STATISTICAL ANALYSIS PLAN

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

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Final Statistical Analysis Plan

Version *1.3, based on Protocol Amendment 6 (08October2020)*

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Table of Contents

List of Abbreviations

AE	Adverse Event
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AR(1)	First order autoregressive
AST	Aspartate aminotransferase
BFI	Brief Fatigue Inventory©
BMB	Bone marrow burden
BMD	Bone mineral density
BPI-SF	Brief Pain Inventory-Short Form©
BUN	Blood urea nitrogen
[redacted]	[redacted]
CRP	C-reactive protein
CSR	Clinical Study Report
DXA	Dual energy x-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study
EOW	Every other week
GCB	Glucocerebrosidase
GGT	Gamma-glutamyl transferase
HCT	Hematocrit
HGT	Human Genetic Therapies
[redacted]	[redacted]
IRR	Infusion-related reactions
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LS	Lumbar spine
[redacted]	[redacted]
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
NHANES	National Health and Examination Survey
OC	Observed case
PT	Preferred term
[redacted]	[redacted]

RBC	Red blood cell
REML	Restricted maximum likelihood estimation
SAE	Serious adverse event
[redacted]	[redacted]
SOC	System organ class
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
US(A)	United States of America
VPRIV	Velaglucerase alfa
WBC	White blood cell
WHO	World Health Organization
β-hCG	Human chorionic gonadotropin

1. Introduction

The purpose of this statistical analysis plan (SAP) is to document technical and detailed specifications for the final analysis of data collected for protocol SHP-GCB-402. Results of the analyses described in this SAP will be included in the Clinical Study Report (CSR). Any post-hoc or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective SAP will be clearly identified in the CSR.

1.1. Background and Study Rationale

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). 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. Bone involvement results in skeletal abnormalities and deformities as well as bone pain and bone crises. Bone pain is a significant problem in Gaucher disease. The disease has been classified into 3 clinical subtypes. Type 1 Gaucher disease, the most common form, accounting for more than 90% of all cases does not involve the central nervous system (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.

[redacted] The effects of VPRIV on the change in lumbar spine (LS) bone mineral density (BMD) as assessed by dual energy x-ray absorptiometry (DXA) and lumbar spine (LS) and femur bone marrow burden (BMB) as assessed by magnetic resonance imaging (MRI) were assessed previously in the clinical development program and will be evaluated as primary and key secondary objectives in this study as well.

Objectives

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 LS BMD Z-score as measured by DXA after 24 months of treatment.

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 of treatment

- BMD as measured by the change from baseline in g/cm^2 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 the 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
- WHO BMD classification (normal bone density, osteopenia, osteoporosis) based on LS T-scores after 12 and 24 months of treatment
- Safety

[redacted]

2. Investigational Plan

2.1. 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.

2.2. Study Endpoints

2.2.1. Primary Endpoint

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.

2.2.2. Secondary Endpoints

The secondary efficacy endpoints of this study 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) in BMD reported as g/cm^2. Assessments will be performed at the screening visit and Weeks 51 and 103 (end of study).
- 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).
- 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 visit 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 the 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 (assessed on screening visit) and Weeks 51 and 103 (end of study).
- Safety Endpoints:
    - Adverse events (AE)
    - 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

2.2.3. Exploratory Endpoints

[redacted]

2.3. Treatments

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.

3. General Statistical Considerations

All statistical analyses will be performed by PPD using SAS® software version 9.3 or later (SAS Institute, Cary, N.C., USA).

Statistical analyses will be based on the intent-to-treat (ITT) principle for all efficacy variables. 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.

Data will be plotted as appropriate, tabulated and listed. 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 patients changes from baseline will be examined using one sample t-test or Wilcoxon signed rank test. Statistical significance will be defined at the 0.05 level. Study schedule of each assessment is available in Appendix IV. Baseline is defined as last data collected prior to the first administration of study drug.

The significant digits specified for the summary statistics (eg, mean, standard deviation) will be consistent with the measured precision of the experiment used; specific programming conventions are outlined in Appendix V. For samples associated with the same visit but collected at different times or for multiple tests performed at the same visit (e.g. ECG), the

latest valid result will be utilized in the analyses. Appendix VI documents the algorithm for handling and reporting data collected at end of study visits for patients who discontinued the study early and for data collected at unscheduled visits.

No formal statistical tests will be performed on the safety parameters.

3.1. Sample Size

A total of 13 evaluable patients will provide 90% 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 was based on the following assumptions:

- A 2-sided t-test with alpha of 0.05
- A standard deviation of the change is 0.6 (based on data from Study HGT-GCB-044)

With consideration of 30% early discontinuation up to 2 years, at least 19 patients will be enrolled in order to have 13 evaluable patients for the primary analysis.

3.2. Randomization and Blinding

Not applicable; this is a single arm, open-label study.

3.3. Analysis Populations

3.3.1. All Enrolled Population

The all enrolled population includes every patient who signed informed consent.

3.3.2. Intent-to-Treat (ITT) Population

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

3.3.3. Safety Population

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

3.3.4. [redacted]

[redacted]

4. Patient Disposition

Patient disposition for those enrolled, treated, completed, or discontinued/withdrew will be presented in summary tables using the number and percentage of patients per category; reasons for discontinuation/withdrawal will be presented. The number of patients who completed study per protocol and the number of patients who have extended treatment period due to COVID-19 will be summarized. In addition, the start and end dates of COVID-19 impact of each country will be presented. The start date of COVID pandemic is defined as the date of first case that was reported in a specific country:

Country	Start Date of COVID Pandemic
Spain	N.A. Last subject from Spain completed study in Oct 2019.
United Kingdom	30th Jan 2020 (Lillie PJ, et al, 2020)
Israel	21st Feb 2020 (Last M, 2020)
United States of America	20th Jan 2020 (Holshue, et al, 2020)

Patient disposition, patients completing and prematurely discontinued during the study, and study analysis sets will be listed by patient for All Enrolled Population.

5. Protocol Violations and Deviations

An incident involving noncompliance with the protocol, but one which typically does not have significant effects on the patient's rights, safety, or welfare, or the integrity of the resultant data will be considered a protocol deviation. An incident involving noncompliance with the protocol which may affect the patient's rights, safety, or welfare, or the integrity of the resultant data will be considered a protocol violation. In particular, any serious deviation that affects the collection of data for the primary endpoints will be considered a protocol violation. 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.

Patients will be examined on a case-by-case basis to determine if conditions set forth in the study protocol have been violated. The complete list of the protocol deviations will not be summarized; however, the protocol violations identified will be tabulated and listed.

6. Demographics and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using either descriptive statistics or frequency distributions, as appropriate.

The following baseline demographics will be summarized: age (at time of consent) in years, weight (kg) and height (cm) at baseline, race, ethnicity and sex.

The following clinical characteristics will be summarized: time from diagnosis of type 1 Gaucher disease to first treatment, age at diagnosis of type 1 Gaucher disease in years (estimated as age at time of consent - time from diagnosis of type 1 Gaucher disease to first treatment, as date of birth is not collected in the CRF), method of Gaucher disease diagnosis, main presenting features at diagnosis, glucocerebrosidase genotype, LS BMD Z-score at baseline, BMD (g/cm^2) at baseline, BMB at baseline, normalized liver and spleen volumes (%Body Weight) at baseline and the centrally analyzed Screening and Baseline values for hemoglobin concentrations (g/dL) and platelet counts (x10^9/L).

The following laboratory tests will be summarized: Vitamin D blood test at screening visit (or baseline, as applicable).

Baseline height and weight are defined as the last assessment prior to the first VPRIV treatment in the study.

A listing will be created to show all the demographics and baseline characteristics for each patient in the Safety Set.

7. Medical History

Medical history will be listed by patient.

8. Concomitant Medications, Therapies, Medical/Surgical Procedures History

All non-protocol treatments, including medications, therapies/interventions administered to patients, and medical/surgical procedures performed on the patients, on entry into the study (at the time of informed consent), or at any time during the study are regarded as concomitant.

The number and percentage of patients who reported use of at least one concomitant medication will be summarized by Therapeutic Class and Preferred Term (Concomitant medications will be mapped using the WHO-Drug Dictionary version 3, 2015).

Patients who took concomitant medication and concomitant therapies will be presented in listings separately. A listing of all patients who required a medical or surgical procedure will also be generated.

9. Treatment Compliance and Extent of Exposure

Treatment compliance and exposure summaries will be presented. For each patient, the patient's percent of compliance, reflecting the patient's willingness to accept the intravenous infusion at each infusion visit, will be calculated as follows for up to 24 months (Week 103 [end of study]) and for up to the end of COVID-19 extended treatment period.:

Compliance = [(Number of Complete Infusions Received) /(Expected Number of Infusions)]*100

Note: Expected number of infusions is defined as the number of infusions that the patient would have received up to the date of the patient's withdrawal or completion from the study.

The number and percentage of patients who received ≥80% of scheduled infusions (not including partial infusions) will be reported. In addition, the total number of missed infusions will be categorized as 0, 1, 2 to 5, and >5 and summarized by n and the percentage in each category.

The duration (in months) of drug exposure to VPRIV will be calculated as follows:

Exposure (months) = [(Date of the last dose – Date of first dose) + 1]/30.4375

The exposure data and the total number of infusions received will be summarized by descriptive statistics. The actual dose and per protocol dose amount (U/kg) are defined as the weight adjusted actual dose. For actual dose amount, weight is the last available dose on or prior to each infusion date. For protocol dose amount, the first dose of VPRIV will be based on the patient's weight at screening. A change in patient weight of ±5% from screening or the last weight used to recalculate the dose will require a new dose recalculation. The actual and per protocol dose amounts (U/kg) and durations of infusion (minutes) will be averaged across the non-missing infusions for each patient and then summarized by the descriptive statistics across all patients. All exposure data will be presented in a by-patient listing.

10. Efficacy Analysis

All efficacy analyses except [redacted] will be performed on the ITT population. [redacted]

10.1. 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.

10.1.1. Primary Analysis

Patients will have DXA of the lumbar spine for determination of bone mineral density. The BMD (g/cm^2) will be compared to that of an established norm or standard taken from the National Health and Examination Survey (NHANES) III database (Looker et al., 1998, Looker et al., 1995) to calculate BMD Z-scores and T-scores using the following formula:

(patient's BMD – mean BMD) / SD

Note: For Z-score mean BMD is the age/gender/ethnicity-matched BMD from NHANES III database, and SD is the age/gender/ethnicity-matched standard deviation from NHANES III database; For T-score, mean BMD and SD are the mean BMD and standard deviation of a [redacted] female from NHANES III database, respectively.

The null hypothesis is that there is no change from baseline to 24 months (Week 103 [end of study]) in LS BMD Z-scores as measured by DXA. 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 observed LS BMD Z-scores with patients whose LS BMD scores are collected after 24 months of treatment. A 95% confidence interval for the mean and median of the change from baseline will also be presented. In this analysis, no data imputation will be used.

Example SAS code for the 95% CI of Median

```
proc univariate data=dataset cipctldf cibasic;
        var aval;
run;
```

The pattern of LS BMD Z-scores over time, baseline value and change from baseline over time will be evaluated both descriptively using summary statistics and graphically using line graph and box plots at the screening visit, Week 51 and 103 (end of study) using observed data.

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

All observed LS BMD Z-score data will be provided in a by-patient listing.

A sensitivity analysis will be performed for primary endpoint. Details are described in section 12.7.1.

10.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints will include evaluations of change in BMB score and LS BMD Z-score, as well as change in hemoglobin concentration and platelet count, and changes in organ volume (liver and spleen).

10.2.1. LS BMD Z-scores

Changes in LS BMD Z-score from baseline to 12 months (Week 51) will be descriptively summarized and tested using one sample t-test or Wilcoxon signed rank test in the same manner as described above for the primary endpoint. A 95% confidence interval for the mean and median of the change from baseline will also be presented.

10.2.2. BMD (g/cm^2)

Changes in BMD (g/cm^2) from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) will be descriptively summarized and tested using one sample t-test or Wilcoxon signed rank test in the same manner as described above for the primary endpoint using observed data. A 95% confidence interval for the mean and median of the change from baseline will also be presented. In addition, this analysis will be repeated using last observation carried forward (LOCF) method.

The change and percentage of change from baseline in BMD will be evaluated both descriptively using summary statistics and graphically using line graphs at the baseline visit and Weeks 51 and 103 (end of study) using OC and LOCF data.

All observed BMD data will be provided in a by-patient listing.

10.2.3. BMB score

Bone marrow burden raw scores will be entered into eCRF by two independent radiologists, after reviewing MRIs of the LS and femurs. In the event of the sufficient discrepancy is found in the analysis (defined as a difference in the total sum of BMB scores between readers being $\geqslant$3), the independent radiologists will proceed with consensus adjudication process and discuss the data together. The mutually agreed upon BMB scores will be entered by one radiologist, and signed off by the other. If adjudication is not needed, the scores entered by reader 1 will be used in BMB score calculation. The BMB scores range between 1 and 8 for each location and total BMB range between 2 and 16, based on the method of DeMayo et al (DeMayo et al., 2008). The total lumbar spine score (1-8) is the sum of signal intensity score (0,1,2), T1 signal intensity score (0,1,2,3), infiltration pattern (1,2) and absence of fat in basivertebral vein region (0,1). The total femora score (1-8) is the sum of signal intensity score (0,1,2,3), T1 signal intensity score (0,1,2), site of involvement (1,2,3). Total BMB score is calculated as total lumbar spine score and total femora score.

Changes in BMB score (MRI of LS and femur) from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) will be descriptively summarized and tested using one sample t-test or Wilcoxon signed rank test in the same manner as described above for the primary endpoint. A 95% confidence interval for the mean and median of the change from baseline will also be presented. In this analysis, missing post-baseline data will be imputed using last observation carried forward (LOCF) method.

The change and percentage of change from baseline in BMB score will be evaluated both descriptively using summary statistics and graphically using line graphs at the baseline visit and Weeks 51 and 103 (end of study) using OC and LOCF data.

All observed BMB score data will be provided in a by-patient listing.

10.2.4. Hemoglobin concentration (g/dL) and Platelet count (x10^9/L)

Changes from baseline over time in hemoglobin concentration and platelet count will be descriptively summarized and tested using one sample t-test or Wilcoxon signed rank test at each time point in the same manner as described above for the primary endpoint. For calculating changes from baseline for each patient, the patient's centrally performed hemoglobin concentration and platelet count collected at screening and baseline will be averaged to represent the patient's baseline value. If a baseline result is unavailable, the screening result will be used (or vice versa). A 95% confidence interval for the mean and median of the change from baseline will also be presented. Missing post-baseline data will be imputed using last observation carried forward (LOCF) method.

In addition to changes from baseline, the pattern of hemoglobin concentration and platelet count over time, and the percentage of change from baseline in hemoglobin concentration and platelet count will be evaluated descriptively using summary statistics at the baseline visit and 13, 25, 37, 51, 65, 77, 89, and 103 (end of study) using OC and LOCF data. Line graphs over time will also be provided to summarize the hemoglobin concentration and platelet count over time, changes from baseline and percentages from baseline using OC and LOCF data.

All hemoglobin concentration and platelet count data will be listed separately for each patient.

10.2.5. Normalized liver volume and Normalized spleen volume

Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in normalized liver volume and normalized spleen volume as measured by abdominal MRI will be descriptively summarized and tested using one sample t-test or Wilcoxon signed rank test in the same manner as described above for the primary endpoint. A 95% confidence interval for the mean and median of the change from baseline will also be presented. Missing post-baseline data will be imputed using last observation carried forward (LOCF) method.

The MRIs for measurement of liver and spleen volume are only collected at baseline and Weeks 51 and 103 (end of the study). Liver and spleen volumes will be normalized to body weight measured at baseline and Weeks 51 and 103 (end of the study).

Liver/Spleen size relative to body weight = (Liver/Spleen volume [cc]/Body weight [g])*100

Note: Corresponding body weight for a particular visit will be obtained from the Height/Weight eCRF page and should be from the same visit as liver and spleen measurements; last observation carried forward (LOCF) will be applied for body weight measurement.

The pattern of normalized liver volume and normalized spleen volume over time, the change from baseline over time and the percentage of change from baseline will be evaluated both descriptively using summary statistics and graphically using line graphs at the screening visit and Weeks 51 and 103 (end of study) using OC and LOCF data.

All normalized liver volume and normalized spleen volume data will be listed separately for each patient.

10.2.6. WHO BMD classification

Patients' WHO BMD classification based on LS T-score will be captured and classified as having normal (T-score ≥-1), osteopenia (-2.5< T-score <-1), or osteoporosis (T-score ≤-2.5) BMD. The number and proportion of patients who have shifts in BMD classification based on T-score will be summarized at the baseline visit and Weeks 51 and 103 (end of study).

A listing of the patients who changed BMD WHO classification based on T-score within the first 2 years and beyond will be provided.

10.2.7. Additional Analysis for Secondary Efficacy Endpoints

As an additional analysis, a linear mixed model repeated measures (MMRM) will be used as a repeated measures analysis to investigate the improvement of efficacy over time. The model will include fixed categorical effects for visit week and baseline value of each endpoint, age at baseline and age at diagnosis of type 1 Gaucher disease as continuous covariates. All the non-missing result of each secondary endpoints will be included in the model. SAS Proc Mixed with restricted maximum likelihood estimation (REML) and an unstructured within-patient covariance structure will be used. The MMRM analysis will be performed using OC and LOCF data. If this model fails to converge, a first order autoregressive (AR(1)) covariance structure will be used. From this model, change from baseline in least squares means, p-values and 95% confidence intervals will be estimated for quantitative secondary efficacy endpoints at each time point.

Example SAS code for the MMRM analysis (all post-baseline results will be used).

```
proc mixed data=dataset;
 class avisitn usubjid;
 model chg= avisitn base age adiaggau/s cl;
```

**avisitn is the analysis visit; usubjid is subject ID; chg is the change from baseline result of each endpoint; base is baseline value;; age is age at baseline; adiaggau is age at diagnosis of type 1 Gaucher disease.*

```
 repeated avisitn/type=un subject=usubjid r rcorr;
 lsmeans avisitn/pdiff cl alpha=0.05;
run;
```


10.2.8. Health Economics and Outcomes Research Endpoints

Change from baseline to 12 months (Week 51) and 24 months (Week 103 [end of study]) in overall fatigue as measured by the Brief Fatigue Inventory© (BFI) and bone pain as measured by the questions that were taken from Brief Pain Inventory (Short Form)© (BPI-SF) will be evaluated as health economic and outcomes research endpoints.

The first three questions of BFI evaluate patient fatigue on a 11-point scale ranging from 0 (No fatigue) to 10 (As bad as you can imagine). The last six questions in BFI rate how fatigue has interfered patient's activities on a 11-point scale ranging from 0 (Does not interfere) to 10 (Completely interferes). The global fatigue score will be calculated as average score of all the 9 items on the BFI. Patients must have at least five of nine items in order to calculate the global fatigue score.

Questions from BPI-SF include 2 subscales: pain severity [Item 3-6, score range 0 (No pain) - 10 (As bad as you can image)] and pain interference [Item 9A-9G, score range 0 (Does not interfere) to 10 (Completely interferes)]. The two subscale scores will be computed as the average score of all the items from that subscale. Patients must have non-missing responses to all

4 pain severity items and at least four of seven pain interference items in order to calculate the subscale scores. The questions 2, 7, and 8 of the BPI-SF have been removed from the questionnaire.

The observed values of BFI global fatigue score, BPI-SF subscale scores and individual item scores will be descriptively summarized and tested using one sample t-test or Wilcoxon signed rank test at baseline visit and at Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study) in the same manner as described above for the primary endpoint. A 95% confidence interval for the mean and median of the change from baseline will also be presented.

The descriptive summary statistics of the change from baseline and percentage change from baseline for BFI and questions from BPI-SF will also be generated at each time point. All questions from BPI-SF and BFI data for individuals will be listed.

10.3. Other Assessments or Analyses ([redacted])

[redacted]

11. Safety Analysis

11.1. Adverse Events

11.1.1. Treatment-emergent Adverse Events

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.

An incomplete or partial AE onset date may consist of either 1) only the year is available or 2) only the month and year are available. In general, an AE will be deemed a treatment-emergent AE if it cannot be definitively categorized as a pre-treatment AE after considering the relation of the available components (day, month, year) of the AE onset date with respect to the date of the first dose. If the partial AE onset date is not sufficient to categorize an AE as a treatment-emergent or pre-treatment AE, the available components (day, month, year) of the AE resolution date should be considered with respect to the date of the first dose.

In summary, imputation of the AE onset date is not needed to deem an AE as treatment-emergent or not. Based on the information available, one can compare the components (day, month, year) of the AE onset date (and of the AE resolution date if needed) with the date of the first infusion. In the end, if an AE cannot be conclusively categorized as a pre-treatment AE, then it must be categorized as a treatment-emergent AE.

AE tabular summaries will be based on all treatment-emergent AEs. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 18.1 or later.

An overall safety summary of treatment-emergent AEs will be presented. This summary table will display the number of patients and associated percentage in each of the following categories:

- Patients who experienced no AEs
- Patients who experienced at least one AE
- Patients who experienced at least one drug- related AE
- Patients who experienced at least one infusion-related AE
- Patients who experienced at least one severe AE
- Patients who experienced at least one drug-related severe AE
- Patients who experienced at least one life-threatening AE
- Patients who experienced at least one drug-related life-threatening AE
- Patients who experienced at least one serious AE (SAE)
- Patients who experienced at least one drug-related SAE
- Patient discontinuation from the study due to an AE(s)
- Patient deaths.

AEs will be summarized by system organ class (SOC) and preferred term (PT). The number and proportion of patients experiencing an AE will be tabulated overall; recurrent AEs observed within a patient will be counted once. Within each SOC, the PT will be sorted in descending frequency by the overall number of patients experiencing an AE. All AEs will be listed.

AEs that led to permanent discontinuation from the study will be summarized by SOC and PT. A listing of all patients who permanently discontinued due to an AE(s) will be provided and given a table number.

11.1.2. Serious Adverse Events

A SAE is any AE that results in any of the following outcomes: death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, a persistent or

significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The number and percentage of patients reporting treatment-emergent SAEs will be presented by SOC and PT. In addition, all SAEs will be presented in a by-patient listing and given a table number. A listing of all patients who died during the study will also be provided and given a table number.

11.1.3. Relationship of Treatment-emergent Adverse Events to Study Drug

The investigator should report on the AE eCRF if the AE is a study drug-related AE. If the relationship is missing, it will be imputed as "Related". The relationship will be determined by the investigator. 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 number and percentage of patients reporting a study drug-related AE will be presented by SOC and PT. In addition, AEs by SOC and PT will be tabulated by relationship to study drug by reporting the episode with the closest relationship to study drug.

11.1.4. Infusion-related (IRR) Adverse Events

An infusion-related reaction (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 by the investigator as related to study drug. Infusion-related Adverse Events will be presented by SOC and PT.

11.1.5. Severity of Treatment-emergent Adverse Event

AEs by SOC and PT will be tabulated by severity. In the case of multiple occurrences of the same AE (at the PT level) in an individual patient, the AE that is classified as the most severe (i.e., maximum severity) will be identified for the analysis by severity.

11.2. Clinical Laboratory Evaluations

The continuous laboratory data (serum chemistry, hematology, urinalysis and coagulation) will be descriptively summarized at the baseline visit and at Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study). In addition, the change from baseline to Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study) will be descriptively summarized. A laboratory retest, if available, that was performed at a scheduled visit, will be used in the analysis. If a baseline laboratory result is unavailable and a retest was not performed, the result will be replaced by the screening result if available.

The change from baseline to the end of study (EOS) measurement will be summarized using a shift table presented in terms of Normal (N), Out of Range and Not Clinically Significant (NCS), Out of Range and Clinically Significant (CS), or Missing (not done or not applicable). Clinical significance is based on the investigator's assessment and captured on the electronic case report form. If a patient prematurely discontinues the study, then all subsequent measurements will be marked as not applicable. The summary will be based on all available data. All the laboratory data (serum chemistry, hematology, urinalysis and coagulation) will be listed by patient.

Serum Chemistry:

- 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

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

Coagulation

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

Hemoglobin concentration and platelet count will be reported as secondary endpoints and they will not be included in the summary of laboratory assessments.

11.3. Vital Sign Measurements

Infusion vital signs will be recorded at every visit when an infusion is given. Vital signs parameters include pulse (bpm), blood pressure (systolic [mmHg] / diastolic [mmHg]), respiration rate (breaths per min), temperature (ºC) and pulse oxygen measurement (%).

For each infusion, the vital signs parameters will be recorded at the following time points: start of infusion (within 10 minutes prior to start of infusion), during the infusion (30 minutes after the start of infusion, plus or minus 5 minutes), after infusion (within 5 minutes after completing the infusion; 30 minutes after completing the infusion plus or minus 5 minutes; and 60 minutes after completing the infusion plus or minus 5 minutes). 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 infusion vital sign parameters will be summarized by reporting the number and proportion of patients experiencing at least one above normal (and at least one below normal) change during

the study in each vital sign parameter during or after the infusion. For each infusion vital sign parameter, the denominator for calculating this percent will only consider those patients who experienced at least one normal pre-infusion result during the study for that vital sign parameter. Results will be presented as above normal and below normal for each vital sign parameter overall.

A by-patient listing of all vital sign assessments will be provided.

Normal ranges for each vital sign parameter are provided below.

Sitting and Supine		
Systolic BP (mm Hg)	HIGH and INCREASE	≥ 140 and increase of 20 from baseline value
	LOW and DECREASE	< 90 and decrease of 20 from baseline value
Diastolic BP (mm Hg)	HIGH and INCREASE	≥ 90 and increase of 15 from baseline value
	LOW and DECREASE	< 50 and decrease of 15 from baseline value
Heart Rate (bpm)	HIGH and INCREASE	≥ 100 and increase of > 15 from baseline value
	LOW and DECREASE	< 45 and decrease of > 15 from baseline value

11.4. Physical Examination

A physical examination is to be performed at baseline and Weeks 13, 25, 37, 51, 65, 77, 89 and 103 (end of study). For the baseline Physical Exam, any clinically significant conditions will be recorded on the Medical History form. For all subsequent Physical Exams, any new or worsening conditions from baseline abnormal findings identified during the Exam will be recorded on the Adverse Event page. No summary table will be presented. A by-patient listing of all physical examination assessments will be provided.

11.5. 12-lead Electrocardiogram

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 a qualified cardiologist. ECGs will include assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, and assessment of pulse rate (PR), QRS, QT and corrected QT (QTc) intervals. QTc interval will be calculated using both Bazett (QTcB=QT/(RR)1/2) and Fridericia (QTcF=QT/(RR)1/3) corrections.

The measurements of PR, QRS, QT, QTc, and heart rate and the change from baseline to Week 103 (end of study) at scheduled visits will be summarized by descriptive statistics. Sinus rhythm and atrial or ventricular hypertrophy will be summarized using a shift table from baseline to EOS. A by-patient listing of ECG assessments will be provided.

11.6. Antibody Assessments

Anti-velaglucerase alfa antibody results, including anti-velaglucerase antibodies (ADA) and neutralizing anti-velaglucerase antibodies (NAb) will be summarized. The Anti-velaglucerase antibody status will be summarized as categorical variable by positive and negative at baseline, by

transient positive and persistent positive during the study period, and by treatment-induced positive and treatment-boosted positive at each post baseline visits. The anti-velaglucerase antibody titer will be summarized as continuous variable at baseline, and by any positive, by treatment-induced positive and treatment-boosted positive each post baseline visits.

Treatment-induced positive is defined as subject was positive for ADA or NAb at a study visit post baseline in a subject who is negative for ADA, NAb at baseline; Treatment-boosted positive is defined as subject's ADA or NAb titer was boosted to a higher level post baseline (greater than or equal to the baseline titer by fourfolds or more) at a study visit in a subject who is ADA or NAb positive at baseline; Transient positive is defined as subject tested positive for ADA or NAb once during treatment period (excluding last test), or positive for ADA or NAb two times or more where the first and last time points for ADA or NAb positive are separated by a period less than 16 weeks and the subject's last test is negative; Persistent positive is defined as subject tested ADA or NAb positive two times or more (more than 16 weeks apart) during study period including last time point tested. Antibody assessments will also be provided in a by-patient listing.

11.7. Pregnancy Testing

Female patients' pregnancy test results will be listed by patient for the safety population.

12.Statistical/Analytic Issues

12.1. Interim Analyses and Data Monitoring

Not applicable.

12.2. Adjustment for Covariates

Prognostic and predictive demographic and baseline factors may be incorporated in the repeated measures analyses. Unless otherwise specified, all repeated measures models that model the change from baseline over time will include baseline age, age at diagnosis of type 1 Gaucher disease in years, and the corresponding baseline value of the outcome parameter of interest as a factor. Tabular and graphical summaries obtained from the repeated measures models will identify the factors included in the statistical models.

12.3. Multi-center Studies

The summary results will not be presented by individual centers due to a small number of patients at each center.

12.4. Statistical Assumptions

No test will be performed for statistical assumptions.

12.5. Multiple Comparisons/Multiplicity

Not applicable.

12.6. Examination of Subgroups and Interactions

A COVID-19 subgroup analyses is planned for the outcome measurements per section 12.7.2.

12.7. Sensitivity Analysis

The following sensitivity analyses will be performed:

12.7.1. Last Observation Carried Forward (LOCF) Method

As a sensitivity analysis, the primary and secondary 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. If all post-baseline assessments are missing, the assessment at baseline will not be carried forward for the analysis.

12.7.2. COVID-19 Sensitivity Analysis

A subgroup analysis for patients who completed study per protocol and patients who have extended treatment period due to COVID-19 will be performed for the following summaries and figures to assess the impact of COVID-19 pandemic:

- Protocol violations
- Treatment compliance and extent of exposure
- Primary efficacy endpoint,
- Secondary efficacy endpoints, excluding BMD scores at month 12 (Week 51)
- [redacted]

For the summaries of adverse events, the subgroup analyses will be repeated for pre- and during COVID-19 pandemic phases. For any AE that occurred on or after the start of the pandemic, it will be considered as the event during COVID-19 pandemic phases. If the AE started before the start of the pandemic, it will be considered as pre-COVID-19 pandemic event. The protocol violations, patient exposure, Brief Pain Inventory outcomes and [redacted] measurements will be listed by patients who completed study per protocol and patients who have extended treatment period due to COVID-19.

12.7.3. Sensitivity Analysis for MRI Results

Site [redacted] has changed the MRI machine during the study, resulting in subject [redacted] having the baseline MRI performed on the old machine, and post-baseline MRI performed on the new machine. To evaluate the impact of MRI machine on the test results, the summaries of BMB score, normalized liver volume and normalized spleen volume will be repeated excluding subject [redacted].

12.7.4. Statistical Methods and Sensitivity Analyses for Estimand

For subjects who discontinued from the study due to treatment emergent adverse event (TEAE) or lack of efficacy (LOE), the missing data following discontinuation will be imputed under the hypothetical strategy using multiple imputation (MI) method, assuming discontinuation due to TEAE or LOE would not occur.

Multiple imputation (MI) method will utilize the SAS procedures PROC MI and PROC MIANALYZE, based on the assumption of missing at random (MAR) to assign missing LS BMD scores. Missing LS BMD Z-score as measured by DXA at Week 103 will be imputed using MI. The imputation model by FCS regression method will include age at baseline, age at diagnosis of type 1 Gaucher disease, LS BMD Z-score at baseline and at Week 51 as effect. [redacted] and number of imputations will be set as 50. The change from baseline in LS BMD Z scores at Week 103 will be calculated from the imputed 50 datasets. The 50 imputed datasets will be analyzed using the primary analysis methods. Results from analysis of each imputed dataset will be combined using Rubin's imputation rules to produce a pooled estimate of mean change from baseline. PROC MIANALYZE will be used to combine the results from each imputed dataset.

12.7.5. Sensitivity Analysis for Brief Fatigue Inventory© (BFI) and bone pain as measured by the questions that were taken from Brief Pain Inventory (Short Form)© (BPI-SF) Results

For Brief Fatigue Inventory© (BFI) and questions that were taken from Brief Pain Inventory (Short Form)© (BPI-SF), some of the Week 0 assessments were collected after the first infusion. A sensitivity analysis will be performed to include these post-infusion results as baseline and repeat for the analysis in section 10.2.8.

12.8. Handling of Missing Data

Imputation of missing data post-baseline will be employed using last observation carried forward (LOCF) for the endpoints of the change from baseline to subsequent time points in LS BMD Z-score as measured by DXA, BMB score, hemoglobin concentration, platelet count, normalized liver volume and normalized spleen volume. No data imputation will be used for the categorical analyses of WHO BMD classification based on LS T-scores, bone pain as measured by the questions from BPI-SF, and overall fatigue as measured by the BFI.

Patients who discontinue the study prematurely will be asked to undergo all safety and efficacy evaluations required for the end of study visit. If these data meet the algorithm outlined in Appendix VI, Algorithm to Handle End of Study and Unscheduled Visits, efficacy data collected at these visits will be incorporated in the analyses.

12.9. Definitions

Term	Definition

Term	Definition
Baseline	Data collected prior to the first administration of study drug (Day -3 through Day 0, where Day 0 is the day prior to first infusion)
Modified baseline	The average of data collected at screening and baseline. The non-missing values will be used to average.
Change from baseline	Post-baseline visit value minus baseline visit value or Modified baseline value
Percent Change from Baseline	(Change from baseline * 100) ÷ baseline or Modified baseline
Follow-up	30 days after the final infusion

13.References

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14.Appendices

14.1. Appendices I - List of Statistical Tables

Table No	Table Title
10.1.1	Patient Disposition All Enrolled Population
10.1.2	Demographic and Baseline Characteristics Safety Population
10.1.3a	Protocol Violations ITT Population
10.1.3b	Protocol Violations by COVID-19 Subgroup ITT Population
10.1.4a	Exposure to Study Drug and Treatment Compliance Safety Population
10.1.4b	Exposure to Study Drug and Treatment Compliance by COVID-19 Subgroup Safety Population
10.1.5	Concomitant Medications by Therapeutic Class and Preferred Term Safety Population
10.2.1.1a	Lumbar Spine BMD Z-Scores: Actual Values, Change from Baseline and Percentage Change from Baseline at 24 Months ITT Population – OC
10.2.1.1b	Lumbar Spine BMD Z-Scores: Actual Values, Change from Baseline and Percentage Change from Baseline at 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.1.1c	Lumbar Spine BMD Z-Scores: Sensitivity Analysis of Change from Baseline at 24 Months with Multiple Imputation for Missing Data ITT Population – OC
10.2.1.2a	Lumbar Spine BMD Z-Scores: Actual Values, Change from Baseline and Percentage Change from Baseline at 24 Months ITT Population – LOCF
10.2.1.2b	Lumbar Spine BMD Z-Scores: Actual Values, Change from Baseline and Percentage Change from Baseline at 24 Months by COVID-19 Subgroup ITT Population – LOCF
10.2.2.1a	BMB Scores: Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population – LOCF
10.2.2.1b	BMB Scores: Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population – LOCF
10.2.2.1c	BMB Scores: Sensitivity Analysis of Actual Values, Change from Baseline and Percentage Change from Baseline within 24 ITT Population without Subject [redacted] – LOCF
10.2.2.1d	BMB Scores: Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population – OC
10.2.2.1e	BMB Scores: Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.2.1f	BMB Scores: Sensitivity Analysis of Actual Values, Change from Baseline and Percentage Change from Baseline within 24 ITT Population without Subject [redacted] – OC
10.2.2.2a	BMB Scores: Repeated Measures Analysis of Change from Baseline ITT Population - OC
10.2.2.2b	BMB Scores: Repeated Measures Analysis of Change from Baseline by

Table No	Table Title
	COVID-19 Subgroup ITT Population - OC
10.2.2.2c	BMB Scores: Sensitivity Analysis of Repeated Measures Analysis of Change from Baseline ITT Population without Subject [redacted] - OC
10.2.2.2d	BMB Scores: Repeated Measures Analysis of Change from Baseline ITT Population - LOCF
10.2.2.2e	BMB Scores: Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - LOCF
10.2.2.2f	BMB Scores: Sensitivity Analysis of Repeated Measures Analysis of Change from Baseline ITT Population without Subject [redacted] - LOCF
10.2.3.1	Lumbar Spine BMD Z-Scores: Actual Values, Change from Baseline and Percentage Change from Baseline within 12 Months ITT Population – OC
10.2.3.2	Lumbar Spine BMD Z-Scores: Actual Values, Change from Baseline and Percentage Change from Baseline within 12 Months ITT Population – LOCF
10.2.3.3a	Lumbar Spine BMD Z-Scores: Repeated Measures Analysis of Change from Baseline ITT Population - OC
10.2.3.3b	Lumbar Spine BMD Z-Scores: Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - OC
10.2.3.3c	Lumbar Spine BMD Z-Scores: Repeated Measures Analysis of Change from Baseline ITT Population - LOCF
10.2.3.3d	Lumbar Spine BMD Z-Scores: Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - LOCF
10.2.3.4a	Lumbar Spine BMD (g/cm2) : Actual Values, Change from Baseline and Percentage Change from Baseline at 24 Months ITT Population – OC
10.2.3.4b	Lumbar Spine BMD (g/cm2): Actual Values, Change from Baseline and Percentage Change from Baseline at 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.3.5a	Lumbar Spine BMD (g/cm2): Actual Values, Change from Baseline and Percentage Change from Baseline at 24 Months ITT Population – LOCF
10.2.3.5b	Lumbar Spine BMD (g/cm2): Actual Values, Change from Baseline and Percentage Change from Baseline at 24 Months by COVID-19 Subgroup ITT Population – LOCF
10.2.3.6	Lumbar Spine BMD (g/cm2): Actual Values, Change from Baseline and Percentage Change from Baseline within 12 Months ITT Population – OC
10.2.3.7	Lumbar Spine BMD (g/cm2): Actual Values, Change from Baseline and Percentage Change from Baseline within 12 Months ITT Population – LOCF
10.2.3.8a	Lumbar Spine BMD (g/cm2): Repeated Measures Analysis of Change from Baseline ITT Population - OC
10.2.3.8b	Lumbar Spine BMD (g/cm2): Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - OC
10.2.3.8c	Lumbar Spine BMD (g/cm2): Repeated Measures Analysis of Change from Baseline ITT Population - LOCF
10.2.3.8d	Lumbar Spine BMD (g/cm2): Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - LOCF
10.2.4.1a	Hemoglobin Concentration (g/dL): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population – LOCF

Table No	Table Title
10.2.4.1b	Hemoglobin Concentration (g/dL): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population – LOCF
10.2.4.1c	Hemoglobin Concentration (g/dL): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population – OC
10.2.4.1d	Hemoglobin Concentration (g/dL): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.4.2a	Hemoglobin Concentration (g/dL): Repeated Measures Analysis of Change from Baseline ITT Population - OC
10.2.4.2b	Hemoglobin Concentration (g/dL): Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - OC
10.2.4.2c	Hemoglobin Concentration (g/dL): Repeated Measures Analysis of Change from Baseline ITT Population - LOCF
10.2.4.2d	Hemoglobin Concentration (g/dL): Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - LOCF
10.2.5.1a	Platelet Count (x 10^9/L): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population – LOCF
10.2.5.1b	Platelet Count (x 10^9/L): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population – LOCF
10.2.5.1c	Platelet Count (x 10^9/L): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population – OC
10.2.5.1d	Platelet Count (x 10^9/L): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.5.2a	Platelet Count (x 10^9/L): Repeated Measures Analysis of Change from Baseline ITT Population - OC
10.2.5.2b	Platelet Count (x 10^9/L): Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - OC
10.2.5.2c	Platelet Count (x 10^9/L): Repeated Measures Analysis of Change from Baseline ITT Population - LOCF
10.2.5.2d	Platelet Count (x 10^9/L): Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - LOCF
10.2.6.1a	Normalized Liver Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population – LOCF
10.2.6.1b	Normalized Liver Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population – LOCF
10.2.6.1c	Sensitivity Analysis of Normalized Liver Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population without Subject [redacted] – LOCF
10.2.6.1d	Normalized Liver Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT

Table No	Table Title
	Population – OC
10.2.6.1e	Normalized Liver Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.6.1f	Sensitivity Analysis of Normalized Liver Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population without Subject [redacted] – OC
10.2.6.2a	Normalized Liver Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline ITT Population - OC
10.2.6.2b	Normalized Liver Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - OC
10.2.6.2c	Sensitivity Analysis of Normalized Liver Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline ITT Population without Subject [redacted] – OC
10.2.6.2d	Normalized Liver Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline ITT Population - LOCF
10.2.6.2e	Normalized Liver Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - LOCF
10.2.6.2f	Sensitivity Analysis of Normalized Liver Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline ITT Population without Subject [redacted] – OC
10.2.7.1a	Normalized Spleen Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population – LOCF
10.2.7.1b	Normalized Spleen Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population – LOCF
10.2.7.1c	Sensitivity Analysis of Normalized Spleen Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population without Subject [redacted] – LOCF
10.2.7.1d	Normalized Spleen Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population – OC
10.2.7.1e	Normalized Spleen Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.7.1f	Sensitivity Analysis of Normalized Spleen Volume (% of Body Weight): Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population without Subject [redacted] – OC
10.2.7.2a	Normalized Spleen Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline ITT Population - OC
10.2.7.2b	Normalized Spleen Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - OC
10.2.7.2c	Sensitivity Analysis of Normalized Spleen Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline ITT Population without

Table No	Table Title
	Subject [redacted] – OC
10.2.7.2d	Normalized Spleen Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline ITT Population - LOCF
10.2.7.2e	Normalized Spleen Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline by COVID-19 Subgroup ITT Population - OC
10.2.7.2f	Sensitivity Analysis of Normalized Spleen Volume (% of Body Weight): Repeated Measures Analysis of Change from Baseline ITT Population without Subject [redacted] – OC
10.2.8.1a	Shifts in WHO Classification of Lumbar Spine BMD T-Scores ITT Population - OC
10.2.8.1b	Shifts in WHO Classification of Lumbar Spine BMD T-Scores by COVID-19 Subgroup ITT Population - OC
10.2.9.1a	Brief Fatigue Inventory©: Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population - OC
10.2.9.1b	Brief Fatigue Inventory©: Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.9.1c	Brief Fatigue Inventory©: Actual Values, Change from Baseline and Percentage Change from Baseline (Including Post-Infusion Week 0 Assessments) within 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.10.1a	Questions Taken from Brief Pain Inventory (Short Form)©: Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months ITT Population - OC
10.2.10.1b	Questions Taken from Brief Pain Inventory (Short Form)©: Actual Values, Change from Baseline and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population - OC
10.2.10.1c	Questions Taken from Brief Pain Inventory (Short Form)©: Actual Values, Change from Baseline (Including Post-Infusion Week 0 Assessments) and Percentage Change from Baseline within 24 Months by COVID-19 Subgroup ITT Population - OC
10.2.11.1a	[redacted]
10.2.11.1b	
10.2.11.2a	
10.2.11.2b	
10.2.11.3a	
10.2.11.3b	

Table No	Table Title
	[redacted]
10.2.11.4a	
10.2.11.4b	
10.2.11.5a	
10.2.11.5b	
10.2.11.6a	
10.2.11.6b	
10.2.11.7a	
10.2.11.7b	
10.2.11.8a	
10.2.11.8b	
10.2.11.9a	
10.2.11.9b	
10.2.11.10	
10.2.11.11	
10.2.11.12	
10.2.11.13	
10.3.1.1a	Overall Summary of Treatment-Emergent Adverse Events Safety Population
10.3.1.1b	Overall Summary of Treatment-Emergent Adverse Events by COVID Phases Safety Population
10.3.1.2a	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Population
10.3.1.2b	Summary of Treatment-Emergent Adverse Events by System Organ Class,

Table No	Table Title
	Preferred Term and COVID Phase Safety Population
10.3.1.3a	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug Safety Population
10.3.1.3b	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Relationship to Study Drug and COVID Phase Safety Population
10.3.1.4a	Summary of Treatment-Emergent Infusion-Related Adverse Events by System Organ Class and Preferred Term Safety Population
10.3.1.4b	Summary of Treatment-Emergent Infusion-Related Adverse Events by System Organ Class, Preferred Term and COVID Phase Safety Population
10.3.1.5a	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity Safety Population
10.3.1.5b	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Severity and COVID Phase Safety Population
10.3.2.1a	Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term Safety Population
10.3.2.1b	Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and COVID Phase Safety Population
10.3.2.2a	Summary of Treatment-Emergent Adverse Events Leading to Permanent Study Discontinuation by System Organ Class and Preferred Term Safety Population
10.3.2.2b	Summary of Treatment-Emergent Adverse Events Leading to Permanent Study Discontinuation by System Organ Class, Preferred Term and COVID Phase Safety Population
10.4.1.1	Clinical Chemistry Laboratory: Actual Values and Change from Baseline by Scheduled Visit Safety Population
10.4.1.2	Clinical Chemistry Laboratory: Shifts from Baseline to EOS Safety Population
10.4.2.1	Hematology Laboratory: Actual Values and Change from Baseline by Scheduled Visit Safety Population
10.4.2.2	Hematology Laboratory: Shifts from Baseline to EOS Safety Population
10.4.3.1	Urinalysis Laboratory: Actual Values and Change from Baseline by Scheduled Visit Safety Population
10.4.3.2	Urinalysis Laboratory: Shifts from Baseline to EOS Safety Population
10.4.4.1	Coagulation Laboratory: Actual Values and Change from Baseline by Scheduled Visit Safety Population
10.4.4.2	Coagulation Laboratory: Shifts from Baseline to EOS Safety Population
10.5.1	Proportion of Patients Experiencing at Least One Abnormal Change in an Infusion Vital Sign Parameter (Safety Population)
10.6.1	12-Lead Electrocardiogram: Actual Values, Change from Baseline and Percentage Change from Baseline by Scheduled Visit Safety Population
10.6.2	12-Lead Electrocardiogram:: Shifts from Baseline to EOS Safety Population
10.7.1	Summary of Anti-velaglucerase Alfa Antibody Status by Scheduled Visit Safety Population
10.7.2	Summary of Anti-velaglucerase alfa Antibody Titer by Scheduled Visit Safety Population

14.2. Appendices II - List of Statistical Figures

Figure No	Figure Title
10.2.1.1a	Line Graph of Mean (+/- SE) Lumbar Spine BMD Z-Scores Within 24 Months ITT Population - OC
10.2.1.1b	Line Graph of Mean (+/- SE) Lumbar Spine BMD Z-Scores Within 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.1.2a	Box Plot of Change from Baseline in Lumbar Spine BMD Z-Scores Within 24 Months ITT Population - OC
10.2.1.2b	Box Plot of Change from Baseline in Lumbar Spine BMD Z-Scores Within 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.1.3a	Line Graph of Mean (+/- SE) Lumbar Spine BMD Z-Scores Within 24 Months ITT Population - LOCF
10.2.1.3b	Line Graph of Mean (+/- SE) Lumbar Spine BMD Z-Scores Within 24 Months by COVID-19 Subgroup ITT Population - LOCF
10.2.1.4a	Line Graph of Mean (+/- SE) Lumbar Spine BMD (g/cm2) Within 24 Months ITT Population - OC
10.2.1.4b	Line Graph of Mean (+/- SE) Lumbar Spine BMD (g/cm2) Within 24 Months by COVID-19 Subgroup ITT Population – OC
10.2.1.5a	Line Graph of Mean (+/- SE) Lumbar Spine BMD (g/cm2) Within 24 Months ITT Population - LOCF
10.2.1.5b	Line Graph of Mean (+/- SE) Lumbar Spine BMD Z-Scores (g/cm2) Within 24 Months by COVID-19 Subgroup ITT Population - LOCF
10.2.2.1a	Line Graph of Mean (+/- SE) BMB Scores Within 24 Months ITT Population - LOCF
10.2.2.1b	Line Graph of Mean (+/- SE) BMB Scores Within 24 Months by COVID-19 Subgroup ITT Population - LOCF
10.2.2.1d	Line Graph of Mean (+/- SE) BMB Scores Within 24 Months ITT Population - OC
10.2.2.1e	Line Graph of Mean (+/- SE) BMB Scores Within 24 Months by COVID-19 Subgroup ITT Population - OC
10.2.4.1a	Line Graph of Mean (+/- SE) Hemoglobin Concentration (g/dL) Within 24 Months Results ITT Population - LOCF
10.2.4.1b	Line Graph of Mean (+/- SE) Hemoglobin Concentration (g/dL) Within 24 Months Results by COVID-19 Subgroup ITT Population - LOCF
10.2.4.1c	Line Graph of Mean (+/- SE) Hemoglobin Concentration (g/dL) Within 24 Months Results ITT Population - OC
10.2.4.1d	Line Graph of Mean (+/- SE) Hemoglobin Concentration (g/dL) Within 24 Months Results by COVID-19 Subgroup ITT Population - OC
10.2.5.1a	Line Graph of Mean (+/- SE) Platelet Count (x 10^9/L) Within 24 Months Results ITT Population - LOCF

Figure No	Figure Title
10.2.5.1b	Line Graph of Mean (+/- SE) Platelet Count (x 10^9/L) Within 24 Months Results by COVID-19 Subgroup ITT Population - LOCF
10.2.5.1c	Line Graph of Mean (+/- SE) Platelet Count (x 10^9/L) Within 24 Months Results ITT Population - OC
10.2.5.1d	Line Graph of Mean (+/- SE) Platelet Count (x 10^9/L) Within 24 Months Results by COVID-19 Subgroup ITT Population - OC
10.2.6.1a	Line Graph of Mean (+/- SE) Normalized Liver Volume (% of Body Weight) Within 24 Months Results ITT Population - LOCF
10.2.6.1b	Line Graph of Mean (+/- SE) Normalized Liver Volume (% of Body Weight) Within 24 Months Results by COVID-19 Subgroup ITT Population - LOCF
10.2.6.1d	Line Graph of Mean (+/- SE) Normalized Liver Volume (% of Body Weight) Within 24 Months Results ITT Population - OC
10.2.6.1e	Line Graph of Mean (+/- SE) Normalized Liver Volume (% of Body Weight) Within 24 Months Results by COVID-19 Subgroup ITT Population - OC
10.2.7.1a	Line Graph of Mean (+/- SE) Normalized Spleen Volume (% of Body Weight) Within 24 Months Results ITT Population - LOCF
10.2.7.1b	Line Graph of Mean (+/- SE) Normalized Spleen Volume (% of Body Weight) Within 24 Months Results by COVID-19 Subgroup ITT Population - LOCF
10.2.7.1d	Line Graph of Mean (+/- SE) Normalized Spleen Volume (% of Body Weight) Within 24 Months Results ITT Population - OC
10.2.7.1e	Line Graph of Mean (+/- SE) Normalized Spleen Volume (% of Body Weight) Within 24 Months Results by COVID-19 Subgroup ITT Population - OC
10.2.9.1a	Line Graph of Mean (+/- SE) Brief Fatigue Inventory© Within 24 Months Results ITT Population - OC
10.2.9.1b	Line Graph of Mean (+/- SE) Brief Fatigue Inventory© Within 24 Months Results by COVID-19 Subgroup ITT Population - OC
10.2.10.1a	Line Graph of Mean (+/- SE) Questions Taken from Brief Pain Inventory (Short Form)© Within 24 Months Results ITT Population - OC
10.2.10.1b	Line Graph of Mean (+/- SE) Questions Taken from Brief Pain Inventory (Short Form)© Within 24 Months Results by COVID-19 Subgroup ITT Population - OC

14.3. Appendices III - List of Statistical Listings

Listing No	Listing Title
10.1.1	Listing of Patient Disposition All Enrolled Population
10.1.2	Listing of Demographic and Baseline Characteristics Safety Population
10.1.3a	Listing of Protocol Violations ITT Population
10.1.3b	Listing of Protocol Violations by COVID-19 Subgroup ITT Population
10.1.4a	Listing of Patient Exposure Safety Population
10.1.4b	Listing of Patient Exposure by COVID-19 Subgroup Safety Population

Listing No	Listing Title
10.1.5	Listing of Medical History Safety Population
10.1.6	Listing of Prior and Concomitant Medications Safety Population
10.1.7	Listing of Prior and Concomitant Therapies Safety Population
10.1.8	Listing of Prior and Concomitant Medical/Surgical Procedures Safety Population
10.2.1.1	Listing of Lumbar Spine BMD Z-Scores Within 24 Months ITT Population
10.2.2.1	Listing of BMB Scores Within 24 Months ITT Population
10.2.3.1	Listing of Lumbar Spine BMD (g/cm2) Within 24 Months ITT Population
10.2.4.1	Listing of Hemoglobin Concentration (g/L) Within 24 Months ITT Population
10.2.5.1	Listing of Platelet Count (x 10^9/L) Within 24 Months ITT Population
10.2.6.1	Listing of Normalized Liver Volume (% of Body Weight) Within 24 Months ITT Population
10.2.7.1	Listing of Normalized Spleen Volume (% of Body Weight) Within 24 Months ITT Population
10.2.8.1	Listing of Lumbar Spine BMD T-Scores Within 24 Months ITT Population
10.2.9.1	Listing of Brief Fatigue Inventory Within 24 Months ITT Population
10.2.10.1a	Listing of Brief Pain Inventory Within 24 Months ITT Population
10.2.10.1b	Listing of Brief Pain Inventory Within 24 Months by COVID-19 Subgroup ITT Population
10.2.11.1a	[redacted]
10.2.11.1b	[redacted]
10.2.12.1	Listing of Bone Pathology Within 24 Months ITT Population
10.3.1.1	Listing of Adverse Events Safety Population
10.3.2.1	Listing of Serious Adverse Events Safety Population
10.3.2.2	Listing of Treatment-Emergent Adverse Events Leading to Permanent Study Discontinuation Safety Population
10.3.2.3	Listing of Deaths Safety Population
10.4.1.1	Listing of Clinical Chemistry Laboratory Evaluations Safety Population
10.4.2.1	Listing of Hematology Laboratory Evaluations Safety Population
10.4.3.1	Listing of Urinalysis Laboratory Evaluations Safety Population
10.4.4.1	Listing of Coagulation Laboratory Evaluations Safety Population
10.5.1	Listing of Vital Sign Evaluations Safety Population
10.5.2	Listing of Physical Examination Evaluations Safety Population
10.5.3.1	Listing of 12-Lead ECG Evaluations Safety Population
10.5.4	Listing of Anti-velaglucerase alfa Antibody Status Safety Population
10.5.5	Listing of Pregnancy Results Safety Population

14.4. Appendices IV - Schedule of Study Procedures

Assessment	Study Schedule of Events
LS BMD Z-score	Screening, Weeks 51 and 103 (end of study)
BMB score	Baseline, Weeks 51 and 103 (end of study)
Hemoglobin concentration	Baseline, Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study)
Platelet count	Baseline, Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study)
Normalized liver volume	Baseline, Weeks 51 and 103 (end of study)
Normalized spleen volume	Baseline, Weeks 51 and 103 (end of study)
Questions from BPI-SF	Baseline, Weeks 13, 25, 37, 51, 65, 77, 89, and 103 (end of study).
BFI	Baseline, Weeks 13, 25, 37, 51, 65, 77, 89 and 103 (end of study).
WHO BMD	Screening, Weeks 51 and 103 (end of study).
[redacted]	Baseline, Weeks 13, 25, 37, 51, 65, 77, 89 and 103 (end of study).
Clinically laboratory tests	Baseline, Weeks 13, 25, 37, 51, 65, 77, 89 and 103 (end of study).
HBsAg, HCV, HIV, 25-hydroxyvitamin D	Screening
Physical examination	Baseline, Weeks 13, 25, 37, 51, 65, 77, 89 and 103 (end of study).
ECG	Baseline, Weeks 25, 51, 77 and 103 (end of study)
Serum anti-velaglucerase alfa antibody	Baseline, Weeks 13, 25, 37, 51, 65, 77, 89 and 103 (end of study).

14.5. Appendices V - Programming Conventions

- Use single space within a variable and double space between variables
- Do no split variables across a page; add a page break
- For categorical variables in the baseline characteristics table, medical/surgical procedures table, and concomitant therapy table, please add a "Missing" row if needed
- Algorithm to use for Therapeutic Class for conmeds: Use ATC4 if not missing; if ATC4 is missing or coded as "…", then use ATC3. If both ATC4 and ATC3 are missing or coded as "…", then use ATC2. If ATC4, ATC3, and ATC2 are missing or coded as "…", then use ATC1
- The general conventions for decimal points are:
    - Proportions (%) should be presented to 1 decimal point
    - If a p-value is less than 0.00005, then this will be presented as a p-value of '<0.0001'. All other p- values will be rounded to 4 decimal places

14.6. Appendices VI- Algorithm to Handle End of Study and Unscheduled Visits

End of Study (EOS) Visits

For the efficacy analysis, if the EOS visit date for patients who discontinue the study early is on or within 17 days after the last infusion date then we will derive the visit number for the EOS visit as last infusion week plus 2 weeks.

Unscheduled Visits

For the efficacy analysis, compare the unscheduled visit date to the closest infusion date; if the unscheduled visit occurred on or within +/- 7 days of that infusion date then we assign the infusion week as the visit week for the unscheduled visit. If the unscheduled visit was completed between two infusion weeks and the distances are same, the visit week will be assigned as the infusion week before unscheduled visit. The assessment result from the unscheduled visit will be used to replace the missing result for that visit week. If using the algorithm, multiple unscheduled visits fall into the same visit then the one closest to the infusion date will be used to replace the missing result for the visit week. If the multiple unscheduled visits that fall into the same visit are equal distant from the infusion date then the one before the infusion date will be used.

For vital sign measurements, physical examination, 12-lead ECG and antibody assessments, compare the unscheduled visit date to the infusion date of the closest safety assessment visit. If the unscheduled visit occurred within +/- 30 days of that infusion date then we assign the infusion week as the visit week for the unscheduled visit. The assessment result from the unscheduled visit will be used to replace the missing result for that visit week. If using the algorithm, multiple unscheduled visits fall into the same visit then the one closest to the infusion date will be used to replace the missing result for the visit week. If the multiple unscheduled visits that fall into the same visit are equal distant from the infusion date then the one before the infusion date will be used.

Based on the algorithms above, for the efficacy parameters only, the EOS and unscheduled visits that fall into the visit window will be carried forward when LOCF analysis is performed.

14.7. Appendices VII – Estimand and Intercurrent Events

Possible intercurrent events are presented below:

Label	Intercurrent Event Type
IcEv1 (Discontinue TEAE)	Discontinuation from study due to treatment emergent adverse event (TEAE).
IcEv2 (Discontinue LOE)	Discontinuation from study due to lack of efficacy (LOE).
IcEv3 (Prohibited medications)	Use of prohibited medications.
IcEv4 (Compliance)	Poor compliance (>=3 consecutively missing dose, or 5 total).

Primary efficacy estimand with rationale and strategies to address intercurrent events are presented below:

Estimand Label	Estimand (Primary)
Estimand Description	Mean change in LS BMD Z-score as measured by DXA from baseline to 24 months (Week 103 [end of study]) in treatment-naïve patients with type 1 Gaucher disease irrespective of using prohibited medication or poor compliance and assuming patients did not discontinue treatment due to TEAE or LOE. A hypothetical strategy is used to estimate the change of LS BMD Z-score assuming discontinuation due to TEAE or LOE would not occur. A treatment policy strategy is used for assessing change of LS BMD Z-score irrespective of using prohibited medication or poor compliance.
Target Population	Treatment-naïve Patients with Type 1 Gaucher Disease patients who received at least one study drug infusion (full or partial).
Endpoint	The change from baseline to 24 months (Week 103 [end of study]) in LS BMD Z-score as measured by DXA.
Treatment Condition(s)	Velaglucerase alfa 60 U/kg every other week (EOW) by a minimum 60-minute intravenous infusion
Population-Level Summary	Change in means
Intercurrent Event Strategy	
IcEv1 (Discontinue TEAE)	Hypothetical strategy
IcEv2 (Discontinue LOE)	Hypothetical strategy
IcEv3 (Prohibited medications)	Treatment Policy Strategy
IcEv4 (Compliance)	Treatment Policy Strategy
Rationale for Strategies	A hypothetical strategy for discontinuation due to TEAE or LOE to ascertain the efficacy prior to treatment discontinuation. A treatment policy strategy for use of prohibited medication or poor compliance as this is relevant to clinical practice