited Treatment

The following medications and treatments are prohibited at any time prior and throughout the course of the study:

1. FABRAZYME (agalsidase beta) and its biosimilars
2. GLYSET (miglitol)
3. GALAFOLD (migalastat)
4. Any investigational product for treatment of Fabry disease

The following medications should not be administered at any time during this study because these substances have the potential to inhibit intracellular GLA:

1. Chloroquine
2. Amiodarone
3. Monobenzone
4. Gentamicin

6.7 Protocol Considerations for Unavoidable Circumstances Such as the COVID-19 Pandemic

On a temporary basis, in order to maintain subject safety, confidentiality, and study integrity in the context of healthcare delivery challenges presented by unavoidable circumstances, such as the COVID-19 pandemic, subjects who may be impacted should contact clinical sites and

investigators to determine the best course of action. Depending on the impact, in some cases it may be possible to arrange for alternative solutions as permitted by local regulations. Any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the study team and the medical monitor, while maintaining subject safety and confidentiality as the priority.

Missing data, remote visits, changes to assessment approaches, and altered visit windows during unavoidable circumstances such as the COVID-19 public health emergency may affect the study results. Thus, it is important to identify all protocol deviations and altered data collection or assessment methods. Any protocol deviations, missing visits, or missing assessments related to COVID-19 restrictions will be recorded and reported in the clinical study report.

The following procedural changes may be considered:

- If necessary, informed consent (and assent if applicable) from a potential or current study subject may be obtained via electronic informed consent capabilities, or an electronic face-to-face consent interview when potential subjects are unable to travel to the site.
- Subjects who discontinued from screening due to COVID-19-related factors but were otherwise qualified to participate in the study may be rescreened if the medical monitor agrees.
- Remote checks instead of site visits (if appropriate) may be performed as a safety check on subject well-being.
- Transfer to clinical sites away from risk zones to complete required visits.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Investigational Product

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 52 (Table 1) will be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified safety follow-up 14 days (+7 days) after the last dose/infusion. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for discontinuation, date of discontinuation of the investigational product, and the total amount of investigational product administered must be recorded in the source documents.

7.2 Reasons for Discontinuation

The primary reason for discontinuation must be determined by the investigator and recorded in the subject's source document and the appropriate eCRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject (by a parent(s) or legal guardian for pediatric subjects)
- Lost to follow-up
- Lack of efficacy
- Death
- Pregnancy
- Other (If "Other" is selected, the investigator must specify in the eCRF)

7.3 Withdrawal from the Study

Withdrawal from the study means that the subject is no longer taking study treatment and does not return for further study visits. A subject may withdraw from the study at any time and for any reason without prejudice to his/her future medical care by the physician or at the institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible. Subjects who discontinue or withdraw will not be replaced.

7.4 Subjects "Lost to Follow-up" Prior to the Last Scheduled Contact/Visit

A minimum of 3 documented attempts must be made to contact any subject (or their legally authorized representative) who is lost to follow-up at any time point prior to the last scheduled contact (in person or by phone or video). These contact attempts should be documented in the medical record.

8. STUDY ASSESSMENTS AND PROCEDURES

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent (and assent if applicable) from the subject (as per local requirements). There must be documentation of consent (and assent if applicable) as per local requirements indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions, prior to performing any study-related procedures.

8.1 Study Periods

See Table 1 for the schedule of study activities. Study assessments are detailed in Section 8.2.

8.1.1 Screening Period (Week -7 to Week -2)

The duration of the screening period is up to 42 days where study subjects will undergo all procedures listed for the screening period in Table 1. The screening period can occur over multiple days to allow for the evaluation of subject's eligibility for inclusion in the study.

Written informed consent, and assent if applicable, to participate in the study will be obtained by the investigator from each subject before the performance of any protocol-specific procedure. The screening period starts when subjects sign informed consent/assent.

At screening, each subject will be reviewed for eligibility against the study inclusion/exclusion criteria. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study, and the reason(s) for the subject's ineligibility will be documented.

A screen failure is a subject who has given informed consent but who fails to meet the inclusion and/or exclusion criteria and has not been administered investigational product(s).

Subjects who fail screening due to a single laboratory test result that does not meet eligibility criteria may have that laboratory test repeated at the discretion of the investigator. This will include a repeat of only the failed assessment rather than a repeat of all screening assessments (rescreening). In these cases, a new Subject Identification Code (SIC) is not required. The repeat of a single screening assessment is allowed only once. A repeat assessment must take place within 42 days of the initial screening for any subject requiring repeat of a screening assessment.

If this timeframe is exceeded, then all screening assessments must be repeated and the subject assigned a new SIC. Exemptions may be provided if the timeframe is exceeded due to administrative reasons.

Subjects who still do not meet eligibility criteria may not have the laboratory test repeated a second time unless a justification can be provided.

8.1.2 Baseline Visit Period (Week -1)

Study subjects will undergo all procedures listed for the baseline visit in Table 1 prior to receiving the first infusion of REPLAGAL. Subject eligibility will be confirmed at baseline on the basis of review of the study entrance criteria (see Section 8.2.1.5). Subjects should not proceed to treatment period unless they continue to meet all inclusion/exclusion criteria at the baseline visit. The reason(s) for the subject's ineligibility for the study will be documented. Screening assessment for serum chemistry, hematology, urinalysis, and ECG may be used as baseline if assessment is performed within 7 days prior to baseline.

8.1.3 Treatment Period

8.1.3.1 REPLAGAL Infusion EOW (±4 days) from Week 0 Through Week 52

The treatment period will be up to 52 weeks during which subjects will receive EOW (±4 days) IV infusions of REPLAGAL at the clinical site. The first dose of REPLAGAL will be based on the subject's weight at baseline. A change in subject weight of ≥5% from baseline or the last weight used to recalculate the dose will require a recalculation of the dose by the clinical site.

8.1.3.2 Evaluation Visits at Week 8, 16, 28, 40, and 52

At evaluation visits, all study procedures, assessments (except for post-infusion vital signs), and sample collection (except for post-infusion PK sample collection on Week 28) outlined in Table 1 should be completed prior to administering an infusion, except on Week 40 and 52 visits where REPLAGAL infusion should maintain the ±4 days window period while the evaluation procedures can be done within the ±7 days window period. If REPLAGAL is discontinued, regardless of the reason, the evaluations listed for Week 52 will be performed as completely as possible. Subject may visit the clinical site at schedules other than the scheduled visits for assessments as clinically warranted; these will be recorded as unscheduled visit. Unscheduled visit(s) will be recorded in the eCRF.

8.1.4 Safety Follow-up Period (End of Study)

The safety follow-up period (end of study) is 14 days (+7 days) after EOT infusion (or the last infusion for early treatment discontinued subjects). During this period, there will be a telephone call/scheduled visit to query for AEs, SAEs, and concomitant medications. Subjects who experienced SAEs or mild, moderate, or severe AEs may be requested to report to the clinical site for further examination. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Appendix 3.2).

8.1.5 Additional Care of Subjects after the Study

No aftercare is planned for this study.

8.2 Study Assessments

Detailed descriptions of subject procedures and evaluations required for this protocol are described in this section. The timing for the performance of these evaluations is specified in the Schedule of Activities (Table 1).

8.2.1 Demographic and Other Baseline Characteristics

Subject demographic information including gender, age, and race will be collected prior to the subject receiving the first dose of investigational product.

8.2.1.1 Height and Weight

Height and weight will be measured and recorded in the subject's source documents.

For subjects <18 years of age at screening, height should be measured at screening, baseline, and every evaluation visit during the treatment period.

For subjects ≥18 years of age at screening, height should be measured only at the baseline visit.

Weight is a critical measurement as it determines the dosing of REPLAGAL. Weight will be measured at screening, baseline, and every visit during the treatment period, as specified in the Schedule of Activities (Table 1), with any dosing adjustments completed prior to the dose administration (Section 6.2.5).

BMI should be calculated by the investigator using the weight and height measured during the baseline visit and will be recorded in the source documents as well as in EDC.

8.2.1.2 Medical History

Medical history (including documentation of diagnosis of Fabry disease) will be collected and recorded in the subject's source documents. Medical history will include a review of the subject's medical status and documentation of current and prior medical/surgical procedures. The subject will be queried on the following:

- Relevant intercurrent illness and chronic disease update
- Disease-specific review of symptoms concerning to the following organs and systems:
    - Head, neck, and thyroid
    - Eyes, ears, nose, and throat

- Chest and lungs
- Heart
- Lymph nodes
- Abdomen
- Anorectal
- Genitourinary
- Skin
- Musculoskeletal
- Endocrine
- Neurological
- Other

8.2.1.3 Prior and Concomitant Treatment

All non-study treatment including, but not limited to, herbal treatments, vitamins, behavioral treatment, or non-pharmacological treatment, such as psychotherapy, received within 30 days prior to screening period through the end of the safety follow-up period must be recorded in the subject's source document and on the appropriate eCRF page.

Prior treatment includes all treatment received within 30 days prior to the screening period through the date of the first dose of investigational product. Prior treatment information must be recorded on the subject's source documentation and on the appropriate eCRF page.

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded in the subject's source document and on the appropriate eCRF page.

8.2.1.4 Viral Testing

Viral testing will be performed at screening to ensure that subjects do not present with viral infections that might compromise their ability to safely complete the study and confound later interpretation of the study findings. Viral tests include hepatitis B surface antigen with confirmation by hepatitis B viral DNA load, HCV antibody with confirmation by HCV-ribonucleic acid polymerase chain reaction testing, and human immunodeficiency virus (HIV) antibody.

8.2.1.5 Confirmation of Study Eligibility

At screening, each subject will be reviewed for eligibility against the study inclusion/exclusion criteria. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study, and the reason(s) for the subject's ineligibility will be documented; the subject will be considered a screen failure (see Section 8.1.1).

Subject eligibility will be confirmed at baseline on the basis of review of the study entrance criteria. Subjects should not be administered study medication unless they continue to meet all inclusion/exclusion criteria at the time of dosing. For any subjects who do not continue to meet the study entrance criteria, the reason(s) for the subject's ineligibility for the study will be documented and the subject will be considered a screen failure.

An Eligibility Form and required supporting documentation, as allowed by local regulations, should be sent to the sponsor's medical monitor or designee as soon as the baseline procedures are completed for confirmation of patient eligibility. Confirmation of patient eligibility by the sponsor's medical monitor or designee is required before first dose administration.

8.2.2 Efficacy

8.2.2.1 Estimated Glomerular Filtration Rate

For subjects ≥18 years old, the serum creatinine is tested and eGFR is calculated by a Takeda-designated central laboratory from serum creatinine using the CKD-EPI equation. The CKD-EPI equation, expressed as a single equation, is:

$$eGFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Where, Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

For subjects <18 years old, the serum creatinine is tested and eGFR is calculated by a Takeda-designated central laboratory from serum creatinine using the Counahan–Barratt equation. The Counahan–Barratt equation, expressed as a single equation, is:

$$eGFR = (0.43 \times \text{height in cm})/Scr$$

Where, Scr is serum creatinine (mg/dL).

8.2.2.2 Brief Pain Inventory-Short Form

The BPI-Short Form is a validated self-report measure that includes valid scales of pain intensity and pain related interference with various domains of functioning (see Appendix 5). The instrument is well validated in cancer pain populations and was used to characterize pain in subjects with terminal illnesses. Using a 1-week frame of reference, pain intensity "on average", "at its worst", "at its least", and "pain right now", are measured on separate 10-point numerical rating scales. Similar rating scales are used to estimate the degree to which pain interferes with general activity, mood, walking ability, normal work, sleep, relations with other people, and enjoyment of life. These 7 scales can be summed to generate an overall index of functional interference due to pain. Pain at worst will be the primary variable for assessing improvement in neuropathic pain. Subjects must be 12 years of age or older to complete the BPI-Short Form assessment on their own. Prior to 12 years of age, the subject's parent(s)/legally authorized representative will complete this with the subject. The inventory is to be completed in its entirety prior to infusions at baseline, Weeks 8, 16, 28, 40, and 52 visits. No questions should be omitted at the discretion of the investigator and the form should not be modified in any way to include the name provided by the author.

8.2.2.3 Urine Protein/Creatinine Ratio

An early morning spot urine sample will be obtained to measure protein and creatinine levels. Measurement of urine protein/creatinine ratio will be performed as part of urinalysis (see Appendix 2 for details on urinalysis).

8.2.2.4 Echocardiography

Echocardiography will be used to assess cardiac LVMI and LVEF. Echocardiography will be performed in accordance with the clinical site's standard practice(s) at time points specified in the Schedule of Activities (Table 1). An echocardiogram performed within 14 days prior to baseline visit may be used as the baseline echocardiogram. Echocardiography will be read locally at the clinical site by the investigator or a qualified designee.

8.2.2.5 Audiology Testing

For subjects <18 years old, audiology testing will be performed. Audiology testing will include pure tone conduction and bone conduction for each ear using 4 different pure tone frequencies (500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz) and will be performed at visits specified in the Schedule of Activities (Table 1). Any changes in threshold will be categorized as conductive, sensorineural, or unknown.

8.2.3 Safety

8.2.3.1 Physical Examination

A full physical examination will be performed by the investigator with a thorough review of body systems. Physical examinations will include a review of the subject's general appearance as well as evaluation of the body systems including, but not limited to, endocrine, head and neck, cardiovascular, eyes, abdomen, ears, genitourinary, nose, skin, throat, musculoskeletal, chest and lungs, and neurological. Abnormalities identified at the screening visit and at subsequent study visits will be recorded in the subject's source documents. All subsequent physical examinations should assess clinically significant changes from the baseline physical examination (defined as the assessment before first dose of study drug). Physical examination information should be entered on the Physical Examination eCRF, including interpretation of Normal; Abnormal, Not Clinically Significant; or Abnormal, Clinically Significant.

8.2.3.2 Adverse Events

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events will be collected from the time informed consent is signed. See Appendix 3 for AE definitions (including TEAEs, SAEs, IRRs), assessment, collection time frame, and reporting procedures.

8.2.3.3 Vital Signs

The following vital signs will be collected at all study visits: pulse, blood pressure, respiratory rate, and temperature. On visits where a subject is scheduled to receive an infusion, vital signs should be recorded as outlined in Table 5. In the event that a scheduled infusion does not occur at one of these visits, vital signs should still be collected. The vital signs that were taken within 10 minutes prior to the start of the expected infusion should be documented in the eCRF.

If there are no IRRs reported during the first 3 infusions, the observation and vital signs after infusion can be omitted at the discretion of the investigator.

The investigator will assess whether a change from baseline visit in vital signs is clinically significant, and whether the change should be considered and recorded as an AE.

Table 5. Schedule for Recording of Vital Signs at Infusion

Timing Relative to Infusion	Schedule of Assessments
Start of Infusion	Within 10 minutes prior to start of infusion
During Infusion	20 minutes (±5 minutes) after start of infusion

Table 5. Schedule for Recording of Vital Signs at Infusion

Timing Relative to Infusion	Schedule of Assessments
After Infusion[a]	10 minutes (±5 minutes) after completing the infusion 30 minutes (±5 minutes) after completing the infusion

[a] If there are no infusion-related reactions during the first 3 infusions, the observation and vital signs after infusion can be omitted at the discretion of the investigator.

8.2.3.4 Clinical Laboratory Tests

All clinical laboratory tests will be performed according to the laboratory's standard procedures. Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value is not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

A complete list of the clinical laboratory tests (serum chemistry, hematology, and urinalysis) to be performed is provided in Appendix 2.

8.2.3.5 Pregnancy Test

Female subjects of childbearing potential will have a pregnancy test administered at screening, baseline visit, and evaluation visits outlined in Table 1.

At screening, pregnancy testing will be performed using a urine test, and if needed, a serum beta-human chorionic gonadotropin (β-hCG) test. The urine pregnancy test should be administered by the site before any other screening procedures (except for signature of informed consent) are completed. If the urine pregnancy test is negative, screening procedures will be completed as outlined in Table 1; serum β-hCG testing is no longer required. If the urine test is positive, a blood sample will be collected for serum β-hCG testing and sent to either local laboratory or the central laboratory for analysis; no additional screening procedures should be completed until the result of the serum pregnancy test is available. Female subjects of childbearing potential must have a negative urine pregnancy test, or a negative serum β-hCG test when a urine test is positive at screening to be eligible for the study. A positive serum β-hCG test would result in the subject being a screen failure.

At baseline, the urine pregnancy test should be administered by the site before any other baseline procedures are completed. If the urine test is positive, a blood sample will be collected for serum β-hCG testing and sent to either local laboratory or the central laboratory for analysis; no additional baseline procedures will be completed until the result of the serum pregnancy test is

available. If the serum β-hCG result is positive, the subject will not be dosed with REPLAGAL and would be considered a screen failure or discontinued from the study.

At all other visits during the treatment period, a urine pregnancy test will be performed prior to the completion of any study procedures. If the urine test is positive, a blood sample will be collected for serum β-hCG testing and sent to either local laboratory or central laboratory for analysis; the subject will not receive any additional investigational product infusions until the result of the serum pregnancy test is available. If the serum β-hCG result is positive, no additional doses of the investigational product are to be administered. For details on pregnancy reporting, see Appendix 3.8.

8.2.3.6 Electrocardiogram

Twelve-lead ECGs will be performed in accordance with the clinical site's standard practice(s) at time points specified in the Schedule of Activities (Table 1). The ECG recordings will be read locally at the clinical site by the investigator or a qualified designee. The ECGs will include assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, and assessment of PR, QRS, QT, and corrected QT intervals. Identification of any clinically significant findings and/or conduction abnormalities will be recorded in the eCRF.

8.2.3.7 Anti-drug Antibody Testing

Blood samples will be collected for all subjects for the determination of anti-agalsidase alfa antibodies prior to the subject receiving the REPLAGAL infusion at time points specified in the Schedule of Activities (Table 1). Blood samples collected for anti-agalsidase alfa antibody determination will be evaluated at a Takeda-designated central laboratory. These samples will be analyzed for anti-REPLAGAL binding antibodies. Confirmed positive samples will undergo assessment for NAbs. Sample collection, processing, and shipping instructions will be detailed in the study laboratory manual provided by the laboratory.

8.2.4 Other Assessments

8.2.4.1 Pharmacodynamic Assessment: Plasma Globotriaosylsphingosine (Lyso-Gb3) Level

Blood samples will be collected for plasma lyso-Gb3 assessment prior to the subject receiving the REPLAGAL infusion at time points specified in the Schedule of Activities (Table 1). Plasma lyso-Gb3 will be analyzed at a Takeda-designated central laboratory using a validated assay.

8.2.4.2 Pharmacokinetic Assessment

Subjects to be enrolled in this study will provide either intensive or sparse PK samples. Blood samples for PK analysis will be collected at Day 1 (Week 0) and Week 28 visits (Table 1). The intensive and sparse PK blood sample collection time points are presented in Table 2 and Table 3. The PK sample analysis will be conducted in the Takeda-designated central laboratory.

The intensive PK set will enable the accurate estimation of PK parameters including AUC_{0-t} and C_{max}. Five adult subjects and 5 pediatric subjects will provide the full set of serial PK samples (**intensive sampling**). Other subjects will follow a reduced/sparse PK sampling schedule (total of 3 samples: predose - 0 min, end of infusion - 40 min, and 120 min after start of infusion) (**sparse sampling**). Subject weight, REPLAGAL dose (in mg) administered, date and time of start and end of infusion, and date and time of PK samples will be collected. Pharmacokinetic parameters will be determined in subjects providing intensive PK using noncompartmental analysis and include, but are not limited to, the following:

- AUC_{0-last} (min*U/mL): Area under the concentration-time curve from the time of dosing to the last measurable concentration
- $AUC_{0-\infty}$ (min*U/mL): Area under the concentration-time curve from time zero extrapolated to infinity
- CL (mL/min): Serum clearance of administered dose (Dose/AUC)
- CL (mL/min/kg): Serum clearance of administered dose normalized for body weight
- C_{max}: Maximum concentration observed
- $t_{1/2}$ (min): Terminal elimination half-life, defined as the natural log of 2 divided by the terminal rate constant (λz)
- t_{max} (min): Time of maximum observed concentration sampled post dose
- V_{ss} (mL): Volume of distribution at steady state
- V_{ss} (%BW): Estimate of volume of distribution at steady state normalized for body weight
- AUC_{last}/dose (AUC_{last}/[U/kg]): Area under the concentration-time curve at the last sample (AUC_{last}) normalized for the dose of enzyme activity
- $AUC_{0-\infty}$/dose ($AUC_{0-\infty}$/[U/kg]): Area under the concentration-time curve at infinity ($AUC_{0-\infty}$) normalized for the dose of enzyme activity
- C_{max}/dose (C_{max}/[U/kg]): Maximum serum concentration (C_{max}) normalized for the dose of enzyme activity

8.2.5 Volume of Blood to Be Drawn from Each Subject

The amount of blood to be collected for each assessment tested at the Takeda-designated laboratory is provided in the central laboratory manual. The amount of blood to be collected for each assessment tested at the local laboratory follows each selected site's requirement. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is

to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

The study will be analyzed by the sponsor or its designee.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513) version 9.4 or higher.

9.2 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

No interim analysis, adaptive design, or data monitoring committee is planned for this study.

9.3 Sample Size and Power Considerations

A sample size of 20 safety evaluable subjects is planned to be enrolled in this study to descriptively provide an estimate of the serious TEAE rate. No formal sample size calculations have been done and the sample size is based on feasibility.

9.4 Statistical Analysis Set

The statistical analysis will include the following analysis sets:

- The **intent-to-treat (ITT) set** will include all subjects who sign the ICF, are enrolled in the study, and have received at least 1 study drug infusion (full or partial).
- The modified intent-to-treat (mITT) set will include all enrolled subjects (all subjects from the ITT set) who have received at least 1 dose of investigational product and completed at least 1 post-baseline efficacy assessment of the endpoints. The mITT set will be used for efficacy analyses.

- The **safety set** will include all subjects in the ITT set who receive at least 1 dose of REPLAGAL. The safety set will be used for the analysis of safety endpoints.
- The **per-protocol (PP) set** will include all subjects in the mITT set excluding subjects with major protocol deviations. The PP set will be identified by a team consisting of, at a minimum, a physician and a statistician from Takeda. The PP set will be used for an efficacy sensitivity analysis.
- The **pharmacokinetic (PK) set** will include all subjects in the ITT who receive at least 1 dose of investigational product and provide intensive or sparse PK samples. The **intensive PK set** will include subjects in the PK set who provide intensive sampling. Five adult subjects and 5 pediatric subjects will be included in this set. Pharmacokinetic parameters will be derived from the intensive PK set.

9.5 Efficacy Analyses

Continuous variables will be summarized with descriptive statistics including the mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized with the frequency and percentage of subjects falling within each category. Subsequently, longitudinal data will be analyzed using mixed-effects model for repeated measures, using both the mITT and PP sets (using the PP set will serve as a sensitivity analysis).

The observed values, the change from baseline, the change over time, and the percentage change from baseline for the efficacy measurements (eGFR, urine protein/creatinine ratio, plasma lyso-Gb3, LVMI, and LVEF) will be summarized by sex and visit.

Subject listings will be provided for clinical outcomes from the BPI-Short Form measurement.

Audiology results will be produced at baseline and (if applicable) for each post-baseline evaluation visit.

Audiology data will also be presented in the form of individual subject listings.

Efficacy analyses will be based on the mITT set, with the PP set as a sensitivity analysis.

9.6 Safety Analyses

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities coding dictionary. Treatment-emergent AEs will be summarized for overall and by system organ class (SOC) and preferred term (PT). Analysis of AEs will be performed at both

subject level and AE level. Similar displays will be provided for IRRs. The AEs will be summarized by severity, seriousness, and relation to investigational product.

Subjects will be counted once per SOC and once per PT. Multiple events of the same type will be combined for each subject and, when doing this, the worst severity or outcome for each event type will be presented for the analysis. When calculating event rates, the denominator will be the total population size, irrespective of dropouts over the course of follow-up.

Tabular summaries of other safety endpoints (eg, vital signs, blood tests, concomitant medications [coded using the World Health Organization Drug Dictionary], anti-agalsidase alfa antibody status, and infusion information) will be produced at baseline and, if applicable, for each post-baseline visit.

Changes in the results of physical examination from the baseline will be presented by visit and body system in the form of a shift table.

The observed values and the change from baseline for ECG parameters (PR, QRS, QT, QTc, and heart rate) will be summarized by visit. The number of subjects with normal and abnormal ECG results during the study period will be summarized by visit in the form of a shift table.

Laboratory data will be listed by subject. Subjects with newly occurring abnormalities outside the normal range will be flagged, listed separately, and summarized. The mean change from baseline in laboratory values or a shift table also will be provided at each visit. Change from baseline will be calculated by subtracting the baseline value from the post-baseline value.

Vital sign data will be listed by subject, and any newly occurring changes outside the reference range from baseline will be flagged. Mean changes from baseline for vital sign data will be summarized. Subjects with notable abnormal values will be identified and listed separately along with their values.

The number and percentage of subjects reporting at least one use of concomitant medication during the study will be reported. Subject listings will be provided describing the reason(s) for study discontinuation.

Antibody data, including NAbs, will also be presented in the form of individual subject listings.

Safety analyses will be based on the safety set.

9.7 Pharmacokinetic Analyses

Statistical analysis of PK data will be based on the PK set as well as the intensive PK set.

For the PK set, individual concentrations will be listed and summarized by scheduled time points for all subjects and by age (eg, ≥18 years vs <18 years). For the intensive PK set, individual concentration will be summarized for all subjects and by age. Individual PK parameters of REPLAGAL will be listed and summarized by treatment for all subjects as well as by age with descriptive statistics (number, arithmetic mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, and CV of geometric mean). Pharmacokinetic parameter estimates will be computed, where appropriate, from individual serum-concentration time data using noncompartmental methods and actual times. Figures of individual and mean (±SD) concentration-time profiles of REPLAGAL will be generated based on nominal time points for all subjects and by age.

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Appendix 1 Regulatory, Ethical, and Study Oversight Considerations

Appendix 1.1 Regulatory and Ethical Considerations

This study is conducted in accordance with current applicable regulations including ICH E6, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

Appendix 1.2 Sponsor's Responsibilities

Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, source documents, and eCRFs in accordance with current GCP and the respective local and national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to applicable parties as necessary.

Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information. The timing for study registration and results summary posting must be in accordance with applicable local and national requirements.

Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

Appendix 1.3 Investigator's Responsibilities

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guidelines E6 (1996) and E6 R2 (2017) and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The investigator and any sub-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

Documentation and Retention of Records

Case Report Forms

Electronic case report forms are completed for each subject and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded into eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

The eCRFs should be approved by the investigator per study specifications and the sponsor's data delivery requirements.

Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to, subject's medical file and original clinical laboratory reports.

All key data must be recorded in the subject's source documents.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The ICF includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US Food and Drug Administration [FDA], European Medicines Agency [EMA], UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The

following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

Appendix 1.4 Data Management Considerations

Data Collection

The investigators' authorized site personnel must enter the information required by the study eCRF Completion Guidelines or similar for all data requiring transcription of the source. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered in the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting.

Data Management

Data are to be entered into a clinical database as specified in the Takeda data management plan or similar. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

Appendix 1.5 Ethical Considerations

Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed

consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent and assent forms must remain in each subject's study file and must be available for verification at any time.

Pediatric subjects reaching the legal age during the study, ie, turning 18 years old (legal age in China is 18 years old) should sign an ICF at the earliest feasible opportunity additionally to the one provided by their parent(s)/legally authorized representative at the beginning of the study.

Within the source documents, site personnel should document instruction of and understanding by the parent(s)/legally authorized representative/caregiver of the safe, responsible administration of investigational product to the study subject.

Institutional Review Board or Ethics Committee

It is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement. Investigational product supplies will not be released until the sponsor has received written IRB/EC approval.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue. If required by local law, substantial amendments to the protocol must also be approved by the appropriate regulatory agency prior to implementation.

The investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. The investigator must also keep the local IRB/EC informed of any serious and significant AEs as required by IRB/EC procedures.

Privacy and Confidentiality

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market REPLAGAL; national or local regulatory authorities; and the IRB/EC which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities. Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

Study Results/Publication Policy

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form. The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other investigators prior to publication or oral presentations of the study results on an individual basis. The site agrees not to publish or present the site's study results until such time as either the aggregate multisite study results are published in a cooperative publication or for a period of one (1) year after termination or completion of the study at all participating sites, whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results

from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the sponsor by the site for review. Upon the sponsor's request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the sponsor time to file any patent application(s). All publications of the study results shall appropriately reference the multisite study publication, if any, or the fact that the study results are a subset of data resulting from a larger multisite study.

Takeda is committed to transparent dissemination of all scientific, technical and medical manuscripts generated from Shire-supported research. Therefore, after January 1, 2018, Takeda will require the submission of all Takeda-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an investigator does not confer any rights to authorship of publications.

Appendix 2 Clinical Laboratory Tests

The following clinical laboratory assessments will be performed (unless otherwise specified, these assessments will be performed in the local laboratory):

Chemistry

- Sodium (Na^+)
- Potassium (K^+)
- Chloride (Cl^-)
- Bicarbonate
- Total calcium (Ca^{2+})
- Magnesium (Mg^{2+})
- Phosphate
- Creatinine (Takeda-designated central laboratory)
- Blood urea nitrogen
- Glucose
- Albumin
- Total bilirubin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Triglycerides
- Cholesterol (total, low density lipoprotein, high density lipoprotein)

Hematology

Complete blood count

- Leukocytes
- Hematocrit [Hct]
- Platelets
- Neutrophils
- Eosinophils
- Lymphocytes/leukocytes (%)
- Monocytes/leukocytes (%)
- Neutrophils/leukocytes (%)
- Erythrocytes
- Hemoglobin [Hb]
- Lymphocytes
- Monocytes
- Basophils
- Eosinophils/leukocytes (%)
- Basophils/leukocytes (%)

Urinalysis

- Standard urinalysis (turbidity, color, pH, specific gravity, protein, glucose, ketones, bilirubin, occult blood, leukocytes, erythrocytes, bacteria, casts, crystals)
- Urine protein/creatinine ratio (early morning spot urine)

Viral Testing

- Hepatitis B surface antigen (HBsAg)
- Hepatitis B virus DNA

Other Tests

- Serum anti-drug antibody (ADA) and neutralizing antibodies (Takeda-designated central laboratory)

- Hepatitis C virus (HCV) antibody with confirmation by HCV ribonucleic acid polymerase chain reaction testing
- Human immunodeficiency virus (HIV) antibody
- Plasma lyso-Gb3 (Takeda-designated central laboratory)

Pregnancy test

- Serum β-hCG test (local laboratory or the central laboratory)
- Urine pregnancy test

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Appendix 3.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this investigational product or medicinal product. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not causality is suspected (ICH Guidance E2A 1995).

Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the investigational product or medicinal product until the end of the safety follow-up period.

Serious Adverse Event

A serious adverse event (SAE) is any untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to investigational product or not) and at any dose:

- Results in death.
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of hospitalization. Note: Hospitalizations that are the result of elective or previously scheduled investigations procedures or surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs.

  For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity.
- Results in a congenital abnormality/birth defect.

- Is an important medical event. Note: 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 subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include:

  Bronchospasm associated with anaphylaxis requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

  Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus, hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V).

Infusion-related Reaction

An IRR will be defined as an event that:

1. Begins either during or within 24 hours after the start of the infusion
2. Is judged as related to treatment with the investigational product.

An IRR can be serious or nonserious. Adverse events that are considered IRRs will be noted as such in the subject's source documentation. Other AEs which occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (eg, laboratory testing and physical examinations), which were performed prior to the infusion, will not be considered as IRRs.

A list of the most common IRRs that have been reported in patients with Fabry disease during REPLAGAL infusions is included in the current version of the REPLAGAL IB.

Management of Infusion-related Reactions

The management of IRRs should be based on the severity of the reaction, and at the discretion of the investigator. If mild or moderate acute infusion reactions occur, medical attention must be sought immediately, and appropriate actions instituted. The infusion can be temporarily interrupted (5 to 10 minutes) until symptoms subside and the infusion may then be restarted, or the infusion rate can be slowed. Some mild and transient effects may not require medical treatment or discontinuation of the infusion.

Oral or IV pretreatment with antihistamines and/or corticosteroids, from 1 to 24 hours prior to infusion, may prevent subsequent reactions in those cases where symptomatic treatment was previously required. Pretreatment of infusion reactions is left to the clinical judgment of the investigator.

If further analysis of IRRs is necessary, additional clinical laboratory samples may be collected at the discretion of the investigator and in consultation with the study medical monitor.

Unexpected Adverse Event

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB and/or prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the product but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to investigational product (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to investigational product

Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected disease progression and are part of the efficacy or

effectiveness data collected in the study. Significant worsening of symptoms should be recorded as an AE.

Pre-existing conditions prior to randomization or initiation of study medication are described in the medical history, and those that manifest with the same severity, frequency, or duration after drug exposure, are not to be recorded as AEs. However, when there is an increase in the severity, duration or frequency of a pre-existing condition, the event must be described in the AE eCRF.

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter, physical examination finding, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the pretreatment evaluation observed closest to the start of investigational product, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value, vital sign, or ECG parameter is clinically significant and represents an AE.

The ECG assessment is conducted and reported by the local laboratory.

Appendix 3.2 Collection of Adverse Events

All AEs/SAEs are collected from the time the informed consent document is signed until the defined follow-up period stated in Section 8.1.4. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered.

All AEs/SAEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained.

Appendix 3.3 Assessment of Adverse Events

Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity is captured as a new event. Worsening medical conditions, signs or symptoms present prior to initiation of investigational product, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the investigational product, and the dyspepsia becomes severe and more frequent after first dose a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source and appropriate eCRF.

The medical assessment of severity is determined by using the following definitions:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the

occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

The following additional guidance may be helpful:

Table A1. Adverse Event Relationship Categorization

Related	The temporal relationship between the event and the administration of the investigational product is compelling enough and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

Outcome Categorization

The outcome of AEs must be documented in the source during the course of the study. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

Appendix 3.4 Safety Reporting

Reference Safety Information

The RSI for this study is the IB which the sponsor has provided under separate cover to all investigators.

Reporting Procedures

The investigator should complete an SAE electronic Case Report Form (eCRF) in English or report via the paper safety report form (as back-up in case transmission of an SAE is not feasible) within 24 hours of becoming aware of any SAE. It is applicable to all initial and follow-up SAE reports. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Appendix 3.9) unless they result in an SAE.

The CRO/Takeda medical monitor should receive notification once there is new or update on SAE eCRF or paper SAE report form.

Appendix 3.5 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.1.4 and must be reported to the Takeda Global Patient Safety Evaluation Department and the CRO/Takeda medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Takeda Global Patient Safety Evaluation Department within 24 hours of the reported first becoming aware of the event.

Appendix 3.6 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms reported by the subject after signing the informed consent form or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

Appendix 3.7 Fatal Outcome

Any SAE that results in the subject's death (eg, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

Appendix 3.8 Pregnancy

All pregnancies are reported from the time informed consent is signed until the defined follow-up period stated in Section 8.1.4.

Any report of pregnancy for any female study subject must be reported to Takeda Global Patient Safety Evaluation Department within 24 hours of the first awareness of the event using the paper Pregnancy Report Form. The fax number and e-mail address are provided in the Form Completion Instruction.

A copy of the Takeda Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Takeda medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study subject must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days and 1 year post-partum.

Pregnancy complications such as abortion/miscarriage, or congenital abnormality are considered SAEs and must be reported according to the SAE reporting procedure.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE according to the SAE reporting procedure as well as the Takeda Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

Appendix 3.9 Abuse, Misuse, Overdose and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Appendix 3.1.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- Misuse – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- Overdose – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product, errors relating to rate of drug administration dilution, use of inappropriate diluent, and longer than recommended time frames within which drug must be used after dilution should be considered as a reportable medication errors.

All investigational product provided to pediatric subjects should be supervised by the parent(s)/legally authorized representative/caregiver.

Appendix 3.10 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm, these do not constitute de facto deviation from the protocol. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial subjects from immediate hazard to their health and safety

The investigator may implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the sponsor. In the event(s) of an apparent direct hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, and within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

Appendix 3.11 Regulatory Agency, Institutional Review Board, Ethics Committee and Site Reporting

The sponsor/CRO is responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable (serious) adverse drug reactions to regulatory authorities, investigators and ECs/institutions as applicable, in accordance with national regulations in the countries where the study is conducted. The sponsor/CRO will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial.

In addition, the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the TAK-675 program.

The investigator is responsible for notifying the local IRB/EC of all safety reports or significant safety findings that occur at his or her site as required by IRB/EC procedures and applicable national regulations (see Appendix 1.5).

Appendix 4 Contraceptive Guidance

Female subjects:

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below.

Highly Effective Contraceptive Methods That Are User Dependent[a] ***Failure rate of <1% per year when used consistently and correctly.***
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Contraceptive Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) **Bilateral tubal occlusion**
Vasectomized partner[c]
Sexual abstinence[d]
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of investigational product. [c] A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the female of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. [d] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the investigational product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

Appendix 5 Scales and Assessments

The following scales/assessments will be utilized in this study:

Full Title of Scale/Assessment
Brief Pain Inventory (BPI)-Short Form

A separate master file containing each scale/assessment listed above will be provided to the site.

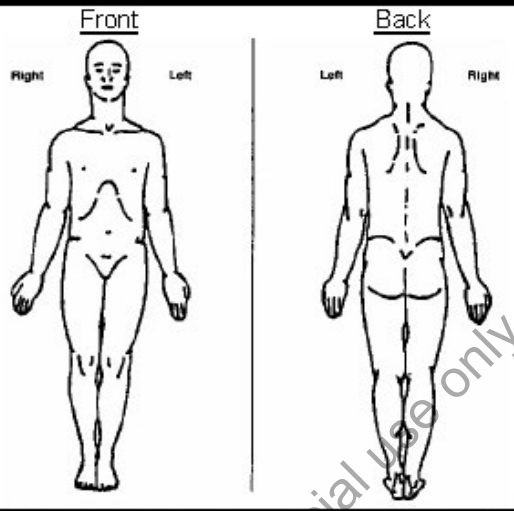
Brief Pain Inventory-Short Form

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

B. Mood

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

C. Walking ability

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

E. Relations with other people

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

F. Sleep

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

G. Enjoyment of life

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

Appendix 6 Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AUC	area under the curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero extrapolated to infinity
AUC_{0-last}	area under the concentration-time curve from the time of dosing to the last measurable concentration
β-hCG	beta-human chorionic gonadotropin
BPI	Brief Pain Inventory
BW	body weight
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology
CL	serum clearance
C_{max}	maximum concentration observed
COVID-19	coronavirus disease
CRF	case report form
CRO	contract research organization
CV	coefficient of variation
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
EOW	every other week
ERT	enzyme replacement therapy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLA	α-galactosidase A

Abbreviation	Definition
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
LVEF	left ventricular ejection fraction
LVMI	left ventricular mass index
lyso-Gb3	globotriaosylsphingosine
M6P	mannose-6-phosphate
mITT	modified intent-to-treat
NAb	neutralizing antibody
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per protocol
PT	preferred term
QoL	quality of life
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SIC	Subject Identification Code
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Definition
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time of maximum observed concentration
UK	United Kingdom
US	United States
V_{ss}	volume of distribution at steady state

Appendix 7 Protocol History

Document	Date	Global/Country/Site Specific
Amendment 2.0	23 May 2023	China
Amendment 1.0	07 Feb 2022	China
Original Protocol	17 Mar 2021	China

Protocol Amendment 1.0 and Rationale

The table below provides an overview of the changes from the original protocol (dated 17 Mar 2021) to the original protocol Amendment 1.0.

The primary reasons for the Amendment 1 are to:

- Provide clarification regarding inclusion criteria and activities adjustment for subjects <18 years old;
- Add left ventricular mass index (LVMI) and left ventricular ejection fraction (LVEF) measured by echocardiography as a secondary objective to investigate the efficacy of REPLAGAL on cardiac parameters;
- Change infusion-related adverse event (IRAE) to infusion-related reaction (IRR) consistently throughout the protocol and update the definition of IRR to keep consistent with the Investigator's Brochure (IB).

Grammatical, typographical, or minor edits for clarity, administrative, and general formatting revisions are not identified.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number 1.0	**Amendment Date 07 Feb 2022**	**China**
Section(s) Affected by Change	**Description of Each Change**	**Rationale for Change**
Section 1.1 Synopsis Section 1.2 Schedule of Activities Table 1 Schedule of Activities Section 3.1.2 Secondary Objectives Section 3.2 Study Endpoints Section 8.2.2.4 Echocardiography Section 9.5 Efficacy Analyses	Added cardiac LVMI and LVEF assessed by echocardiography test as one of the efficacy assessments. Echocardiography test to be performed during baseline visit period, at Week 16 visit, and at Week 52 visit (EOT or early discontinuation visit).	Added to investigate the efficacy of REPLAGAL on LVMI and LVEF.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number 1.0	**Amendment Date 07 Feb 2022**	**China**
Section(s) Affected by Change	**Description of Each Change**	**Rationale for Change**
Section 1.1 Synopsis Section 5.1 Inclusion Criteria	For inclusion criterion #8, clarified that eGFR of 45 to 120 mL/min/1.73 m^2 is only applicable to the adult subjects (⩾ 18 years old).	The specified eGFR range is applicable to adult subjects (≥18 years old) only.
Section 1.1 Synopsis Section 5.2 Exclusion Criteria	Added the exception of non-systemic use for medications in exclusion criterion #7.	Local administration without systemic absorption is allowed.
Section 1.1 Synopsis Section 9.4 Statistical Analysis Set Section 9.5 Efficacy Analyses	Added mITT analysis set.	Added and clarified that the mITT analysis set will be used for efficacy analyses, instead of the ITT set. The mITT analysis set will be used as the basis set for the PP set.
Section 1.2 Schedule of Activities Table 1 Schedule of Activities	Updated height and weight measurements, clinical laboratory tests, and procedures at REPLAGAL infusion visit in the Schedule of Activities. See Table 1 for details.	Added the details and revised for clarity.
Section 2.2 Product Background and Clinical Information	Updated integrated clinical study datasets according to the latest edition of the IB. Updated the identified and potential safety risks of REPLAGAL according to the latest edition of the IB.	Revised to be consistent with the latest edition of the IB.
Section 4.3 Duration of Subject Participation	Added the definition of study completion.	Added the mandatory standard language per protocol template.
Section 7.2 Reasons for Discontinuation	Updated wording to indicate only primary reason for discontinuation will be recorded in the subject's source document and appropriate eCRF.	For clarity.
Section 7.3 Withdrawal from the Study	Added the definition of 'withdrawal from the study'.	For clarity.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number 1.0	**Amendment Date 07 Feb 2022**	**China**
Section(s) Affected by Change	**Description of Each Change**	**Rationale for Change**
Section 7.4 Subjects "Lost to Follow-up" Prior to the Last Scheduled Contact/Visit	Updated the communication methods to contact any subject who is lost to follow-up.	Revised to be more executable.
Section 8.1.1 Screening Period (Week -7 to Week -2)	Added the definition of screen failure.	For clarity.
Section 8.2.1.1 Height and Weight	Updated time points for height and weight measurement	Height is needed for eGFR calculation for subjects <18 years old. Weight measurement is necessary at screening.
Section 8.2.1.3 Prior and Concomitant Treatment	Added the description of prior treatment.	For clarity.
Section 8.2.1.5 Confirmation of Study Eligibility	Added the description of confirmation of study eligibility.	For clarity.
Section 8.2.2.3 Urine Protein/Creatinine Ratio Appendix 2 Clinical Laboratory Tests	Specified early morning spot urine should be collected for urine protein/creatinine ratio assessment.	Added the requirement that early morning spot urine sample will be used for urine protein/creatinine ratio.
Section 8.2.3.5 Pregnancy Test	Updated time points needed for pregnancy tests.	Revised for correctness.
Section 8.2.4.1 Pharmacodynamic Assessment: Plasma Globotriaosylsphingosine (Lyso-Gb3) Level	Removed the requirement that subjects need to fast for at least 8 hours prior to the blood draw for plasma lyso-Gb3 assessment.	Revised for correctness.
Appendix 2 Clinical Laboratory Tests	Specified laboratory assessments to be performed in the local laboratory and central laboratory.	For clarity.
Appendix 3.1 Adverse Event Definitions	Changed IRAE to IRR and updated definition of IRR. Removed the requirement to confirm ECG result by a central laboratory.	Changed IRAE to IRR for consistency. Revised the IRR definition to keep consistent with latest edition of the IB. Central ECG result confirmation is not applicable for this study.
Appendix 3.8 Pregnancy Appendix 3.11 Regulatory Agency, Institutional Review	Updated the wording regard safety report for pregnancy.	Updated per the applicable safety reporting procedure.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **1.0**	**Amendment Date** **07 Feb 2022**	**China**
Section(s) Affected by Change	**Description of Each Change**	**Rationale for Change**
Board, Ethics Committee and Site Reporting		

ECG=electrocardiogram; eCRF=electronic Case Report Form; eGFR=estimated glomerular filtration rate; EOT=end of treatment; IB=investigator's brochure; IRAE=infusion-related adverse event; IRR=infusion-related reaction; ITT=intent-to-treat; LVEF=left ventricular ejection fraction; LVMI=left ventricular mass index; lyso-Gb3=globotriaosylsphingosine; mITT=modified intent-to-treat; PP=per-protocol.