Clinical Study Protocol

NCT Number: NCT05529992

Title: A Multicenter, Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Velaglucerase Alfa in Chinese Subjects With Type 1 Gaucher Disease

Study Number: TAK-669-3001

Document Version and Date: Amendment 1.0, 02 August 2022

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-669-3001
Title:	A Multicenter, Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Velaglucerase alfa in Chinese Subjects With Type 1 Gaucher Disease
Short Title:	Safety, Efficacy, and Pharmacokinetics of Velaglucerase alfa in Chinese Subjects With Type 1 Gaucher Disease
Study Phase:	Phase 3b
Drug:	Velaglucerase alfa (VPRIV)
IND Number:	Non-IND
EUDRACT Number:	Non-EUDRACT
Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Ave, Lexington, MA 02421, USA
Principal/ Coordinating Investigator:	[redacted]
Protocol History:	Original Protocol: 22 Nov 2021 Protocol Amendment 1: 02 Aug 2022

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

DocuSigned by:

[redacted]

Date:

Investigator's Acknowledgement

I have read this protocol for Study TAK-669-3001.

Title: A Multicenter, Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Velaglucerase alfa in Chinese Subjects With Type 1 Gaucher 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 Registration of 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:
(please hand print or type)

_____

_____

Signature: _____ *Date:* _____

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

A summary of the changes incorporated into Amendment 1 is provided in the table below. Any minor revisions in grammar, spelling, punctuation, and format are not reflected in the summary of changes.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **1**	**Amendment Date** **02 Aug 2022**	**China**
Description of Each Change and Rationale		**Section(s) Affected by Change**
Added details regarding contact information cards and changed the section heading as per the updated protocol template.		Contacts
Increased the frequency of the body weight test as body weight changes requires to recalculate the dose of investigational product.		Section 1.1 Synopsis Table 1 Schedule of Activities Section 6.2.3 Dosing
Added a window duration for the infusion to +10 minutes over a period of 60 minutes to provide the additional operational flexibility. The window duration of infusion should not be applicable on Day 1 (Week 1) and Week 37 as the PK sample collection are scheduled during these visits and the PK sampling timepoints are the nominal timepoints based on a 60-minute infusion.		Section 1.1 Synopsis Table 1 Schedule of Activities, footnote 'l' Section 6.2 Administration of Investigational Product
Added the sentence that QoL assessment is not applicable for subjects <5 years of age for clarification.		Section 1.1 Synopsis Table 1 Schedule of Activities, footnote 'x' Section 4.1 Overall Design Section 8.2.4.3 Quality of Life
Specified the minimum number of enrolled subjects in the study who should be <18 and ≥18 years old for better clarification.		Section 1.1 Synopsis Table 2 Pharmacokinetic Sampling Time Points Section 4.1 Overall Design
Removed the dose of VPRIV as the switch subjects may use different dose in the study than already defined (60 U/kg body weight).		Section 1.1 Synopsis Section 3.1.1 Primary Objective Section 4.1 Overall Design Section 4.2 Scientific Rationale for Study Design Section 6.2.3 Dosing
Increased the number of clinical sites from '5 to 6' to 'at least 8' to increase the recruitment capability.		Section 1.1 Synopsis Section 4.5 Sites and Regions

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Amendment Number **1**	**Amendment Date** **02 Aug 2022**	**China**
Description of Each Change and Rationale		**Section(s) Affected by Change**
Updated the previous inclusion criterion#3 and #4 as the subject needs to meet any 1 criterion to be eligible for the study and merged it as inclusion criterion#3. Reported the details of previous inclusion criterion#3 (b and c) as inclusion criterion#4 and #5 for better clarity and to specify how to assess splenomegaly and hepatomegaly.		Section 1.1 Synopsis Section 5.1 Inclusion Criteria
Changed the size of in-line sterilizing filter from '0.2 µm' through '0.22 µm' in consistent with the China label.		Section 1.1 Synopsis Section 6.2 Administration of Investigational Product
Added the body weight test during the screening period as it is used for normalized liver and spleen volume calculation measured by abdominal radiology scan (MRI or CT scan). Updated the frequency of height to match with the frequency of abdominal radiology scan (MRI or CT scan) which will be used for normalized liver and spleen volume calculation.		Table 1 Schedule of Activities
Added the details for the initial dose calculation for subject who received Imiglucerase ERT within the 12 months prior to screening for consistency with other sections of the protocol.		Table 1 Schedule of Activities, footnote 'l'
Clarified that vital signs and 12-lead ECG will be measured/collected prior to blood draw and/or initiation of infusion following 5 minutes of rest as per the standard operational requirements.		Table 1 Schedule of Activities, footnote 'm' Table 1 Schedule of Activities, footnote 'o' Section 8.2.3.3 Vital Signs Section 8.2.3.6 12-lead Electrocardiogram
Removed the test 'subtypes for creatine kinase' as some sites could not perform this test and based on the previous results, it is not critical to evaluate the safety of VPRIV. Specified the name of 'blood urea nitrogen' as '(blood) urea nitrogen or (blood) urea' to allow flexibility at sites. Removed the tests of 'iron-binding capacity, transferrin saturation, and unsaturated iron-binding capacity' as some sites could not perform this test and these tests are not critical tests to distinguish iron-deficiency-related anemia and Gaucher disease-related anemia.		Table 1 Schedule of Activities, footnote 'r' Appendix 2
Added criteria for defining hepatomegaly and moderate splenomegaly and to enable eligibility at local clinical site.		Table 1 Schedule of Activities, footnote 'v' Section 8.2.2.2 Liver and Spleen Magnetic Resonance Imaging or Computed Tomography Scan

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Amendment Number **1**	**Amendment Date** **02 Aug 2022**	**China**
Description of Each Change and Rationale		**Section(s) Affected by Change**
Widen the allowed PK sample collection window to facilitate the study execution without impacting the integrity of the PK assessment. Removed the predose PK sample in 4 through 11 years old subject to reduce the blood collection times/volume. Changed the PK sample collection window for the start of infusion to 0 (-30 minutes) and end of infusion to 60 (-3 minutes) and added footnotes 'a' and 'b' that 'a PK sample should be collected within 30 min prior to the start of 60 minutes infusion' and 'a PK sample should be collected within 3 minutes prior to the end of 60 minutes infusion', respectively for better clarification. Added a footnote "the PK sampling timepoints are the nominal timepoints based on a 60-minute infusion" to clarify the PK sample collections relative to the infusion duration.		Table 2 Pharmacokinetic Sampling Time Points
Added the details of restricted items of which female and male subjects should refrain from for the duration of the study and for 30 days after the last dose of study treatment per the study requirements.		Section 5.4.1 Female Contraception Section 5.4.2 Male Contraception
Added the details to clarify the responsibility of an investigator if a subject experiences an infusion-related AEs. Added the sentence that "site specific discharge requirements should be followed if any" to increase the operational flexibility.		Section 6.2 Administration of Investigational Product
Removed the term 'destruction at site tracking' as the study drug will be destructed at the central depot designated by sponsor.		Section 6.2.1 Interactive Response Technology for Investigational Product Management
Added a sentence "A daily temperature log of the drug storage area must be maintained every working day" to clearly define the requirement of study drug temperature record.		Section 6.3.3 Storage
Added additional details for review of subject eligibility at baseline visit due to the complex inclusion criteria and reduce screening failure rate.		Section 8.1.2 Baseline Visit (Day –3 Through Day 0)
Updated the number of blood samples for children (4 through 11 years old) from '7 blood samples' to '6 blood samples' as predose PK sample has been removed to reduce the blood collection times/volume. Specified that listed PK parameters are only for Day 1 (Week 1) based on serial PK sampling.		Section 8.2.4.1 Pharmacokinetics
Added a sentence that alternative approaches such as remote source data review via phone or video could be used for monitoring purpose per the updated protocol template.		Appendix 1.3
Updated the existing questionnaire with the standard questionnaires from the license holder.		Appendix 5 Scales and Assessments

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Amendment Number **1**	**Amendment Date** **02 Aug 2022**	**China**
Description of Each Change and Rationale		**Section(s) Affected by Change**
Minor grammatical and administrative changes, rewording and updates have been made for consistency, to remove redundancies, and to improve readability, and clarity of the protocol.		Throughout the document

AE=adverse event; CT=computed tomography; ECG=electrocardiogram; ERT=enzyme replacement therapy; PK=pharmacokinetic; QoL=quality of life; MRI=magnetic resonance imaging; SAE=serious adverse event; VPRIV=velaglucerase alfa.

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

CONTACTS

Contacts

Certain events and study-related activities will require the investigator and/or subject to have appropriate contact information. The sponsor or contract research organization (CRO) will provide investigators with emergency medical contact information cards to be carried by each subject.

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 backup) 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 PPD medical monitor:

Hotline number (24 hours a day/7 days a week): + 44 1223 374 240

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or nonmedical complaints to Takeda within 1 business day. If requested, the 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.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: TAK-669-3001	**Drug:** Velaglucerase alfa (VPRIV)
Title of the study: A Multicenter, Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Velaglucerase alfa in Chinese Subjects With Type 1 Gaucher Disease	
Short title: Safety, Efficacy, and Pharmacokinetics of Velaglucerase alfa in Chinese Subjects With Type 1 Gaucher Disease	
Study phase: Phase 3b	
Number of subjects (total): The study is anticipated to enroll a total of 20 subjects.	
Investigator: [redacted]	
Sites and region: The study is planned to be conducted in at least 8 clinical sites in China.	
Study period (planned): 2022 to 2025	**Clinical phase:** 3b
Objectives: **Primary:** The primary objective of the study is to evaluate the safety of VPRIV by assessing the incidence of serious treatment-emergent adverse events (TEAEs) when administered every other week (EOW) up to 51 weeks by intravenous (IV) infusion in Chinese subjects with type 1 Gaucher disease. **Secondary:** The secondary objectives of the study are to assess: • Other safety parameters of VPRIV (including the incidence of TEAEs and infusion-related reactions [IRRs] and rates of antibody formation) • The effect of VPRIV on hematologic manifestations • The effect of VPRIV on the liver and spleen volume • The effect of VPRIV on quality of life (QoL) • The pharmacokinetics (PK) of VPRIV • The effect of VPRIV on disease biomarkers	
Rationale: On 27 Apr 2021, VPRIV received approval of its New Drug Application from China's National Medical Products Administration for the treatment of type 1 Gaucher disease. As part of the approval requirements of China's Health Authority, this Phase 3b interventional post approval commitment study is planned to evaluate the safety, efficacy, and PK of VPRIV in Chinese subjects with type 1 Gaucher disease.	

Investigational product, dose, and mode of administration:

Investigation product

The investigational product, VPRIV, will be provided in single-use, 4-mL vials containing 11 mg or 440 U velaglucerase alfa after reconstitution and provides 10 mg or 400 U for infusion use, and the solution should be clear to slightly opalescent and colorless for IV infusion.

Dose

Velaglucerase alfa (VPRIV) infusions will occur at the clinical site. Subjects will receive VPRIV as an IV infusion EOW (±3 days). For treatment-naive subjects, the initial dose of VPRIV will be calculated based on the subject's body weight determined at baseline. For subjects who received Imiglucerase enzyme replacement therapy (ERT) within the 12 months prior to screening, the initial dose will be determined by the investigator after discussing with the sponsor and recording in appropriate document based on the subject's specific treatment and situation at the time of enrollment, according to the subject's benefit and risk assessment. Weight will be measured every 6 weeks (Weeks 7, 13, 19, 25, 31, 37, 43, and 49) throughout the study before starting the study drug infusion. For all dosed subjects, a change in body weight of ±5% from baseline or the previous body weight used to recalculate the dose will require a new dose recalculation by the clinical site.

Mode of administration

Velaglucerase alfa should be administered through a 0.22 μm in-line sterilizing filter over a period of 60 (+10) minutes; on Day 1 (Week 1) and Week 37, the infusion should be administered over a period of 60 minutes. The infusion should be completed within 24 hours of reconstitution of the vials. Velaglucerase alfa should not be infused with other products in the same infusion tubing, as the compatibility in solution with other products has not been evaluated.

Methodology:

This is a China only, Phase 3b, multicenter, nonrandomized, open-label, single-arm study to evaluate the safety, efficacy, and PK of VPRIV in Chinese subjects who have confirmed diagnosis of type 1 Gaucher disease. The study is anticipated to enroll a total of 20 subjects with a documented diagnosis of type 1 Gaucher disease, including at least 12 subjects who have not received any Gaucher disease treatment within 12 months prior to enrollment and up to 8 subjects who have been treated with Imiglucerase for Gaucher disease within 12 months prior to enrollment. The study is eligible for subjects aged 2 years and above, and the attempts should be made to enroll at least 3 subjects who are <18 years old and at least 3 subjects who are ≥18 years old in the naive subjects group.

After signing the informed consent form (ICF), subjects will have the study procedures required during the screening period (Day –21 through Day –4). After completion of the baseline procedures and assessments during the baseline visit period (Day –3 through Day 0), eligible subjects will receive IV infusions of VPRIV EOW (±3 days) from Week 1 through Week 51 during the treatment period (except at Week 1 where the time window is +3 days [Day 1 through Day 3]), followed by the end-of-treatment (EOT) visit at Week 53.

Additionally, for subjects ≥4 years old, PK assessments and sample collections will occur on Day 1 (Week 1) and Week 37 (±3 days) at the required timepoints. Pharmacokinetic samples will be collected only for the naive subjects who have not received any Gaucher disease treatment within the 12 months prior to enrollment. Pharmacokinetic parameters, including the maximum serum concentration (C_{max} [ng/mL]), time to maximum concentration (T_{max} [min]), area under the curve from time 0 to infinity (AUC_{inf} [ng•min/mL]), half-life ($T_{1/2}$ [min]), clearance (CL [mL/min/kg]), and apparent steady-state volume of distribution (V_{ss} [mL/kg]), will be determined, where appropriate, from individual serum-concentration time data using noncompartmental methods and actual sampling times.

All subjects will undergo safety assessments throughout the study until completion of the follow-up period of approximately 30 days (±7 days) from completion of the treatment infusion (or the last infusion for early treatment discontinued subjects). Safety assessments will include monitoring of AEs, use of concomitant treatment(s), clinical laboratory values, antibody formation, vital signs, physical examinations, and electrocardiogram (ECG) results.

Efficacy assessments in terms of hemoglobin concentration and platelet count will be required at baseline and every 6 weeks from Week 7 during the study treatment period and EOT visit. Liver and spleen volume evaluation will be performed at screening, Week 25, and the EOT visit. A questionnaire on QoL will be performed at baseline, Week 25, and the EOT visit. Quality-of-life assessment will include Short Form-36, version 2 (SF-36; for subjects ≥18 years of age) or Childhood Health Questionnaire-Parent Form 50 (CHQ-PF50; for subjects ≥5 and <18 years of age); QoL assessment is not applicable for subjects <5 years of age. Biomarker assessments, such as chemokine (C-C motif) ligand 18 (CCL18) and glucosylsphingosine (Lyso-Gb1), may be assessed from samples collected at the baseline, Week 13, Week 25, Week 37, and EOT visits.

Inclusion and exclusion criteria:

Inclusion criteria:

Each subject has to meet the following criteria to be eligible for the study:

1. Has a documented, confirmed diagnosis of type 1 Gaucher disease based on the following, as determined by the investigator:
   a. Decreased glucocerebrosidase (GCB) activity level that is ≤30% of normal or
   b. Decreased GCB activity level that is >30% of normal, but with confirmation of genetic mutation test
2. Is at least 2 years of age, inclusive, at screening
3. Is naive to treatment for Gaucher disease (Has not received treatment for Gaucher disease [investigational or approved products] within the 12 months prior to screening)

   OR

   Is receiving or has recently received Imiglucerase ERT (Has received Imiglucerase treatment within the 12 months prior to screening and not within the 14 days prior to screening)
4. Has Gaucher disease-related hematological abnormalities, defined as
   - Hemoglobin levels of ≥1 g/dL below the lower limit of normal for their age and gender

     AND/OR
   - A platelet count of $<90 \times 10^9$/L below the lower limit of normal for their age and gender
5. Has Gaucher disease-related viscera abnormalities, defined as the following:
   - Subject has at least moderate splenomegaly, assessed by palpation (2 to 3 cm below the left costal margin), or by abdominal radiology scan (magnetic resonance imaging [MRI] or computed tomography [CT] scan, with spleen volume >5 times normal)

     AND/OR
   - Subject has hepatomegaly, assessed by palpation or by abdominal radiology scan (MRI or CT scan); subjects who have undergone splenectomy must have satisfied these criteria for this study.
6. If a female of childbearing potential, must agree to use a medically acceptable method of contraception at all times during the study and for 30 days following the last dose of the investigational product and must have a negative pregnancy test result at the time of screening and throughout their participation in the study. Male subjects must agree to use a medically acceptable method of birth control at all times during the study and for 30 days following the last dose of the investigational product and are required to report the pregnancy of a partner.
7. The subject (and/or their legally authorized representative) must voluntarily sign an Institutional Review Board-/Ethics Committee-approved written ICF after all relevant aspects of the study have been explained and discussed with the subject. Subjects who are <18 years old must provide assent **AND** their parents/legally authorized representative should sign the ICF accordingly.
8. Must be sufficiently cooperative to participate in the study as judged by the investigator

Exclusion criteria:

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

1. Has type 2 or 3 Gaucher disease or is suspected of having type 3 Gaucher disease as assessed by the investigator (eg, subject has Gaucher disease-related central nervous system manifestations or abnormal electroencephalogram [EEG] examinations).
2. Has had a splenectomy or an active, clinically significant spleen infarction within the 12 months prior to screening.
3. Has received treatment with any investigational drug or device within 30 days prior to screening or within 5 half-lives of that investigational product, whichever is greater; such treatment during the study will not be permitted.

4. Is currently receiving red blood cell growth factor (eg, erythropoietin), chronic systemic corticosteroids, or has been on such treatment within the 6 months prior to screening.
5. Has a positive test result at screening for hepatitis B surface antigen (HBsAg) with detectable hepatitis B viral DNA load, hepatitis C virus (HCV) antibody with confirmation by HCV RNA polymerase chain reaction testing, and HIV antibody.
6. Presents with non-Gaucher disease-related exacerbated anemia at screening (eg, due to iron, folic acid, and/or vitamin B_{12} deficiency or infectious/immune-mediated causes). Subjects who have a folic acid deficiency, vitamin B_{12}-deficiency–related anemia, or iron-deficiency–related anemia during screening do not meet the study entry criteria and will be considered a screening failure. Subjects may be treated for the underlying disease and be rescreened as judged by investigator. Rescreening will be permitted once only.
7. Subject, subject's parent(s), or subject's legal guardian(s) is/are unable to understand the nature, scope, and possible consequences of the study.
8. Has a significant comorbidity, in the opinion of the investigator, that might affect the study data or confound the study results (eg, malignancies, primary biliary cirrhosis, or autoimmune liver disease)
9. Is unable to comply with the protocol (eg, has a clinically relevant medical condition making implementation of the protocol difficult, an uncooperative attitude, is unable to return to the site for safety evaluations, or is otherwise unlikely to complete the study), as determined by the investigator
10. Is a pregnant and/or lactating female
11. Has experienced a severe (grade 3 or higher) infusion-related hypersensitivity reaction (anaphylactic or anaphylactoid reaction) to any ERT (approved or investigational)

    Note: Subjects with a historical positive antibody result to Imiglucerase but without a severe infusion-related hypersensitivity reaction will not be excluded.

Maximum duration of subject participation in the study: The maximum duration of participation is expected to be 59 weeks:

- Screening period: Day –21 through Day –4
- Baseline: Day –3 through Day 0 (prior to the first dose)
- Treatment period: Week 1 (Day 1; first dose) through Week 51 (a total of 26 infusions will be administered per subject)
- End-of-treatment visit: Week 53 or 2 weeks (±7 days) after the last infusion for early withdrawal or discontinuation of subjects
- Safety follow-up period: 30 days (±7 days) after the last infusion

Statistical analysis:

Analysis sets

- **The intent-to-treat (ITT) set** will include all subjects who sign the ICF (and assent form if applicable) and are eligible for the study based on the defined inclusion/exclusion criteria. The ITT 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 VPRIV. The safety set will be used for analysis of the safety endpoints.
- **The per-protocol (PP)** set will include all subjects in the ITT set excluding subjects with major protocol deviations. The PP set will be identified by a team consisting of, at a minimum, a physician and statistician from Takeda. The PP set will be used for an efficacy sensitivity analysis.
- **The PK set** will include all subjects in the ITT set who receive at least 1 dose of VPRIV and provide evaluable PK concentration data.

Sample size and power considerations

A sample size of 20 safety evaluable subjects is planned to be enrolled in the 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.

Study endpoints

Primary:

- Incidence rate of serious TEAEs throughout the study

Secondary:

- Incidence rate of other safety parameters of VPRIV throughout the study:
  a) TEAEs
  b) IRRs
  c) Development of anti-VPRIV antibodies, including neutralizing antibodies
- Other safety aspects measured by laboratory assessments, vital signs, and ECG results
- Change from baseline to Week 53 in hemoglobin concentration and platelet count (time frame: 53 weeks)
- Change from baseline to Week 53 in normalized liver and spleen volume (percent of body weight) (time frame: 53 weeks)
- Change from baseline to Week 53 in the QoL questionnaire assessment (including SF-36, version 2 for subjects ≥18 years of age or CHQ-PF50 for subjects ≥5 and <18 years of age) (time frame: 53 weeks)
- The PK parameters of VPRIV at Week 1 and single serumdrug concentration at the end of the infusion at Week 37
- Percentage change from baseline to Week 53 in biomarkers (such as plasma CCL18 and Lyso-Gb1) (time frame: 53 weeks)

Efficacy analyses

Continuous variables will be summarized with descriptive statistics including the mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum. Categorical data will be summarized with the frequency and percentage of subjects falling within each category.

The observed values, change from baseline, change over time, and percentage change from baseline for the efficacy measurements (hematologic manifestations and liver and spleen volume) will be summarized by sex and visit. Subject listings will be provided for the clinical outcomes from the QoL questionnaires.

Efficacy analyses will be based on the ITT set, with the PP set as a sensitivity analysis. Data from the subjects who previously received Imiglucerase ERT and treatment-naive populations will be analyzed separately, as well as pooled.

Safety analyses

Adverse events will be coded using the most recent version of MedDRA. Treatment-emergent AEs will be summarized overall and by system organ class (SOC) and preferred term (PT). Analysis of AEs will be performed at both the subject and AE levels. Similar displays will be provided for IRRs. The AEs will be summarized by severity, seriousness, and relation to the 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 the worst severity or outcome for each event type will be presented for the analysis. When calculating the event rates, the denominator will be the total population size, irrespective of dropouts over the course of follow-up.

Tabular summaries of other safety parameters (eg, vital signs, blood tests, concomitant treatments [coded using WHODrug Global], anti-VPRIV antibody status, and infusion information) will be produced at baseline and, if applicable, for each postbaseline evaluation visit.

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

The observed values and change from baseline for ECG parameters (PR, QRS, QT, and corrected QT intervals and heart rate) will be summarized by visit. The number of subjects with normal and abnormal ECG results during the study 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 will be provided for each visit. The change from baseline will be calculated by subtracting the baseline value from the postbaseline value.

Vital sign data will be listed by subject, and any newly occurring changes outside the reference range from baseline will be flagged. The 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 1 use of concomitant treatment during the study will be reported. Subject listings will be provided describing the reason(s) for study discontinuation.

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

Safety data will be analyzed using the safety set. Safety data will be analyzed separately for subjects who previously received Imiglucerase ERT and treatment-naive populations, as well as pooled.

Other analyses

Pharmacokinetic analyses:

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

For the PK set, individual concentrations will be listed and summarized by visit and scheduled time points for naive subjects with PK assessments and by age (eg, ≥18 years vs 12 through 17 years vs 4 through 11 years). Individual PK parameters of VPRIV at Week 1 will be listed and summarized by treatment for all PK subjects, as well as by age, with descriptive statistics (number, arithmetic mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, and CV [95% CI] of the 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 VPRIV will be generated based on nominal time points.

Health-related quality-of-life analyses:

The change over time in subject rating of QoL will be analyzed using the SF-36, version 2 for subjects ≥18 years of age and CHQ-PF50 for subjects ≥5 and <18 years of age.

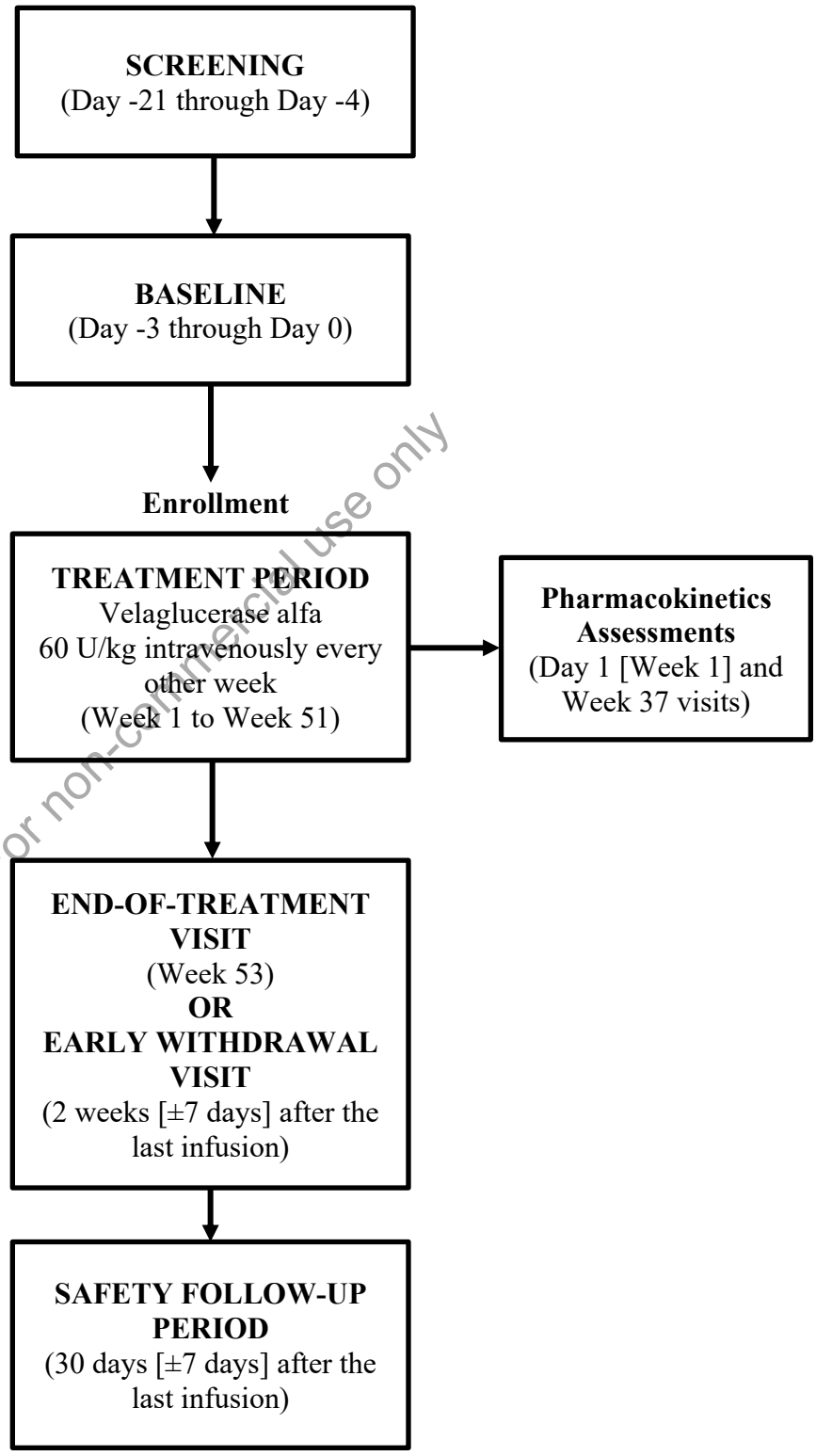
Initially, simple summary statistics will be produced for the overall score and (if available) any subscale score of each patient-reported outcome measure. Continuous variables will be summarized using the following descriptive statistics: mean, SD, median, Q1, Q3, minimum, and maximum. The number and percentage of observed levels will be reported for all categorical measures.

Biomarker analyses:

Circulating biomarker data will be summarized using descriptive statistics.

1.2 Schema

Figure 1. Study Schematic Diagram



1.3 Schedule of Activities

Table 1. Schedule of Activities

Procedure	Screening[a]	Baseline[b]	Treatment Period Study Week[c]																										EOT (Week 53) OR Early Withdrawal (2 weeks ±7 days after the last infusion)[d]	Safety Follow-up Period (30 days ±7 days after the last infusion)[e]
	Day –21 through Day –4	Day –3 through Day 0	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51		
Informed consent	X																													
Confirmation of study eligibility[f]	X	X																												
Demographics	X																													
Medical history, including surgical procedures[g]	X																													
Immunology[h]	X																													
Electroencephalogram[i]	X																													
Physical examination[j]	X	X							X						X						X								X	
Prior and concomitant treatments[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational product infusion[l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body weight	X	X				X			X			X			X			X			X			X			X		X	
Height[n]	X														X														X	

Table 1. Schedule of Activities

Procedure	Screening[a]	Baseline[b]	Treatment Period Study Week[c]																										EOT (Week 53) OR Early Withdrawal (2 weeks ±7 days after the last infusion)[d]	Safety Follow-up Period (30 days ±7 days after the last infusion)[e]
	Day –21 through Day –4	Day –3 through Day 0	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51		
12-Lead electrocardiogram[o]		X							X						X						X								X	
Pregnancy test[p]	X	X			X		X		X		X		X		X		X		X		X		X		X		X		X	
Urinalysis[q, i]		X							X						X						X								X	
Serum chemistry[r, i]		X							X						X						X								X	
Hematology (for safety laboratory)[s, i]	X	X							X						X						X								X	
Hemoglobin concentration and platelet count[s, t]		X				X			X			X			X			X			X			X			X		X	
Serum anti-VPRIV antibody[t]		X							X						X						X								X	
Circulating biomarkers[t, u]		X							X						X						X								X	
Liver and spleen volume (MRI or CT scan)[v, i]	X														X														X	
X-ray of bilateral femoral neck and distal femur (procedural imaging)[w]		X																												
Quality-of-life assessment[x]		X													X														X	

Table 1. Schedule of Activities

Procedure	Screening[a]	Baseline[b]	Treatment Period Study Week[c]																									EOT (Week 53) OR Early Withdrawal (2 weeks ±7 days after the last infusion)[d]	Safety Follow-up Period (30 days ±7 days after the last infusion)[e]
	Day –21 through Day –4	Day –3 through Day 0	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51		
PK assessments[y]			X																		X								

AE=adverse event; β-hCG=beta-human chorionic gonadotropin; CT=computed tomography; eCRF=electronic Case Report Form; EOT=end of treatment; ERT=enzyme replacement therapy; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; MRI=magnetic resonance imaging; PK=pharmacokinetic(s); QoL=quality of life; SAE=serious adverse event; VPRIV=velaglucerase alfa.

[a] Screening assessments and procedures can be performed over multiple days within a period of up to 18 days following the subject's signature of the ICF.

[b] All baseline assessments and procedures must be completed prior to the first VPRIV infusion and will be performed at the clinical site.

[c] A window of ±3 days is allowed around the infusion interval to facilitate subject scheduling, except at Week 1 where the time window is +3 days (Day 1 through Day 3).

[d] For subjects who discontinue the study prior to the Week 53 visit, all EOT assessments and procedures should be performed as completely as possible.

[e] The safety follow-up period is 30 (±7) days after the last infusion at Week 51 (or the last infusion for early discontinued subjects). During this period, there will be a telephone call or scheduled visit to the site to query for AEs, SAEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure or return to the baseline level or explained by the investigator if the AE and/or SAE will not be resolved as documented in the subject's source documents.

[f] Study eligibility will be confirmed by review of the study entrance criteria at screening, including the subject's hemoglobin concentration, platelet level, and liver and spleen volume (analyzed at the local laboratory). Confirmation of the eligibility at baseline includes the subject's hemoglobin concentration and platelet level (analyzed at the local laboratory).

[g] Medical history, including surgical procedures within the 30 days prior to signing the ICF, will be collected and recorded in the subject's source documents and on the appropriate eCRF page.

[h] Immunology tests include HBsAg, HCV, and HIV. Tests for HBsAg with detectable hepatitis B viral DNA load, HCV antibody with confirmation by HCV RNA polymerase chain reaction testing, and HIV antibody will be performed at the local laboratory or Takeda-designated laboratory.

[i] Will be performed at the local laboratory.

[j] A complete physical examination will include, at a minimum, assessments of the following organs and systems: eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatologic, musculoskeletal, extremities, lymph nodes, nervous system (eg, eye movement disorder), and other.

[k] Prior treatments received within the 30 days prior to signing the ICF will be collected and recorded in the subject's source documents and on the appropriate eCRF page.

[l] The VPRIV infusions will be administered at the clinical site. For treatment-naive subjects, the initial dose of VPRIV will be calculated based on the subject's body weight determined at baseline. For subjects who received Imiglucerase ERT within the 12 months prior to screening, the initial dose will be determined by the investigator after discussing with the sponsor and recording in appropriate document based on the subject's specific treatment and situation at the time of enrollment, according to the subject's benefit and risk assessment. For all dosed subjects, a change in body weight of ±5% from baseline or the previous body weight assessment at Weeks 7, 13, 19, 25, 31, 37, 43, or 49 used to recalculate the dose will require a new dose recalculation by the clinical site. Velaglucerase alfa should be administered over a period of 60 (+10) minutes; on Day 1 (Week 1) and Week 37, the infusion should be administered over a period of 60 minutes.

[m] Vital signs include pulse rate, blood pressure, respiratory rate, temperature, body weight, and height. Measurement of pulse rate, blood pressure, respiratory rate, and temperature will be taken prior to blood draw and/or initiation of infusion following 5 minutes of rest. Vital signs should be recorded as outlined in Table 4 and will be recorded in the subject's source documents and on the appropriate eCRF page. If there are no infusion-related reactions observed during the first 3 infusions, vital signs assessment for the subsequent infusions can be omitted at the discretion of the investigator.

[n] Height will be measured as part of the vital sign assessments and for calculation of normalized liver and spleen volume which will be measured by abdominal radiology scan (MRI or CT scan) at screening, at Week 25, and the EOT visit.

[o] Electrocardiogram parameters (PR, QRS, QT, and corrected QT intervals and heart rate) will be collected prior to blood draw and/or initiation of infusion following 5 minutes of rest.

[p] Female subjects of childbearing potential will have a pregnancy test. Pregnancy testing will be performed using a urine sample and, if needed, a serum β-hCG sample. If the urine pregnancy test is negative, the study assessments and procedures will be completed; serum β-hCG testing will not be required. If the urine test is positive, a blood sample will be collected for serum β-hCG testing and sent to either the local laboratory or Takeda-designated laboratory for analysis. No additional study assessments or procedures should be completed until the result of the serum pregnancy test is available. Female subjects of childbearing potential must have a negative serum β-hCG test 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. The pregnancy test at the baseline visit can be waived if it had been performed within 7 days of the previous test during the screening visit.

[q] Urinalysis parameters include bilirubin, color, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, and urobilinogen.

[r] Serum chemistry laboratory tests include albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, (blood) urea nitrogen or (blood) urea, calcium, creatinine, creatine kinase, ferritin, γ-glutamyl transferase glucose, lactate dehydrogenase, potassium, serum iron, sodium, total bilirubin, and total protein. Subjects who have folic acid deficiency, vitamin B_{12}-deficiency–related anemia, or iron-deficiency–related anemia at screening do not meet the study entry criteria and will be considered a screening failure. Subjects may be treated for the underlying disease and be rescreened as judged by the investigator. Rescreening will be permitted once only. Subjects who enter the study receiving iron supplement therapy will continue receiving iron supplement therapy throughout their participation in the study.

[s] Hematology laboratory tests for safety include hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, white blood cell count with differential, neutrophils, basophils, lymphocytes, monocytes, and eosinophils. Assessments of hemoglobin concentration and platelet count are included as components of the hematology laboratory panel at screening, baseline (Day –3 through Day 0) and Weeks 13, 25, 37, and 53 (EOT). For statistical analysis purposes, an additional blood sample will be collected and sent to a central laboratory for evaluation of hemoglobin concentration and platelet count at baseline (Day –3 through Day 0) and Weeks 7, 13, 19, 25, 31, 37, 43, 49, and 53 (EOT).

[t] The sample will be collected before the VPRIV infusion and evaluated at a Takeda-designated laboratory.

[u] Circulating biomarkers include glucosylsphingosine and chemokine (C-C motif) ligand 18.

[v] Liver and spleen volume will be confirmed by an abdominal MRI or CT scan. All imaging modalities should remain consistent for all subject at all timepoints throughout the study. Investigator is responsible to perform eligibility check for presence of at least hepatomegaly and/or moderate splenomegaly (spleen volume >5 times normal). The multiples of normal (MN) for splenomegaly is given by spleen volume (MN) = spleen volume (cm^3) / 2 x subject's weight (kg). The multiples of normal for hepatomegaly is given by liver volume (MN) = liver volume (cm^3) / 25 x subject's weight (kg). To evaluate VPRIV efficacy, the volumes of liver and spleen will be analyzed and calculated centrally by sending the MRI/CT images to a Takeda-designated imaging vendor.

[w] X-ray test can be waived if it has been performed within the 30 days prior to the baseline visit.

[x] Quality-of-life assessments include Short Form-36, version 2 (for subjects ≥18 years of age) or Childhood Health Questionnaire-Patient Form 50 (for subjects ≥5 and <18 years of age); QoL assessment is not applicable for subjects <5 years of age.

[y] The PK sampling schedule is specified in Table 2. Pharmacokinetic samples will be evaluated at a Takeda-designated laboratory.

Table 2. Pharmacokinetic Sampling Time Points

	Day 1 (Week 1)										Week 37
Age Group	**Before the infusion**	**During the Infusion**		**End of the Infusion**	**After the infusion**						**End of the Infusion**
	0 (-30) min[a]	**20 (±1) min**	**40 (±2) min**	**60 (-3) min[b]**	**65 (±3) min**	**70 (±3) min**	**80 (±4) min**	**90 (±4) min**	**105 (±5) min**	**120 (±6) min**	**60 (-3) min[b]**
≥18 years old	X	X	X	X	X	X	X	X	X	X	X
12 through 17 years old	X	X	X	X		X	X	X		X	X
4 through 11 years old		X		X		X	X	X			X

min=minute(s).

Notes: The study is anticipated to enroll 12 naive subjects (attempts should be made to enroll at least 3 subjects who are <18 years old and at least 3 subjects who are ≥18 years old) for pharmacokinetic assessment. Pharmacokinetic assessments will occur for subjects ≥4 years old. Pharmacokinetic samples will be collected only for the naive subjects who have not received any Gaucher disease treatment within the 12 months prior to enrollment. Pharmacokinetic blood samples must not be drawn from the arm being used for the infusion.

The PK sampling timepoints are the nominal timepoints based on a 60-minute infusion.

[a] A PK sample should be collected within 30 min prior to the start of 60-min infusion.

[b] A PK sample should be collected within 3 min prior to the end of 60-min infusion.

2. INTRODUCTION

2.1 Indication and Current Treatment Options

Gaucher disease, a panethnic, autosomal, recessive disease (Cox and Schofield 1997) is the most common glycosphingolipid storage disorder (Cox et al. 2003). The disease occurs when an inherited deficiency of the lysosomal enzyme glucocerebrosidase (GCB) leads to progressive accumulation of glucocerebroside within macrophages and subsequent tissue and organ damage. In China, domestic experts estimate that the prevalence rate of Gaucher disease in the Chinese population is lower than the global average, with only 0.2 to 0.5 cases per 100,000 people (prevalence is approximately 1/500,000 to 1/200,000), speculated from neonatal prevalence (Zhang 2020). In 2018, Gaucher disease had been listed in the Catalogue of Rare Diseases in China (http://www.gov.cn/zhengce/zhengceku/2018-12/31/content_5435167.htm, Notice of Releasing First Batch of Rare Disease List, Accessed 11 Nov 2021).

Gaucher disease is a multisystem disorder, with clinical features reflective of the distribution of abnormal macrophages (Gaucher cells) in the liver, spleen, bone marrow, skeleton, lungs, and occasionally, lymph nodes (Beutler and Grabowski 2001). Accumulation of glucocerebroside-containing cells (mainly macrophages or macrophage-like cells) in the liver and spleen leads to secondary changes, including organomegaly, which can be massive, particularly in the case of the spleen. Bone involvement results in skeletal abnormalities and deformities, as well as bone pain and crises. Deposits in the bone marrow and splenic sequestration lead to dysfunction with clinically significant anemia and thrombocytopenia.

The disease has been classified into 3 clinical subtypes based on the presence or absence of neurological symptoms and severity of neurological symptoms (Beutler and Grabowski 2001). Global statistics show that type 1 patients account for about 95%, type 2 patients account for 1%, and type 3 patients account for approximately 2% to 3%. Type 1 Gaucher disease, the most common form, does not involve the central nervous system; typical manifestations include hepatomegaly, splenomegaly, thrombocytopenia, bleeding tendencies, anemia, hypermetabolism, skeletal pathology, growth retardation, pulmonary disease, and decreased quality of life (QoL) (Pastores et al. 2004). Patients with type 2 Gaucher disease present with acute neurological deterioration, and those with type 3 disease typically display a more subacute neurological course. In Northeast Asia, including China, Japan, and South Korea, the proportion of type 2 and type 3 is relatively high and, according to expert predictions, may reach approximately 30% to 50%, mainly related to gene mutations (Zhang 2020).

Most of the research effort to date has focused on strategies for augmenting enzyme levels to compensate for the underlying defect; enzyme replacement therapy (ERT) has remained the cornerstone of treatment for Gaucher disease since the early 1990s and is highly effective in

improving many of the clinical manifestations of this disease (Cox et al. 2003). Data from the International Collaborative Gaucher Group show that approximately 90% of all patients with Gaucher disease who have anemia should achieve normal hemoglobin concentrations within 2 years of initiation of ERT (Weinreb et al. 2002). Enzyme replacement therapy reduces organomegaly, improves hematological parameters, and positively affects health-related QoL (Barton et al. 1991, Masek et al. 1999, Weinreb et al. 2002). In China, the use of ERT has more than 20 years of real-world experience. Enzyme replacement therapy specifically supplements the lack of enzymes in the patient's body, reduces the accumulation of glucocerebrosides in the body, and is a specific treatment for Gaucher disease.

2.2 Product Background and Clinical Information

Velaglucerase alfa (VPRIV) is a human GCB that catalyzes the hydrolysis of glucocerebroside, reducing the amount of accumulated glucocerebroside and correcting the pathophysiology of Gaucher disease. It is produced by gene activation in a human cell line. In order to produce an enzyme that is readily taken up by the mannose receptors of phagocytic cells, VPRIV is manufactured to contain predominantly high-mannose type N-linked glycans.

Velaglucerase alfa is approved as a long-term ERT for the treatment of type 1 Gaucher disease in pediatric and adult subjects. The initial approval was on 26 Feb 2010 in the United States (US), and approval in the European Union (EU) was granted on 26 Aug 2010 under the trade name VPRIV. Global commercialization is ongoing with approval in 66 countries as of 27 Jul 2021. Orphan drug designation has been received in the US, the EU, Switzerland, Australia, Japan, South Korea, Mexico, and Taiwan. In China, VPRIV was listed as the First List of Overseas New Drugs in Urgent Clinical Need in 2018 and was given conditional approval in Apr 2021.

As of 25 Feb 2020, a total of 355 subjects have received VPRIV in the clinical studies. Clinical safety, efficacy, and pharmacokinetic (PK) data from 4 core Phase 1/2 to 3 studies (TKT025, TKT032, TKT034, and HGT-GCB-039) supported the global commercialization of VPRIV. Three of the core studies (TKT025, TKT032, and HGT-GCB-039) were conducted in treatment-naive subjects; the fourth core study (TKT034) was performed in subjects previously treated with Imiglucerase and then switched to VPRIV at the same dose. The core studies were extended via 2 extension studies (TKT025EXT and HGT-GCB-044) to evaluate long-term safety and efficacy. In the core studies, VPRIV was administered intravenously (IV) over 60 minutes at doses ranging from 15 to 60 U/kg every other week (EOW). The youngest subject receiving VPRIV in these studies was 4 years of age.

Overall data from the studies to date support the finding that long-term ERT with VPRIV is generally well tolerated at all doses tested in adult or pediatric, male or female subjects with type 1 Gaucher disease. Adverse event (AE) profiles are consistent between treatment-naive

subjects and subjects who switch from prior treatment with Imiglucerase. Very common adverse drug reactions (ADRs), defined as those occurring at a frequency of at least 1 in 10 subjects, comprised headache, dizziness, abdominal pain/upper abdominal pain, bone pain, arthralgia, back pain, infusion-related reactions (IRRs), asthenia/fatigue, and pyrexia/body temperature increased.

2.3 Study Rationale

On 27 Apr 2021, VPRIV received approval of its New Drug Application from China's National Medical Products Administration for the treatment of type 1 Gaucher disease. As part of the approval requirements of China's Health Authority, this Phase 3b interventional post approval commitment study is planned to evaluate the safety, efficacy, and PK of VPRIV in Chinese subjects with type 1 Gaucher disease.

2.4 Benefit/Risk Assessment

Velaglucerase alfa is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by widely distributed proteolytic enzymes. Therefore, no studies have been conducted to evaluate the metabolism of VPRIV. Efficacy data from previous core studies demonstrated that increases in hemoglobin concentration and platelet count and decreases in normalized liver and spleen volume were seen in treatment-naive adult and pediatric subjects with type 1 Gaucher disease. Response based on increases in hemoglobin concentration for VPRIV treatment was shown to be noninferior to that of Imiglucerase, and no statistically significant treatment difference was seen between VPRIV and Imiglucerase for the increase in platelet count or decrease in liver or spleen volumes. An exploratory analysis showed an increase in the bone mineral density of the lumbar spine in adult subjects following treatment with VPRIV and suggested a beneficial effect on the linear growth of children with Gaucher disease. Hemoglobin concentration, platelet count, and liver and spleen volumes observed after long-term treatment with Imiglucerase were maintained in adult and pediatric subjects when these subjects were switched from Imiglucerase to VPRIV at the same dose. Similar improvements in visceral manifestations to those seen in subjects with type 1 Gaucher disease were also observed in treatment-naive pediatric subjects with type 3 Gaucher disease.

To date, VPRIV has shown an overall favorable safety profile in the clinical studies in a total of 355 subjects. Infusion-related reactions were the most commonly observed adverse reactions in subjects treated with VPRIV in the clinical studies. Most of the IRRs were mild in severity. The management of IRRs is based on the severity of the reaction, and may include slowing the infusion rate, treatment with medications such as antipyretics and/or corticosteroids, and/or stopping and resuming treatment with an increased infusion time. Subjects were not routinely premedicated prior to infusion of VPRIV during the clinical studies.

The most serious adverse reactions in subjects treated with VPRIV were hypersensitivity reactions. As with any IV protein product, hypersensitivity reactions, including symptoms consistent with anaphylaxis, are possible. Treatment with VPRIV should be approached with caution in subjects who have exhibited symptoms of hypersensitivity to the active ingredient, excipients in the drug product, or other ERT. Appropriate medical support should be readily available when VPRIV is administered. If a severe reaction occurs, current medical standards for emergency treatment are to be followed.

In the clinical studies, 4 serious AEs (SAEs) were reported that were considered to be related to VPRIV. These SAEs included 1 subject with grade 3 allergic dermatitis that resolved during the 9-month study (HGT-GCB-039). This subject continued treatment with VPRIV in the extension study (HGT-GCB-044) with no recurrence. One switched subject experienced an SAE of an anaphylactoid reaction: this subject permanently discontinued treatment with VPRIV in Study TKT034. One subject in Study HGT-GCB-058 had an SAE of a migraine, which was considered mild in severity. One subject in Study HGT-GCB-087, conducted in Japan, had an SAE of retinal detachment. This subject had 2 nonrelated SAEs of vitreous opacities and 2 nonrelated SAEs of retinal detachment during participation in the Extension Study HGT-GCB-091, continued to receive treatment, and completed the study.

There have been no deaths considered related to VPRIV. One pediatric subject with a history of seizures died during participation in a clinical study following extended treatment with VPRIV. The cause of death was convulsions and considered by the investigator as not related to VPRIV.

A tiered approach was used for immunogenicity monitoring. In the core studies (TKT025, TKT032, TKT034, and HGT-GCB-039), 1 of 94 subjects (1.1%) who received VPRIV developed antibodies. The neutralizing antibodies were detected by an enzymatic activity assay. No IRRs were reported for this subject. In the extension studies (TKT025EXT and HGT-GCB-044), 1 of 105 subjects (1.0%) developed anti-VPRIV antibodies. In Study HGT-GCB-058, 1 of 167 assessable subjects (0.6%) in the treatment protocol developed antibodies. In Study HGT-GCB-068, 1 of 6 assessable subjects developed anti-VPRIV antibodies that were not neutralizing. In the core studies, extension studies, and Study HGT-GCB-058, positive subject samples were also tested for the presence of immunoglobulin (Ig)E anti-VPRIV antibodies. No subjects in these studies developed IgE anti-VPRIV antibodies. No subjects in the Japanese studies (HGT-GCB-087 and HGT-GCB-091) developed anti-VPRIV antibodies. In the ongoing study (SHP-GCB-402), 3 subjects developed anti-VPRIV antibodies. One of the subjects showed a persistent anti-VPRIV antibody response from Week 25 onwards with low antibody titers. The second subject had positive results for anti-VPRIV antibodies at baseline and all time points tested; antibody titers were within a 2-step dilution of the baseline titer of 80. For this subject, neutralizing antibodies were transiently seen at Week 51. The third

subject developed anti-VPRIV antibody response at Week 25 through Week 51 and again at Week 77 through the end of the study. No SAEs were reported for these subjects, and the AEs reported were in alignment with the known safety profile of VPRIV.

The safety profile of VPRIV in the postmarketing setting is consistent with that seen in the clinical development program. No new safety concerns have been identified.

Always refer to the latest version of the VPRIV investigator's brochure (IB) for the overall benefit/risk assessment and most accurate and current information regarding drug metabolism, PK, efficacy, and safety of VPRIV.

2.5 Compliance Statement

The study will be conducted in accordance with this protocol, the International Council for Harmonization 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 are described fully in Appendix 1.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to evaluate the safety of VPRIV by assessing the incidence of serious treatment-emergent AEs (TEAEs) when administered EOW up to 51 weeks by IV infusion in Chinese subjects with type 1 Gaucher disease.

3.1.2 Secondary Objectives

The secondary objectives of the study are to assess:

- Other safety parameters of VPRIV (including the incidence of TEAEs and IRRs and rates of antibody formation)
- The effect of VPRIV on hematologic manifestations
- The effect of VPRIV on the liver and spleen volume
- The effect of VPRIV on QoL
- The PK of VPRIV
- The effect of VPRIV on disease biomarkers

3.2 Study Endpoints

Table 3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety of VPRIV by assessing the incidence of serious TEAEs	• Incidence rate of serious TEAEs throughout the study
Secondary	
• To assess other safety parameters of VPRIV	• Incidence rate of other safety parameters of VPRIV throughout the study: a) TEAEs b) Infusion-related reactions c) Development of anti-VPRIV antibodies, including neutralizing antibodies • Other safety aspects measured by laboratory assessments, vital signs, and electrocardiogram results

Table 3. Objectives and Endpoints

Objectives	Endpoints
• To assess the effect of VPRIV on hematologic manifestations	• Change from baseline to Week 53 in hemoglobin concentration and platelet count (time frame: 53 weeks)
• To assess the effect of VPRIV on the liver and spleen volume	• Change from baseline to Week 53 in normalized liver and spleen volume (percent of body weight) (time frame: 53 weeks)
• To assess the effect of VPRIV on QoL	• Change from baseline to Week 53 in the QoL questionnaire assessment (including Short Form-36, version 2 for subjects ≥18 years of age or Childhood Health Questionnaire-Parent Form 50 for subjects ≥5 and <18 years of age) (time frame: 53 weeks)
• To assess the PK of VPRIV	• The PK parameters of VPRIV at Week 1 and single serum drug concentration at the end of the infusion at Week 37
• To assess the effect of VPRIV on disease biomarkers	• Percentage change from baseline to Week 53 in biomarkers (such as plasma chemokine [C-C motif] ligand 18 and glucosylsphingosine) (time frame: 53 weeks)

PK=pharmacokinetic(s); QoL=quality of life; TEAE=treatment-emergent adverse event; VPRIV=velaglucerase alfa.

4. STUDY DESIGN

4.1 Overall Design

This is a China only, Phase 3b, multicenter, nonrandomized, open-label, single-arm study to evaluate the safety, efficacy, and PK of VPRIV in Chinese subjects who have confirmed diagnosis of type 1 Gaucher disease. The study is anticipated to enroll a total of 20 subjects with a documented diagnosis of type 1 Gaucher disease, including at least 12 subjects who have not received any Gaucher disease treatment within 12 months prior to enrollment and up to 8 subjects who have been treated with Imiglucerase for Gaucher disease within 12 months prior to enrollment. The study is eligible for subjects aged 2 years and above, and the attempts should be made to enroll at least 3 subjects who are <18 years old and at least 3 subjects who are ≥18 years old in the naive subjects group.

After signing the informed consent form (ICF), subjects will have the study procedures required during the screening period (Day –21 through Day –4). After completion of the baseline procedures and assessments during the baseline visit period (Day –3 through Day 0), eligible subjects will receive IV infusions of VPRIV EOW (±3 days) from Week 1 through Week 51 during the treatment period (except at Week 1 where the time window is +3 days [Day 1 through Day 3]), followed by the end-of-treatment (EOT) visit at Week 53.

Additionally, for subjects ≥4 years old, PK assessments and sample collections will occur on Day 1 (Week 1) and Week 37 (±3 days) at the required timepoints (Table 2). Pharmacokinetic samples will be collected only for the naive subjects who have not received any Gaucher disease treatment within the 12 months prior to enrollment. Pharmacokinetic parameters, including maximum serum concentration (C_{max} [ng/mL]), time to maximum concentration (T_{max} [min]), area under the curve from time 0 to infinity (AUC_{inf} [ng•min/mL]), half-life ($T_{1/2}$ [min]), clearance (CL [mL/min/kg]), and apparent steady-state volume of distribution (V_{ss} [mL/kg]), will be determined, where appropriate, from individual serum-concentration time data using noncompartmental methods and actual sampling times.

All subjects will undergo safety assessments throughout the study until completion of the follow-up period of approximately 30 days (±7 days) from completion of the treatment infusion (or the last infusion for early treatment discontinued subjects). Safety assessments will include monitoring of AEs, use of concomitant treatment(s), clinical laboratory values, antibody formation, vital signs, physical examinations, and electrocardiogram (ECG) results.

Efficacy assessments in terms of hemoglobin concentration and platelet count will be required at baseline and every 6 weeks from Week 7 during the study treatment period and EOT visit. Liver and spleen volume evaluation will be performed at screening, Week 25, and the EOT visit. A

questionnaire on QoL will be performed at baseline, Week 25, and the EOT visit. Quality-of-life assessment will include Short Form-36, version 2 (SF-36; for subjects ≥18 years of age) or Childhood Health Questionnaire-Parent Form 50 (CHQ-PF50; for subjects ≥5 and <18 years of age); quality-of-life assessment is not applicable for subjects <5 years of age. Biomarker assessments, such as chemokine (C-C motif) ligand 18 (CCL18) and glucosylsphingosine (lyso-Gb1), may be assessed from samples collected at the baseline, Week 13, Week 25, Week 37, and EOT visits.

4.2 Scientific Rationale for Study Design

In order to facilitate the broadest evaluation of the efficacy and safety of VPRIV, the enrolled patient population will be as diverse as possible. In this nonrandomized, open-label, multicenter, China only study, both treatment-naive patients (untreated within the 12 months prior to screening) and patients switched from Imiglucerase ERT (treated within the 12 months prior to screening and not within the 14 days prior to screening) will be enrolled. Clinical activity of gene-activated human GCB will be measured by measuring the change in hemoglobin concentration and platelet count, along with reduction in the liver and spleen volume. Biomarkers will also be measured.

4.3 Justification for Dose

Velaglucerase alfa has been approved in 60 countries as of 25 Feb 2020 for the treatment of type 1 Gaucher disease in pediatric and adult subjects. Velaglucerase alfa will be administered at the globally approved dose of 60 U/kg body weight EOW as a 60-minute IV infusion.

4.4 Duration of Subject Participation

The maximum duration of participation is expected to be 59 weeks:

- Screening period: Day –21 through Day –4
- Baseline: Day –3 through Day 0 (prior to the first dose)
- Treatment period: Week 1 (Day 1; first dose) through Week 51 (a total of 26 infusions will be administered per subject)
- End-of-treatment visit: Week 53 or 2 weeks (±7 days) after the last infusion for early withdrawal or discontinuation of subjects
- Safety follow-up period: 30 (±7) days after the last infusion

4.5 Sites and Regions

The study is planned to be conducted in at least 8 clinical sites in China.

5. STUDY POPULATION

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

5.1 Inclusion Criteria

Each subject has to meet the following criteria to be eligible for the study:

1. Has a documented, confirmed diagnosis of type 1 Gaucher disease based on the following, as determined by the investigator:
    a. Decreased GCB activity level that is ≤30% of normal or
    b. Decreased GCB activity level that is >30% of normal, but with confirmation of genetic mutation test
2. Is at least 2 years of age, inclusive, at screening
3. Is naive to treatment for Gaucher disease (Has not received treatment for Gaucher disease [investigational or approved products] within the 12 months prior to screening

    OR

    Is receiving or has recently received Imiglucerase ERT (Has received Imiglucerase treatment within the 12 months prior to screening and not within the 14 days prior to screening)
4. Has Gaucher disease-related hematological abnormalities, defined as
    - Hemoglobin levels of ≥1 g/dL below the lower limit of normal for their age and gender

      AND/OR
    - A platelet count of <90 × 10^9/L below the lower limit of normal for their age and gender
5. Has Gaucher disease-related viscera abnormalities, defined as the following:
    - Subject has at least moderate splenomegaly, assessed by palpation (2 to 3 cm below the left costal margin), or by abdominal radiology scan (magnetic resonance imaging [MRI] or computed tomography [CT] scan, with spleen volume >5 times normal)

      AND/OR

- Subject has hepatomegaly, assessed by palpation or by abdominal radiology scan (MRI or CT scan); Subjects who have undergone splenectomy must have satisfied these criteria for this study.

6. If a female of childbearing potential, must agree to use a medically acceptable method of contraception at all times during the study and for 30 days following the last dose of the investigational product and must have a negative pregnancy test result at the time of screening and throughout their participation in the study. Male subjects must agree to use a medically acceptable method of birth control at all times during the study and for 30 days following the last dose of the investigational product and are required to report the pregnancy of a partner.
7. The subject (and/or their legally authorized representative) must voluntarily sign an Institutional Review Board (IRB)/Ethics Committee (EC)-approved written ICF after all relevant aspects of the study have been explained and discussed with the subject. Subjects who are <18 years old must provide assent **AND** their parents/legally authorized representative should sign the ICF accordingly.
8. Must be sufficiently cooperative to participate in the study as judged by the investigator

5.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met.
Has type 2 or 3 Gaucher disease or is suspected of having type 3 Gaucher disease as assessed by the investigator (eg, subject has Gaucher disease-related central nervous system manifestations or abnormal electroencephalogram [EEG] examinations).

2. Has had a splenectomy or an active, clinically significant spleen infarction within the 12 months prior to screening
3. Has received treatment with any investigational drug or device within 30 days prior to screening, or within 5 half-lives of that investigational product, whichever is greater; such treatment during the study will not be permitted.
4. Is currently receiving red blood cell growth factor (eg, erythropoietin), chronic systemic corticosteroids, or has been on such treatment within the 6 months prior to screening
5. Has a positive test result at screening for hepatitis B surface antigen (HBsAg) with detectable hepatitis B viral DNA load, hepatitis C virus (HCV) antibody with confirmation by HCV RNA polymerase chain reaction testing, and HIV antibody
6. Presents with non-Gaucher disease-related exacerbated anemia at screening (eg, due to iron, folic acid, and/or vitamin B_{12} deficiency or infectious/immune-mediated causes).

Subjects who have a folic acid deficiency, vitamin B_{12}-deficiency–related anemia, or iron-deficiency–related anemia during screening do not meet the study entry criteria and will be considered a screening failure. Subjects may be treated for the underlying disease and be rescreened as judged by investigator. Rescreening will be permitted once only.

7. Subject, subject's parent(s), or subject's legal guardian(s) is/are unable to understand the nature, scope, and possible consequences of the study
8. Has a significant comorbidity, in the opinion of the investigator, that might affect the study data or confound the study results (eg, malignancies, primary biliary cirrhosis, or autoimmune liver disease)
9. Is unable to comply with the protocol (eg, has a clinically relevant medical condition making implementation of the protocol difficult, an uncooperative attitude, is unable to return to the site for safety evaluations, or is otherwise unlikely to complete the study), as determined by the investigator
10. Is a pregnant and/or lactating female
11. Has experienced a severe (grade 3 or higher) infusion-related hypersensitivity reaction (anaphylactic or anaphylactoid reaction) to any ERT (approved or investigational). Note: Subjects with a historical positive antibody result to Imiglucerase but without a severe infusion-related hypersensitivity reaction will not be excluded.

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 30 days following the last dose of the 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 30 days following the last dose of the 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 urine and/or serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use the acceptable methods of contraception.

Female adult subjects should be either:

- Postmenopausal (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 have passed since sterilization, or
- Of childbearing potential with a negative urine and/or serum β-hCG pregnancy test at screening. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use the acceptable methods of contraception.

Acceptable methods of contraception (see Appendix 4 for guidance) 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 of contraception noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

Female subjects must agree not to become pregnant, breastfeed a baby or donate an egg or eggs (ova) for the duration of the study and for 30 days after the last dose of study treatment.

5.4.2 Male Contraception

Males, including males who are surgically sterile (vasectomy), with female partners of childbearing potential must agree to be abstinent or use a medically acceptable form of contraception (see Appendix 4 for guidance) from screening through 30 days after the last dose of the investigational product.

Male subjects must refrain from donating sperm for the duration of the study and for 30 days after the last dose of study treatment.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The investigational product, VPRIV, will be provided in single-use, 4-mL vials containing 11 mg or 440 U velaglucerase alfa after reconstitution and provides 10 mg or 400 U for infusion use, and the solution should be clear to slightly opalescent and colorless for IV infusion.

Additional information is provided in the VPRIV IB.

6.1.2 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

Velaglucerase alfa is a sterile lyophilized powder that requires reconstitution and dilution and is intended for IV infusion only. Velaglucerase alfa contains no preservatives, and vials are for single use only; once reconstituted, the product should be used immediately. Refer to the VPRIV IB for reconstitution instructions. If immediate use is not possible, the reconstituted or diluted product may be stored for up to 24 hours at 2 to 8 ºC (36 to 46 ºF); it should be protected from light and should not be frozen. Any unused solution should be discarded in accordance with local regulations.

Velaglucerase alfa should be administered through a 0.22 µm in-line sterilizing filter over a period of 60 (+10) minutes; on Day 1 (Week 1) and Week 37, the infusion should be administered over a period of 60 minutes. The infusion should be completed within 24 hours of reconstitution of the vials. Velaglucerase alfa should not be infused with other products in the same infusion tubing, as the compatibility in solution with other products has not been evaluated.

If a subject experiences an infusion-related AE (as defined in Appendix 3.1) during the infusion of investigational product, the investigator should decide, based on his or her clinical judgment, whether the infusion should be slowed or temporarily or permanently discontinued.

Investigational product infusions are to occur on approximately the same day of the week but may occur every 14 (±3) days in order to facilitate subject scheduling. If at all possible, missed infusions should be avoided. If a subject is not dosed within 17 days from their scheduled dose, the subject should receive the next infusion as soon as possible after approval from the medical monitor for the subject to continue in the study. It may be acceptable to give the next infusion as early as 11 days after the previous infusion. Subsequent infusions will return to the original schedule.

Subjects will be discharged from the clinic 1 hour following completion of the infusion if they are clinically stable. However, on infusion days when PK assessments are scheduled, subjects will be discharged from the clinic approximately 3 hours after completion of the infusion if they are clinically stable. Site specific discharging requirement should be followed if any.

6.2.1 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, and return of the investigational product. Please refer to the separate instruction manual that outlines the operating procedures regarding the IRT.

6.2.2 Allocation of Subjects to Treatment

This is an open-label, nonrandomized study, where all subjects will be enrolled to receive VPRIV. Subject numbers are assigned to all subjects as they consent to take part in the study. At each site, the subject number will be assigned to subjects according to the sequence of presentation for study participation.

6.2.3 Dosing

Velaglucerase alfa (VPRIV) infusions will occur at the clinical site. Subjects will receive VPRIV as an IV infusion EOW (±3 days). For treatment-naive subjects, the initial dose of VPRIV will be calculated based on the subject's body weight determined at baseline. For subjects who received Imiglucerase ERT within the 12 months prior to screening, the initial dose will be determined by the investigator after discussing with the sponsor and recording in appropriate document based on the subject's specific treatment and the situation at the time of enrollment, according to the subject's benefit and risk assessment. Weight will be measured every 6 weeks (Weeks 7, 13, 19, 25, 31, 37, 43, and 49) throughout the study before starting the study drug infusion. For all dosed subjects, a change in body weight of ±5% from baseline or the previous body weight used to recalculate the dose will require a new dose recalculation by the clinical site.

6.2.4 Unblinding the Treatment Assignment

Not applicable.

6.2.5 Dose Modification

Not applicable.

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

Velaglucerase alfa (VPRIV) is supplied in individually packaged borosilicate glass vials, which are closed with a butyl rubber stopper with a fluorescein coating and an aluminum overseal with a flip-off plastic cap. Each vial contains 11 mg or 440 U velaglucerase alfa after reconstitution and provides 10 mg or 400 U for infusion use. Velaglucerase alfa will be supplied by Takeda and shipped by a qualified distributor to the clinical site.

6.3.1 Labeling

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

6.3.2 Packaging

The investigational product is packaged according to applicable local and regulatory requirements for investigational studies.

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

6.3.3 Storage

Velaglucerase alfa should be stored in a refrigerator at 2 to 8 °C (36 to 46 °F) and should not be frozen. The vial should be protected from light. Velaglucerase alfa should not be used beyond the expiration date on the vial.

The investigator has overall responsibility for ensuring that the investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or a member of the study team, but this delegation must be documented.

The 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 an established temperature range.

The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained. A daily temperature log of the drug storage area must be maintained every working day; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified minimum/maximum thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established

range, and the temperature excursion must be recorded in IRT immediately. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and investigational product is deemed appropriate for use by the sponsor.

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 investigational product, eg, fumigation of a storage room.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out the study 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 the 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 on the protocol and 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 dispense and administer the investigational product only to the subjects included in the study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment dose assignment. All administered and dispensed medication will be documented in the subject's source documents and/or other investigational product record.

No investigational product stock or returned inventory from a Takeda-sponsored study may be removed from the site where it was 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 will be destroyed centrally by a

Takeda-designated supplier. In this case, destruction records identifying what was destroyed, when, and how must be obtained, with copies provided to the sponsor. Destruction of the investigational product must be in accordance with local, state, and national laws.

Based on entries on the site drug accountability forms, it must be possible to reconcile the 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

In this study, VPRIV will be administered only to eligible subjects under the supervision of the investigator or identified subinvestigator(s) at a clinical site.

6.6 Permitted and Prohibited Treatment

6.6.1 Permitted Treatment

Treatments for the common ailments (eg, common cold and allergy remedies) or medications that are considered necessary for the welfare of the subject are permissible, provided they are not included in the list of prohibited treatments (see Section 6.6.2).

Every effort should be made to keep supportive Gaucher's disease treatment (ie, treatments for bone disease and hematologic symptoms) constant throughout the study; however, changes in these medications are acceptable if necessary, according to clinical judgment. Any change(s) must be recorded on the appropriate electronic Case Report Form (eCRF) page.

Subjects may receive iron supplement therapy. The treatment regimen for iron supplement therapy will be based on the investigator's assessment on a per-subject basis. Subjects who enter the study receiving iron supplement therapy will continue receiving iron supplement therapy throughout their participation in the study.

6.6.2 Prohibited Treatment

The following medications and treatments are prohibited throughout the course of the study:

- Drugs that are indicated to treat anemia or thrombocytopenia (such as red blood cell growth factor or proprietary Chinese medicine)
- Any other investigational drug or device
- Any additional treatment for type 1 Gaucher disease
- Chronic systemic corticosteroids

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

If study treatment is discontinued, regardless of the reason, the assessments and procedures listed for the EOT visit will be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified assessments and procedures at the safety follow-up visit. 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 total amount of investigational product administered must be recorded in the source documents.

7.1.1 Reasons for Discontinuation

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

Reasons for discontinuation include, but are not limited to, the following:

- Adverse event
- Protocol deviation
- Withdrawal by subject (by a parent or both parents/legal guardian for pediatric subjects)
- Lost to follow-up
- Lack of efficacy
- Pregnancy in female subjects
- Study termination
- Other (if "Other" is selected, the investigator must specify the reason on the eCRF)

7.2 Withdrawal From the Study

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.

7.3 Subjects "Lost to Follow-up" Prior to the Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject who is lost to follow-up at any time point prior to the last scheduled contact (site visit or telephone contact).

8. STUDY ASSESSMENTS AND PROCEDURES

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

8.1 Study Periods

The study schedule includes a screening period, baseline visit, treatment period, end-of-treatment visit, and safety follow-up period.

The study completion date is defined as the date on which the last subject in the study completes the final protocol-defined assessments. This includes the safety follow-up visit or contact, whichever is later (see Section 8.1.5).

8.1.1 Screening Period (Day –21 Through Day –4)

Informed consent and assent (when applicable) must be obtained for all subjects participating in the study prior to performing any study-related assessments and procedures. Subjects may withdraw their consent at any time and for any reason. Participation in the study may be terminated at any time without the subject's consent as determined by the investigator. The screening assessments and procedures can be performed over multiple days within a period of up to 18 days following the subject's signature of the ICF.

The investigator or qualified site personnel will confirm that all of the inclusion criteria (Section 5.1) and none of the exclusion criteria (Section 5.2) have been met.

Subjects who fail screening due to a single laboratory test result that does not meet the eligibility criteria may have that laboratory test repeated at the discretion of the investigator. This includes a repeat of only the failed assessment (retesting) rather than a repeat of all screening assessments, which is allowed only once within 2 weeks of the initial screening.

Subjects who fail screening will be permitted rescreening once only; they must sign the new ICF and will be assigned a new subject number.

Subjects who have folic acid deficiency, vitamin B_{12}-deficiency–related anemia, or iron-deficiency–related anemia during screening do not meet study entry criteria and will be considered a screening failure. Subjects may be treated for the underlying disease and be rescreened as judged by investigator. Rescreening will be permitted once only.

8.1.2 Baseline Visit (Day –3 Through Day 0)

All assessments and procedures listed for the baseline visit in Table 1 must be completed prior to the first VPRIV infusion and will be performed at the clinical site. Subject eligibility will be reconfirmed at baseline on the basis of review of the study entrance criteria. Subjects should not

proceed to the treatment period unless they continue to meet all inclusion/exclusion criteria. Subjects who do not meet all eligibility criteria at the baseline visit can be retested once only. The reason(s) for the subject's ineligibility for the study will be documented. Takeda and/or its delegates will review subject eligibility remotely before first infusion. The investigator sites will provide summary information on the subject's eligibility, which is consistent with the required information on the eCRF (see Appendix 1.3). Source documents will be shared only in accordance with local regulations and subject to confidentially measures.

All medical decisions are the responsibility of the investigator and Takeda and/or its delegates cannot in any way influence such medical decisions.

8.1.3 Treatment Period (Week 1 Through 51)

The treatment period will be up to 51 weeks, during which time the subjects will receive an IV infusion of VPRIV EOW at the clinical site. A window of ±3 days is allowed around the infusion interval to facilitate subject scheduling, except at Week 1 where the time window is +3 days (Day 1 through Day 3). For treatment-naive subjects, the first dose of VPRIV will be based on the subject's body weight determined at baseline. For subjects who received Imiglucerase treatment within the 12 months prior to screening, the initial dose will be determined by the investigator after discussing with the sponsor and recording in appropriate document based on the subject's specific treatment and situation at the time of enrollment, according to the subject's benefit and risk assessment.

During the treatment period, safety assessments, including monitoring of AEs, use of prior and concomitant treatments, clinical laboratory values, antibody formation, vital signs, physical examinations, ECGs, and pregnancy tests will be conducted at visits as outlined in Table 1. Efficacy assessments in terms of hemoglobin concentration and platelet count will performed every 6 weeks starting from Week 7. The evaluation for circulating biomarker, liver and spleen volume (MRI or CT scan), QoL assessments, and PK assessments will be conducted at visits as outlined in Table 1.

8.1.4 End-of-Treatment Visit (Week 53) or Early Withdrawal Visit

After completion of the treatment period, the subject will return to the site at Week 53 for the EOT visit assessments and procedures. If VPRIV treatment is discontinued early or the subject is withdrawn from the study, regardless of the reason, the assessments and procedures listed for Week 53 will be performed as completely as possible within 2 weeks (±7 days) after the last infusion (early withdrawal visit).

The subject may visit the clinical site at visits other than those scheduled for assessments and procedures as clinically warranted; these will be recorded as unscheduled visits.

8.1.5 Safety Follow-up Period

The safety follow-up period for the study is 30 (±7) days after the last infusion at Week 51 (or the last infusion for early discontinued subjects). During this period, there will be a telephone call or scheduled visit to the site to query for AEs, SAEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure or return to baseline level or explained by the investigator if the AE and/or SAE will not be resolved as documented in the subject's source documents (see Appendix 3.2).

8.1.6 Additional Care of Subjects After the Study

No aftercare is planned for this study.

8.1.7 COVID-19–related Protocol Considerations

On a temporary basis, in order to maintain subject safety, confidentiality, and study integrity in the context of health care delivery challenges presented by 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 medical monitor while maintaining subject safety and confidentiality as the priority.

Missing data, remote visits, changes to assessment approaches, and altered visit windows during 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. It is crucial that any deviations related to COVID-19 be clearly identified as such in the eCRF.

The following procedural changes may be considered:

- If necessary, informed consent from a potential or current trial 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 trial 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.
- The subject may be transferred to an investigational site away from the risk zones to complete the required visits.

- If the screening period exceeds 18 days due to COVID-19–related factors, the subject may be rescreened.

8.2 Study Assessments

Detailed descriptions of the study assessments and procedures required are described in this section. The timing for the performance of these assessments and procedures is presented 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 the investigational product.

8.2.1.1 Medical History

At screening, the subject's complete medical history, including surgical procedures within the 30 days prior to signing the ICF, will be collected and recorded in the subject's source documents and on the appropriate eCRF page. This will include a review of body systems and documentation of current and prior medical procedures.

8.2.1.2 Prior and Concomitant Treatments

All nonstudy treatment including, but not limited to, herbal treatments, vitamins, behavioral treatment, or nonpharmacological treatment, such as psychotherapy, received within the 30 days prior to signing ICF through the end of the safety follow-up period must be recorded in the subject's source documents and on the appropriate eCRF page. For the subjects who have not been treated for Gaucher disease within the 12 months prior to screening, verification for treatment will be conducted; for the subjects who have received Imiglucerase ERT within the 12 months prior to screening, the dose and frequency must be recorded.

Concomitant treatment refers to all treatment received between the date of signing the ICF and the end of the safety follow-up period, inclusive. Concomitant treatment information must be recorded in the subject's source documents and on the appropriate eCRF page.

8.2.1.3 Immunology

Immunology 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.

Immunology tests include HBsAg, HCV, and HIV. Tests for HBsAg with detectable hepatitis B viral DNA load, HCV antibody with confirmation by HCV RNA polymerase chain reaction

testing, and HIV antibody will be performed at the local laboratory or Takeda-designated laboratory.

Subjects with a positive result are to be excluded from the study.

8.2.1.4 Electroencephalogram

The EEG will be performed at screening at the local laboratory to exclude subjects who are at the early stage of type 3 Gaucher disease. Subjects with abnormal EEG examinations will be excluded from the study.

8.2.2 Efficacy Assessments

8.2.2.1 Hemoglobin Concentration and Platelet Count

Efficacy assessments in terms of hemoglobin concentration and platelet count will be required at baseline and every 6 weeks starting from Week 7 during the study treatment period through Week 53. These assessments are included as components of the hematology laboratory panel.

Hemoglobin concentration and platelet count will be evaluated at a Takeda-designated laboratory.

8.2.2.2 Liver and Spleen Magnetic Resonance Imaging or Computed Tomography Scan

Subjects will have an MRI or CT scan of the liver and spleen at screening, Week 25, and Week 53. All imaging modalities should remain consistent for all subject at all timepoints throughout the study. The MRI or CT scan will be performed at local laboratory. Investigator is responsible to perform the eligibility check for presence of at least of hepatomegaly and/or moderate splenomegaly. To evaluate VPRIV efficacy, the volumes of liver and spleen will be analyzed and calculated centrally by sending the MRI/CT images to a Takeda-designated imaging vendor. Image collection and preparation procedures are provided in the imaging manual.

8.2.3 Safety Assessments

8.2.3.1 Physical Examination

A complete physical examination will be performed. A complete physical examination will include, at a minimum, assessments of the following organs and systems: eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, dermatologic, musculoskeletal, extremities, lymph nodes, nervous system (eg, eye movement disorder), and other.

Any abnormal change in the physical findings will be recorded as an AE in the subject's source documents and on the appropriate eCRF page.

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 the ICF is signed.

See Appendix 3 for definitions; assessments; collection time frames; and reporting procedures of AEs, TEAEs, serious TEAEs, and other events.

8.2.3.3 Vital Signs

Vital signs include pulse rate, blood pressure, respiratory rate, temperature, body weight, and height. Measurement of pulse rate, blood pressure, respiratory rate, and temperature will be taken prior to blood draw or initiation of infusion following 5 minutes of rest. Vital signs should be recorded as outlined in Table 4 and will be recorded in the subject's source documents and on the appropriate eCRF page.

If there are no IRRs observed during the first 3 infusions, vital signs assessment for the subsequent infusions can be omitted at the discretion of the investigator.

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

Table 4. Schedule for Recording of Vital Signs on Infusion Days

Timing Relative to the Infusion	Schedule of Activities
Start of the Infusion	Within 10 minutes prior to the start of the infusion
During the Infusion	30 (±5) minutes after the start of the infusion
After the Infusion[a]	Within 10 minutes after completing the infusion, 30 (±5) minutes after completing the infusion, and 60 (±5) minutes after completing the infusion

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

8.2.3.3.1 Body Weight and Height

Body weight and height will be measured as part of vital signs assessments at the time points presented in the schedule of activities (Table 1).

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 that 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 or is not clinically significant. Abnormal clinical laboratory values that 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.

Hemoglobin concentration and platelet count tests for efficacy assessment will be performed at a Takeda-designated laboratory. Serum chemistry tests, hematology tests for safety assessment, and urinalysis tests will be performed at the local laboratory. See Section 8.1.1 for rescreening of subjects who have folic acid deficiency, vitamin B_{12}-deficiency–related anemia, or iron-deficiency–related anemia at screening.

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

8.2.3.5 Pregnancy Test

Female subjects of childbearing potential must have a negative pregnancy test at all visits indicated in Table 1 to be eligible for the study.

Pregnancy testing will be performed using a urine sample and, if needed, a serum β-hCG sample. If the urine pregnancy test is negative, the study assessments and procedures will be completed; serum β-hCG testing will not be required. If the urine test is positive, a blood sample will be collected for serum β-hCG testing and sent to either the local laboratory or Takeda-designated laboratory for analysis. No additional study assessments or procedures should be completed until the result of the serum pregnancy test is available. A positive serum β-hCG test would result in the subject being a screen failure or discontinued from the study.

The pregnancy test at the baseline visit can be waived if it had been performed within 7 days of the previous test during the screening visit.

8.2.3.6 12-lead Electrocardiogram

12-lead ECGs will be performed prior to blood draw and/or initiation of infusion following 5 minutes of rest and in accordance with the clinical site's standard practice(s) at visits 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. Electrocardiogram parameters (PR, QRS, QT, and corrected QT intervals and heart rate) will be collected following 5 minutes of rest. Identification of any clinically significant findings and/or conduction abnormalities will be recorded as an AE in the subject's source documents and on the appropriate eCRF page.

8.2.3.7 Serum Anti-velaglucerase Alfa Antibody

All subjects will have a blood sample collected at the visits specified in the schedule of activities (Table 1) for determination of serum anti-VPRIV antibodies. During the treatment period, these

blood samples will be collected prior to the VPRIV infusion and evaluated at a Takeda-designated laboratory. Sample collection, preparation, and shipping procedures are provided in the laboratory manual.

8.2.3.8 X-ray of Bilateral Femoral Neck and Distal Femur (Procedural Imaging)

X-ray images of the bilateral femoral neck and distal femur will be taken at baseline to test the bone density and determine the severity of the bone disease. X-ray test can be waived if it has been performed within the 30 days prior to the baseline visit. If any bone pain or damage occurs during the study, X-rays will be used to judge the relevance of AEs.

8.2.4 Other Assessments

8.2.4.1 Pharmacokinetics

Blood samples for PK analysis will be collected on Day 1 (Week 1) and at Week 37; the PK sampling time points are specified in Table 2. Pharmacokinetic samples will be collected only for the naive subjects who have not received any Gaucher disease treatment within the 12 months prior to enrollment. A total of 11 blood samples will be collected from adult subjects (≥18 years old). A total of 9 blood samples will be collected from adolescent subjects (12 through 17 years old). A total of 6 blood samples will be collected from children (4 through 11 years old). Pharmacokinetic blood samples must not be drawn from the arm being used for the infusion. Sample collection, processing, and shipping information is provided in the laboratory manual. Serum samples will be analyzed for VPRIV using a validated analytical method (eg, enzyme-linked immunosorbent assay) at a Takeda-designated laboratory.

The PK parameters on Day 1 (week 1) will include:

- C_{max} (ng/mL)
- T_{max} (min)
- AUC_{inf} (ng•min/mL)
- $T_{1/2}$ (min)
- CL (mL/min/kg)
- V_{ss} (mL/kg)

8.2.4.2 Circulating Biomarkers

Plasma lyso-Gb1 and serum CCL18 will be assessed at baseline, Weeks 13, 25, and 37 and EOT visits specified in the schedule of activities (Table 1). The sample will be collected before the VPRIV infusion and evaluated at a Takeda-designated laboratory.

8.2.4.3 Quality of Life

At baseline, Week 25, and Week 53 visits, subject's QoL will be assessed using validated, Chinese versions of SF-36, version 2 (for subjects ≥18 years of age) and CHQ-PF50 (for subjects ≥5 and <18 years of age); QoL assessment is not applicable for subjects <5 years of age. The SF-36, version 2 will be completed by the subject, while the CHQ-PF50 will be completed by the subject's parent or caregiver.

During treatment period, the SF-36, version 2 and CHQ-PF50 questionnaires should be completed prior to any testing or discussion with the investigator. The subject and/or subject's parent or caregiver should be given sufficient space and time to complete the questionnaires. The questionnaires are intended to be self-reported and should not be interviewer-administered.

The SF-36, version 2 is a self-administered, validated questionnaire designed to measure generic health-related QoL. This 36-item questionnaire measures 8 domains, including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Two summary scores, including the Physical Component Score and Mental Component Score, will be calculated. Additionally, the scores can be calculated based on each of the 8 domains. Higher scores indicate better health status. The subject should complete the questionnaire on their own without any assistance from the study staff or a caregiver.

The CHQ-PF50 will assess the parent(s) or caregiver's impression of the following scales: global health, physical functioning, role/social limitations (emotional/behavioral and physical), bodily pain/discomfort, behavior, global behavior, mental health, self-esteem, general health perceptions, change in health, parental impact (emotional and time), family activities, and family cohesion. An increase in the CHQ-PF50 score indicates a more favorable assessment by the proxy of the child's health and/or well-being. The subject's parent or caregiver should complete the questionnaire on their own without any assistance from the study staff.

Sample questionnaires for QoL assessments included in the study are provided in Appendix 5.

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 collected 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, the assessments may be combined if they require the same type of tube.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

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

A statistical analysis plan (SAP) will provide the statistical methods and definitions for 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 treatments. 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 statistical software, version 9.4 or higher (SAS Institute).

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

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

9.3 Sample Size and Power Considerations

A sample size of 20 safety evaluable subjects is planned to be enrolled in the 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 Sets

The statistical analysis will include the following analysis sets:

- The **intent-to-treat (ITT) set** will include all subjects who sign the ICF (and assent form, if applicable) and are eligible for the study based on the defined inclusion/exclusion criteria. The ITT 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 VPRIV. The safety set will be used for analysis of the safety endpoints.

- The **per-protocol (PP) set** will include all subjects in the ITT set excluding subjects with major protocol deviations. The PP set will be identified by a team consisting of, at a minimum, a physician and statistician from Takeda. The PP set will be used for an efficacy sensitivity analysis.

- The **PK set** will include all subjects in the ITT set who receive at least 1 dose of VPRIV and provide evaluable PK concentration data.

9.5 Analysis of Disposition

The number of subjects enrolled, completing, or withdrawing from the study, along with the reasons for withdrawal, will be tabulated for the ITT set.

9.6 Medical History

Medical history will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for the ITT set.

9.7 Demographics and Baseline Characteristics Analyses

Baseline and demographic variables will be descriptively summarized for the ITT set.

9.8 Treatment Compliance and Extent of Exposure

Treatment compliance and the extent of exposure will be described by calculating the percentage of planned doses and total number of actual doses received by the subject and summarized for the ITT set.

9.9 Efficacy Analyses

The efficacy endpoints are described in Table 3.

Continuous variables will be summarized with descriptive statistics including the mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum. Categorical data will be summarized with the frequency and percentage of subjects falling within each category.

The observed values, change from baseline, change over time, and percentage change from baseline for the efficacy measurements (hematologic manifestations and liver and spleen volume) will be summarized by sex and visit. Subject listings will be provided for the clinical outcomes from the QoL questionnaires.

Efficacy analyses will be based on the ITT set, with the PP set as a sensitivity analysis. Data from subjects who previously received Imiglucerase ERT and treatment-naive populations will be analyzed separately, as well as pooled.

9.10 Safety Analyses

The safety endpoints are described in Table 3.

Adverse events will be coded using the most recent version of MedDRA. Treatment-emergent AEs will be summarized overall and by SOC and PT. Analysis of AEs will be performed at both the subject and AE levels. Similar displays will be provided for IRRs. The AEs will be summarized by severity, seriousness, and relation to the 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 the worst severity or outcome for each event type will be presented for the analysis. When calculating the event rates, the denominator will be the total population size, irrespective of dropouts over the course of follow-up.

Tabular summaries of other safety parameters (eg, vital signs, blood tests, concomitant treatments [coded using WHODrug Global], anti-VPRIV antibody status, and infusion information) will be produced at baseline and, if applicable, for each postbaseline evaluation visit.

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

The observed values and change from baseline for ECG parameters (PR, QRS, QT, and corrected QT intervals and heart rate) will be summarized by visit. The number of subjects with normal and abnormal ECG results during the study 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 will be provided for each visit. The change from baseline will be calculated by subtracting the baseline value from the postbaseline value.

Vital sign data will be listed by subject, and any newly occurring changes outside the reference range from baseline will be flagged. The 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 1 use of concomitant treatment during the study will be reported. Subject listings will be provided describing the reason(s) for study discontinuation.

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

Safety data will be analyzed using the safety set. Safety data will be analyzed separately for subjects who previously received Imiglucerase ERT and treatment-naive populations, as well as pooled.

9.11 Other Analyses

The PK, QoL, and biomarker endpoints are described in Table 3.

9.11.1 Pharmacokinetic Analyses

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

For the PK set, individual concentrations will be listed and summarized by visit and scheduled time points for naive subjects with PK assessments and by age (eg, ≥18 years vs 12 through 17 years vs 4 through 11 years). Individual PK parameters of VPRIV at Week 1 will be listed and summarized by treatment for all PK subjects, as well as by age, with descriptive statistics (number, arithmetic mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, and CV [95% CI] of the 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 VPRIV will be generated based on nominal time points.

9.11.2 Health-related Quality-of-Life Analyses

The change over time in subject rating of QoL will be analyzed using the SF-36, version 2 for subjects ≥18 years of age and CHQ-PF50 for subjects ≥5 and <18 years of age.

Initially, simple summary statistics will be produced for the overall score and (if available) any subscale score of each patient-reported outcome measure. Continuous variables will be summarized using the following descriptive statistics: mean, SD, median, Q1, Q3, minimum, and maximum. The number and percentage of observed levels will be reported for all categorical measures.

9.11.3 Biomarker Analyses

Circulating biomarker data will be summarized using descriptive statistics.

10. REFERENCES

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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, contract research organization [CRO]) used in this study will be maintained in the investigator and sponsor 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 and 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, and eCRFs in accordance with current GCP guidelines and the respective local and (inter)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 the release of the 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 prior to 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 the CRO 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 the study completion date for pediatric studies and 1 year for nonpediatric 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 the applicable sites, regulatory agencies, and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study that 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 Guideline 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 subinvestigators 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 coordinating principal investigator (multicenter study), in compliance with ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The investigator and any subinvestigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met the 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, or coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

Documentation and Retention of Records

Electronic Case Report Forms

Electronic Case Report Forms are supplied by theCRO 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 on the eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic Case Report Forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the eCRF.

The clinical research associate/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries will be sent for corrections or verification of data. Alternative approaches may be used to ensure data quality, data integrity, and subject safety (eg, remote source data review via phone or video) as permitted by regional and local regulations. Additional details are in the monitoring plan.

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, the 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 have direct access to original source records relevant to this study, regardless of media.

The clinical research associate/study monitor (and auditors and IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form 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, and X-rays).

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), and United Kingdom 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 the investigational product; or any significant equity interest in the sponsor or subsidiaries as defined in 21 Code of Federal Regulations 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 the source data and data entered on 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 sponsor's 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, where applicable, from all study subjects prior to any study-related assessments and procedures,

including screening. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's parent/legally authorized representative, as applicable, is requested to sign and date the ICF 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 subject's rights and responsibilities. A copy of the ICF and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or subject's legally authorized representative and/or parent(s) or caregiver, as applicable. This document may require translation into the local language. Signed ICFs must remain in each subject's study file and be available for verification at any time.

The principal investigator will provide the sponsor with a copy of the ICF and assent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to the study start that another party (ie, the sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

Institutional Review Board or Ethics Committee

It is the responsibility of the investigator to submit this protocol, the ICF (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 documents 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 IRB/EC must approve any revisions of all informed consent/assent 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 will review 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 VPRIV; national or local regulatory authorities; and the IRB/EC that 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 that may not afford the same level of protection that applies within the country where this study is conducted. The purpose of any such transfer would include to support regulatory submissions, conduct new data analyses to publish or present the study results, or 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 1 year after termination or completion of the study at all participating sites, whichever occurs first. After that time, the site may publish the site's study results in scientific journals or present the study results at a 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 60 days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication must 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 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.

The sponsor is committed to transparent dissemination of all scientific, technical, and medical manuscripts generated from Takeda-supported research. Therefore, after 01 Jan 2018, the sponsor 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 point of entry, online availability of published research output with, where available, rights of reuse 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 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:

Serum chemistry:

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- (Blood) Urea nitrogen or (blood) urea
- Calcium
- Creatinine
- Creatine kinase
- Ferritin
- γ-glutamyl transferase glucose
- Lactate dehydrogenase
- Potassium
- Serum iron
- Sodium
- Total bilirubin
- Total protein

Hematology:

- Hematocrit
- Hemoglobin
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- Platelet count
- Red blood cell count
- White blood cell count with differential
- Neutrophils
- Basophils
- Lymphocytes
- Monocytes
- Eosinophils

Urinalysis:

- Bilirubin
- Color
- Glucose
- Ketones
- Nitrite
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen

Others:

- HIV and hepatitis (B surface antigen and C antibody)
- Pregnancy test
- Serum anti-velaglucerase alfa antibody
- Plasma chemokine (C-C motif) ligand 18
- Glucosylsphingosine
- Pharmacokinetic test (velaglucerase assay)

Appendix 3 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Appendix 3.1 Adverse Event Definitions

An 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 the investigational 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 the investigational product, whether or not causality is suspected (ICH Guidance E2A 1995).

Treatment-emergent Adverse Event

A TEAE is defined as any event emerging or manifesting at or after the initiation of the investigational product or any existing event that worsens in either intensity or frequency following exposure to the investigational product.

Serious Adverse Event

An SAE is any untoward clinical manifestation of signs, symptoms, or outcomes (whether considered related to the 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 that hypothetically might have caused death if it was more severe.
- Requires in-patient hospitalization or prolongation of hospitalization. Note: Hospitalizations that are the result of elective or previously scheduled investigations procedures or surgery for preexisting 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 hospitalization for an elective or previously scheduled surgery that meets serious criteria must be reported as an SAE.
- 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 require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

  - Bronchospasm associated with anaphylaxis requiring intensive treatment at an emergency department or home; blood dyscrasias or convulsions that do not result in in-patient hospitalization; or the development of drug dependency or abuse.
  - Reviewed and confirmed seroconversion for HIV, hepatitis A virus, hepatitis B virus, HCV, hepatitis E virus, or parvovirus B19

Infusion-related Adverse Event

An infusion-related AE will be defined as an AE that 1) begins either during or within 12 hours after the start of the infusion and 2) is judged as possibly or probably related to the study treatment.

If a subject has an infusion-related AE during the infusion of the study medication, the investigator should decide, based on his/her clinical judgment, whether the infusion should be slowed or temporarily or permanently discontinued. Infusion-related AEs that occur after the infusion should be assessed and treated in a similar manner.

Subjects experiencing recurrent infusion-related AEs may be premedicated. If infusions continue without incident, then tapering of medications may be considered. The investigator and medical monitor will evaluate reduction or discontinuation of premedications after the first 3 months of treatment.

For severe infusion-related AEs, the investigator should consult with the medical monitor prior to the subject's next dose to determine the appropriate course of action for future infusions.

Unexpected Adverse Event

An unexpected adverse event is an AE that's 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 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

A suspected unexpected serious adverse reaction (SUSAR) is defined as any suspected adverse reaction to the study treatment that is both serious and unexpected.

The event must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to the study treatment

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.

Preexisting conditions prior to screening 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 be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting condition, the event must be described on the AE eCRF.

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of the investigational product, a shift of a parameter is observed from a value in the normal 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; duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product; and range of variation of the respective parameter within its reference range should also be considered.

If, at the end of the treatment period, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values that were not present at baseline, 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 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.

Appendix 3.2 Collection of Adverse Events

All AEs/SAEs will be collected from the time the informed consent document is signed until the safety follow-up period (Section 8.1.5). This includes events occurring during screening, regardless of whether or not the investigational product has been administered.

All AEs/SAEs must be followed to closure (when 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 is 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 the initiation of the 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 the first dose, a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source.

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, significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship Categorization

A physician/investigator must make the assessment of the relationship to the investigational product for each AE. The investigator should decide whether, in his/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 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 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 an accident.
Not related	The event can be readily explained by other factors, such as the subject's underlying medical condition, concomitant therapy, or an accident, and no plausible temporal or biologic relationship exists between the investigational product and 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 eCRF in English or report via the paper SAE report form (as a backup) 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.

Appendix 3.5 Serious Adverse Event Collection Time Frame

All SAEs (regardless of the relationship to the investigational product) are collected from the time the subject signs the ICF until the safety follow-up period (Section 8.1.5) and must be reported to the Takeda Global Patient Safety Evaluation (GPSE) and CRO/Takeda medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE 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 GPSE Department within 24 hours of the first awareness 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, date the symptoms resolve, or 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 ICF, 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 the 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 of signing the ICF until the safety follow-up period (Section 8.1.5).

Any report of pregnancy in any female subject or the female partner of a male subject must be reported within 24 hours of the first awareness of the pregnancy to the Takeda GPSE using the paper Pregnancy Report Form. The fax number and email 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 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 postpartum.

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

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the same procedure as describing the SAE reporting, 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 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 the investigational product when used for a nonmedical 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 the 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 the investigational product higher than the protocol-prescribed dose
- Medication error: An error made in prescribing, dispensing, administration, and/or use of the 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 should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/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 to the 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 subjects from an immediate hazard to their health and safety

The investigator may implement urgent safety measures to protect subjects from immediate hazard to their health or safety. The measures should be implemented immediately and do not require prior authorization from the sponsor. In the event 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 IRB/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 SUSARs and any other applicable (serious) ADRs to regulatory authorities, investigators, and ECs/institutions, as applicable, in accordance with safety 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 product or would be sufficient to consider changes to the investigational product administration or 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 VPRIV program.

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

Appendix 4 CONTRACEPTIVE GUIDANCE

Female subjects:

Female subjects of childbearing potential are eligible to participate in the study if they are not pregnant or lactating and agree to use a highly effective method of contraception consistently and correctly as described in the following table:

Highly Effective Contraceptive Methods That Are User Dependent[a] With a failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • 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 • Intrauterine hormone-releasing system
Bilateral tubal occlusion
Vasectomized partner[c]
Sexual abstinence[d]

[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 study treatment, 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 the study treatment.

[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 study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and preferred and usual lifestyle of the subject.

Male subjects:

Male subjects with female partners of childbearing potential are eligible to participate if they agree to use one of the following:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a female of childbearing potential who is not currently pregnant

Male subjects with a pregnant or lactating partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration during the protocol-defined time frame (from screening through 30 days after the last dose of the investigational product).

Male subjects must refrain from donating sperm for the duration of the study and for 30 days after the last dose of study treatment.

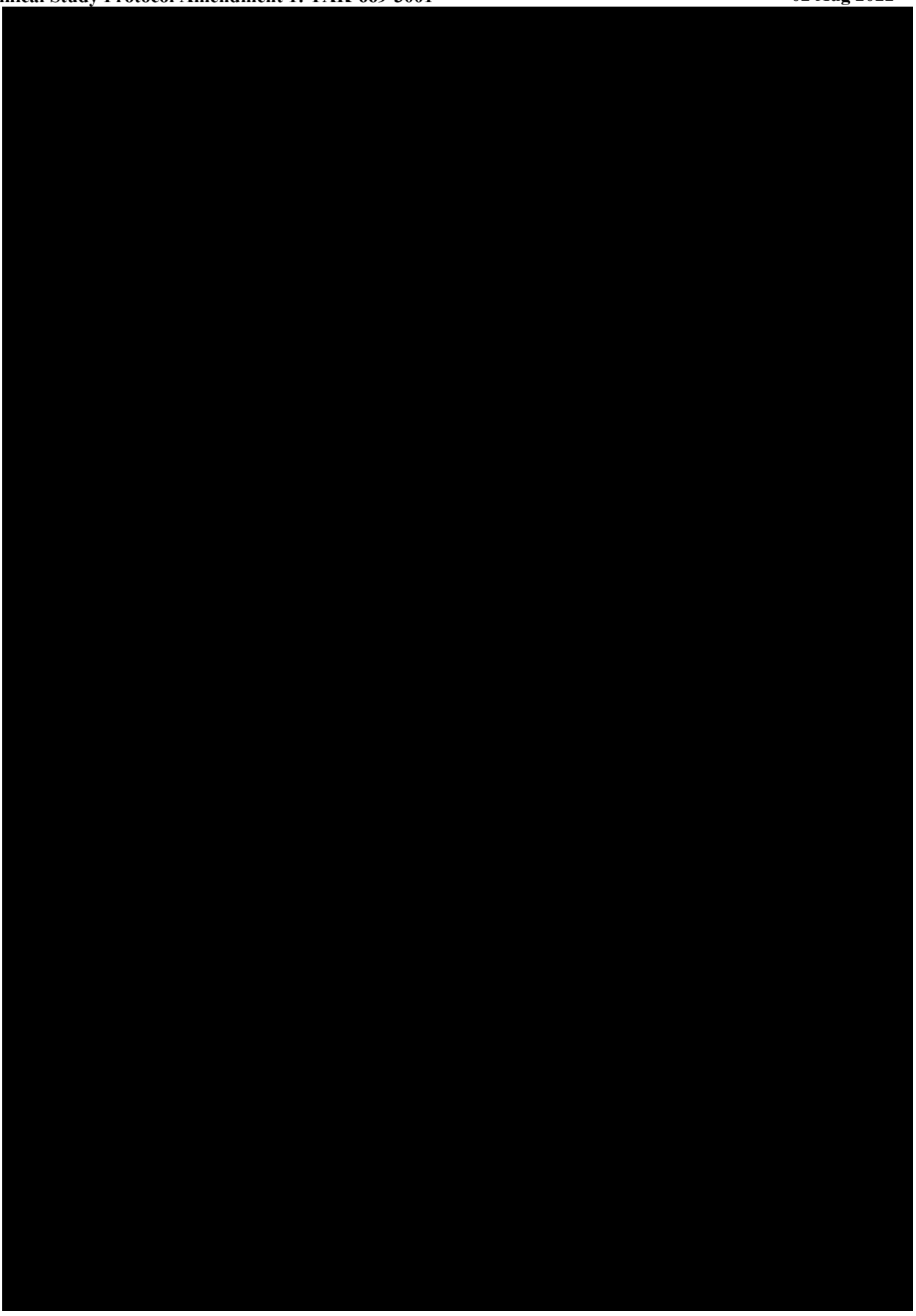
Appendix 5 SCALES AND ASSESSMENTS

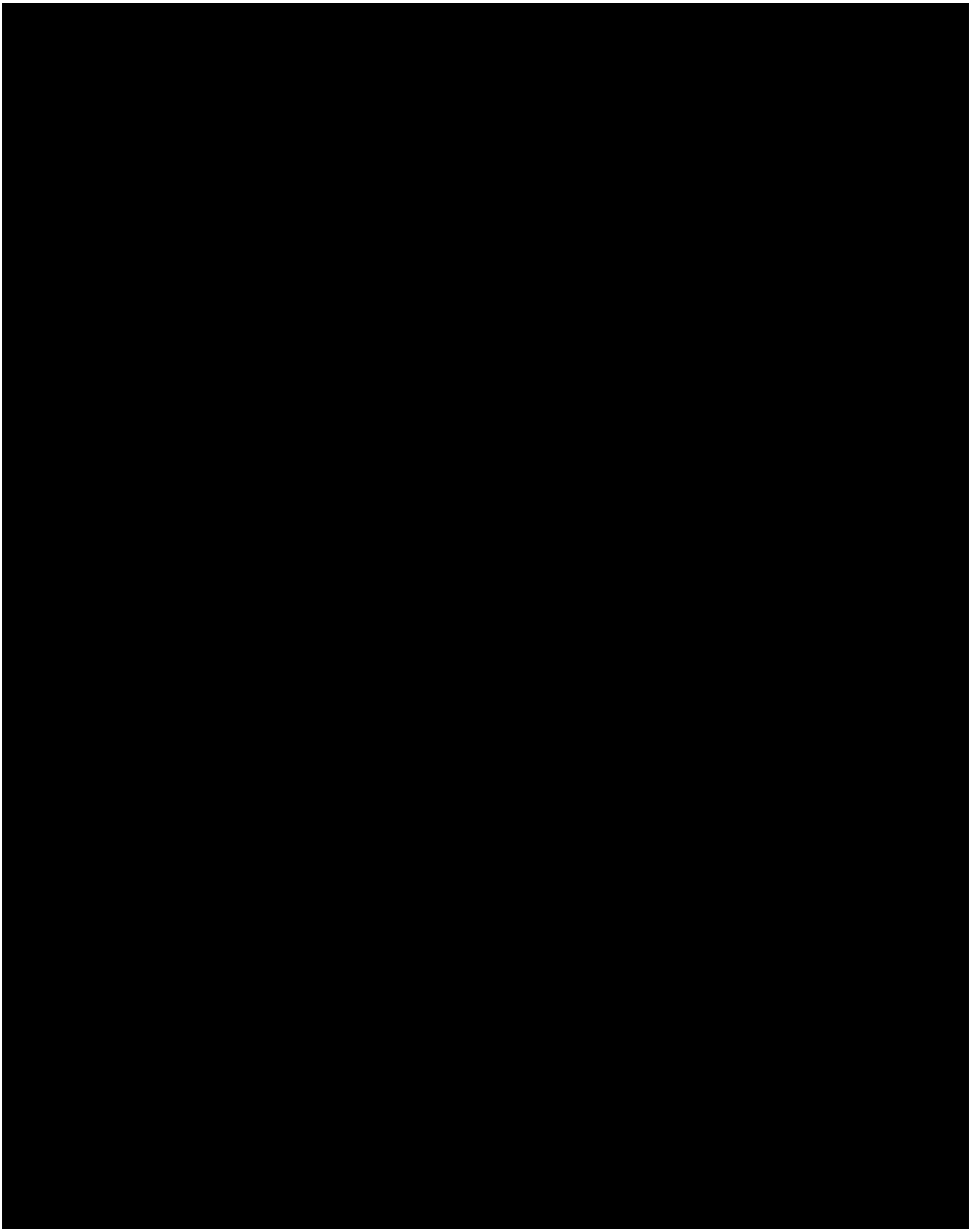
The following scales/assessments in the Chinese language (ie, validated, Chinese version of QoL instruments) will be utilized in this study:

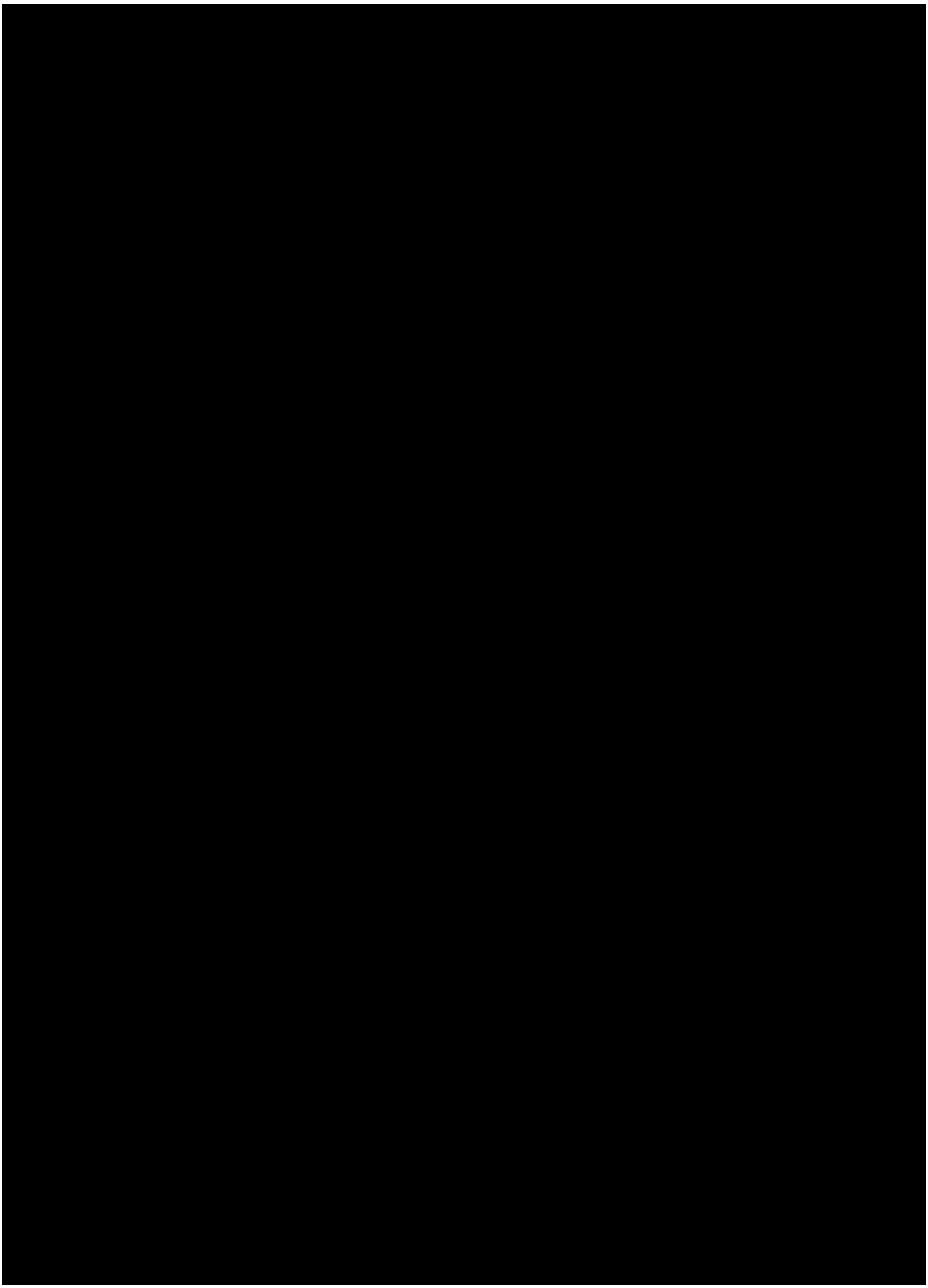
Full Title of Scale/Assessment	Age
Short Form 36 Version 2	≥18 years
Child Health Questionnaire-Parent Form 50	≥5 to <18 years

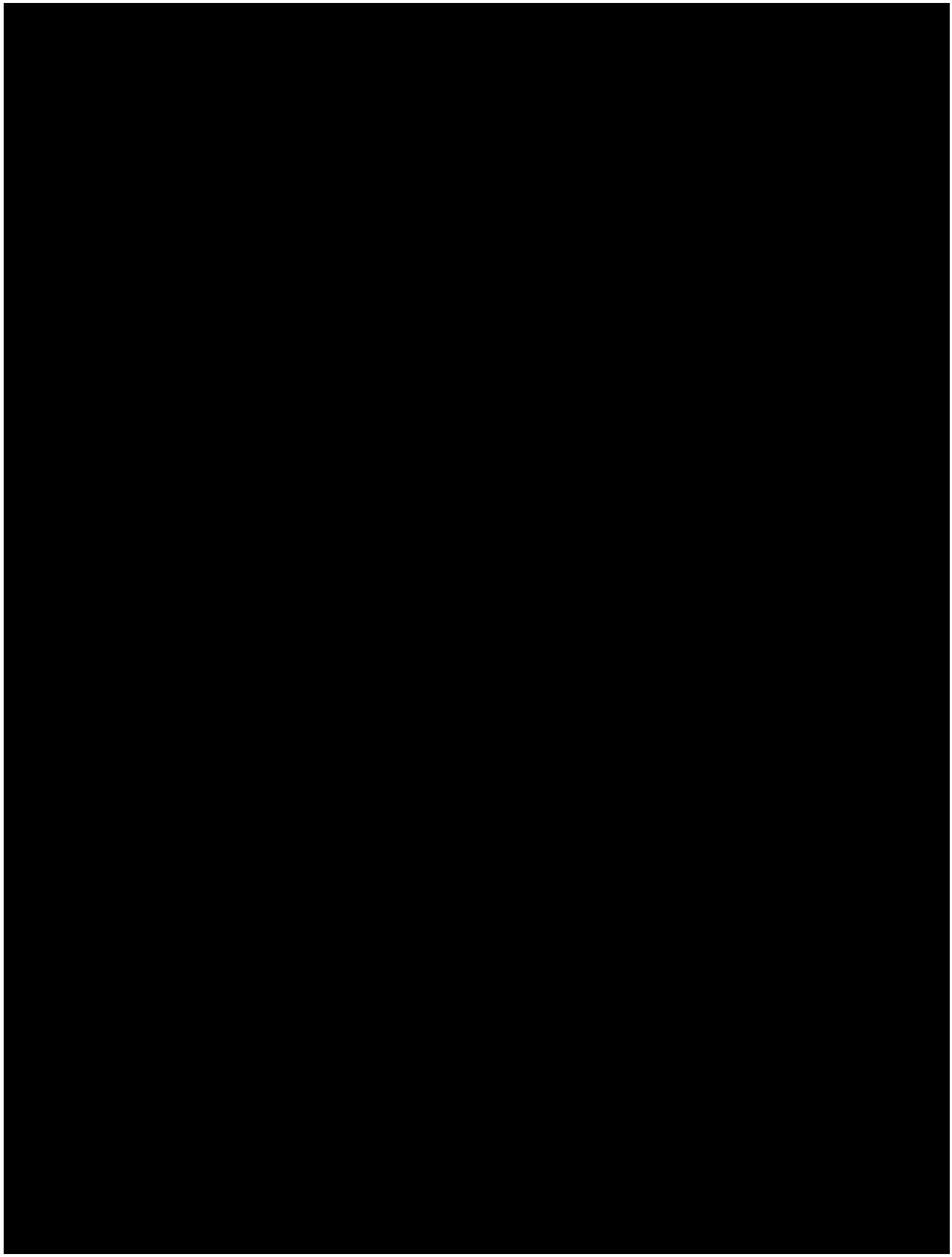
A separate master file containing each scale/assessment will be provided to the site. Updates to the scales/assessments during the study (if applicable) will be documented in the table above, and a new master file containing the revised scale/assessment will be provided to the site.

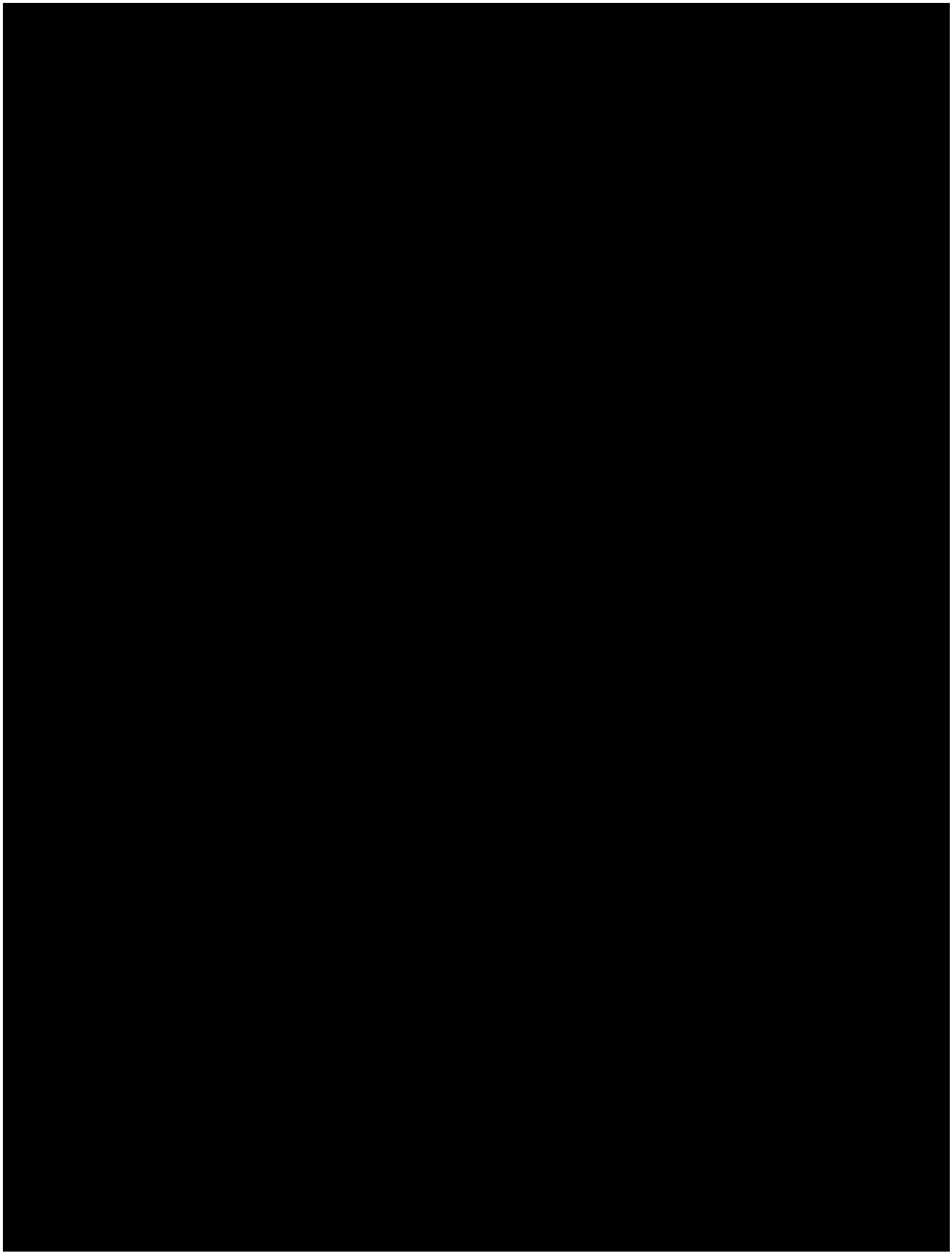
Short Form 36 Version 2

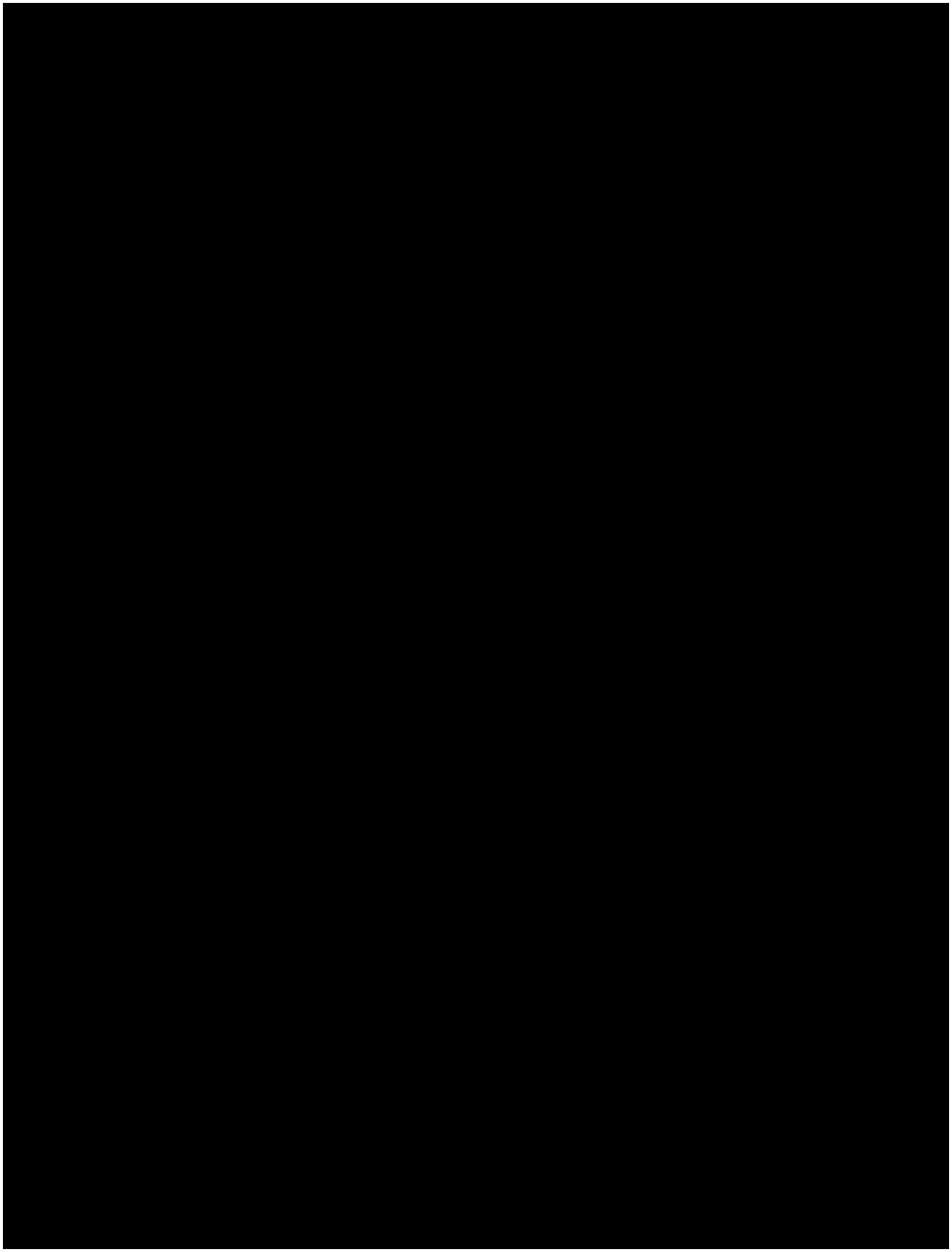












Child Health Questionnaire-Parent Form 50

Appendix 6 ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AUC_{inf}	area under the curve from time 0 to infinity
β-hCG	β-human chorionic gonadotropin
CCL18	chemokine (C-C motif) ligand 18
CHQ-PF50	Childhood Health Questionnaire-Parent Form 50
CL	clearance
C_{max}	maximum serum concentration
CRO	contract research organization
CT	computed tomography
CV	coefficient of variation
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EEG	electroencephalogram
EMA	European Medicines Agency
EOT	end of treatment
EOW	every other week
ERT	enzyme replacement therapy
EU	European Union
FDA	Food and Drug Administration
GCB	glucocerebrosidase
GCP	Good Clinical Practice
GPSE	Global Patient Safety Evaluation
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
IB	investigator's brochure
ICF	informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Ig	immunoglobulin
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
lyso-Gb1	glucosylsphingosine
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PK	pharmacokinetic(s)
PP	per-protocol
PT	preferred term
QoL	quality of life
Q1	first quartile
Q3	third quartile
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
US	United States
VPRIV	velaglucerase alfa
V_{ss}	apparent steady-state volume of distribution

Appendix 7 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	22 Nov 2021	China
Protocol Amendment 1	02 Aug 2022	China