CLINICAL STUDY PROTOCOL

NCT Number: NCT02574286

Study Title: An Open-label, Multicenter, Single-arm, Phase 4 Study of the Effect of Treatment with Velaglucerase alfa on Bone-related Pathology in Treatment-naïve Patients with Type 1 Gaucher Disease

Study Number: SHP-GCB-402

Protocol Version and Date:

Original Protocol: 30 Apr 2015

Amendment 1: 14 Sep 2015

Amendment 2: 02 Jun 2016

Amendment 3: 06 Jul 2016

Amendment 4: 04 May 2017

Amendment 5: 26 Jul 2018

Amendment 6: 02 Nov 2020

CLINICAL TRIAL PROTOCOL: SHP-GCB-402

Study Title:	An Open-label, Multicenter, Single-arm, Phase 4 Study of the Effect of Treatment with Velaglucerase alfa on Bone-related Pathology in Treatment-naïve Patients with Type 1 Gaucher Disease
Study Number:	SHP-GCB-402
Study Phase:	4
EudraCT Number:	2015-001578-17
Product Name:	velaglucerase alfa (VPRIV®)
Indication:	Long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease
Investigators:	Multicenter
Sponsor:	Shire Human Genetic Therapies, Inc., a wholly owned subsidiary of Takeda Pharmaceuticals Company Limited
Sponsor Contact:	300 Shire Way Lexington, MA 02421 USA [redacted]
Medical Monitor:	[redacted], DDS, PhD

	Date
Amendment 6:	02 November 2020
Amendment 5:	26 July 2018
Amendment 4:	04 May 2017
Amendment 3:	06 July 2016
Amendment 2:	02 June 2016
Amendment 1:	14 September 2015
Original Protocol:	30 April 2015

PROTOCOL SIGNATURE PAGE

Study Title:	An Open-label, Multicenter, Single-arm, Phase 4 Study of the Effect of Treatment with Velaglucerase alfa on Bone-related Pathology in Treatment-naïve Patients with Type 1 Gaucher Disease
Study Number:	SHP-GCB-402
Final Date:	02 November 2020

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire Medical Monitor

[redacted] 02-Nov-2020 | 08:36:53 EST

_____
Signatu **Date**

[redacted], DDS, PhD
_____
Printed Name

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **6**	**Amendment Date** **02 October 2020**	**Global**
Protocol Amendment Summary and Rationale: A summary of updates made to Clinical Protocol SHP-GCB-402 Amendment 6 are itemized below.		
Section(s) Affected by Change	**Description of Change**	**Rationale**
Title Page, Synopsis	Added that Shire is now a wholly owned subsidiary of Takeda Pharmaceuticals Company Limited	To provide updated and correct information
Title Page, Protocol Signature Page, Emergency Contact Information	[redacted] added as medical monitor	To provide updated and correct information
Synopsis, Section 2.2, Section 3.2.1, Section 10.7.2	Two new objectives and endpoints were added. Objectives: • BMD as measured by the change from baseline in g/cm^2 after 12 months of treatment. • BMD as measured by the change from baseline in g/cm^2 after 24 months of treatment. Endpoints: • Change from baseline to 12 months (Week 51) in BMD reported as g/cm^2. Assessments will be performed at the screening visit and Weeks 51. • Change from baseline to 24 months (Week 103 [end of study]) in BMD reported as g/cm^2. Assessments will be performed at the screening visit and Week 103 (end of study).	The study is already set up to obtain g/cm^2, as Z-scores are derived from the original output of g/cm^2. The objectives are being added to assess the original BMD output from the DXA scans.
Synopsis, throughout protocol and appendices	The Brief Pain Inventory – Short Form was updated to "Questions taken from the BPI-SF©"	Updated to accurately reflect the questions used in Study SHP-GCB-402. Questions 2, 7, and 8 of this assessment were not used.
Synopsis, Section 5.3	Exclusion criterion #6, "The patient has had a splenectomy" was updated to clarify that it is not meant to exclude subjects who have accessory spleens.	Updated for clarity

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **6**	**Amendment Date** **02 October 2020**	**Global**
Protocol Amendment Summary and Rationale: A summary of updates made to Clinical Protocol SHP-GCB-402 Amendment 6 are itemized below.		
Section(s) Affected by Change	**Description of Change**	**Rationale**
Synopsis, Section 3.3, Section 7.11.8.1, Section 10.8	[redacted]	[redacted]
Emergency Contact Information	Global Drug Safety was updated to Global Patient Safety Evaluation	To provide updated and correct information.
Section 6.3	The following text was added: "When a weight change of ±5% is identified, the dose should be adjusted as soon as possible, but no later than the next bi-weekly study visit. If the dose can be adjusted prior to the infusion on the same day, this adjustment should be performed; however, if the dose cannot be adjusted on the same day, the dose must be adjusted prior to the next bi-weekly infusion. It is acceptable for the dose adjustment to occur at either of the following times in the study: 1) The dose adjustment to occur on the same day a weight change of ±5% from the screening weight or weight at last dose adjustment is identified at the clinic site (Wk13, 25, 37, 51, 65, 77, 89); or 2) The dose adjustment to occur at the next bi-weekly study visit after a weight change of ±5% from the screening weight or weight at last dose adjustment is identified at the clinic site (Wk13, 25, 37, 51, 65, 77, 89).	To clarify when and how to adjust study drug dose in the event of a weight change of ±5%

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **6**	**Amendment Date** **02 October 2020**	**Global**
Protocol Amendment Summary and Rationale: A summary of updates made to Clinical Protocol SHP-GCB-402 Amendment 6 are itemized below.		
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 6.6; Appendix 1 Study Schedule of Events: Study Week 41 to Study Week 89, footnote d; Appendix 9	Added the optional transfer of study visit weeks 77 and/or 89 to home therapy and the addition of dose continuation infusions due to the COVID-19 pandemic	Added to ensure subject safety, allow subject and site staff greater flexibility, and to mitigate impact to the study timing from COVID-19
Section 7.8	Added that infusion of VPRIV may be delivered intravenously with an in-line sterilizing filter that has a rated pore size of 0.22 µm	Per FDA Guidance below, 0.2 µm and 0.22 µm filters are considered to have interchangeable nominal pores size ratings. FDA Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. September 2004. Page 27, B. Filtration Efficacy and footnote #18
Appendix 8	The Brief Fatigue Inventory assessment has been added to the appendix	Assessment was inadvertently omitted from the prior amendment's appendices

SYNOPSIS

Sponsor:
Shire Human Genetic Therapies, Inc. (Shire), a wholly owned subsidiary of Takeda Pharmaceuticals Company Limited

Name of Finished Product: velaglucerase alfa (VPRIV®)

Study Title:
An Open-label, Multicenter, Single-arm, Phase 4 Study of the Effect of Treatment with Velaglucerase Alfa on Bone-related Pathology in Treatment-naïve Patients with Type 1 Gaucher Disease

Study Number: SHP-GCB-402

Study Phase: 4

Investigational Product, Dose, and Mode of Administration:
Velaglucerase alfa 60 U/kg every other week (EOW) by a minimum 60-minute intravenous infusion

Concomitant Medication, Dose, and Mode of Administration:
All patients will also receive 800 IU vitamin D (oral) daily starting at the week 1 visit

Comparator, Dose, and Mode of Administration: Not applicable

Primary Objective:
The primary objective is: To evaluate the effect of VPRIV therapy (60 U/kg EOW) in treatment-naïve patients with type 1 Gaucher disease on change from baseline in lumbar spine (LS) bone mineral density (BMD) Z-score as measured by dual energy x-ray absorptiometry (DXA) after 24 months of treatment

Secondary Objectives:
The secondary objectives are to evaluate the effect of VPRIV therapy (60 U/kg EOW) over time in treatment-naïve patients with type 1 Gaucher disease on:

- BMD as measured by the change from baseline in LS BMD Z-score after 12 months of treatment
- BMD as measured by the change from baseline in g/cm^2 after 12 months and after 24 months of treatment
- Bone marrow burden (BMB) as measured by magnetic resonance imaging (MRI) of the LS and femur after 12 and 24 months of treatment
- Hemoglobin concentration after 12 and 24 months of treatment
- Platelet count after 12 and 24 months of treatment
- Liver volume measured by abdominal MRI after 12 and 24 months of treatment
- Spleen volume measured by MRI after 12 and 24 months of treatment
- Bone pain as measured by questions taken from the Brief Pain Inventory-Short Form© (BPI-SF) after 12 and 24 months of treatment
- Fatigue measured by the Brief Fatigue Inventory (BFI) after 12 and 24 months of treatment
- World Health Organization (WHO) BMD classification (normal bone density, osteopenia, osteoporosis) based on LS T-scores after 12 and 24 months of treatment
- Safety

Exploratory Objectives:

[redacted]

Study Endpoints:
The primary endpoint is:

- Change from baseline to 24 months (Week 103 [end of study]) in LS BMD Z-score as measured by DXA.

The secondary efficacy endpoints are:

- Change from baseline to 12 months (Week 51) in LS BMD Z-score. Assessments will be performed at the screening visit and Weeks 51 and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103, end of study) in LS BMD in g/cm^2.
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in BMB score (MRI of LS and femur). Assessments will be performed at the baseline visit and Weeks 51 and 103 (end of study).
- Change from baseline over time in hemoglobin concentration. Assessments will be performed at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
- Change from baseline over time in platelet count. Assessments will be performed at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in normalized liver volume as measured by abdominal MRI. Assessments will be performed at the baseline visit and Weeks 51 and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in normalized spleen volume as measured by MRI. Assessments will be performed at the baseline visit and Weeks 51 and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in bone pain as measured by questions taken from the BPI-SF©. Assessments will be performed at the baseline visit and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in overall fatigue as measured by the BFI. Assessments will be performed at the baseline visit and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
- Shifts in WHO BMD classifications (normal bone density, osteopenia, osteoporosis) based on LS T-scores. Assessments will be performed at baseline (screening visit) and Weeks 51 and 103 (end of study).

Study Population:
At least 19 patients (≥18 and ≤70 years of age) with type 1 Gaucher disease who are naïve to enzyme replacement therapy (ERT)/substrate reduction therapy (SRT) are planned to be recruited to achieve 13 evaluable patients. To be considered evaluable, a patient must have an eligible DXA score at Baseline and at 24 months (Week 103 [end of study]).

Study Design: Multicenter, open-label, single-arm, Phase 4 study design

Study Duration:
Patients will be dosed for 101 weeks (51 infusions), preceded by a Screening/baseline period of up to 28 days and followed by a 30-day Safety Follow-up Period.

Study Inclusion and Exclusion Criteria:
Inclusion criteria
Each patient must meet all the following criteria to be enrolled in this study:
1. The patient has a documented diagnosis of type 1 Gaucher disease, as documented by deficient glucocerebrosidase (GCB) activity in leukocytes (whole blood only) or cultured skin fibroblasts. Diagnosis by only dry blood spot test is insufficient. Diagnosis may be based on results obtained prior to Screening if documented in the patient's medical history.
2. Patients must have a LS BMD Z-score <-1 or BMD T-score of <-1 as measured by DXA during the screening phase.
3. Patient is treatment-naïve, ie, should not have received ERT or SRT in the 12 months prior to enrollment.
4. The patient is ≥18 and ≤70 years of age.
5. Female patients of childbearing potential must agree to use a medically acceptable method of contraception at all times during the study. (See Section 6.8.3 for acceptable methods of contraception).
6. The patient, or patient's legally authorized representative(s), if applicable, understands the nature, scope, and possible consequences of the study and has provided written informed consent that has been approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC).
7. The patient must be sufficiently cooperative to participate in this clinical study as judged by the investigator.

Exclusion criteria
Patients who meet any of the following criteria will be excluded from the study:
1. Neurological symptoms indicating that the patient may have type 3 Gaucher disease.
2. A significant comorbidity, which, as determined by the investigator, might compromise study assessment, affect study data or confound the study results (eg, malignancies, primary biliary cirrhosis, autoimmune liver disease, etc).
3. Any osteoporosis-specific treatment (eg, bisphosphonates) or treatment with erythropoietin (or erythropoietin-like substances) during the past year.
4. Structural, joint-associated bone damage of such extent and severity that the investigator deems it could impact participation in the study and assessment of relevant study endpoints (eg, pain).
5. The patient is pregnant or lactating.
6. The patient has had a splenectomy. (This criterion is not meant to exclude subjects who have accessory spleens.)
7. The patient is enrolled in another clinical study that involves clinical investigations or use of any investigational product (drug or device) within 30 days prior to study enrollment or at any time during the study.
8. Severe vitamin D deficiency to the level that would be expected to result in osteomalacia (vitamin D <10 ng/mL [25 nmol/L]). If there is mild vitamin D insufficiency at screening (vitamin D >10 and <30 ng/mL) treat with 4000 IU vitamin D per day for 1 month and rescreen.

9. The patient has previously interrupted ERT for safety reasons.
10. The patient has had hypersensitivity to the active substance or to any of the excipients.

Pharmacokinetic Variables: Not applicable

Pharmacodynamic Assessments: Not applicable

Efficacy Assessments:
Bone-related disease will be assessed over time by measuring BMD, BMB, and bone pain as follows:

- Bone mineral density of the lumbar spine will be measured by DXA, and the results converted to Z-scores appropriate for age, sex, and race. Lumbar spine T-scores/WHO classifications of normal bone density, osteopenia, osteoporosis will also be assessed.
- Bone marrow involvement of the LS and femurs will be measured by MRI and through blinded analysis by 2 independent radiologists, converted to BMB scores between 0 and 8 based on the method of DeMayo et al.
- Bone pain will be measured by questions taken from the BPI-SF©.

Non–bone-related disease will be assessed by measuring:

- Hemoglobin concentration
- Platelet count
- Liver and spleen volume (and a determination of splenic lesions) measured by abdominal MRI and normalized to body weight
- Overall fatigue measured by the BFI

[redacted]

Safety Assessments:
Safety will be assessed over time by monitoring the following:

- Adverse events
- Use of concomitant medications
- Laboratory tests (hematology, serum chemistry, coagulation, and urinalysis)
- Positive anti-velaglucerase alfa antibody status, including assessment of neutralizing activity for confirmed antibody positive samples

Statistical Methods:
Statistical analyses will be based on the intent-to-treat (ITT) principle for all efficacy variables. The ITT analysis will be based on all enrolled patients who received at least 1 study drug infusion (full or partial). Summary statistics will be provided for the changes and percent changes from baseline for each parameter. Two-sided 95% confidence intervals in the mean changes and mean percent changes from baseline will be presented for each endpoint.

Continuous data collected at baseline and subsequent study visits will be summarized, and the mean, standard deviation, minimum, maximum, and median values for each variable will be tabulated to facilitate the search for trends over time that may be attributable to study drug. Categorical variables will be presented in terms of frequencies and percent. Within patient changes from baseline will be examined using 1 sample t-test or Wilcoxon signed rank test. Statistical significance will be defined at the 0.05 level.

Demographic and baseline characteristics will be summarized as frequencies and percentages, and data will be presented using descriptive statistics.

In general, descriptive statistics and graphs will be used for the presentation of study results including, if relevant, graphs showing the treatment effect over time for patients individually and overall.

The safety population will be used for all safety analyses and is defined as all enrolled patients who received at least 1 study drug infusion (full or partial). Safety will be evaluated on the basis of AEs reported, clinical laboratory data, use of concomitant medications, vital signs, and physical examinations. In addition, blood samples will be analyzed for determination of the presence of anti-velaglucerase alfa antibodies.

Sample Size Determination
In a previous protocol version (Amendment 4), approximately 40 patients were planned for enrollment in order to achieve a total of 34 evaluable patients (driven by the key secondary efficacy endpoint), assuming a 15 % drop-out rate. A total of 34 evaluable patients provided 99% power to detect a significant change in LS BMD Z-score from baseline after 24 months of treatment (primary efficacy endpoint) when in fact there is a +0.6 change (improvement) in Z-score. The calculation assumed an alpha of 0.05 2-sided t-test) and a standard deviation of change of 0.6 based on data from study HGT-GCB-044. The 34 evaluable patients also conferred 80% power to detect a significant change in one of the key secondary endpoints, namely the change from baseline in LS BMD Z-score after 12 months of treatment. Assumptions for the key secondary endpoint power calculation were also based on study HGT-GCB-044 in which a +0.25 change in in Z-score at 12 months was reported with a standard deviation of 0.5.

In the previous amendment (Amendment 5), the number of patients planned for enrolment was revised based on the patient recruitment and retention experience to date to allow for a more realistic and achievable recruitment target. Cumulative enrollment data collected from study initiation to date indicate a suboptimal enrollment rate of 0.5 patient per month.

Study enrollment is hindered by the considerable prevalence of screen failures (approximately 50%) resulting from the limited global pool of naïve patients with Gaucher disease who demonstrate bone involvement at baseline and who meet the eligibility criteria of this study. Based on this information, the number of patients planned for enrollment was reduced to at least 19 patients in order to yield 13 evaluable patients. To be considered evaluable, a patient must have an eligible DXA score at Baseline and at 24 months (Week 103 [end of study]). The number of evaluable patients was determined assuming a drop-out rate of 30% based on the rate of early discontinuations reported during the first 2 years of the study. With 13 evaluable patients and assuming the same effect size (increase in LS BMD Z-score of +0.6) and standard deviation (0.6) values at 24 months from study HGT-GCB-044, the study will be 90% powered to detect significant changes (alpha 0.05) in LS BMD Z-score at 24 months (primary efficacy endpoint). As the revised sample size no longer provides adequate statistical power for the detection of significant changes in the key secondary endpoints defined in the previous protocol version, those were demoted to secondary endpoints in the current amendment.

Date of Original Protocol: 30 April 2015
Date of Amendment 1: 14 September 2015
Date of Amendment 2: 02 June 2016
Date of Amendment 3: 06 July 2016
Date of Amendment 4: 04 May 2017
Date of Amendment 5: 26 July 2018
Date of Amendment 6: 02 November 2020

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form within 24 hours to the Shire Global Patient Safety Evaluation Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by fax or e-mail using the details below.

Fax: [redacted]

Email: [redacted]

For protocol- or safety-related issues the investigator must contact the Shire Medical Monitor:

[redacted], DDS, PhD

Telephone: [redacted]

Fax: N/A

Mobile: [redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
1, 25 OH vitamin D	1, 25 dihydroxycholecalciferol
25 OH vitamin D	25 hydroxycholecalciferol
AE	adverse event
BFI	Brief Fatigue Inventory
BMB	bone marrow burden
BMD	bone mineral density
BMP-2	bone morphogenic protein-2
[redacted]	[redacted]
CFR	Code of Federal Regulations
CNS	central nervous system
CRP	c-reactive protein
DXA	dual energy x-ray absorptiometry
eCRF	electronic case report form
ECG	electrocardiogram
EOW	every other week
ERT	enzyme replacement therapy
FDA	Food and Drug Administration
FDP	fibrinogen degradation product
GCB	glucocerebrosidase
GCP	Good Clinical Practice
GSL	glycosphingolipid
β-hCG	human chorionic gonadotropin
ICGG	International Collaborative Gaucher Group
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
[redacted]	[redacted]
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	infusion-related reactions
ITT	intent-to-treat
LOCF	last observation carried forward
LS	lumbar spine
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MRI	magnetic resonance imaging
PT	preferred term
QoL	quality of life
Questions taken from the BPI-SF©	Questions taken from the Brief Pain Inventory-Short Form©
[redacted]	[redacted]
SAE	serious adverse event
[redacted]	[redacted]
SOC	system organ class
SRT	substrate reduction therapy
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
VPRIV	velaglucerase alfa
WHO	World Health Organization

1 INTRODUCTION

1.1 Bone Pathology in Gaucher Disease - An Unmet Medical Need

Gaucher disease, a pan-ethnic, autosomal, recessive disease with an estimated 30,000 persons with type 1 disease worldwide (Cox and Schofield, 1997), is the most common glycosphingolipid (GSL) storage disorder (Cox et al., 2003). Despite the pan-ethnicity of the disorder, there is a particularly high prevalence in the Ashkenazi Jewish population. 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. Glucocerebrosidase is required for hydrolysis of glucocerebroside to glucose and cerebroside.

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 bone 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). Type 1 Gaucher disease, the most common form accounting for more than 90% of all cases, (Pastores et al., 2004) does not involve the CNS; 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.

Most research effort to date has focused on strategies for augmenting enzyme levels to compensate for the underlying defect; enzyme replacement therapy (ERT) has been the cornerstone of treatment for Gaucher disease since the early 1990s and is highly effective in improving many of the clinical manifestations (Cox et al., 2003).

1.2 Experience with ERT for Bone-related Complications of Gaucher Disease

Data from the International Collaborative Gaucher Group (ICGG) demonstrate that approximately 90% of all patients with Gaucher disease should achieve normal hemoglobin concentration within 2 years of initiation of treatment (Cox et al., 2003). Enzyme replacement therapy reduces organomegaly, improves hematological parameters, and positively impacts health-related QoL (Weinreb et al., 2002; Masek et al., 1999).

Despite the availability since 1991 of the first ERT for Gaucher disease, the management of the skeletal manifestations of the disease remains a significant unmet medical need. Skeletal complications are a frequent occurrence in patients with Gaucher disease.

Of 1698 patients with Gaucher disease, treated or untreated, who were included in the ICGG Gaucher Registry, 94% were reported to have radiological evidence of bone disease, including Erlenmeyer flask deformity (46%) or osteopenia (42%) (Charrow et al., 2000). Data from this ICGG Gaucher Registry also showed that within the first year prior to the initiation of treatment with ERT, 56% of patients reported bone pain and 23% reported bone crisis (Charrow et al., 2007), which might include acute episodes of severe skeletal pain and fever (Charrow et al., 2007; Goker-Alpan, 2011). This high rate of skeletal complications and their progressive nature, combined with the irreversible and debilitating nature of bone destruction, call for aggressive and early treatment and careful monitoring (Goker-Alpan, 2011; Deegan et al., 2011). Published therapeutic goals for adult patients with Gaucher disease include the following targets for improvement of skeletal complications (Pastores et al., 2004):

- Lessen or eliminate bone pain within 1 to 2 years
- Prevent bone crises
- Prevent osteonecrosis and subchondral joint collapse
- Improve bone mineral density (BMD)
- Increase trabecular BMD by 3 to 5 years

Using data from the ICGG Gaucher Registry, improvements in BMD Z-scores following initiation of ERT with imiglucerase have been shown to be dose dependent. A linear mixed model suggests that the BMD Z-scores of the population as a whole approached normal for patients who received 60 U/kg; however, this was only after 8 years of treatment and included many patients who at baseline had normal Z-scores. Many patients with Z-scores <-1 did not normalize (Maas et al., 2003). This retrospective approach relies on data voluntarily entered into the database. These data reflect the standard of care provided by individual treating physicians and not any defined clinical protocol. As a result, the data are characterized by heterogeneity in treatment, dose, regimen, and the assessments used to monitor the course of Gaucher disease. In addition, there is no opportunity to correct for the calibration of multiple dual energy x-ray absorptiometry (DXA) scanners over long observation periods.

[redacted]

[redacted] The effects of VPRIV on the change in lumbar spine BMD and lumbar spine and femur BMB as assessed by MRI were assessed previously in the clinical development program and will be evaluated as primary or key secondary objectives in this new study as well.

A new assessment, bone pain as measured by questions taken from the BPI-SF©, was added as a secondary objective. The questions taken from the BPI-SF© are used to assess the severity of pain and the impact of pain on daily functions. The questions taken from the BPI-SF© have been used in patients with pain from chronic diseases or conditions such as cancer, osteoarthritis, and low back pain, or with pain from acute conditions such as postoperative pain. Of specific relevance here is that questions taken from the BPI-SF© have been used to assess pain in several studies of Fabry patients (Cleeland, 2002; Schiffmann et al., 2001; Ries et al., 2003; Hoffmann et al., 2005; Deegan and Cox, 2005).

Questions taken from the BPI-SF© will assess the severity of pain, impact of pain on daily function, location of pain, pain medications, and amount of pain relief in the past 24 hours or the past week, and questions taken from the BPI-SF© have been shown to respond to both behavioral and pharmacological pain interventions. In this study, questions have been taken from the BPI-SF©, which takes about 5 minutes to complete (see Appendix 7).

Bone pain is a significant problem in Gaucher disease. Even if ERT has beneficial effects on other parameters, low to moderate bone pain may remain in a significant number of patients following ERT treatment (Rosenbloom and Weinreb, 2014; Weinreb et al., 2008). The current study will assess pain in patients with type 1 Gaucher disease before and during treatment with ERT. Using a validated instrument, such as the BPI-SF©, the impact of any pain on QoL will be assessed and can be compared to that of other conditions with chronic pain.

[redacted]

Please refer to the current edition of the investigator's brochure for further information concerning the safety and clinical development of VPRIV.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

To evaluate the effect of VPRIV therapy (60 U/kg every other week [EOW]) in treatment-naïve patients with type 1 Gaucher disease on change from baseline in lumbar spine (LS) BMD Z-score as measured by DXA after 24 months of treatment.

2.2 Secondary Objectives

The secondary objectives are to evaluate the effect of VPRIV therapy (60U/kg EOW) over time in treatment-naïve patients with type 1 Gaucher disease on:

- BMD as measured by the change from baseline in LS BMD Z-score after 12 months of treatment
- BMD as measured by the change from baseline in g/cm^2 after 12 months and after 24 months of treatment
- BMB as measured by magnetic resonance imaging (MRI) of the LS and femur after 12 and 24 months of treatment
- Hemoglobin concentration after 12 and 24 months of treatment
- Platelet count after 12 and 24 months of treatment
- Liver volume measured by abdominal MRI after 12 and 24 months of treatment
- Spleen volume measured by MRI after 12 and 24 months of treatment
- Bone pain as measured by questions taken from the BPI-SF© after 12 and 24 months of treatment
- Fatigue measured by the Brief Fatigue Inventory (BFI) after 12 and 24 months of treatment
- WHO BMD classification (normal bone density, osteopenia, osteoporosis) based on LS T-scores after 12 and 24 months of treatment
- Safety

2.3 Exploratory Objectives

[redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is:

Change from baseline to 24 months (Week 103 [end of study]) in LS BMD Z-score as measured by DXA.

3.2 Secondary Endpoints

3.2.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Change from baseline to 12 months (Week 51) in LS BMD Z-score. Assessments will be performed at the screening visit and Weeks 51 and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103, end of study) in LS BMD in g/cm^2.
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in BMB score (MRI of lumbar spine and femur). Assessments will be performed at the baseline visit and Weeks 51 and 103 (end of study).
- Change from baseline over time in hemoglobin concentration. Assessments will be performed at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
- Change from baseline over time in platelet count. Assessments will be performed at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in normalized liver volume as measured by abdominal MRI. Assessments will be performed at the baseline visit and Weeks 51 and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in normalized spleen volume as measured by MRI. Assessments will be performed at the baseline visit and Weeks 51 and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in bone pain as measured by questions taken from the BPI-SF©. Assessments will be performed at the baseline visit and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in overall fatigue as measured by the BFI. Assessments will be performed at the baseline visit and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
- Shifts in WHO BMD classifications (normal bone density, osteopenia, and osteoporosis) based on LS T-scores. Assessments will be performed at baseline (screening visit) and Weeks 51 and 103 (end of study).

3.2.2 Safety Endpoints

The safety endpoints are:

- AEs
- Use of concomitant medications
- Clinically abnormal laboratory tests (hematology, serum chemistry, coagulation, and urinalysis)
- Positive anti-velaglucerase alfa antibody status, including assessment of neutralizing activity for confirmed antibody positive samples

3.3 Exploratory Endpoints

[redacted]

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multicenter, open-label, single-arm, Phase 4 study to prospectively evaluate the effect of VPRIV on bone-related pathology in treatment-naïve patients with type 1 Gaucher disease. In order to yield 13 evaluable patients, at least 19 patients will be enrolled to receive VPRIV at the recommended starting dose for treatment-naïve patients of 60 U/kg EOW by a minimum 60-minute intravenous infusion. To be considered evaluable, a patient must have an eligible DXA score at Baseline and at 24 months (Week 103 [end of study]).

The primary endpoint is the change from baseline to 24 months (Week 103 [end of study]) in LS BMD Z-score. Bone mineral density will be measured using DXA, and the results will be converted to Z-scores appropriate for the patient's age, sex, and race.

See Appendix 1 for the Study Schedule of Events table.

4.2 Rationale for Study Design and Comparator Group

Bone-related problems are a critical unmet medical need in Gaucher disease and there is reason to believe that treatment with VPRIV may lead to significant bone and bone-related effects as early as 12 months after initiation of treatment in ERT-naïve patients. Twenty-one treatment-naïve patients received initial VPRIV therapy at a dose of 60 U/kg in Study TKT032 or HGT-GCB-039 and showed a mean increase in LS BMD Z-score that was statistically significant at the first post-baseline assessment (9 months for those patients in Study HGT-GCB-039 and 12 months for those patients in Study TKT032).

In consideration of the rarity of Gaucher disease, a single-arm study was chosen because a placebo-controlled trial would not be feasible or ethical for the proposed indication.

4.3 Study Duration

It is expected that the duration of study participation for each subject will be approximately 110 weeks, including 101 weeks of treatment (51 infusions), additional screening/baseline assessments taking up to 4 weeks, and 4 weeks of safety follow up after treatment is completed. It is expected that 24 months of treatment is sufficient to observe statistically significant changes in lumbar spine BMD, based on previous experience in Study TKT025EXT and Study HGT-GCB-044.

5 STUDY POPULATION SELECTION

5.1 Study Population

It is planned that at least 19 patients with type 1 Gaucher disease who are at least 18 years of age but no more than 70 years of age and who are naïve to ERT/substrate reduction therapy (SRT) will be enrolled. Patients will have a documented diagnosis of type 1 Gaucher disease, as documented by deficient GCB activity in leukocytes (whole blood only) or cultured skin fibroblasts and a LS BMD Z-score <-1 or BMD T-score of < -1 as measured by DXA during the screening phase.

5.2 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. The patient has a documented diagnosis of type 1 Gaucher disease, as documented by deficient GCB activity in leukocytes (whole blood only) or cultured skin fibroblasts. Diagnosis by only dry blood spot test is insufficient. Diagnosis may be based on results obtained prior to screening if documented in the patient's medical history.
2. Patients must have a LS BMD Z-score <-1 or BMD T-score of <-1 as measured by DXA during the screening phase.
3. Patient is treatment-naïve, ie, has not received ERT or SRT in the 12 months prior to enrollment.
4. The patient is ≥18 and ≤70 years of age.
5. Female patients of childbearing potential must agree to use a medically acceptable method of contraception at all times during the study. (See Section 6.8.3 for acceptable methods of contraception).
6. The patient, or patient's legally authorized representative(s), if applicable, understands the nature, scope, and possible consequences of the study and has provided written informed consent that has been approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC).
7. The patient must be sufficiently cooperative to participate in this clinical study as judged by the investigator.

5.3 Exclusion Criteria

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

1. Neurological symptoms indicating that the patient may have type 3 Gaucher disease.
2. A significant comorbidity, which, as determined by the investigator, might affect study data or confound the study results (eg, malignancies, primary biliary cirrhosis, autoimmune liver disease, etc).
3. Any osteoporosis-specific treatment (eg, bisphosphonates) or treatment with erythropoietin (or erythropoietin-like substances) during the past year.
4. Structural, joint-associated bone damage of such extent and severity that the investigator deems it could impact participation in the study and assessment of relevant study endpoints (eg, pain).

5. The patient is pregnant or lactating.
6. The patient has had a splenectomy. (This criterion is not meant to exclude subjects who have accessory spleens.)
7. The patient is enrolled in another clinical study that involves clinical investigations or use of any investigational product (drug or device) within 30 days prior to study enrollment or at any time during the study.
8. Severe vitamin D deficiency to the level that would be expected to result in osteomalacia (vitamin D <10 ng/mL [25 nmol/L]). If there is mild vitamin D insufficiency at screening (vitamin D >10 and <30 ng/mL) treat with 4000 IU vitamin D per day for 1 month and rescreen.
9. The patient has previously interrupted ERT for safety reasons.
10. The patient has had hypersensitivity to the active substance or to any of the excipients.

6 STUDY TREATMENT

6.1 Description of Treatment

6.1.1 Investigational Product

The investigational product to be used in this study is VPRIV for intravenous infusion. Velaglucerase alfa is supplied as a sterile, preservative-free, lyophilized powder in single-use vials.

6.1.2 Comparator

Not applicable.

6.2 Treatment Administered

All enrolled patients will receive VPRIV by a minimum 60-minute intravenous infusion at the recommended approved starting dose for treatment-naïve patients of 60 U/kg EOW. Patients will continue to receive 60 U/kg EOW for 24 months (101 weeks). A 30-day follow-up period is planned after the final dose.

6.3 Selection and Timing of Dose for Each Patient

All enrolled patients will receive VPRIV at the same dose, ie, 60 U/kg EOW, which is the recommended approved starting dose for patients who are naïve to ERT and SRT for Gaucher disease. The first dose of VPRIV will be based on the patient's weight at screening (Days -28 to Day -4). A change in patient weight of ±5% from screening or the last weight used to recalculate the dose will require a new dose recalculation by the clinical site. Weight will be measured every 12 weeks throughout the study, with any dosing adjustment to be completed prior to the next dose. When a weight change of ±5% is identified, the dose should be adjusted as soon as possible, but no later than the next bi-weekly study visit. If the dose can be adjusted prior to the infusion on the same day, this adjustment should be performed; however, if the dose cannot be adjusted on the same day, the dose must be adjusted prior to the next bi-weekly infusion. It is acceptable for the dose adjustment to occur at either of the following times in the study:

1) The dose adjustment to occur on the same day a weight change of ±5% from the screening weight or weight at last dose adjustment is identified at the clinic site (Weeks 13, 25, 37, 51, 65, 77, 89); or
2) The dose adjustment to occur at the next bi-weekly study visit after a weight change of ±5% from the screening weight or weight at last dose adjustment is identified at the clinic site (Weeks 13, 25, 37, 51, 65, 77, 89).

For dosing calculations, patient weight can be rounded to the nearest 0.5 kg, VPRIV dose to the nearest Unit, and dose volume to the nearest 0.1 mL

Study drug infusions are to occur on approximately the same day of the week, but may occur every 14 days (± 7 days) of the target day in order to facilitate patient scheduling. If at all possible, missed infusions should be avoided.

If a patient is not dosed within 21 days from their scheduled dose, the patient should receive the next infusion as soon as possible. It may be acceptable to give the next infusion as early as 7 days after the previous infusion. Subsequent infusions will return to the original schedule.

6.4 Method of Assigning Patients to Treatment Groups

Not applicable; single-armed study, all enrolled patients are to receive the same dose of VPRIV.

6.5 Blinding

Not applicable; this is an open-label study.

6.6 Home Infusion of Velaglucerase alfa

The first three velaglucerase alfa infusions are to be administered at the clinical site. After the first 3 doses, patients who have not experienced a treatment-related serious adverse event or an infusion-related adverse event of more than mild severity may receive their subsequent infusions at home by qualified and trained medical personnel, per the discretion and direction of the Investigator. Patients who have experienced an infusion-related adverse event of more than mild severity may be re-evaluated at a later time point during the study for consideration to transition to home infusions. Patients receiving velaglucerase alfa as home therapy will be required to return to the clinical site at Weeks 13, 25, 37, 51, 65, 77, 89, and 103. Please refer to Appendix 9 for information on transferring visits at Weeks 77 and 89 to home therapy and the addition of dose continuation infusions due to the COVID-19 pandemic.

The qualified, trained medical personnel will follow the instruction manual provided separately from this protocol that outlines all operating procedures to be followed for this study including drug transport, reconstitution and the required patient assessments before, during, and after infusion of study drug. Clinical evaluations will remain under the medical supervision of the Investigator. Appropriate medical support including adequately trained personnel in emergency measures, should be readily available when velaglucerase alfa is administered. If anaphylactic or other acute severe reactions occur, immediately discontinue the infusion and initiate appropriate medical treatment.

In the home setting, vital signs and documentation of adverse events will be collected at each visit. The qualified, trained medical personnel will evaluate and report to the study site the occurrence of adverse events. Study site personnel will report SAEs as described in Section 7.15.2. In addition, a urine pregnancy test will be conducted at each home infusion visit for women of childbearing potential. If the result is positive, the infusion will not be administered, and a blood sample will be collected for serum pregnancy testing. The next infusion of velaglucerase alfa will not be administered until the results of the serum pregnancy test are received. If the serum human chorionic gonadotropin (β -hCG) result is also positive, the Investigator is to contact the Shire Medical Monitor to determine the appropriate course of action.

If there are no infusion-related reactions (IRRs) during the first 3 infusions the observation and vital signs post-infusion can be omitted at the discretion of the investigator.

If an infusion-related adverse event of more than mild severity occurs while a patient is receiving treatment at home, the qualified, trained medical personnel will maintain contact with the investigator for treatment advice. The infusion should not be restarted in the home setting after an infusion-related adverse event of more than mild severity. Home therapy can only then resume at subsequent infusions after agreement is reached by the investigator and the Shire Medical Monitor.

6.7 Infusion Reactions and Management

Infusions of proteins can be associated with reactions to the infusion that may or may not be immune mediated. Thus, potential reactions to the infusion of the investigational drug are unpredictable. Symptoms suggestive of hypersensitivity, including anaphylaxis, have been observed in patients receiving ERT. Symptoms included pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension.

The management of IRRs should be based on the severity of the reaction. Such management may include, at the discretion of the investigator, slowing the infusion rate, treatment with medications such as antihistamines, antipyretics, and/or corticosteroids and/or stopping and resuming treatment with prolonged infusion duration.

Pretreatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was previously required. Pretreatment of infusion reactions is left to the clinical judgment of the investigator.

In cases when required and at the discretion of the study site, additional clinical laboratory samples may be collected for further analysis of IRRs. Suggested laboratory evaluation includes complete blood count, complete metabolic panel including liver and renal function tests, CH50, C3, C4, C1 inhibitor, C3a and C5a, total tryptase, histamine, immune complex and serum IgE levels.

6.8 Restrictions

6.8.1 Prior Therapy

The use of any osteoporosis-specific treatment (eg, bisphosphonates) or treatment with erythropoietin within the past year is an exclusion criterion. To be eligible for the study, patients are to be treatment-naïve (ie, have not received ERT or SRT in the 12 months prior to study enrollment).

6.8.2 Concomitant Therapy

Patients who enter the study receiving supplemental therapy (eg, supplemental iron, calcium) must remain on a constant dose and regimen throughout the study. All patients will receive 800 IU vitamin D (oral) daily starting at the week 1 visit for the duration of the study. Initiation of osteoporosis-specific therapy or treatment with erythropoietin during the trial is prohibited.

6.8.3 Contraception

Female patients of childbearing potential must agree to use a medically acceptable method of contraception at all times during the study.

One of the following methods would be acceptable:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
2. Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)
5. Bilateral tubal occlusion
6. Vasectomized partner
7. Sexual abstinence

6.8.4 Fluid and Food Intake

No restrictions or requirements.

6.8.5 Patient Activity Restrictions

The patient is restricted from enrolling in another clinical study that involves clinical investigations or use of any investigational product (drug or device) within 30 days prior to study enrollment or at any time during the study.

6.9 Treatment Compliance

During this study, VPRIV will be administered under controlled conditions; therefore, full patient compliance with study treatment is anticipated to be high.

6.10 Packaging and Labeling

Velaglucerase alfa is a sterile, preservative-free, lyophilized powder requiring reconstitution and further dilution prior to use. It is supplied in individually packaged glass vials, which are closed with a butyl rubber stopper with a fluororesin coating and are sealed with an aluminum overseal with a flip-off plastic cap. The vials are intended for single use only. Velaglucerase alfa is available as 400 U/vial.

All packaging and labeling will be in accordance with applicable regulatory requirements.

6.11 Storage and Accountability

The following information should be considered when storing and using the investigational product.

Velaglucerase alfa should be stored in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). The shelf life is 36 months. Do not use velaglucerase alfa after the expiration date on the vial. Do not freeze. Protect the vials from light.

The disposition of all investigational product delivered to a principal investigator must be recorded on a patient-by-patient basis by completing the Clinical Trial Material Accountability Log or local accountability log. The date and time of administration of the investigational product must be documented on the appropriate eCRF.

The principal investigator, clinical research coordinator, or designee (eg, pharmacist, third party vendor, etc.) must ensure that all documentation regarding investigational product receipt, storage, dispensing, loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the unused investigational product is available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

6.12 Investigational Product Retention at Study Site

The process for return and destruction of investigational product must be determined and documented during the study start-up phase. If the sites do not have an Investigational Product Returns Process/Policy, the Sponsor or designee must provide guidelines to the sites. Sites must retain copies of these documents within the Site Regulatory Binder.

If the investigational product is to be destroyed by the sites or a third party vendor, the sites or third party vendor must follow their own process/policy that describes such activities. The site or third party vendor must retain copies of these documents within the Site Regulatory Binder. The site or third party vendor must ensure that the Clinical Trial Material Accountability and Destruction Log is complete, accurate, and ready for review and/or audit at each monitoring visit.

All manifests documenting shipments of investigational product must be retained as well as copies of any investigational product return forms.

See the Pharmacy Manual for additional details.

7 STUDY PROCEDURES

Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks (±7 days) of the study (Study Schedule of Events table in Appendix 1).

All data collected are to be recorded on the appropriate electronic case report form (eCRF).

7.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent must be obtained from the patient, or the patient's legally authorized representative(s) and assent from the patient (if applicable).

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the patient, or the patient's legally authorized representative(s) by the investigator or designee in accordance with the guidelines described in Section 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.

7.2 Study Entrance Criteria

At screening, each patient will be reviewed for eligibility against the study entrance criteria (Section 5.2 and Section 5.3). Patients who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the patient's ineligibility for the study will be documented.

7.3 Confirmation of Study Eligibility

Patient eligibility according to the study inclusion and exclusion criteria will be confirmed at the baseline visit on the basis of review of the study entrance criteria.

7.4 Demographics

Patient demographic information including sex, age, and race will be collected prior to the patient receiving the first dose of investigational product.

7.5 Medical History

Medical history will include a review of the patient's medical status, documentation of current and prior medical procedures, documentation of current and prior medication usage (including non-Gaucher disease-related investigational drugs or devices, if any), and Gaucher disease diagnosis (including documentation of deficient GCB activity in leukocytes relative to normal [as measured in whole blood only] or cultured skin fibroblast).

7.6 Glucocerebrosidase Genotype Analysis

At screening, all patients will have a blood sample collected for Gaucher disease (GBA) gene sequencing; however, GBA sequencing is not required at screening if documented results are available in the medical history. The sample will be sent to a central laboratory for analyzing and reporting. The results will be used for statistical analysis purposes.

7.7 Height and Weight

Height and weight will be recorded for all patients.

The measurements for height will be collected by way of a calibrated stadiometer. Height measurements will be collected 3 times for each patient at the specified study visits, and the average of the 3 measurements will be determined and recorded at the site.

The clinical site staff will be instructed to use calibrated scales for weight measurement.

7.8 Investigational Product Administration

All doses of VPRIV will be administered by continuous intravenous infusion. Study drug infusions are to occur on approximately the same day of the week but may occur every 14 days (±7 days of the target day) in order to facilitate patient scheduling. If at all possible, missed infusions should be avoided. If a patient is not dosed within 21 days from their scheduled dose, the patient should receive the next infusion as soon as possible. It may be acceptable to give the next infusion as early as 7 days after the previous infusion. Subsequent infusions will return to the original schedule.

The infusion time will be at least 60 minutes (1 hour). For example, a 60 U/kg dose will be delivered at a rate of at least 1 U/kg/minute. The infusion of VPRIV will be delivered intravenously with an in-line sterilizing filter (0.2 micron or 0.22 micron).

The dose of VPRIV will be calculated based on the patient's weight determined at screening. A change in weight of ±5% from screening or the previous weight assessment in the study will require recalculation of the dose.

If a patient experiences an infusion-related AE (as defined in Section 7.14.1.7) 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.

Patients experiencing recurrent infusion-related AEs may be pre-medicated, as described in Section 6.6. If infusions continue without incident, then tapering of medications can be considered.

7.9 Pharmacokinetic Assessments

Not applicable.

7.10 Pharmacodynamic ([redacted]) Assessments

Not applicable. [redacted]

7.11 Efficacy Assessments

7.11.1 Bone Mineral Density

Patients will have DXA of the lumbar spine for determination of bone mineral density. Device calibration procedures and image collection, preparation, and transfer instructions will be provided to clinical sites.

7.11.2 Bone Marrow Burden

Bone marrow burden scores will be calculated from MRIs of the LS and femurs, and through blinded analysis by 2 independent radiologists, converted to BMB scores between 0 and 8 based on the method of DeMayo et al (DeMayo et al., 2008). Image collection, preparation, and transfer instructions will be provided to clinical sites.

7.11.3 Bone Pain

Bone pain will be assessed using questions taken from the BPI-SF©.

7.11.4 Overall Fatigue

Overall fatigue will be assessed using the BFI.

7.11.5 Hemoglobin Concentration

Blood samples will be collected for measurement of hemoglobin concentration. Note: The measurement of hemoglobin concentration is included as a component of hematology laboratory testing at the baseline visit and Weeks 13, 25, 37, 51, 65, 77, 89, and 103.

7.11.6 Platelet Count

Blood samples will be collected for measurement of platelet count. Note: The measurement of platelet count is included as a component of hematology laboratory testing at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103.

7.11.7 Liver and Spleen Volume

Liver and spleen volume (and a determination of splenic lesions) will be measured by abdominal MRI and normalized to body weight. Image collection, preparation, and transfer instructions will be provided to the clinical sites. Reading of the MRIs will be performed by a central reader.

7.11.8 Exploratory Measures of Potential Relevance in Gaucher Disease

[redacted]

7.11.8.1 [redacted]

[redacted]

7.11.9 Concomitant Medications, Therapies, and Medical/Surgical Interventions Assessments

All medications, therapies/interventions administered to, and medical/surgical procedures performed on the study patients from the time of informed consent through the follow-up contact are regarded as concomitant and will be documented on the appropriate pages of the eCRF. These include medications, therapies/interventions administered to patients, and medical/surgical procedures performed on the patients.

7.11.10 Physical Examination

A full physical examination will be performed by the investigator with a thorough review of body systems on specified study visits.

Physical examinations will include a review of the patient's general appearance, neurological examination, as well as evaluation of the following body systems (Table 7-1). Any abnormal change in findings will be recorded as an AE on the appropriate eCRF.

Table 7-1 Assessments for Physical Examinations

Assessment	Assessment
General appearance	Endocrine
Head and neck	Cardiovascular
Eyes	Abdomen
Ears	Genitourinary
Nose	Skin
Throat	Musculoskeletal
Chest and lungs	Neurological

7.11.11 Adverse Event Collection

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 are collected from the time informed consent is signed. (Please refer to Section 7.15, Serious Adverse Event Procedures.

7.11.12 Vital Signs

Vital signs are to be recorded for all patients and will include pulse, blood pressure, respiration rate, temperature, and pulse oxygen measurement.

The schedule included in Table 7-2 will be followed for recording vital signs at home or clinic infusion visits.

Table 7-2 Schedule for Recording of Vital Signs at Infusion

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

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

7.11.13 Electrocardiography

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

7.11.14 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing. All blood samples will be collected via venipuncture. Patients will be in a seated or supine position during blood collection.

Clinical laboratory tests will include the following (Table 7-3). Any clinically significant finding as determined by the investigator will be recorded as an AE on the appropriate eCRF.

Table 7-3 List of Laboratory Tests

Hematology:

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differentials
- Neutrophils
- Basophils
- Lymphocytes
- Monocytes
- Eosinophils

Urinalysis:

- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Nitrite
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen

Urine human chorionic gonadotropin (hCG) (only for females who are not diagnosed as postmenopausal)

Serum Chemistry:

- Vitamin D (screening and Weeks 51 and 103 only)
  - 25-hydroxycholecalciferol
  - 1, 25-dihydroxycholecalciferol
- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium
- C-reactive protein (CRP)
- Creatinine
- Creatine kinase
- Ferritin
- Gamma-glutamyl transferase (GGT)
- Glucose
- Iron binding capacity
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Serum iron
- Sodium (Na)
- Total bilirubin
- Total protein
- Transferrin saturation
- Unsaturated IBC

Coagulation:

- Prothrombin time
- Activated partial thromboplastin time (aPTT)
- D-dimer

The following safety laboratory tests will be performed at Screening:

- Vitamin D blood test

The following laboratory tests will be performed at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103:

- Coagulation
  - Prothrombin time

- Activated partial thromboplastin time (aPTT)
- D-dimer

The laboratory tests for Hematology, Serum Chemistry, and Urinalysis are to be performed as indicated in Section 7.11.5 and Section 7.11.6 and the Appendix 1 Schedule of Events (at Baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103).

7.11.15 Antibody Assessments

Blood samples will be collected for all patients for the determination of anti-velaglucerase alfa antibodies prior to the patient receiving the first dose of VPRIV at the baseline visit and at specified time points throughout the study (Weeks 13, 25, 37, 51, 65, 77, 89 and 103).

Blood samples collected for anti-velaglucerase alfa antibody determination will be evaluated at Shire Bioanalytical and Biomarker Development or a contract research laboratory designated by the Sponsor. These samples will be analyzed for anti-therapeutic protein binding antibodies. Confirmed positive samples will undergo assessment of neutralizing activity.

7.11.16 Pregnancy Testing

Female patients of childbearing potential will have a pregnancy test at each study visit.

At screening, pregnancy testing will be conducted using a urine test and a serum human chorionic gonadotropin (β-hCG) test. Patients with a positive result for either test will not be eligible for this study. The screening urine pregnancy test will be performed locally, and the screening serum pregnancy test will be analyzed at the central laboratory responsible for this study.

At all other visits, pregnancy testing will be performed with a urine test. If the urine test is positive, a blood sample will be collected for serum β-hCG testing. The clinical site's local laboratory will analyze and report all subsequent urine and serum pregnancy testing results.

If, during the Treatment Period (Week 1 to Week 103), a urine pregnancy test result is positive, the patient will not receive the planned infusion(s) until the result of the serum test is available. If the serum β-hCG result is also positive, no additional doses of the investigational product are to be administered and the investigator must contact the Shire Medical Monitor. Any report of pregnancy for any female study participant must be reported within 1 business day.

7.12 Sample Collection, Storage, and Shipping

All samples will be stored and secured in a way that ensures that unauthorized access is prohibited, and the samples are not lost, allowed to deteriorate, or are accidentally or illegally destroyed. Detailed sample collection, processing and shipping, and storage procedures will be provided in the Study Operations and/or Laboratory Manuals.

7.13 [redacted]

[redacted]

7.14 Adverse Events Assessments

7.14.1 Definitions of Adverse Events, Period of Observation, Recording of Adverse Events

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 this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 8.5. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

7.14.1.1 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 should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

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

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

7.14.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

7.14.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

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

7.14.1.4 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 progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

7.14.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pre-treatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

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

7.14.1.6 Pregnancy

Any report of pregnancy for a female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the/Shire Medical Monitor using the details specified in the emergency contact information section of the protocol.

The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant for every pregnant female study participant withdrawn from the study and for pregnant partners of male study participants. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

Pregnancy and lactation are exclusion criteria for this study. Any report of pregnancy for a female study participant or the partner of a male study participant during the course of the study and through 30 days after the patient's last dose of VPRIV must be reported to the Sponsor. Pregnancy is not to be reported as an AE; the Investigational and Marketed Products Pregnancy Report Form should be used to report the pregnancy. The pregnancy will be followed up through delivery or final outcome.

7.14.1.7 Infusion-related Adverse Event Definition

An IRR will be defined as an AE that 1) begins either during or within 24 hours after the start of the infusion and 2) is judged as related to study drug.

Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as IRRs. All AEs should be recorded together with a causality assessment.

7.14.1.8 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 7.15.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of investigational medicinal product 10% higher than the protocol-specified dose.
- **Medication Error** – A mistake made in prescribing, dispensing, administration, and/or use of the investigational medicinal product
  - 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.

7.15 Serious Adverse Event Procedures

7.15.1 Reference Safety Information

The reference for safety information for this study is the investigator's brochure for US investigator sites and the Summary of Product Characteristics for European investigator sites, which the sponsor has provided under separate cover to all investigators.

7.15.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 7.14.1.8) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Global Drug Safety Department. A copy of the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports) must also be sent to the Shire Medical Monitor using the details specified in the emergency contact information section of the protocol.

7.15.3 Serious Adverse Event Definition

A ***Serious Adverse Event*** **(SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death.
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

7.15.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.5 and must be reported to the Shire Global Drug Safety Department and the CRO/Shire Medical Monitor within 24 hours of the first awareness of the event.

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

7.15.5 Serious Adverse Event Onset and Resolution Dates

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.5 and must be reported to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.

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

7.15.6 Fatal Outcome

Any SAE that results in the subject's death (ie, 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.

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

7.15.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor or sponsor designee is responsible for notifying the relevant regulatory authorities/US central IRBs/EU central ECs of related, unexpected SAEs.

In addition, the sponsor or the sponsor's designee is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the velaglucerase alfa program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

7.16 Removal of Patients from the Trial or Investigational Product

A patient's participation in the study may be discontinued at any time at the discretion of the investigator. The following may be justifiable reasons for the investigator to remove a patient from the study:

- Non-compliance, including failure to appear at 1 or more study visits
- The patient was erroneously included in the study
- The patient develops an exclusion criterion
- The patient suffers an intolerable AE
- The patient requests to be discontinued from the study
- The study is terminated by the Sponsor
- Pregnancy

The patient, or the patient's legally authorized representative(s), acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment.

If a patient, or the patient's legally authorized representative(s) acting on behalf of the patient, discontinues participation in the study or the patient is discontinued by the investigator, reasonable efforts will be made to follow the patient through the end of study assessments. The reason for refusal will be documented on the eCRF. Any AEs experienced up to the point of discontinuation must be documented on the AE eCRF. If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

7.17 Other Study Procedures

7.17.1 Safety-related Study Stopping Rules

This study will be stopped and safety data reviewed if any patient experiences a life-threatening SAE or a death occurs, if either is considered related to the investigational product.

Following the review of safety data, the study will be either:

- Resumed unchanged
- Resumed with modifications to the protocol
- Terminated

Patient safety will be monitored on a continuous basis during this study until the last patient completes his or her last scheduled study visit/assessment. For patients who discontinue or are withdrawn prior to the Week 103 end of study visit, a follow-up assessment for safety will occur 30 (±7) days after their last infusion. This follow-up assessment may be conducted over the telephone.

7.18 Appropriateness of Measurements

Standard assessments will be used to monitor safety in the study. The efficacy measures are well established in the general Gaucher disease patient population.

8 STUDY ACTIVITIES

Study procedures will be conducted only after patients have provided written informed consent to participate in the study.

Detailed descriptions of patient evaluations required for this protocol are described below. The Study Schedule of Events is provided in Appendix 1.

All data collected are to be recorded on the appropriate eCRF page. Complete instructions for eCRF completion will be provided separately from this protocol.

8.1 Screening Visit (Days -28 to -4)

- Informed consent (prior to any study-related procedures)
- Study entrance criteria
- Medical history
- Concomitant medications
- AEs
- SAEs
- Vital signs
- Height
- Weight
- Vitamin D blood test
- Pregnancy test
- DXA of lumbar spine

8.2 Baseline (Days -3 to 0)

Note: The baseline visit may be combined with the Week 1 (within 7 days after baseline) Treatment Period visit.

- Confirmation of study eligibility
- Neurological assessment
- Concomitant medications
- AEs
- SAE and IRRs
- Physical examination
- Vital signs
- Pregnancy test
- ECG
- Serum chemistry
- Hematology/Coagulation
- Urinalysis

- Serum anti-velaglucerase alfa antibody
- MRI to determine liver and spleen volume
- MRI of the lumbar spine and whole femur
- [redacted]
- Questions taken from the BPI-SF©
- BFI

8.3 Treatment Period (Week 1 to Week 101)

8.3.1 Weeks 1, 3, 5, 7, 9, 11, 15, 17, 19, 21, 23, 27, 29, 31, 33, 35, 39, 41, 45, 43, 47, 49, 53, 55, 57, 59, 61, 63, 67, 69, 71, 73, 75, 79, 81, 83, 85, 87, 91, 93, 95, 97, 99, and 101

- VPRIV infusion
- Concomitant medications
- AEs
- SAE and IRRs
- Vital signs
- Pregnancy test

8.3.2 Weeks 13, 37, 65, and 89

- VPRIV infusion
- Concomitant medications
- AEs
- SAE and IRRs
- Physical examination
- Vital signs
- Pregnancy test
- Height
- Weight
- Serum chemistry
- Hematology/Coagulation
- Urinalysis
- Serum anti-velaglucerase alfa antibody
- [redacted]
- Questions taken from the BPI-SF©
- BFI

8.3.3 Weeks 25 and 77

- VPRIV infusion
- Concomitant medications

- AEs
- SAE and IRRs
- Physical examination
- Vital signs
- Pregnancy test
- Height
- Weight
- ECG
- Serum chemistry
- Hematology/Coagulation
- Urinalysis
- Serum anti-velaglucerase alfa antibody
- [redacted]
- Questions taken from the BPI-SF©
- BFI

8.3.4 Week 51

- Neurological assessment
- VPRIV infusion
- Concomitant medications
- AEs
- SAE and IRRs
- Physical examination
- Vital signs
- Pregnancy test
- Height
- Weight
- Vitamin D blood test
- ECG
- Serum chemistry
- Hematology/Coagulation
- Urinalysis
- Serum anti-velaglucerase alfa antibody
- MRI to determine liver and spleen volume
- MRI of the LS and whole femur
- DXA of LS
- [redacted]
- Questions taken from the BPI-SF©
- BFI

8.4 End of Study (Week 103)/Early Termination Procedures

- Neurological assessment
- Concomitant medications
- AEs
- SAE and IRRs
- Physical examination
- Vital signs
- Pregnancy test
- Height
- Weight
- Vitamin D blood test
- ECG
- Serum chemistry
- Hematology/Coagulation
- Urinalysis
- Serum anti-velaglucerase alfa antibody
- MRI to determine liver and spleen volume
- MRI of the LS and whole femur
- DXA of LS
- [redacted]
- Questions taken from the BPI-SF©
- BFI

8.5 30-day Safety Follow-up Visit

- AEs
- SAEs and IRRs
- Concomitant medications

9 QUALITY CONTROL AND ASSURANCE

Training will occur at an investigator meeting or at the site initiation visit or both, and instruction manuals will be provided to aid consistency in data collection and reporting across sites.

Clinical sites will be monitored by the Sponsor or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the FDA 21 CFR Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role(s) in the study, through a password-protected environment.

Data entered in the system will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the Sponsor or its designee. If necessary, the study site will be contacted for corrections or clarifications; all missing data will be accounted for.

SAE information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance and Risk Management database.

10 PLANNED STATISTICAL METHODS

10.1 General Considerations

This is a multicenter, open-label study designed to evaluate the effect of VPRIV on bone-related pathology in adult treatment-naïve patients with Type 1 Gaucher disease.

Statistical analyses will be based on the intent-to-treat (ITT) principle for all efficacy variables. The ITT analysis will be based on all enrolled patients who received at least 1 study drug infusion (full or partial). Summary statistics will be provided for the changes and percent changes from baseline for each parameter. Two-sided 95% confidence intervals in the mean changes and mean percent changes from baseline will be presented for each endpoint.

Continuous data collected at baseline and subsequent study visits will be summarized, and the mean, standard deviation, minimum, maximum, and median values for each variable will be tabulated to facilitate the search for trends over time which may be attributable to study drug. Categorical variables will be presented in terms of frequencies and percent. Within patient changes from baseline will be examined using 1 sample t-test or Wilcoxon signed rank test. Statistical significance will be defined at the 0.05 level.

Demographic and baseline characteristics will be summarized as frequencies and percentages, and data will be presented using descriptive statistics.

In general, descriptive statistics and graphs will be used for the presentation of study results including, if relevant, graphs showing the treatment effect over time for patients individually and overall.

Safety will be evaluated on the basis of AEs reported, clinical laboratory data, use of concomitant medications, vital signs, and physical examinations. In addition, blood samples will be analyzed for determination of the presence of anti-velaglucerase alfa antibodies.

All statistical analyses will be performed using SAS® software. Any changes to the analyses proposed in this protocol will be described in the statistical analysis plan and/or the clinical study report.

10.2 Determination of Sample Size

In a previous protocol version (Amendment 4), approximately 40 patients were planned for enrollment in order to achieve a total of 34 evaluable patients (driven by the key secondary efficacy endpoint), assuming a 15 % drop-out rate. A total of 34 evaluable patients provided 99% power to detect a significant change in LS BMD Z-score from baseline after 24 months of treatment (primary efficacy endpoint) when in fact there is a +0.6 change (improvement) in Z-score. The calculation assumed an alpha of 0.05 (2-sided t-test) and a standard deviation of change of 0.6 based on data from study HGT-GCB-044. The 34 evaluable patients also conferred 80% power to detect a significant change in one of the key secondary endpoints, namely the change from baseline in LS BMD Z-score after 12 months of treatment.

Assumptions for the key secondary endpoint power calculation were also based on study HGT-GCB-044 in which a +0.25 change in in Z-score at 12 months was reported with a standard deviation of 0.5.

In the previous amendment (Amendment 5), the number of patients planned for enrolment was revised based on the patient recruitment and retention experience to date to allow for a more realistic and achievable recruitment target. Cumulative enrollment data collected from study initiation to date indicate a suboptimal enrollment rate of 0.5 patient per month. Study enrollment is hindered by the considerable prevalence of screen failures (approximately 50%) resulting from the limited global pool of naïve patients with Gaucher disease who demonstrate bone involvement at baseline and who meet the eligibility criteria of this study. Based on this information, the number of patients planned for enrollment was reduced to at least 19 patients in order to yield 13 evaluable patients. To be considered evaluable, a patient must have an eligible DXA score at Baseline and at 24 months (Week 103 [end of study]). The number of evaluable patients was determined assuming a drop-out rate of 30% based on the rate of early discontinuations reported during the first 2 years of the study. With 13 evaluable patients and assuming the same effect size (increase in LS BMD Z-score of +0.6) and standard deviation (0.6) values at 24 months from study HGT-GCB-044, the study will be 90% powered to detect significant changes (alpha 0.05) in LS BMD Z-score at 24 months (primary efficacy endpoint). As the revised sample size no longer provides adequate statistical power for the detection of significant changes in the key secondary endpoints defined in the previous protocol version, those were demoted to secondary endpoints in the current amendment.

10.3 Analysis Populations

The ITT population will be used for all efficacy analyses and is defined as all enrolled patients who received at least 1 study drug infusion (full or partial). The safety population will be used for all safety analyses and is defined as all enrolled patients who received at least 1 study drug infusion (full or partial).

10.4 Patient Disposition

Patient disposition for those enrolled, treated, completed, or discontinued/withdrew will be presented in summary tables using number and percentage of patients per category; reasons for discontinuation/withdrawal will be presented.

10.5 Demographics and Baseline Characteristics

Demographic (eg, age, sex, and race) and baseline characteristics (eg, medical history, disease history, and bone pathology) will be analyzed using the safety population. Demographic and baseline characteristics will be summarized using either descriptive statistics or frequency distributions, as appropriate.

10.6 Primary Endpoint

10.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to 24 months (Week 103 [end of study]) in LS BMD Z-score as measured by DXA. The null hypothesis is that there is no change from baseline to 24 months in LS BMD Z-scores. A statistically significant change in BMD after 24 months of treatment is highly clinically relevant in this patient population. One sample t-test or Wilcoxon signed rank test will be applied for the change from baseline of LS BMD Z-scores with patients whose LS BMD scores are collected after 24 months of treatment. A 95% confidence interval for the mean of the change from baseline will also be presented.

As a sensitivity analysis, the primary efficacy analysis will be repeated by applying last observation carried forward (LOCF) method. That is, if the LS BMD score is missing at 24 months (Week 103 [end of study]), the last non-missing score before 24 months will be carried forward, and the score at baseline will not be carried forward for the analysis.

The descriptive summary statistics of the percentage of change from baseline of the LS BMD Z-score will also be generated.

10.7 Secondary Endpoints

10.7.1 Safety Endpoints

All patients who receive at least 1 study drug infusion (full or partial) will be assessed for clinical safety and tolerability. The safety population will be used for the analyses of the safety endpoints. No formal statistical tests will be performed on the safety parameters.

The number and proportion of patients for the following parameters will be descriptively summarized:

- Study drug-related AEs
- Infusion-related AEs
- Serious AEs
- Use of concomitant medication
- Clinically abnormal laboratory tests (hematology, serum chemistry, and urinalysis)
- Positive anti-velaglucerase alfa antibody test

AEs will be coded using the MedDRA, and tabular summaries of AEs will be based on all TEAEs recorded. A TEAE is defined as any AE that occurred on or after the time of the first infusion of study drug until 30 days after the last infusion of study drug.

The number and proportion of patients experiencing an AE will be tabulated for the following:

- Overall summary of AEs: Recurrent AEs observed within a patient will be counted once.
- AEs by system organ class (SOC) and preferred term (PT).

- AEs by SOC, PT, and severity: In the case of multiple occurrences of the same AEs (at the PT level) in an individual patient, the AE that is classified as the most severe (ie, maximum severity) will be identified.
- AEs by SOC, PT, and relationship: The AE with the closest relationship to the study drug in the same PT level will be reported.
- SAEs, infusion-related AEs, and AEs that led to permanent discontinuation, by SOC and PT.

Furthermore, an SAE listing and a listing of all patients who permanently discontinued due to an AE(s) will be provided. An infusion-related AE is defined as an AE that begins either during or within 24 hours after the start of the infusion and is judged as related to the investigational product.

Anti-velaglucerase alfa antibody results will also be summarized. For this study, once the patient becomes antibody positive to velaglucerase alfa, they will be considered positive for the remainder of the study.

Any newly occurring abnormalities or worsening from baseline in vital signs, ECG, physical examination, or clinical laboratory test data will be flagged. In addition, the number and proportion of patients with any shifts in vital signs from normal before infusion to abnormal after infusion will be presented. Changes in laboratory parameters will also be summarized using shift tables based on a classification of values as low, normal, or high with respect to the reference range.

10.7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following evaluations:

- Change from baseline to 12 months (Week 51) in LS BMD Z-score. Assessments will be performed at the screening visit and Weeks 51 and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103, end of study) in LS BMD in g/cm^2.
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in BMB score (MRI of LS and femur). Assessments will be performed at the baseline visit and Weeks 51 and 103 (end of study).
- Change from baseline over time in hemoglobin concentration. Assessments will be performed at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
- Change from baseline over time in platelet count. Assessments will be performed at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in normalized liver volume as measured by abdominal MRI. Assessments will be performed at the baseline visit and Weeks 51 and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in normalized spleen volume as measured by MRI. Assessments will be performed at the baseline visit and Weeks 51 and 103 (end of study).

- Shifts in WHO BMD classification (normal bone density, osteopenia, osteoporosis), based on LS T-scores. Assessments will be performed at the baseline visit and Weeks 51 and 103 (end of study).

For WHO BMD classification based on LS T-score endpoint, the number and proportion of patients classified as having normal (T-score ≥-1), osteopenia (-2.5< T-score <-1), or osteoporosis(T-score ≤-2.5) BMD will be captured; patient shifts in BMD classification based on T-score will be reported.

For the remaining secondary efficacy parameters, 1 sample t-test or Wilcoxon signed rank test will be applied for the change from baseline of each endpoint at each time point. In this analysis, the LOCF method for missing values will be applied. As an additional analysis, a linear mixed-effects model will be used as a repeated measures analysis to investigate the improvement of efficacy over time. This model uses all the clinical information obtained on a patient while allowing for the repeated measurements to exhibit correlation between observations within the same patient. Estimates for the clinical parameters obtained over time will account for the baseline measurements and will be adjusted for demographic and baseline factors. This linear mixed-effects model will be described in more detail in a statistical analysis plan.

The descriptive summary statistics of the percentage of change from baseline for the quantitative efficacy endpoints will also be generated.

10.7.3 Other Secondary Efficacy Endpoints (Health Economics and Outcomes Research Endpoints)

Health economic and outcomes research endpoints are secondary endpoints. These include the following:

- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in overall fatigue as measured by the BFI. Assessments will be performed at the baseline visit and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
- Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in bone pain as measured by questions taken from the BPI-SF©.
- Assessments will be performed at the baseline visit and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).

For the health economics and outcomes parameters, 1 sample t-test or Wilcoxon signed rank test will be applied for the change from baseline of each endpoint at each time point. In this analysis, the LOCF method for missing values will be applied.

The descriptive summary statistics of the percentage of change from baseline for the quantitative efficacy endpoints will also be generated.

10.8 Other Assessments or Analyses (Exploratory Measures Research)

[redacted]

10.9 Interim Analysis

No interim analyses are planned for the study.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

Before initiation of the study, the investigators must provide the Sponsor with a completed form FDA 1572, Investigator Agreement, or other applicable regulatory documentation. Investigational product may be administered only under the supervision of the investigators listed on these forms. Curriculum vitae must be provided for the investigators and sub-investigators listed on form FDA 1572 or other regulatory documentation, as applicable.

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions. The investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

11.2 Institutional Review Board or Independent Ethics Committee Approval

Before initiation of the study, the investigator must provide the Sponsor with a copy of the written IRB/IEC approval of the protocol and the informed consent form. This approval must refer to the informed consent form and the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC at least once per year. The IRB/IEC must be notified of completion of the study. Within 3 months of study completion or termination, a final report must be provided to the IRB/IEC. A copy of these reports will be sent to the study clinical monitor. The investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. AEs which are reported to the US FDA or other regulatory agencies (IND safety reports) must be submitted promptly to the IRB/IEC.

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and investigators abide by GCP as described in the 21 CFR Parts 50, 56, and 312 and the ICH GCP Guidelines. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

11.4 Patient Information and Consent

Before enrolling in the clinical study, the patient or legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. Only informed consent forms approved by an IRB or IEC may be used.

An informed consent form that includes information about the study will be prepared and given to the patient or legally authorized representative(s). This document will contain all FDA and ICH-required elements. The informed consent form must be in a language understandable to the patient or legally authorized representative(s) and must specify who informed the patient, or the patient's legally authorized representative(s).

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

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

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

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

A model of the informed consent form to be used in this study will be provided to the sites separately from this protocol.

11.5 Patient Confidentiality

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

11.6 Study Monitoring

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

The study will be monitored by the Sponsor or its designee. Monitoring will be performed by a representative of the Sponsor (clinical study monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

11.7 Case Report Forms and Study Records

Case report forms (paper or electronic) are provided for each patient. All forms must be filled out by authorized study personnel. All corrections to the original eCRF entry must indicate the reason for change. The investigator is required to sign the eCRF after all data have been captured for each patient. If corrections are made after review and signature by the investigator, he or she must be made aware of the changes, and his or her awareness documented by re-signing the eCRF.

11.7.1 Critical Documents

Before Shire initiates the trial (ie, obtains informed consent from the first patient), it is the responsibility of the investigator to ensure that the following documents are available to Shire or its designee:

- Applicable local regulatory documentation (eg, completed FDA form 1572 [statement of Investigator]), signed, dated, and accurate
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed within 24 months of study initiation)
- Copy of investigator and sub-investigator(s) current medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed by name, number, and date of approval or re-approval: protocol, any amendments, subject information/informed consent form, and any other written information to be provided regarding patient recruitment procedures
- Copy of IRB/IEC-approved subject information/informed consent form, any other written information, advertisement (with IRB approval stamp and date of approval)
- Current list of IRB/IEC members/constitution (dated within 12 months prior to study initiation)
- Financial disclosure form signed by investigator and sub-investigator(s)
- Current laboratory reference ranges (if applicable)
- Certification/Quality Assurance scheme/other documentation (if applicable)

Regulatory approval and notification as required must also be available; these are the responsibility of Shire or their designee.

11.8 Data Monitoring Committee

There will be no data monitoring committee.

11.9 Protocol Violations/Deviations

The investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

A record of patients screened, but not entered into the study, is also to be maintained. No protocol exemption will be granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC.

Protocol modifications will only be initiated by the Sponsor and must be approved by the IRB/IEC and submitted to the FDA or other applicable international regulatory authority before initiation.

11.10 Premature Closure of the Study

If the Sponsor, investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between the Sponsor and the investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure of the investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the investigator to protocol requirements

11.11 Access to Source Documentation

Regulatory authorities, the IRB/IEC, or the Sponsor may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters may be performed.

11.12 Data Generation and Analysis

The clinical database will be developed and maintained by a contract research organization or an electronic data capture technology provider as designated by Shire. Shire or its designee will be responsible for performing study data management activities.

Adverse events will be coded using the MedDRA. Concomitant medication will be coded using the WHO-Drug Dictionary. Centralized laboratories will be employed as described in the study manual to aid in consistent measurement of efficacy and safety parameters.

11.13 Retention of Data

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

11.14 Financial Disclosure

The investigator should disclose any financial interests in the Sponsor as described in 21 CFR Part 54 prior to beginning this study. The appropriate form will be provided to the investigator by the Sponsor, which will be signed and dated by the investigator prior to the start of the study. The investigator should promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study.

11.15 Publication and Disclosure Policy

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

It is understood by the investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

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

12 LIST OF REFERENCES

Beutler, E. & Grabowski, G. 2001. Gaucher Disease. *In:* Scriver CR, B. A., Sly WS, Valle D (ed.) *The Metabolic and Molecular Basis of Inherited Disease, 8th Edition.* New York: McGraw-Hill.

Charrow, J., Andersson, H. C., Kaplan, P., Kolodny, E. H., Mistry, P., Pastores, G., Rosenbloom, B. E., Scott, C. R., Wappner, R. S., Weinreb, N. J. & Zimran, A. 2000. The Gaucher registry: demographics and disease characteristics of 1698 patients with Gaucher disease. *Arch Intern Med,* 160, 2835-43.

Charrow, J., Dulisse, B., Grabowski, G. A., Weinreb, N. J. C. I. N. C. G. A. & author reply, P. 2007. The effect of enzyme replacement therapy on bone crisis and bone pain in patients with type 1 Gaucher disease. *Clinical genetics,* 71, 205-11.

Cleeland, C. S. 2002. Pain assessment: the advantages of using pain scales in lysosomal storage diseases. *Acta Paediatr Suppl,* 91, 43-7.

Cox, T. M., Aerts, J. M., Andria, G., Beck, M., Belmatoug, N., Bembi, B., Chertkoff, R., Vom Dahl, S., Elstein, D., Erikson, A., Giralt, M., Heitner, R., Hollak, C., Hrebicek, M., Lewis, S., Mehta, A., Pastores, G. M., Rolfs, A., Miranda, M. C. & Zimran, A. 2003. The role of the iminosugar N-butyldeoxynojirimycin (miglustat) in the management of type I (non-neuronopathic) Gaucher disease: a position statement. *J Inherit Metab Dis,* 26, 513-26.

Cox, T. M. & Schofield, J. P. 1997. Gaucher's disease: clinical features and natural history. *Baillieres Clin Haematol,* 10, 657-89.

Deegan, P. B. & Cox, T. M. 2005. Clinical evaluation of biomarkers in Gaucher disease. *Acta paediatr (Oslo, Norway: 1992). Suppl,* 94, 47-50; discussion 37-8.

Deegan, P. B., Pavlova, E., Tindall, J., Stein, P. E., Bearcroft, P., Mehta, A., Hughes, D., Wraith, J. E. & Cox, T. M. 2011. Osseous manifestations of adult Gaucher disease in the era of enzyme replacement therapy. *Medicine,* 90, 52-60.

DeMayo, R. F., Haims, A. H., McRae, M. C., Yang, R. & Mistry, P. K. 2008. Correlations of MRI-based bone marrow burden score with genotype and spleen status in Gaucher's Disease. *Am J Roentgenol,* 191, 115-123.

Goker-Alpan, O. 2011. Therapeutic approaches to bone pathology in Gaucher disease: past, present and future. *Molecular genetics and metabolism,* 104, 438-47.

Hoffmann, B., Garcia de Lorenzo, A., Mehta, A., Beck, M., Widmer, U. & Ricci, R. 2005. Effects of enzyme replacement therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry Outcome Survey). *J Med Genet,* 42, 247-52.

Maas, M., van Kuijk, C., Stoker, J., Hollak, C. E., Akkerman, E. M., Aerts, J. F. & den Heeten, G. J. 2003. Quantification of bone involvement in Gaucher disease: MR imaging bone marrow burden score as an alternative to Dixon quantitative chemical shift MR imaging--initial experience. *Radiology,* 229, 554-61.

Masek, B. J., Sims, K. B., Bove, C. M., Korson, M. S., Short, P. & Norman, D. K. 1999. Quality of life assessment in adults with type 1 Gaucher disease. *Qual Life Res,* 8, 263-8.

Mikosch, P. & Hughes, D. 2010. An overview on bone manifestations in Gaucher disease. *Wien Med Wochenschr,* 160, 609-24.

Pastores, G. M., Weinreb, N. J., Aerts, H., Andria, G., Cox, T. M., Giralt, M., Grabowski, G. A., Mistry, P. K. & Tylki-Szymanska, A. 2004. Therapeutic goals in the treatment of Gaucher disease. *Semin Hematol,* 41, 4-14.

Pavlova, E. V., Deegan, P. B., Tindall, J., McFarlane, I., Mehta, A., Hughes, D., Wraith, J. E. & Cox, T. M. 2011. Potential biomarkers of osteonecrosis in Gaucher disease. *Blood Cells Mol Dis,* 46, 27-33.

Ries, M., Mengel, E., Kutschke, G., Kim, K. S., Birklein, F., Krummenauer, F. & Beck, M. 2003. Use of gabapentin to reduce chronic neuropathic pain in Fabry disease. *J Inherit Metab Dis,* 26, 413-4.

Rosenbloom, B. & Weinreb, N. 2014. Bone disease in patients with Gaucher disease. *Expert Rev Endocrinol Metab,* 9, 153-162.

Schiffmann, R., Kopp, J. B., Austin, H. A., Sabnis, S., Moore, D. F., Weibel, T., Balow, J. E. & Brady, R. O. 2001. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA,* 285, 2743-9.

Weinreb, Charrow, Andersson, Kaplan, Kolodny, Mistry, Pastores, Rosenbloom, Scott, Wappner & Zimran 2002. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *American Journal of Medicine, The,* 113, 112-119.

Weinreb, N., Taylor, J., Cox, T. M., Yee, J. & vom Dahl, S. 2008. A benchmark analysis of the achievement of therapeutic goals for type 1 Gaucher disease patients treated with imiglucerase. *AM J Hematol,* 83, 890-5.

Appendix 1 Study Schedule of Events

Study Schedule of Events: Screening to Study Week 39

Procedure	Screening	Baseline	Treatment Period Study Week (±7 days)																			
	Day –28 to Day –4	Day –3 to Day 0[a]	1[a]	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39
Informed consent[b]	•																					
Study entrance criteria	•																					
Confirmation of study eligibility		•																				
Medical history	•																					
Glucocerebrosidase Genotype Analysis[c]	•																					
Neurological assessment		•																				
VPRIV infusion			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Vitamin D blood test[d]	•																					
Concomitant medications[e]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
SAE and IRRs	•[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Physical examination		•							•						•						•	
Vital signs	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Urine pregnancy test[g]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Serum β-hCG	•																					
Height	•								•						•						•	
Weight	•								•						•						•	
ECG		•													•							
Serum chemistry		•							•						•						•	
Hematology/Coagulation		•							•						•						•	
Urinalysis		•							•						•						•	

Study Schedule of Events: Screening to Study Week 39

Procedure	Screening	Baseline	Treatment Period Study Week (±7 days)																			
	Day –28 to Day –4	Day –3 to Day 0[a]	1[a]	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39
Serum anti-velaglucerase alfa antibody		•							•						•						•	
MRI to determine liver and spleen volume		•																				
MRI of the lumbar spine and whole femur		•																				
DXA of lumbar spine	•																					
[redacted]		•							•						•						•	
Questions taken from the BPI-SF©		•							•						•						•	
Brief Fatigue Inventory		•							•						•						•	

DXA=dual energy x-ray absorptiometry; ECG=electrocardiogram; β-hCG=human chorionic gonadotropin; IRRs=infusion-related reactions; MRI=magnetic resonance imaging; SAE=serious adverse event; VPRIV=velaglucerase alfa

[a] The baseline visit may be combined with the Week 1 (within 7 days after baseline) Treatment Period visit.

[b] Prior to any study-related procedures.

[c] At screening, all patients will have a blood sample collected for Gaucher disease (GBA) gene sequencing; however, GBA sequencing is not required at screening if documented results are available in the medical history.

[d] Vitamin D testing includes analysis for both 25-hydroxycholecalciferol and 1, 25-dihydroxycholecalciferol.

[e] All patients will receive 800 IU vitamin D (oral) daily starting at the week 1 visit for the duration of the study.

[f] Collection of SAEs and IRRs to begin after signed informed consent is obtained. Study site personnel will report SAEs as described in Section 7.15.2.

[g] At the screening visit both urine (local) and serum pregnancy tests (sent to central laboratory) will be performed. Patients with a positive result for either test at screening will not be eligible. Pregnancy testing at subsequent visits for female patients of childbearing potential will be done with a urine test (local). If a patient has a positive urine test result, the infusion will be held and a serum (ß-hCG) test is to be conducted at the local laboratory responsible for the study.

Study Schedule of Events: Study Week 41 to Study Week 89

Procedure	Treatment Period Study Week (±7 days)																								
	41	43	45	47	49	51	53	55	57	59	61	63	65	67	69	71	73	75	77[d]	79	81	83	85	87	89[d]
Neurological assessment						•																			
VPRIV infusion	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Vitamin D Blood Test[a]						•																			
Concomitant medications[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
SAE and IRRs	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Physical examination						•							•						•						•
Vital signs	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Urine pregnancy test[c]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Height						•							•						•						•
Weight						•							•						•						•
ECG						•													•						
Serum chemistry						•							•						•						•
Hematology/Coagulation						•							•						•						•
Urinalysis						•							•						•						•
Serum anti-velaglucerase alfa antibody						•							•						•						•
MRI to determine liver and spleen volume						•																			
MRI of the lumbar spine and whole femur						•																			
DXA of lumbar spine						•																			
[redacted]						•							•						•						•
Questions taken from the BPI-SF©						•							•						•						•
Brief Fatigue Inventory						•							•						•						•

Study Schedule of Events: Study Week 41 to Study Week 89

Procedure	Treatment Period Study Week (±7 days)																							
	41	43	45	47	49	51	53	55	57	59	61	63	65	67	69	71	73	75	77[d]	79	81	83	85	87	89[d]

DXA=dual energy x-ray absorptiometry; ECG=electrocardiogram; β-hCG=human chorionic gonadotropin; IRRs=infusion-related reactions; MRI=magnetic resonance imaging; SAE=serious adverse event; VPRIV=velaglucerase alfa

[a] Vitamin D testing includes analysis for both 25-hydroxycholecalciferol and 1, 25-dihydroxycholecalciferol.

[b] All patients will receive 800 IU vitamin D (oral) daily starting at the week 1 visit for the duration of the study.

[c] Pregnancy testing for female patients of childbearing potential will be done with a urine test. If a patient has a positive urine test result, the infusion will be held and a serum (β-hCG) test is to be conducted at the local laboratory responsible for the study.

[d] Please refer to Appendix 9 for information on transferring visits at Weeks 77 and 89 to home therapy and the addition of dose continuation infusions due to the COVID-19 pandemic.

Study Schedule of Events: Study Week 91 to End of Study (Week 103)/Early Termination and the 30-day Safety Follow-up

Procedure	Study Week (±7 days)							
	Treatment Period						End of Study (Week 103)/ Early Termination	30-day Safety Follow-up[a]
	91	93	95	97	99	101		
Neurological assessment							•	
VPRIV infusion	•	•	•	•	•	•		
Vitamin D Blood Test[b]							•	
Concomitant medications[c]	•	•	•	•	•	•	•	•
Adverse events	•	•	•	•	•	•	•	•
SAE and IRRs	•	•	•	•	•	•	•	•
Physical examination							•	
Vital signs	•	•	•	•	•	•	•	
Urine pregnancy test[d]	•	•	•	•	•	•	•	
Height							•	
Weight							•	
ECG							•	
Serum chemistry							•	
Hematology/Coagulation							•	
Urinalysis							•	
Serum anti-velaglucerase alfa antibody							•	
MRI to determine liver and spleen volume							•	
MRI of the lumbar spine and whole femur							•	
DXA of lumbar spine							•	
[redacted]							•	
Questions taken from the BPI-SF©							•	
Brief Fatigue Inventory							•	

Study Schedule of Events: Study Week 91 to End of Study (Week 103)/Early Termination and the 30-day Safety Follow-up

Procedure	Study Week (±7 days)							
	Treatment Period						End of Study (Week 103)/ Early Termination	30-day Safety Follow-up[a]
	91	93	95	97	99	101		

DXA=dual energy x-ray absorptiometry; ECG=electrocardiogram; β-hCG=human chorionic gonadotropin; IRRs=infusion-related reactions; MRI=magnetic resonance imaging; SAE=serious adverse event; VPRIV=velaglucerase alfa

[a] The 30-day safety follow-up is to occur 30 (±7) days after the last infusion (Week 101) for patients who complete the study (Section 7.17) and 30 (±7) days after the last infusion for patients who discontinue or are withdrawn prior to Week 103. This follow-up assessment may be conducted over the telephone.

[b] Vitamin D testing includes analysis for both 25-hydroxycholecalciferol and 1, 25-dihydroxycholecalciferol.

[c] All patients will receive 800 IU vitamin D (oral) daily for the duration of the study

[d] Pregnancy testing for female patients of childbearing potential will be done with a urine test. If a patient has a positive urine test result, the infusion will be held and a serum (β-hCG) test is to be conducted at the local laboratory responsible for the study.

Appendix 2 Protocol Amendment 5 Summary of Changes

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **26 July 2018**	**Global/Country/Site Specific** **Global**
Protocol Amendment Summary and Rationale: Clinical Protocol SHP-GCB-402 Amendment 5 represents a number of changes to SHP-GCB-402 Amendment 4 (dated 04 May 2017). The main changes include a reduction of the sample size to provide statistical power for the primary endpoint only, a reclassification of the key secondary endpoints into secondary endpoints, and a change in the Bone Marrow Burden scoring method. The significant changes and additions to Protocol Amendment 5 relative to Protocol Amendment 4 and the rationale for each change are summarized below. Grammatical, typographical, punctuation, format, and minor editorial changes are not enumerated in this table.		
Section(s) Affected by Change	**Description of Change**	**Rationale**
Protocol cover and signature pages	• Updated the name of the study medical monitor	• To provide updated and correct information.
Synopsis (investigational product, dose, and mode of administration), Section 4.1 and Section 6.2	• The duration of study drug infusion was clarified to be a minimum of 60 minutes instead of 60 minutes.	• To provide clear guidance to the investigators.
Synopsis (secondary objectives) and Section 2.2	• The key secondary objectives were re-classified as secondary objectives. • Time points for evaluation of change from baseline were specified for each of the secondary objectives.	• To reflect that the change in the key secondary endpoints is no longer a consideration in the sample size determination and that sample size is calculated based on change in the primary endpoint, only. • For added clarity.
Synopsis (study endpoints), Section 3.2 and Section 10.7.2	• The key secondary endpoints were re-classified as secondary endpoints.	• To reflect that the change in the key secondary endpoints is no longer a consideration in the sample size determination and that sample size is calculated based on change in the primary endpoint, only.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **26 July 2018**	**Global/Country/Site Specific** **Global**
Protocol Amendment Summary and Rationale: Clinical Protocol SHP-GCB-402 Amendment 5 represents a number of changes to SHP-GCB-402 Amendment 4 (dated 04 May 2017). The main changes include a reduction of the sample size to provide statistical power for the primary endpoint only, a reclassification of the key secondary endpoints into secondary endpoints, and a change in the Bone Marrow Burden scoring method. The significant changes and additions to Protocol Amendment 5 relative to Protocol Amendment 4 and the rationale for each change are summarized below. Grammatical, typographical, punctuation, format, and minor editorial changes are not enumerated in this table.		
Section(s) Affected by Change	**Description of Change**	**Rationale**
Synopsis (study population) , Section 4.1, Section 5.1 and Section 10.2	• The number of subjects planned for enrollment was reduced from approximately 40 subjects to at least 19 subjects.	• To provide a more realistic and achievable recruitment target considering the high prevalence of screen failures and the resultant low study enrollment rate. The recruitment challenges result from the rarity of Gaucher disease and the limited global pool of naïve patients with bone involvement who meet the eligibility criteria of this study.
	• The number of expected evaluable subjects was decreased from 34 subjects to 13 subjects.	• To ensure adequate statistical power is maintained to detect significant treatment effect on the primary endpoint despite reduction in numbers of enrolled patients and assuming a 30% drop-out rate.
	• A definition was added to clarify that evaluable patients are those patients who have an eligible DXA score at Baseline and at 24 months (Week 103 [end of study]).	• For added clarity

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **26 July 2018**	**Global/Country/Site Specific** **Global**

Protocol Amendment Summary and Rationale:
Clinical Protocol SHP-GCB-402 Amendment 5 represents a number of changes to SHP-GCB-402 Amendment 4 (dated 04 May 2017). The main changes include a reduction of the sample size to provide statistical power for the primary endpoint only, a reclassification of the key secondary endpoints into secondary endpoints, and a change in the Bone Marrow Burden scoring method. The significant changes and additions to Protocol Amendment 5 relative to Protocol Amendment 4 and the rationale for each change are summarized below. Grammatical, typographical, punctuation, format, and minor editorial changes are not enumerated in this table.

Section(s) Affected by Change	Description of Change	Rationale
Synopsis (efficacy assessment) and Section 7.11.2	• The BMB scoring was changed to follow the DeMayo et al. method instead of the Maas et al. method.	• The DeMayo scoring approach will essentially follow the same soring as the one described in the Maas et al. paper with the elimination of the slightly hypointense and markedly hypointense options as scoring choices to the readers as those cannot be observed in STIR images of the marrow. Omission of these scoring choices will reduce the chance of reading errors.
Synopsis (sample size determination) and Section 10.2	• Text describing change in the assumptions underlying sample size determination in the current versus previous protocol version was added.	• To capture that sample size calculation (and assumptions used for calculation) are now driven by detection of significant change in the primary endpoint without consideration of change in the key secondary endpoints.
	• The power provided by the sample size for the detection of change in the primary endpoint was changed from 99% to 90%.	• To reflect the decrease in statistical power as a result of sample size reduction.
	• The early subject discontinuation rate previously estimated at 15% was revised to 30%.	• To provide a more accurate and realistic estimation of the drop-out rate based on the patient retention experience with the study to date.
Emergency contact information page	• Updated emergency contact information.	• To provide updated and correct information.
Section 4.1	• The key secondary endpoints were removed from the description of the overall study design.	• For consistency with the reclassification of the key secondary endpoints into secondary endpoints.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **26 July 2018**	**Global/Country/Site Specific** **Global**
Protocol Amendment Summary and Rationale: Clinical Protocol SHP-GCB-402 Amendment 5 represents a number of changes to SHP-GCB-402 Amendment 4 (dated 04 May 2017). The main changes include a reduction of the sample size to provide statistical power for the primary endpoint only, a reclassification of the key secondary endpoints into secondary endpoints, and a change in the Bone Marrow Burden scoring method. The significant changes and additions to Protocol Amendment 5 relative to Protocol Amendment 4 and the rationale for each change are summarized below. Grammatical, typographical, punctuation, format, and minor editorial changes are not enumerated in this table.		
Section(s) Affected by Change	**Description of Change**	**Rationale**
Section 5.2	• Minor change made to the wording pertaining to Gaucher disease diagnosis by dry blood spot in the first inclusion criterion.	• For consistency of wording between the synopsis and Section 5.2.
Section 5.3	• Minor change made to the wording of the first exclusion criterion.	• For consistency of wording between the synopsis and Section 5.3.
Section 7.8	• The maximum time allowed between 2 doses for patients who miss their scheduled dose was corrected to 21 days.	• To update dose timing based on a change made in the previous amendment but was erroneously not captured in this section.
Section 7.14.1	• Adverse event definition was added.	• To provide clear guidance to the investigators.
Section 8.1	• Viral testing was removed from the list of Screening Visit assessments.	• To clarify that viral testing will not be performed at Screening as per the Schedule of Events.
Appendix 1 (Study Schedule of Events, Week 91 to Week 103/Early Termination and the 30-day Safety Follow-up; footnote a)	• A window of ±7 days was specified for the 30-day safety follow-up of patients who complete the study.	• To provide clear guidance to the investigators.

Appendix 3 Protocol Amendment 4 Summary of Changes

Clinical Protocol SHP-GCB-402 Amendment 4 represents a number of changes to SHP-GCB-402 Amendment 3 (dated 06 July 2016). These include a revision of the definition of infusion-related reactions (IRRs) to match that in the Summary of Product Characteristics, revision of the vitamin D dose, and increase in the subject age range for enrollment as well as other changes that are summarized below.

Changes in grammar, spelling, punctuation, format, minor editorial changes (including changes for consistency and clarity), and updates to the list of abbreviations and cross-references are not enumerated in this summary of changes. The text solely deleted is presented as ~~strikethrough~~ and the text revised or added is presented in **bold** font.

The significant changes and additions to Protocol Amendment 4 from Protocol Amendment 3 along with a rationale for each change are provided in the table below.

Section	Summary of Changes	Rationale for change
Synopsis Concomitant Medication, Dose, and Mode of Administration Section 6.8.2 Concomitant Therapy	All patients will also receive ~~600~~ **800** IU ~~25 hydroxyvitamin~~ **vitamin** D (oral) daily starting at the week 1 visit…	• Switched to 800 IU to facilitate sourcing of vitamin D.
Synopsis Exploratory objectives Section 2.3 Exploratory Objectives	[redacted]	[redacted]

Section	Summary of Changes	Rationale for change
Synopsis Study Endpoints Section 3.1 Primary Endpoint Section 3.2.1 Key Secondary Endpoints Section 3.2.2 Other Secondary Endpoints	The primary endpoint ~~of this study~~ is: • Change from baseline to 24 months (Week 103 [end of study]) in LS BMD Z-score as measured by DXA. ~~Assessments will be performed at the screening visit and Weeks 25, 51, 77, and 103 (end of study).~~ The key secondary endpoints ~~of this study~~ are: • Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in BMB score (MRI of LS and femur). Assessments will be performed at the baseline visit and Weeks ~~25~~ 51~~77~~ and 103 (end of study). • Change from baseline to 12 months (Week 51) in LS BMD Z-score. Assessments will be performed at the screening visit and Weeks ~~25~~ 51~~77~~ and 103 (end of study). Other secondary efficacy endpoints ~~of this study~~ are: • Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in normalized liver volume as measured by abdominal MRI. Assessments will be performed at the baseline visit and Weeks ~~25~~ 51~~77~~ and 103 (end of study). • Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in normalized spleen volume as measured by MRI. Assessments will be performed at the baseline visit and Weeks ~~25~~ 51~~77~~ and 103 (end of study). Shifts in WHO BMD classifications (normal bone density, osteopenia, and osteoporosis) based on LS T-scores. Assessments will be performed at baseline (screening visit) and Weeks ~~25~~ 51~~77~~ and 103 (end of study)	• Revised text to improve clarity. • Revised text to improve clarity. • Eliminated assessments at Weeks 25 and 77 to ease subject burden as data from these visits will not be used in the determination of any endpoints.
Synopsis Study Duration	Patients will be dosed for ~~102~~ 101 weeks (51 infusions), preceded by a Screening/baseline period of up to 28 days and followed by a 30-day Safety Follow-up Period.	• Corrected an error.
Synopsis Study Population	**Approximately** ~~Up to~~ 40 patients (≥18 and ≤~~65~~ **70** years of age) with type 1 Gaucher disease who are naïve to enzyme replacement therapy (ERT)/substrate reduction therapy (SRT) are planned to be recruited to achieve 34 evaluable patients.	• Revised text to improve clarity; increased the upper limit of enrolment age to 70 years to facilitate enrolment.

Section	Summary of Changes	Rationale for change
Synopsis Study Inclusion Criteria Section 5.2 Inclusion Criteria	2. Patients must have a LS BMD Z-score <-1 **or BMD T-score of <-1** as measured by DXA during the screening phase.	• Added criterion of BMD T-score to facilitate enrolment after consideration of this measure as an appropriate alternative to BMD Z-score.
Synopsis Study Inclusion Criteria Section 5.2 Inclusion Criteria	4. The patient is ≥18 and ≤~~65~~ **70** years of age.	• Increased the upper limit of enrolment age to 70 years to facilitate enrolment.
Synopsis Study Exclusion Criteria Section 5.3 Exclusion Criteria	8. Severe vitamin D deficiency to the level that would be expected to result in osteomalacia (~~25-hydroxyvitamin~~**vitamin** D < 10 ng/mL [25 nmol/L]). If there is mild vitamin D insufficiency at screening (~~25-hydroxyvitamin~~**vitamin** D > 10 and < 30 ng/mL) treat with 4000 IU ~~25-hydroxyvitamin~~**vitamin** D per day for 1 month and rescreen.	• Revised text (Vitamin D) for simplicity.
Synopsis Efficacy Assessments	[redacted]	[redacted]

Section	Summary of Changes	Rationale for change
Synopsis Efficacy Assessments Section 3.3 Exploratory Endpoints	[redacted] … [redacted]	[redacted]
Section 4.1 Overall Study Design and Plan	… In order to yield 34 evaluable patients, ~~up to~~ **approximately** 40 patients will be enrolled to receive VPRIV at the recommended starting dose for treatment-naïve patients of 60 U/kg EOW as a 60-minute intravenous infusion.	• Revised text to improve clarity.
Section 4.3 Study Duration	…the duration of study participation for each subject will be approximately 110 weeks, including ~~102~~**101** weeks on treatment (51 infusions),…	• Corrected an error.
Section 5.1 Study Population	It is planned that ~~up to~~ **approximately** 40 patients with type 1 Gaucher disease who are at least 18 years of age but no more than ~~65~~ 70 years of age and who are naïve to ERT/substrate reduction therapy (SRT) will be enrolled. Patients will have a documented diagnosis of type 1 Gaucher disease, as documented by deficient GCB activity in leukocytes (whole blood only) or cultured skin fibroblasts and a LS BMD Z-score <-1 **or BMD T-score of < -1** as measured by DXA during the screening phase.	• Revised text to improve clarity. • Increased the upper limit of enrolment age to 70 years to facilitate enrolment. • Added criterion of BMD T-score to facilitate enrolment after consideration of this measure as an appropriate alternative to BMD Z-score.
Section 6.2 Treatment Administered	Patients will continue to receive 60 U/kg EOW for 24 months (~~102~~ 101 weeks). A 30-day follow-up period is planned after the final dose.	• Corrected an error.

Section	Summary of Changes	Rationale for change
Section 6.3 Selection and Timing of Dose for Each patient	The first dose of VPRIV will be based on the patient's weight at ~~baseline~~ screening (Days ~~-3~~ -28 to Day -4 ~~0~~). A change in patient weight of ±5% from ~~baseline~~ screening or the last weight used to recalculate the dose will require a new dose recalculation by the clinical site. Study drug infusions are to occur on approximately the same day of the week, but may occur every 14 days (±~~3~~ **7** days) of the target day in order to facilitate patient scheduling. If at all possible, missed infusions should be avoided. If a patient is not dosed within ~~17~~ 21 days from their scheduled dose, the patient should receive the next infusion as soon as possible.	• Weight measurement will be performed at screening to allow for calculation of patient doses before baseline/Week 1 visit. • The window was changed to ±7 days to allow for patient rescheduling and to facilitate protocol execution.
Section 6.6 Home Infusion of Velaglucerase alfa	In addition, a urine pregnancy test will be conducted at each home infusion visit **for women of childbearing potential**.	• Added text to improve clarity.
Section 6.7 Infusion Reactions and Management	The management of infusion-related reactions (IRRs) should be based on the severity of the reaction**. Such management may include, at the discretion of the investigator,** eg, slowing the infusion rate, treatment with medications such as antihistamines, antipyretics, and/or corticosteroids and/or stopping and resuming treatment with ~~increased~~ **prolonged** infusion ~~time~~ **duration**. **In cases when required and at site's discretion, additional clinical laboratory samples can be collected for further analysis of IRRs. Suggested laboratory evaluation includes complete blood count, complete metabolic panel including liver and renal function tests, CH50, C3, C4, C1 inhibitor, C3a and C5a, total tryptase, histamine, immune complex and IgE levels.**	• Added or modified text to improve clarity. • Added a description of suggested lab testing for further evaluation of IRRs according to recent expert review of the study protocol.
Section 6.8.3 Contraception	~~8. Double barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)~~	• Removed this method as it is not considered a highly effective method of contraception (<1% failure rate per year) by Clinical Trial Facilitation Group guidance (2014).

Section	Summary of Changes	Rationale for change
Section 6.11 Storage and Accountability	The disposition of all investigational product delivered to a principal investigator must be recorded on a patient-by-patient basis by completing the Clinical Trial Material Accountability Log **or local accountability log**. The date and time of administration of the investigational product must be documented on the appropriate eCRF. The principal investigator, clinical research coordinator, or designee (eg, pharmacist**, third party vendor**, etc.) must ensure that all documentation regarding investigational product receipt, storage, dispensing, loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the **unused** investigational product is available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.	• Added text for clarity.
Section 6.12 Investigational Product Retention at Study Site	If the investigational product is to be destroyed by the sites **or a third party vendor**, the sites **or third party vendor** must follow their own process/policy that describes such activities. The site **or third party vendor** must retain copies of these documents within the Site Regulatory Binder. The site **or third party vendor** must ensure that the Clinical Trial Material Accountability and Destruction Log is complete, accurate, and ready for review and/or audit at each monitoring visit.	• Added text for clarity.
Section 7 STUDY PROCEDURES	Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks (±~~3~~ 7 days) of the study (Study Schedule of Events table in Section 13).	• The window was changed to ±7 days to allow for patient rescheduling and to facilitate protocol execution.
Section 7.8 Investigational Product Administered	All doses of VPRIV will be administered by continuous intravenous infusion. Study drug infusions are to occur on approximately the same day of the week but may occur every 14 days (±~~3~~ 7 days of the target day) in order to facilitate patient scheduling.	• The window was changed to ±7 days to allow for patient rescheduling and to facilitate protocol execution.
Section 7.11.8.1 [redacted]	[redacted]	[redacted]
Section 7.11.8.2 [redacted]	[redacted]	[redacted]

Section	Summary of Changes	Rationale for change
Section 7.11.10 Physical Examination	A full physical examination will be performed **by the investigator** with a thorough review of body systems on specified study visits.	• Added text for clarity.
Section 7.11.13 Electrocardiography	… ECG recordings will be read locally at the clinical site by a ~~qualified cardiologist~~**the investigator or a qualified designee**.	• For the purpose of this assessment, evaluation by a qualified cardiologist is not deemed necessary.
Section 7.11.14 Clinical Laboratory Test	Clinical laboratory tests will include the following (Table 7-3). **Any clinically significant findings as determined by the investigator will be recorded as an AE on the appropriate eCRF.**	• Text added for further details on AE reporting.
Section 7.11.14 Clinical Laboratory Test Table 7-3	Serum Chemistry: - **Vitamin D (screening and Weeks 51 and 103 only)** ➢ 25-hydroxycholecalciferol ➢ 1, 25-dihydroxycholecalciferol ~~Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and human immunodeficiency virus (HIV)~~ The following safety laboratory tests will be performed at Screening: • ~~Hepatitis B surface antigen (HBsAg)~~ • ~~Hepatitis C virus (HCV)~~ • ~~Human immunodeficiency virus (HIV)~~ • ~~25-hydroxyvitamin~~ **Vitamin D** blood test	• Added text (Vitamin D) for clarity. • Removed information on screening test for HBV, HCV and HIV as these are not being performed and are not part of the evaluation of the inclusion/ exclusion criteria. • Revised text (Vitamin D) for simplicity.
Section 7.14.1.7 Infusion-related Adverse Event Definition	An IRR will be defined as an AE that 1) begins either during or within ~~12~~ **24** hours after the start of the infusion and 2) is judged as related to study drug.	• The definition of IRRs has been updated for alignment with global labeling; also, widening the timeframe will ensure IRRs are not underreported.
Section 7.17.1 Safety-related Study Stopping Rules	For patients who discontinue or are withdrawn prior to the Week 103 end of study visit, a follow-up assessment for safety will occur 30 (±7) days after their last infusion. **This follow-up assessment may be conducted over the telephone.**	• The safety follow-up collects information on AE/SAEs, IRRs and concomitant medications, which can be performed over the phone.

Section	Summary of Changes	Rationale for change
Section 8.1 Screening Visit (Days -28 to -4)	**Height** **Weight** ~~25 hydroxyvitamin~~**Vitamin** D blood test	• Weight measurement will be performed at screening visit to allow for calculation of patient doses before baseline/Week 1 visit; height and weight are measured together. • Revised text (Vitamin D) for simplicity.
Section 8.2 Baseline (Days -3 to 0)	~~Height~~ ~~Weight~~	• Weight measurement will be performed at screening visit to allow for calculation of patient doses before baseline/Week 1 visit; height and weight are measured together.
Section 8.3.3 Weeks 25 and 77	~~MRI to determine liver and spleen volume~~ ~~MRI of the LS and whole femur~~ ~~DXA of LS~~	• Eliminated assessments at Weeks 25 and 77 to ease subject burden as data from these visits will not be used in the determination of any endpoints.
Section 8.3.4 Week 51 Section 8.4 End of Study (Week 103)/Early Termination Procedures	**Vitamin D blood test**	• Added this text to conform with the schedule of activities.

Section	Summary of Changes	Rationale for change
Section 10.2 Determination of Sample Size	A total of 34 evaluable patients will provide ~~at least 90~~**99**% power to detect a significant change in LS BMD Z-score from baseline after 24 months of treatment (primary efficacy endpoint) when in fact there is a +0.6 change (improvement) in Z-score. A total of 34 **evaluable** patients will also provide 80% power to detect significant change in LS BMD Z-score from baseline after 12 months of treatment (**one of key** secondary efficacy ~~endpoint). With consideration of 15% early discontinuation up to~~ **endpoints), when there is a +0.25 change in Z-score and a standard deviation of the change is 0.5 based on the data from the Study HGT-GCB-044.** **Considering the potential for appreciable numbers** of early discontinuation**s before** 24 months, ~~up to~~ **it is** planned **that approximately** 40 patients will be enrolled and needed for the primary efficacy analysis.	• Revised text to improve clarity.
Section 10.6.1 Primary Efficacy Endpoint	…~~Assessments will be performed at screening and Weeks 25,51,77, and 103 (end of study).~~	• Revised text to improve clarity.
Section 10.7.1 Safety Endpoints	… An infusion-related AE is defined as an AE that begins either during or within ~~12~~ **24** hours after the start of the infusion and is judged as related to the investigational product.	• The definition of IRRs has been updated for alignment with global labeling; also, widening the timeframe will ensure IRRs are not underreported.
Section 10.7.2 Secondary Efficacy Endpoints	The key secondary endpoints are: • Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in BMB score (MRI of LS and femur). Assessments will be performed at the baseline visit and Weeks ~~25~~ 5177 and 103 (end of study). • Change from baseline to 12 months (Week 51) in LS BMD Z-score. Assessments will be performed at the screening visit and Weeks ~~25~~ 5177 and 103 (end of study). Other secondary efficacy endpoints include the following evaluations: …… • Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in normalized liver volume as measured by abdominal MRI. Assessments will be performed at the baseline visit and Weeks ~~25~~ 5177 and 103 (end of study). • Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in normalized spleen volume as measured by MRI. Assessments will be performed at the	• Eliminated assessments at Weeks 25 and 77 to ease subject burden as data from these visits will not be used in the determination of any endpoints.

<table>
<tr><th>Section</th><th>Summary of Changes</th><th>Rationale for change</th></tr>
<tr><td></td><td>baseline visit and Weeks ~~25~~ 51~~77~~ and 103 (end of study).
Shifts in WHO BMD classification (normal bone density, osteopenia, osteoporosis), based on LS T-scores. Assessments will be performed at the baseline visit and Weeks ~~25, 77,~~51 and 103 (end of study).</td><td></td></tr>
<tr><td>Section 10.8

Other Assessments or Analyses (Exploratory Measures Research)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Section 13 Schedule of Events</td><td>Study Schedule of Events: Screening to Study Week 39
<table>
<tr><td></td><td>Treatment Period
Study Week (~~±3~~ 7 Days)</td></tr>
<tr><td>Procedure</td><td></td></tr>
<tr><td>…</td><td></td></tr>
<tr><td>~~25 hydroxyvitamin~~ Vitamin D blood test</td><td></td></tr>
</table>
<table>
<tr><td rowspan="2">Procedure</td><td>Screening</td><td></td></tr>
<tr><td>Day -28 to -4</td><td>Da</td></tr>
<tr><td>Height</td><td>•</td><td></td></tr>
<tr><td>Weight</td><td>•</td><td></td></tr>
</table>
[d] Vitamin D testing includes analysis for both 25-hydroxycholecalciferol and 1, 25-dihydroxycholecalciferol.
[e] All patients will received ~~600~~ 800 IU ~~25 hydroxyvitamin~~ vitamin D (oral) daily starting at the week 1 visit for the duration of the study.

Study Schedule of Events: Study Week 41 to Study Week 89
<table>
<tr><td></td><td>Treatment Period
Study Week (~~±3~~ 7 Days)</td></tr>
</table>
<table>
<tr><th rowspan="2">Procedure</th><th colspan="7">Treatment Period
Study Week (± 7 days)</th></tr>
<tr><th>41</th><th>43</th><th>45</th><th>47</th><th>49</th><th>51</th><th>53</th></tr>
<tr><td>Vitamin D Blood Test</td><td></td><td></td><td></td><td></td><td></td><td>•</td><td></td></tr>
</table></td><td>• The window was changed to ±7 days to allow for patient rescheduling and to facilitate protocol execution

• Weight measurement will be performed at screening visit to allow for calculation of patient doses before baseline/Week 1 visit; height and weight are measured together.
• Text added for clarity on Vitamin D testing.
• Switched to 800 IU to facilitate sourcing of vitamin D

• The window was changed to ±7 days to allow for patient rescheduling and to facilitate protocol execution.

• Text added for clarity on</td></tr>
</table>

<table>
<tr><th>Section</th><th>Summary of Changes</th><th>Rationale for change</th></tr>
<tr><td></td><td>
[a] Vitamin D testing includes analysis for both 25-hydroxycholecalciferol and 1, 25-dihydroxycholecalciferol.
[b] All patients will received <s>600</s> 800 IU <s>25 hydroxyvitamin</s> vitamin D (oral) daily starting at the week 1 visit for the duration of the study.

Study Schedule of Events: Study Week 91 to End of Study (Week 103)/Early Termination and the 30-day Safety Follow-up
<table>
<tr><td>Study Week (±<s>3</s> 7 Days)</td></tr>
</table>
<table>
<tr><th rowspan="2">Procedure</th><th colspan="8">Study Week (± 7 days)</th></tr>
<tr><th colspan="6">Treatment Period</th><th colspan="2">End of Study (Week 103)/ Early Termination</th></tr>
<tr><td>Vitamin D Blood Test</td><td></td><td></td><td></td><td></td><td></td><td></td><td>•</td><td></td></tr>
</table>
[a] The 30-day safety follow-up is to occur 30 days after the last infusion (Week 101) for patients who complete the study (Section 7.18) and 30 (±7) days after the last infusion for patients who discontinue or are withdrawn prior to Week 103. This follow-up assessment may be conducted over the telephone.
[b] Vitamin D testing includes analysis for both 25-hydroxycholecalciferol and 1, 25-dihydroxycholecalciferol.
[c] All patients will received <s>600</s> 800 IU <s>25 hydroxyvitamin</s> vitamin D (oral) daily for the duration of the study.
</td><td>
Vitamin D testing.
• Switched to 800 IU to facilitate sourcing of vitamin D.

• The window was changed to ±7 days to allow for patient rescheduling and to facilitate protocol execution.

• The safety follow-up collects information on AE/SAEs, IRRs and concomitant medications, which can be performed over the phone.
• Text added for clarity on Vitamin D testing.
• Switched to 800 IU to facilitate sourcing of vitamin D.
</td></tr>
</table>

Appendix 4 Protocol Amendment 3 Summary of Changes

Previous Version: Protocol Amendment 2 (02 June 2016)

Clinical Protocol SHP-GCB-402 Amendment 3 clarifies administrative changes made to protocol SHP-GCB-402, Amendment 2 dated 02 Jun 2016. Clarifications provided in administrative change memo dated 27 Jan 2016 were not included in protocol amendment 2 as an oversight. The minimum age for inclusion has changed to 18; therefore, informed consent by parents has been eliminated.

Changes in grammar, spelling, punctuation, format, minor editorial changes (including changes for consistency and clarity), and updates to the list of abbreviations and cross-references are not enumerated in this summary of changes. The text solely deleted is presented as ~~strikethrough~~ and the text revised or added is presented in **bold** font.

The significant changes and additions to Protocol Amendment 3 from Protocol Amendment 2 are captured in the table below.

Section	Summary of Changes
Synopsis Concomitant Medication, Dose, and Mode of Administration Section 6.8.2 Concomitant Therapy	All patients will also receive 600 IU 25-hydroxyvitamin D (oral) daily **starting at the week 1 visit…**
Synopsis Secondary Objectives	…and **bone marrow burden (**BMB**)** as measured
Synopsis Study Inclusion and Exclusion Criteria	1. The patient has a …blood spot test is not sufficient. Diagnosis **may** be based on results obtained prior to Screening if documented in the patient's medical history.
Synopsis Study Inclusion and Exclusion Criteria Section 5.2 Inclusion Criteria Section 6.8.3 Contraception	5. Female ~~and male patients (with partners)~~ patients of childbearing potential must agree to use a medically acceptable method of contraception at all times during the study.
Synopsis Study Inclusion and Exclusion Criteria Section 5.2 Inclusion Criteria	6. The patient, ~~and the patient's parent(s)~~ or patient's legally authorized representative ~~legal guardian(s)~~, if applicable, understands the nature, scope, and…

Section	Summary of Changes
Section 7.1 Informed Consent	Prior to conducting any study-related procedures, written informed consent must be obtained from the patient, ~~the patient's parent(s),~~ or the patient's legally authorized representative(s) and assent from the patient (if applicable)…. The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the patient, ~~the patient's parent(s),~~ or
Synopsis	[redacted]
Section 5.6 Home Infusion of Velaglucerase alfa	…If the **serum human chorionic gonadotropin** (β-hCG) result is also positive, the Investigator is to contact the Shire Medical Monitor to determine the appropriate course of action…. If there are no IRRs during the first 3 ~~home~~ infusions the observation and vital signs post-infusion can be omitted at the discretion of the investigator.
Section 7.12.4 Vital Signs Table 7-2 Schedule for Recording of Vital Signs at Infusion	The schedule included in Table 7 2 will be followed for recording vital signs at **home or clinic** infusion visits. [a] If there are no infusion-related reactions during the first 3 ~~home~~ infusions, the observation and vital signs post-infusion can be omitted at the discretion of the investigator.
Section 7.12.6 Clinical Laboratory Tests:	**The following safety laboratory tests will be performed at Screening:** • **Hepatitis B surface antigen (HBsAg)** • **Hepatitis C virus (HCV)** • **Human immunodeficiency virus (HIV)** • **25-hydroxyvitamin D blood test** **The following laboratory tests will be performed at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103:** • **Coagulation** o **Prothrombin time** o **Activated partial thromboplastin time (aPTT)** o **D-dimer** **The laboratory tests for Hematology, Serum Chemistry, and Urinalysis are to be performed as indicated in sections 7.11.5 and 7.11.6 and the Schedule of Events (at Baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103).**
Section 7.12.7 Antibody Assessments	…at specified time points throughout the study **(Weeks 13, 25, 37, 51, 65, 77, 89, and 103).**

Section	Summary of Changes
Section 7.12.8 Pregnancy Testing	...Patients with a positive result for either test will not be eligible for this study. **The screening urine pregnancy test will be performed locally and the screening serum pregnancy test will be analyzed at the central laboratory responsible for this study.** …local laboratory will analyze and report all **subsequent urine and serum** pregnancy testing results. …If the **serum** β-hCG result is also positive…
Section 7.17 Removal of Patients from the Trial or Investigational Product	…The patient, ~~the patient's parent(s),~~ or the patient's legally authorized representative… …If a patient~~, the patient's parent(s)~~, or the patient's legally authorized…
Section 8 Study Activities	Study procedures will be conducted only after patients ~~(or parent/legal guardian)~~ have provided written informed consent to participate in the study….
Section 8.1 Screening Visit (Days -28 to -4)	… • SAEs • Vital signs • ~~Hemoglobin concentration~~ • ~~Platelet count~~ • **25-hydroxyvitamin D blood test** • **HBsAg, HCV, HIV**
Section 8.2 Baseline (Days -3 to 0)	Note: The baseline visit may be combined with the Week 1 (**within** 7 days **after baseline)** Treatment Period visit. … • Hematology/**Coagulation**
Section 8.3.1	8.3.1 Weeks 1, 3, 5, **7,** 9, 11, 15, 17**, 19,** 21, 23, 27, 29, **31**, 33, 35, 39, 41, **45**, 43, 47, 49, 53, 55, **57,** 59, 61, 63, 67, 69, **71,** 73, 75, 79, 81, **83**, 85, 87, 91, 93**, 95,** 97, 99, and 101
Section 8.3.2	~~8.3.2 Weeks 7, 19, 31, 45, 57, 71, 83, and 95~~ (merged above) • ~~VPRIV infusion~~ • ~~Concomitant medication~~
Section 8.3.3	• ~~AEs~~ • ~~SAE and IRRs~~ • ~~Vital signs~~
Section 8.3.4	• ~~Pregnancy test~~ ~~8.3.3~~ **8.3.2 Weeks 13, 37, 65, and 89** • Hematology/**Coagulation** ~~8.3.4~~ **8.3.3** Weeks 25 and 77

<table>
<tr><th>Section</th><th>Summary of Changes</th></tr>
<tr><td></td><td>• Hematology/Coagulation
~~8.3.5~~ 8.3.4 Week 51
• Hematology/Coagulation
8.4 End of Study (Week 103)/Early Termination Procedures
• Hematology/Coagulation</td></tr>
<tr><td>Section 10.6.1 Primary Efficacy Endpoint</td><td>The primary efficacy endpoint is the change from baseline to 24 months (Week 103 [end of study]) in LS BMD Z score as measured by DXA. Assessments will be performed at ~~baseline~~ screening and Weeks 25, 51, 77, and 103 (end of study).</td></tr>
<tr><td>Section 11.4 Patient Information and Consent</td><td>Before enrolling in the clinical study, the patient ~~or the patient's parent(s)~~ or legally authorized representative(s) …
… and given to the patient ~~or the patient's parent(s)~~ or legally authorized representative(s).
… understandable to the patient ~~or the patient's parent(s)~~ or legally authorized representative(s) and must specify who informed the patient, ~~the patient's parent(s),~~ or the patient's legally authorized representative(s).

After reading the informed consent document, the patient ~~or the patient's parent(s)~~ or … by the personally dated signature of the patient~~, the patient's parent(s),~~ or the patient's legally authorized representative(s) …

If the patient ~~or the patient's parent(s)~~ or legally authorized representative(s) is unable to read… dated signature of ~~the patient's parent(s) or~~ the patient's legally authorized representative. …

A copy of the signed and dated consent document(s) must be given to the patient ~~or the patient's parent(s)~~ or legal representative(s). …</td></tr>
<tr><td>13 Study Schedule of Events</td><td>
<table>
<tr><th colspan="2">Study Schedule of Events: Screening to Study Week 39</th></tr>
<tr><th rowspan="2">Procedure</th><th>Screening</th></tr>
<tr><th>Day –28
to
Day –4</th></tr>
<tr><td>HBsAg, HCV, HIV</td><td>•</td></tr>
<tr><td>25-hydroxyvitamin D blood test</td><td>•</td></tr>
<tr><td>Serum β-hCG</td><td>•</td></tr>
<tr><td>Hematology/Coagulation</td><td></td></tr>
</table>
Abbreviations: DXA=dual energy x-ray absorptiometry; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus;

[a] The baseline visit may be combined with the Week 1 (within 7 days after baseline) Treatment Period visit….
[d] All patients will receive 600 IU 25-hydroxyvitamin D (oral) daily starting at the week 1</td></tr>
</table>

Section	Summary of Changes
	visit for the duration of the study…. [f] **At the screening visit both urine (local) and serum pregnancy tests (sent to central laboratory) will be performed. Patients with a positive result for either test at screening will not be eligible.** Pregnancy testing **at subsequent visits** for female patients of childbearing potential will be done with a urine test (**local**). If a patient has a positive urine test result, the infusion will be held and a serum (β-hCG) test is to be **conducted at the local laboratory responsible for the study**. ~~At the screening visit both urine and serum pregnancy tests will be performed. Patients with a positive result for either test at screening will not be eligible.~~ **Study Schedule of Events: Study Week 41 to Study Week 89** Hematology/**Coagulation** [a] All patients will receive 600 IU 25-hydroxyvitamin D (oral) daily **starting at the week 1 visit** for the duration of the study…. [b] Pregnancy testing for female patients of childbearing potential will be done with a urine test. If a patient has a positive urine test result, the infusion will be held and a serum (β-hCG) test is to be conducted **at the local laboratory responsible for the study.** **Study Schedule of Events: Study Week 91 to End of Study (Week 103)/Early Termination and the 30-day Safety Follow-up** Hematology/**Coagulation** [a] Pregnancy testing for female patients of childbearing potential will be done with a urine test. If a patient has a positive urine test result, the infusion will be held and a serum (β-hCG) test is to be conducted **at the local laboratory responsible for the study.**

Appendix 5 Protocol Amendment 2 Summary of Changes

Previous Version: Protocol Amendment 1 (14 September 2015)

Clinical Protocol SHP-GCB-402 Amendment 2 has been amended to extend evaluation of the primary endpoint from 12 to 24 months and secondary endpoints from 24 to 12 months, add specific guidance for contraception, update emergency contact information, add concomitant dosing of 600 IU 25-hydroxyvitatmin D daily, [redacted], and revise age range to ≥18 and ≤65 years of age.

NOTE: Changing the IRR definition timeframe from 12 hours to 24 hours was considered in order to align with the post-marketing definition; however, the consensus of the clinical trial team was to remain consistent with the definition used in the most recent clinical studies.

Changes in grammar, spelling, punctuation, format, minor editorial changes (including changes for consistency and clarity), and updates to the list of abbreviations and cross-references are not enumerated in this summary of changes. The text solely deleted is presented as ~~strikethrough~~ and the text revised or added is presented in **bold** font.

The significant changes and additions to Protocol Amendment 2 from Protocol Amendment 1 are captured in the table below.

Section	Summary of Changes
Title Page Appendix 6 Protocol Signature Page	~~Medical Monitor:~~ [redacted]~~, MD, PhD~~ **Medical Monitor:** [redacted]**, MD**
Synopsis Concomitant Medication, Dose and Mode of Administration Section 6.8.2 Concomitant Therapy Appendix 1 Study Schedule of Events Footnotes	**All** patients **will also receive 600 IU 25-hydroxyvitamin D (oral) daily**
Synopsis Primary Objective Section 2.1 Primary Objective	The primary objective is: To evaluate the effect of VPRIV therapy (60 U/kg EOW) in treatment-naïve patients with type 1 Gaucher disease on change from baseline in lumbar spine (LS) bone mineral density (BMD) Z-score as measured by dual energy x-ray absorptiometry (DXA) after ~~12~~ **24** months of treatment

Section	Summary of Changes
Synopsis Secondary Objectives Section 2.2.1 Key Secondary Objective	To evaluate the effect of VPRIV therapy (60 U/kg EOW) on BMD in treatment-naïve patients with type 1 Gaucher disease as measured by the change from baseline in LS BMD Z-score at ~~24~~ **12** months, and bone marrow burden (BMB) as measured by magnetic resonance imaging (MRI) of the LS and femur after 12 and 24 months of treatment
Synopsis Study Endpoints Section 3.1 Primary Endpoint Section 4.1 Overall Study Design and Plan	Change from baseline to ~~12~~ **24** months ~~(Week 51)~~ **(Week 103 [end of study]**) in LS BMD Z-score as measured by DXA. Assessments will be performed at the screening visit and Weeks 25, 51, 77, and 103 (end of study).
Synopsis Study Endpoints Section 3.2.1 Key Secondary Endpoints Section 4.1 Overall Study Design and Plan Section 10.7.2 Secondary Efficacy Endpoints	The key secondary endpoints of this study are: • Change from… • Change from baseline to ~~24 months (Week 103 [end of study])~~ to **12 months (Week 51)** in LS BMD Z-score.
Synopsis Study Endpoints Section 3.2.2 Other Secondary Efficacy Endpoints Section 10.7.2 Secondary Efficacy Endpoints	Other secondary efficacy endpoints of this study are: • ~~Change from baseline over time in hemoglobin concentration. Assessments will be performed at baseline and Weeks 7, 19, 31, 45, 57, 71, 83, and 95.~~ • ~~Change from baseline over time in platelet count. Assessments will be performed at baseline and Weeks 7, 19, 31, 45, 57, 71, 83, and 95.~~ • **Change from baseline over time in hemoglobin concentration. Assessments will be performed at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).** • **Change from baseline over time in platelet count. Assessments will be performed at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).**
Synopsis Efficacy Assessments: [redacted] Section 3.3 Exploratory Endpoints Section 7.11.8 Exploratory	[redacted]

Section	Summary of Changes
Measures of Potential Relevance in Gaucher Disease Section 10.8 Other Assessments or Analyses (Exploratory Measures Research)	[redacted]
Synopsis Efficacy Assessments	[redacted]
Synopsis Inclusion Criteria Section 5.1 Study Population Section 5.2 Inclusion Criteria	~~4. The patient is ≥16 and ≤65 years of age. For patients ≥16 and <18 years of age a Tanner stage of ≥4 must be established.~~ **4. The patient is ≥18 and ≤65 years of age.** 5. Female **and male** patients **(with partners)** of childbearing potential must agree to use a medically acceptable method of contraception at all times during the study.
Synopsis Exclusion Criteria Section 5.3 Exclusion Criteria	**8. Severe vitamin D deficiency to the level that would be expected to result in osteomalacia (25-hydroxyvitamin D < 10 ng/mL [25 nmol/L]). If there is mild vitamin D insufficiency at screening (25-hydroxyvitamin D > 10 and < 30 ng/mL) treat with 4000 IU 25-hydroxyvitamin D per day for 1 month and rescreen.** **9. The patient has previously interrupted ERT for safety reasons.** **10. The patient has had hypersensitivity to the active substance or to any of the excipients.**
Emergency Contact Information Page	EMERGENCY CONTACT INFORMATION ~~Email:~~ [redacted] ~~For protocol- or safety-related issues the investigator must contact the Shire Medical Monitor:~~ [redacted]~~, MD,~~ ~~Telephone:~~ [redacted] ~~Mobile:~~ [redacted] **Email:** [redacted] **For protocol- or safety-related issues the investigator must contact the Shire Medical Monitor:**

Section	Summary of Changes
	[redacted], MD **Telephone: [redacted]** **Mobile: [redacted]**
List of Abbreviations and Definitions of Terms Throughout amendment	**IRR infusion-related reactions**
Section 6.6 Home Infusion of Velaglucerase alfa Appendix 1 Study Schedule of Events Footnote	**Study site personnel will report SAEs as described in Section 7.16.2.**
Section 6.6 Home Infusion of Velaglucerase alfa Table 7-2 Footnote	**If there are no infusion-related reactions during the first 3 ~~home~~ infusions the observation and vital signs post-infusion can be omitted at the discretion of the investigator.** ~~The qualified, trained medical personnel will leave the patient's home no sooner than 1 hour after completion of the infusion.~~
Synopsis Concomitant Medication Section 6.8.2 Concomitant Therapy Appendix 1 Study Schedule of Events Footnote	Patients who enter the study receiving supplemental therapy (eg, supplemental iron, calcium) must remain on a constant dose and regimen throughout the study. **All patients will receive 600 IU 25-hydroxyvitamin D (oral) daily for the duration of the study.**
Section 6.8.3 Contraception	**One of the following methods would be acceptable:** 1. **Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:** • **Oral** • **Intravaginal** • **Transdermal** **2. Progestogen-only hormonal contraception associated with inhibition of ovulation:** • **Oral**

Section	Summary of Changes
	• **Injectable** • **Implantable** **3. Intrauterine device (IUD)** **4. Intrauterine hormone-releasing system (IUS)** **5. Bilateral tubal occlusion** **6. Vasectomized partner** **7. Sexual abstinence** **8. Double barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)**
Section 7.6 Glucocerebro-sidase Genotype Analysis Appendix 1 Schedule of Events Footnote	At screening, all patients will have a blood sample collected for Gaucher disease (GBA) gene sequencing**; however, GBA sequencing is not required at screening if documented results are available in the medical history.**
Section 7.11.5 Hemoglobin Concentration Section 7.11.6 Platelet Count	Blood samples will be collected for measurement of hemoglobin concentration. Note: The measurement of hemoglobin concentration is included as a component of hematology laboratory testing at the baseline visit and Weeks 13, 25, 37, 51, 65, 77, 89, and 103 ~~and hemoglobin concentration and platelet count are assessed separately at the screening visit and Weeks 7, 19, 31, 45, 57, 71, 83, and 95~~. Blood samples will be collected for measurement of platelet count. Note: The measurement of platelet count is included as a component of hematology laboratory testing at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103. ~~, and hemoglobin concentration and platelet count are assessed separately at screening and Weeks 7, 19, 31, 45, 57, 71, 83, and 95.~~
Section 8.1 Appendix 1, Schedule of Events Table	**25-hydroxyvitamin D blood test**
Section 8.2 Appendix 1 Schedule of Events Footnote	**Note: The baseline visit may be combined with the Week 1 Treatment Period visit.**
Section 8.3.2 Weeks 7, 19, 31, 45, 57, 71, 83, and 95	• VPRIV infusion • Concomitant medication • AEs • SAE and IRRs • Vital signs • Pregnancy test

Section	Summary of Changes
	~~• Hemoglobin concentration~~ ~~• Platelet count~~
Section 7.15.1.7 Infusion-related Adverse Event Definition Section 7.18.1 Safety-related Study Stopping Rules Section 10.7.1 Safety Endpoints	…An infusion-related AE is defined as an AE that begins either during or within 12 hours after the start of the infusion and is judged as ~~possibly or probably~~ related to the investigational product.
Section 10.2 Determination of Sample Size	A total of 34 evaluable patients will provide **at least** ~~80%~~**90%** power to detect a significant change in LS BMD Z-score from baseline after 12 months of treatment when in fact there is a ~~+0.2~~ **+0.6** change (improvement) in Z-score. The calculation was based on the following assumptions: **A total of 34 patients will also provide 80% power to detect significant change in LS BMD Z-score from baseline after 12 months of treatment.** With consideration of ~~5%~~ **15%** early discontinuation up to **24 months**, up to 40 planned patients will be enrolled and needed for the primary efficacy analysis
Section 10.6.1 Primary Efficacy Endpoint	The primary efficacy endpoint is the change from baseline to ~~12 months (Week 51)~~ **24 months (Week 103 [end of study])** in LS BMD Z-score as measured by DXA. Assessments will be performed at baseline and Weeks 25, 51, 77, and 103 (end of study). The null hypothesis is that there is no change from baseline to ~~12 months~~ **24 months** in LS BMD Z-scores. A statistically significant change in BMD after ~~1 year~~ **24 months** of treatment is highly clinically relevant in this patient population. One sample t-test or Wilcoxon signed rank test will be applied for the change from baseline of LS BMD Z-scores with patients whose LS BMD scores are collected after ~~1 year~~ **24 months** of treatment. A 95% confidence interval for the mean of the change from baseline will also be presented. As a sensitivity analysis, the primary efficacy analysis will be repeated by applying last observation carried forward (LOCF) method. That is, if the LS BMD score is missing at ~~12 months (Week 51)~~ **24 months (Week 103 [end of study]),** the non-missing score at ~~6 months (Week 25)~~ **12 months (Week 51)** will be carried forward, and the score at baseline will not be carried forward for the analysis.
Appendix 1 Schedule of Events	Treatment Period Study Week **(± 3 days)**
Section 6.3 Selection and Timing of Dose for Each Patient Section 7 Study	study visits **(± 3 days)**

Section	Summary of Changes
Procedures Section 7.8 Investigational Product Administration	
Section 6.3 Selection and Timing of dose for Each Patient	**For dosing calculations, patient weight can be rounded to the nearest 0.5 kg, VPRIV dose to the nearest Unit, and dose volume to the nearest 0.1 mL.**
Section 7.16.1 Reference Safety Information	The reference for safety information for this study is the ~~investigator's brochure~~ **Investigator's Brochure for US investigator sites and the Summary of Product Characteristics for European investigator sites,** which the sponsor has provided under separate cover to all investigators.
Appendix 1 Study Schedule of Events and Footnotes	…Events: Screening to Study Week 39 …Events: Study Week 41 to Study Week 89 …Events: Study Week 91 to End of Study (Week 103)/Early Termination and the 30-day Safety Follow-up

~~Hemoglobin concentration~~[d]	~~●~~					~~●~~					~~●~~						~~●~~					
~~Platelet count~~[d]	~~●~~					~~●~~					~~●~~						~~●~~					

~~a Hemoglobin concentration and platelet count are included as part of the hematology panel but are assessed more frequently (approximately every 6 weeks) than the hematology panel (quarterly); therefore, at some visits, only hemoglobin concentration and platelet count rather than the full hematology panel are assessed (eg, Week 95). For patients receiving home therapy on weeks 7, 19, 31, 45, 57, 71, 83 or 95 samples for hemoglobin concentration and platelet count will not be collected.~~

Appendix 6 Protocol Amendment 1 Summary of Changes

Previous Version: Original Protocol (30 April 2015)

Clinical Protocol SHP-GCB-402 has been amended to incorporate feedback from clinical sites and to update safety language to bring it into alignment with Shire standard language.

Changes in grammar, spelling, punctuation, format, minor editorial changes (including changes for consistency and clarity), and updates to the list of abbreviations and cross-references are not enumerated in this summary of changes. The text solely deleted is presented as ~~strikethrough~~ and the text revised or added is presented in **bold** font.

The significant changes and additions for the protocol Amendment since the original protocol are captured in the table below. Changes from clinical site input are summarized first, followed by changes as a result of alignment with Shire's new safety text.

Changes Requested by Clinical Sites	
Section	Summary of Changes
Synopsis Exploratory Objectives Synopsis Efficacy Assessments Section 2.3 Exploratory Objectives Section 10.8 Other Assessments or Analyses (Exploratory Measures Research)	[redacted]
Synopsis Exploratory Objectives Synopsis Efficacy Assessments Section 7.11.8 Exploratory Measures of Potential Relevance in Gaucher Disease	[redacted]

Changes Requested by Clinical Sites	
Section	Summary of Changes
Emergency Contact Information Page	**EMERGENCY CONTACT INFORMATION** **In the event of an SAE, the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by fax or e-mail using the details below. Fax:** [redacted] **Email:** [redacted] **For protocol- or safety-related issues the investigator must contact the Shire Medical Monitor:** [redacted]**, MD,** **Telephone:** [redacted] **Fax:** [redacted] **Mobile:** [redacted]
Section 3.3 Exploratory Endpoints	[redacted]
Section 6.6 Home Infusion of Velaglucerase alfa (New Section)	**The first three velaglucerase alfa infusions are to be administered at the clinical site. After the first 3 doses, patients who have not experienced a treatment-related serious adverse event or an infusion-related adverse event of more than mild severity may receive their subsequent infusions at home by qualified and trained medical personnel, per the discretion and direction of the Investigator. Patients who have experienced an infusion-related adverse event of more than mild severity may be re-evaluated at a later time point during the study for consideration to transition to home infusions. Patients receiving velaglucerase alfa as home therapy will be required to return to the clinical site at Weeks 13, 25, 37, 51, 65, 77, 89, and 103.** **The qualified, trained medical personnel will follow the instruction manual provided separately from this protocol that outlines all operating procedures to be followed for this study including drug transport, reconstitution and the required patient assessments before, during, and after infusion of study drug. Clinical evaluations will remain under the medical supervision of the Investigator. Appropriate medical support including adequately trained personnel in emergency measures, should be readily available when velaglucerase alfa is administered. If anaphylactic or other acute severe reactions occur, immediately discontinue the**

Changes Requested by Clinical Sites	
Section	Summary of Changes
	infusion and initiate appropriate medical treatment. **In the home setting, vital signs and documentation of adverse events will be collected at each visit. The qualified, trained medical personnel will evaluate and report to the study site the occurrence of adverse events. In addition, a urine pregnancy test will be conducted at each home infusion visit. If the result is positive, the infusion will not be administered and a blood sample will be collected for serum pregnancy testing. The next infusion of velaglucerase alfa will not be administered until the results of the serum pregnancy test are received. If the β-hCG result is also positive, the Investigator is to contact the Shire Medical Monitor to determine the appropriate course of action.** **If an infusion-related adverse event of more than mild severity occurs while a patient is receiving treatment at home, the qualified, trained medical personnel will maintain contact with the investigator for treatment advice. The infusion should not be restarted in the home setting after an infusion-related adverse event of more than mild severity. Home therapy can only then resume at subsequent infusions after agreement is reached by the investigator and the Shire Medical Monitor.** **The qualified, trained medical personnel will leave the patient's home no sooner than 1 hour after completion of the infusion.** Note: Section numbers of all subsequent sections in Section 6 changed as a result
Section 6.8.2 Concomitant Therapy	Was Section 6.6 Concomitant Medications ~~All medications, therapies/interventions administered to, and medical/surgical procedures performed on the study patients from the time of informed consent through the follow-up contact are regarded as concomitant and will be documented on the appropriate pages of the eCRF. These include medications, therapies/interventions administered to patients, and medical/surgical procedures performed on the patients.~~ **Patients who enter the study receiving supplemental therapy (eg, supplemental iron, calcium, vitamin D) must remain on a constant dose and regimen throughout the study. Initiation of osteoporosis-specific therapy or treatment with erythropoietin during the trial is prohibited.**
Section 7.6 Glucocerebrosidase Genotype Analysis	**At baseline, all patients will have a blood sample collected for Gaucher disease (GBA) gene sequencing. The sample will be sent to a central laboratory for analyzing and reporting. The results will be used for statistical analysis purposes.** Note: All subsequent section numbers in Section 7 changed as a result of this addition.
Section 7.11.6 Platelet Count	Note: The measurement of platelet count is included as a component of hematology laboratory testing at baseline and Weeks 13, 25, 37, 51, 65, 77, 89, and 103, and hemoglobin concentration and platelet count are assessed separately at ~~baseline~~ **screening** and Weeks 7, 19, 31, 45, 57, 71, 83, and 95.
Section 10.8 Other Assessments of Analyses (Exploratory	[redacted]

Changes Requested by Clinical Sites	
Section	Summary of Changes
Measures Research)	[redacted]
Appendix 1 Schedule of Events	Glucocerebrosidase Genotype Analysis added to the baseline visit. [redacted] Footnote b (pregnancy) updated: Pregnancy testing for female patients of childbearing potential will be done with a urine test. If a patient has a positive urine test result, the infusion will be held and a serum (β-hCG) test is to be conducted. **At the screening visit both urine and serum pregnancy tests will be performed**. Patients with a positive result for either test at screening will not be eligible. Footnote c (hemoglobin concentration and platelet count) (Footnote b Study Week 41 5o Study Week 89 and Study Week 91 to End of Study) updated: Hemoglobin concentration and platelet count are included as part of the hematology panel but are assessed more frequently (approximately every 6 weeks) than the hematology panel (quarterly); therefore, at some visits, only hemoglobin concentration and platelet count rather than the full hematology panel are assessed (eg, Week 7, 19, 31, and 45). **For patients receiving home therapy on weeks 7, 19, 31, 45, 57, 71, 83 or 95 samples for hemoglobin concentration and platelet count will not be collected.**

Changes to Update Safety Language	
Section	Summary of Changes
Section 7.12.1 Concomitant Medications, Therapies, and Medical/Surgical Interventions Assessments	All medications, therapies/interventions administered to, and medical/surgical procedures performed on the study patients from the time of informed consent through the follow-up contact are regarded as concomitant and will be documented on **the appropriate pages of** the eCRF. **These include medications, therapies/interventions administered to patients, and medical/surgical procedures performed on the patients.**
Section 7.12.3 Adverse Event Collection	**At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (e.g., "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. (Please refer to Section 7.16, Serious Adverse Event Procedures.** Note: Subsequent section numbers in Section 7.12 were adjusted
Section 7.12.5 Electrocardiography	Section title changed from 12-Lead Electrocardiogram

Changes to Update Safety Language	
Section	Summary of Changes
Section 7.15.1 Definitions of Adverse Events Assessment, Period of Observation and Recording of Adverse Events	**All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 8.5. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.** **All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented**.
Section 7.15.1.1 Severity Categorization	~~Mild no limitation of usual activities~~ ~~Moderate some limitations of usual activities~~ ~~Severe Inability to carry out usual activities~~ : Mild: **A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.** Moderate: **A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.** Severe: **A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention**
Section 7.15.1.2 Relationship Categorization	**Table 7-4 Adverse Event Relatedness** ~~**Relationship to Product**~~ ~~**Definition**~~ ~~Not Related~~ ~~Unrelated to the investigational product~~ ~~Possibly Related~~ ~~A clinical event or laboratory abnormality with a reasonable time sequence to administration of the investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.~~ ~~Probably Related~~ ~~A clinical event or laboratory abnormality with a reasonable time sequence to administration of the investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.~~

<table>
<tr><th colspan="2">Changes to Update Safety Language</th></tr>
<tr><td>Section</td><td>Summary of Changes</td></tr>
<tr><td></td><td><s>Definitely related</s> <s>The event follows a reasonable temporal sequence from administration of the investigational product, follows a known or suspected response pattern to the investigational product, is confirmed by improvement upon stopping the investigational product (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the patient to the investigational product; however, the determination of definitely related can only be used when recurrence of the event is observed.</s></td></tr>
<tr><td></td><td>The following additional guidance may be helpful:
<table>
<tr><th>Term</th><th>Relationship Definition</th></tr>
<tr><td>Related</td><td>The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject’s medical condition, other therapies, or accident.</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Not Related</td><td>The event can be readily explained by other factors such as the subject’s underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.</td></tr>
</table></td></tr>
<tr><td>Section 7.15.1.3 Outcome Categorization</td><td>The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:
Fatal
Not Recovered/Not Resolved
Recovered/Resolved
Recovered/Resolved With Sequelae
Recovering/Resolving
Unknown.</td></tr>
<tr><td>Section 7.15.1.4 Symptoms of the Disease Under Study</td><td>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 progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.</td></tr>
<tr><td>Section 7.15.1.5 Clinical Laboratory and Other Safety Evaluations</td><td>A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.</td></tr>
</table>

Changes to Update Safety Language	
Section	Summary of Changes
	If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pre-treatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal values. The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and **whether it** ~~therefore~~ represents an AE.
Section 7.15.1.6 Pregnancy	**Any report of pregnancy must be reported within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the/Shire Medical Monitor using the details specified in the emergency contact information section of the protocol.** **The pregnant female study participant 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 post partum.** **Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form.** **Note: An elective abortion is not considered an SAE.** **In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.** Pregnancy and lactation are exclusion criteria for this study. Any report of pregnancy for a female study participant or the partner of a male study participant during the course of the study and through 30 days after the patient's last dose of VPRIV must be reported to the Sponsor. Pregnancy is not to be reported as an AE; the Investigational and Marketed Products Pregnancy Report Form should be used to report the pregnancy. The pregnancy will be followed up through delivery or final outcome.
Section 7.15.1.8 Abuse, Misuse, overdose, and Medication Error	**Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 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.**

Changes to Update Safety Language	
Section	Summary of Changes

	Abuse – Persistent or sporadic intentional intake of investigational ~~medicinal~~ product ~~at a dose higher than prescribed per protocol (but below the dose defined for overdose) or~~ when used for a non-medical purpose ~~(eg, **altering**~~**.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~~ or unintentional~~ use of investigational~~ medicinal~~ product other than as directed or indicated at any dose~~, which is at or below the dose defined for overdose~~ (Note: this includes a situation where the ~~test article~~**investigational product** is not used as directed at the dose prescribed by the protocol)
	• **Overdose** – Intentional or unintentional intake of a dose of investigational medicinal product 10% higher than the protocol-specified dose.
	• **Medication Error** – A mistake made in prescribing, dispensing, administration, and/or use of the investigational medicinal product
	  • **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.**

Section 7.16.1 Reference Safety Information	**The reference for safety information for this study is the investigator's brochure, which the sponsor has provided under separate cover to all investigators.**
Section 7.16.2 Reporting Procedures	~~Any SAE, regardless of relationship to the investigational product, which occurs in a patient after informed consent should be recorded by the clinical site on an SAE form. The SAE must be completely described on the patient's eCRF, including the judgment of the investigator as to the relationship of the SAE to the investigational product. The investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization) regarding the SAE.~~ ~~The investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the Shire Medical Monitor on an SAE form. This form must be completed and FAXED or EMAILED within 24 hours of the investigator's learning of the event to:~~ **All initial and follow-up SAE reports must be reported by the investigator ~~must report to~~ the Shire Global Pharmacovigilance and Risk Management Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, ~~and~~ or medication errors ~~according to the SAE reporting procedure~~ (see Section 7.15.4.3) unless they result in an SAE.** **The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or**

Changes to Update Safety Language	
Section	Summary of Changes
	e-mail the form to the Shire Global Pharmacovigilance and Risk Management Department. A copy of the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports) must also be sent to the Shire Medical Monitor using the details specified in the emergency contact information section of the protocol.
Section 7.16.3 Serious Adverse Event Definition	~~An SAE is any AE occurring at any dose that results in any of the following outcomes:~~ ~~• Death~~ ~~• Is life-threatening~~ ~~• Requires hospitalization~~ ~~• Requires prolongation of existing hospitalization~~ ~~• A persistent or significant disability or incapacity~~ ~~• A congenital anomaly or birth defect~~ ~~Important medical events that might not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. A life-threatening AE is defined as an AE that placed the patient, in the view of the initial reporter, at immediate risk of death from the AE as it occurred (ie, it does not include an AE that, had it occurred in a more severe form, might have caused death).~~ ~~Hospitalization, which is the result of elective or previously scheduled surgery for a pre-existing condition that has not worsened after initiation of treatment, should not result in an SAE designation. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAEs. Furthermore, this does not apply to device failures resulting in scheduled surgical revisions, which should be reported as SAEs.~~ **A *Serious Adverse Event* (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:** • **Results in death** • **Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.** • **Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).** • **Results in persistent or significant disability/incapacity**

Changes to Update Safety Language	
Section	Summary of Changes
	• **Is a congenital abnormality/birth defect** • **Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.**
Section 7.16.4 Serious Adverse Event Collection Time Frame	~~Any SAE, regardless of relationship to the investigational product, which occurs in a patient after informed consent should be recorded by the clinical site on an SAE form. The SAE must be completely described on the patient's eCRF, including the judgment of the investigator as to the relationship of the SAE to the investigational product. The investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization) regarding the SAE.~~ **All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.5 and must be reported to the Shire Global Pharmacovigilance and Risk Management Department and the CRO/Shire Medical Monitor within 24 hours of the first awareness of the event.** **In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Pharmacovigilance and Risk Management Department within 24 hours of the first awareness of the event.**
Section 7.16.5 Serious Adverse Event Onset and Resolution Dates	**All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.5 and must be reported to the Shire Global Pharmacovigilance and Risk Management Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.** **In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Pharmacovigilance and Risk Management Department within 24 hours of the first awareness of the event**.
Section 7.16.6 Fatal Outcome	~~In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire Medical Monitor by telephone; this is in addition to completing and transmitting the SAE form as stated above. The following provides contact information for the Shire Medical Monitor.~~ **Any SAE that results in the subject's death (ie, 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**

Changes to Update Safety Language	
Section	Summary of Changes
	resolved, without a resolution date recorded. **Action taken with the investigational product should be an active decision by the investigator. For any SAE that results in the subject's death or any ongoing events at the time of death, unless another study drug action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The study drug action of withdrawn should not be selected solely as a result of the subject's death.**
Section 7.16.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting	~~The investigator must promptly report all required information to the IRB/IEC. It is the responsibility of the Sponsor to ensure that each investigator receives a copy of any CIOMS I/MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The investigator or Sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files.~~ **The sponsor or sponsor designee is responsible for notifying the relevant regulatory authorities/US central IRBs/EU central ECs of related, unexpected SAEs.** **In addition the sponsor or the sponsor's designee is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the velaglucerase alfa program.** **The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.**
Section 7.17 Removal of Patients from the Trial or Investigational Product	A patient's participation in the study may be discontinued at any time at the discretion of the investigator. The following may be justifiable reasons for the investigator to remove a patient from the study: • Non-compliance, including failure to appear at 1 or more study visits • The patient was erroneously included in the study • The patient develops an exclusion criterion • The patient suffers an intolerable AE • The patient requests to be discontinued from the study • The study is terminated by the Sponsor • **Pregnancy** The patient, the patient's parent(s), or the patient's legally authorized representative acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. If a patient, the patient's parent(s), or the patient's legally authorized representative(s) acting on behalf of the patient, discontinues participation in the study or the patient is discontinued by the investigator, reasonable efforts will be made to follow the patient through the end of study assessments. The reason for refusal will be documented on the eCRF. Any AEs experienced up to the point of discontinuation must be documented on

Changes to Update Safety Language	
Section	Summary of Changes
	the AE eCRF. If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.
Deleted Sections	The following sections of the original protocol were deleted as the information contained was redundant with updated text: • Section 7.15.1.1 Adverse Events • Section 7.15.1.3 Serious Adverse Events • Section 7.15.2.1 Classification of Adverse Events and Serious Adverse Events • Section 7.15.2.1 Clarification between Serious and Severe • Section 15.3 Relatedness of Adverse Events and Serious Adverse Events • Section 7.15.4 Procedures for Recording and Reporting Adverse Events • Section 7.15.4.1 Adverse Event Monitoring and Period of Observation • Section 7.15.4.2 Reporting Serious Adverse Events to the Sponsor and Medical Monitor

Appendix 7 Questions taken from the BPI-SF©

The graphic below depicts the full Brief Pain Inventory Short Form (BPI-SF©). A subset of questions are taken from this form for use in Study SHP-GCB-402. Questions 2, 7, and 8 are not used.

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

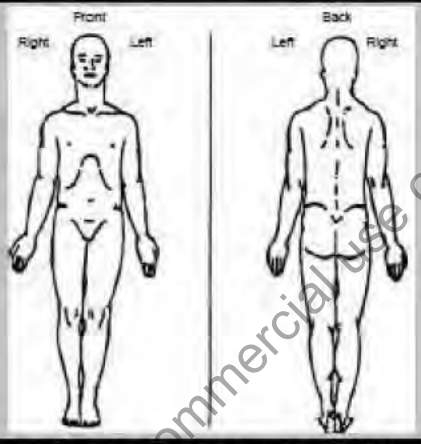
Brief Pain Inventory (Short Form)

Date:____/____/____ Time:_____
Name:_____ _____ _____
Last First Middle Initial

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

1. Yes 2. No

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



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:____/____/____ Time:_____
Name:_____ _____ _____
Last First Middle Initial

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

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

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

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

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

B. Mood

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

C. Walking Ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

Appendix 8 Brief Fatigue Inventory

Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL# _____

Date: ____/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General Activity
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

BFI - English - Formatted March 19, 2008

Appendix 9 Protocol Addendum – COVID-19

Memorandum

To: SHP-GCB-402 Investigators/IRBs/ECs/CAs

CC: Trial Master File

From: [redacted] DDS, PhD

Date: 03 Apr 2020

Subject: Protocol Addendum – Optional transfer of study visit weeks 77 and/or 89 to home therapy and the addition of *Dose Continuation Infusions* due to the COVID-19 pandemic

SHP-GCB-402 - "An Open-label, Multicenter, Single-arm, Phase 4 Study of the Effect of Treatment with Velaglucerase alfa on Bone-related Pathology in Treatment-naïve Patients with Type 1 Gaucher Disease".

The procedures detailed in this addendum have been put in place to ensure subjects continue to receive treatment with Velaglucerase alfa as a study infusion, to ensure subject safety during the COVID-19 pandemic, and to maintain data integrity. These procedures affect the following sections of protocol SHP-GCB-402 amendment 5 (26 July 2018):

- ***Synopsis***
- ***Section 2.1 – Primary Objectives***
- ***Section 2.2 – Secondary Objectives***
- ***Section 3.1 – Primary Endpoints***
- ***Section 3.2 – Secondary Endpoints***
- ***Section 4.1 – Overall Study Design and Plan***
- ***Section 4.3 – Study Duration***
- ***Section 6.2 Treatment Administered***
- ***Section 6.6 - Home Infusion of Velaglucerase alfa***
- ***Section 8.3.2 - Study Activities Weeks 13, 37, 65, and 89, Section 8.3.3 - Study Activities Weeks 25 and 77***
- ***Section 8.4 - Study Activities End of Study (Week 103)/Early Termination Procedures***
- ***Section 10.2 Determination of Sample Size***
- ***Section 10.6.1 Primary Efficacy Endpoint***
- ***Section 10.7.2 Secondary Efficacy Endpoints***
- ***Section 10.7.3 Other Secondary Efficacy Endpoints***
- ***Appendix 1 – Study Schedule of Events***

This protocol addendum is to confirm that, during the COVID-19 pandemic*, if sites are under restrictions that prevent subject visits from being performed onsite, subjects do not wish to travel to the study site, or it is unsafe for visits to occur onsite, as determined by the investigator, the following may be performed:

1. Study visits Week 77 and/or Week 89 can be completed as home therapy visits

2. Infusions with the study drug, Velaglucerase alfa, may be extended beyond Week 101 as *Dose Continuation Infusions*. Subjects may continue to receive their bi-weekly infusions at home every 14 days (± 7 days) until it is safe to complete the End of Study (Week 103)/Early Termination Procedures at the clinical site. *If a subject's need for at home infusions were to extend beyond 3 additional months, the Takeda Medical Monitor should be contacted for evaluation and discussion on a case-by-case basis.*

*This protocol addendum is effective from the date of the memo until written confirmation is received from the site that onsite subject visits can be resumed

**Shire is now part of Takeda

Memorandum

To: SHP-GCB-402 Investigators/IRBs/ECs/CAs

CC: Trial Master File

From: [redacted], DDS, PhD

Date: 03 Apr 2020

Subject: Protocol Addendum – Optional transfer of study visit weeks 77 and/or 89 to home therapy and the addition of *Dose Continuation Infusions* due to the COVID-19 pandemic

Week 77 and/or Week 89 - home therapy visits

- Under this addendum, the following study procedures, previously conducted during an onsite visit as per protocol **Section 8.3.1**, can be conducted during a home therapy visit:
  - VPRIV® infusion
  - Review of concomitant medications
  - Review of Adverse Events (AEs)
  - Review of Serious Adverse Events (SAEs)
  - Review of Infusion-Related Reactions (IRRs)
  - Vital signs
  - Pregnancy test (as applicable)

  The Velaglucerase alfa (VPRIV®) benefit/risk profile has not changed. The continuation of infusions, via a home therapy visit, at weeks 77 and/or 89 visit outweighs the safety risks of any missed safety procedures the subject would have had at an onsite visit at weeks 77 and/or 89.

- Since weight cannot be obtained at the week 77 and/or 89 home therapy visits, the subject's last known weight used for dose calculation should be used until an onsite visit can occur where weight can be obtained.

- The Week 77 and/or Week 89 Brief Fatigue Inventory (BFI) and Brief Pain Inventory (BPI) questionnaires may be collected via phone by the site staff within (±7) days of the associated infusion that occurs as a home therapy visit.

- The following procedures required per protocol **Section 8.3.1** at Week 77 and/or Week 89, that will likely not be performed during the home therapy visit, should be completed as an Unscheduled Visit at the clinical site as soon as it is safe and possible to do so.
  - Weight measurement
  - Height measurement
  - Physical exam
  - ECG
  - Serum Chemistry
  - Hematology/ Coagulation
  - Urinalysis
  - Serum anti- velaglucerase alfa antibody
  - [redacted]
  - Brief Fatigue Inventory (BFI) and Brief Pain Inventory (BPI)-in the event that collection by telephone is not possible

*This protocol addendum is effective from the date of the memo until written confirmation is received from the site that onsite subject visits can be resumed

**Shire is now part of Takeda

Memorandum

To: SHP-GCB-402 Investigators/IRBs/ECs/CAs

CC: Trial Master File

From: [redacted], DDS, PhD

Date: 03 Apr 2020

Subject: Protocol Addendum – Optional transfer of study visit weeks 77 and/or 89 to home therapy and the addition of *Dose Continuation Infusions* due to the COVID-19 pandemic

The site should consult with their monitor regarding any questions concerning the completion and naming of study visits.

***Dose Continuation Infusions* – infusions beyond Week 101**

- This addendum allows subjects to receive infusions beyond week 101 until it safe for the subject to return the clinical site to complete the End of Study (Week 103)/Early Termination Procedures. *For delayed End of Study (Week 103)/Early Termination visits, sites are encouraged to complete the End of Study (Week 103)/Early Termination Procedures as soon as possible.*
- The Velaglucerase alfa (VPRIV®) benefit/risk profile has not changed. The allowance of *Dose Continuation Infusions* does not pose any additional safety risks and allows subjects to receive ongoing treatment with an approved medication for Type 1 Gaucher Disease.
- If a subject's weight was not able to be obtained at the week 77 and/or 89 study visits, the subject's last known weight used for dose calculation should be used for the *Dose Continuation Infusions*.
- The 30-day safety follow-up, as per protocol **Section 8.5,** is to occur 30 (±7) days after the final infusion of study drug. For the purposes of this addendum, this may be a *Dose Continuation Infusion* that extends beyond Week 101.

Any departures from protocol SHP-GCB-402 amendment 5 (26 July 2018) will be documented as deviations as per protocol **Section 11.9**. Deviations that result from circumstances related to COVID-19 pandemic will be so noted.

It is expected that primary and secondary endpoints for some subjects may be extended to greater than 24 months (**Protocol Sections 3, 4, 6, 10, Appendix 1).** It has been deemed that the administration of additional infusions, for a limited period of time, will not significantly affect a number of the study endpoints, and that the safety benefits of these additional infusions outweigh any safety risks. The planned statistical methods, as per protocol **Section 10,** will take into account any data affected by this protocol addendum.

If you have further questions, please do not hesitate to contact your PPD CRA or Shire** directly.

[redacted]

[redacted], DDS, PhD
[redacted], Rare Diseases

*This protocol addendum is effective from the date of the memo until written confirmation is received from the site that onsite subject visits can be resumed.

**Shire is now part of Takeda