Statistical Analysis Plan

NCT Number: NCT05529992

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

Study Number: TAK-669-3001

Document Version and Date: Version 3.0, 13 September 2024

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STATISTICAL ANALYSIS PLAN

Study Number: *TAK-669-3001*

Study Title: *A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Velaglucerase alfa in Chinese Subjects With Type I Gaucher Disease*

Phase: *3b*

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Prepared by: [redacted]

Based on:

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Approved by:

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	03-Oct-2022	Not Applicable
Version 2.0	26-Apr-2024	Update for analysis clarifications and additions.
Version 3.0	13-Sep-2024	Update for clarifications and additions, see section 9.1.

TABLE OF CONTENTS

ABBREVIATIONS

ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
AUC	area under the curve
BMI	body mass index
CHQ-PF50	Childhood Health Questionnaire-Parent Form 50
CI	confidence interval
eCRF	electronic case report form
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end-of-treatment
EOW	every other week
ERT	enzyme replacement therapy
ICF	informed consent form
IRR	infusion-related reaction
ITT	intention-to-treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
Nab	neutralizing antibody
PK	pharmacokinetic
PP	per-protocol
PRO	patient-reported outcomes
PT	Preferred Term (MedDRA)
Q1	25th percentile
Q3	75th percentile
QoL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SD	standard deviation
SF-36	Short Form-36
TEAE	treatment-emergent adverse event

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

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

1.1.2 Secondary Objective(s)

The secondary objectives of the study are to assess:

- *Other safety parameters of VPRIV (including the incidence of TEAEs and infusion-related reactions (IRRs) and rate of antibody formation)*
- *The effect of VPRIV on hematologic manifestations*
- *The effect of VPRIV on the liver and spleen volume*
- *The effect of VPRIV on quality of life (QoL)*
- *The PK of VPRIV*
- *The effect of VPRIV on disease biomarkers*

1.1.3 Additional Objective(s)

Not applicable.

1.2 Endpoints

1.2.1 Primary Endpoint(s)

Primary objective	Primary Endpoint
• *To evaluate the safety of VPRIV by assessing the incidence of serious TEAEs*	• *Incidence rate of serious TEAEs throughout the study*

1.2.2 Secondary Endpoint(s)

1.2.2.1 Key Secondary Endpoints(s)

Secondary objective	Secondary Endpoints
• *To assess other safety parameters of VPRIV*	• *Incidence rate of other safety parameters of VPRIV throughout the study:* *a) TEAEs* *b) Infusion-related reactions* *c) Development of anti-VPRIV antibodies, including neutralizing antibodies* • *Other safety aspects measured by laboratory assessments, vital signs, and electrocardiogram results*
• *To assess the effect of VPRIV on hematologic manifestations*	• *Change from baseline to Week 53 in hemoglobin concentration and platelet count (time frame: 53 weeks)*
• *To assess the effect of VPRIV on the liver and spleen volume*	• *Change from baseline to Week 53 in normalized liver and spleen volume (percent of body weight (BW)) (time frame: 53 weeks)*
• *To assess the effect of VPRIV on QoL*	• *Change from baseline to Week 53 in the QoL questionnaire assessment (including Short Form-36, version 2 for subjects ≥18 years of age or Childhood Health Questionnaire-Parent Form 50 for subjects ≥5 and <18 years of age) (time*

	frame: 53 weeks)
• *To assess the PK of VPRIV*	• *The PK parameters of VPRIV at Week 1 and single serum drug concentration at the end of the infusion at Week 37*
• *To assess the effect of VPRIV on disease biomarkers*	• *Percentage change from baseline to Week 53 in biomarkers (such as plasma chemokine [C-C motif] ligand 18 and glucosylsphingosine) (time frame: 53 weeks)*

1.2.2.2 Other Secondary Endpoint(s)

Not applicable.

1.2.3 Exploratory Endpoint(s)

Not applicable.

1.2.4 Safety Endpoints

Safety endpoints will include the following:

- TEAEs
- Infusion-related reactions (IRRs)
- Antidrug antibody (ADA) against VPRIV assessment, including neutralizing antibody (Nab) status
- Laboratory assessments
- Vital signs
- Electrocardiogram (ECG) results

1.2.5 Other Endpoints

Not applicable.

1.3 Estimands

Not applicable.

2.0 STUDY DESIGN

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

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

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

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

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

visit. Quality-of-life assessment will include Short Form-36, version 2 (SF-36; for subjects ≥18 years of age) or Childhood Health Questionnaire-Parent Form 50 (CHQ-PF50; for subjects 5 through 17 years of age). Biomarker assessments, such as chemokine (C-C motif) ligand 18 (CCL18) and glucosylsphingosine (lyso-Gb1), may be assessed from samples collected at the baseline, Week 13, Week 25, Week 37, and EOT visits.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

No hypothesis will be tested.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

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

5.0 ANALYSIS SETS

5.1 Intent-to-Treat Set

*The **Intent-to-Treat (ITT)** Set will include all subjects who sign the ICF (and assent form, if applicable) and are eligible for the study based on the defined inclusion/exclusion criteria. The ITT Set will be used for efficacy analyses.*

5.2 Per-Protocol Analysis Set

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

5.3 Safety Analysis Set

*The **Safety Set** will include all subjects in the ITT set who receive at least 1 dose of VPRIV. The safety set will be used for analysis of the safety endpoints.*

5.4 Pharmacokinetic Set

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

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

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

Baseline values are defined as the last observed value on or before the first dose of study medication.

Means and medians (and Q1/Q3) will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. CIs intervals will be presented using the same number of decimal places as the parameter estimate.

Continuous variables will be summarized with descriptive statistics including the mean, standard deviation (SD), median, Q1, Q3, minimum and maximum. Categorical data will be summarized with the frequency and percentage of subjects falling within each category. A category for "Missing" will be added, if needed.

The observed values, the change from baseline, the change over time, and the percentage change from baseline for the efficacy measurements (hemoglobin, platelet counts, liver and spleen size) will be summarized by visit and sex.

Subject listings will be provided for clinical outcomes from the QoL assessments.

Efficacy analyses will be based on the ITT Set, with the PP Set as a sensitivity analysis. Data from subjects who previously received Imiglucerase ERT and treatment-naive populations will be analyzed separately, as well as pooled. Data will further be analyzed separately (and pooled) for age groups at informed consent, i.e., age <18 years (age <12 years and age ≥12 to <18 years) and age ≥18 years.

6.1.1 Handling of Treatment Misallocations

Not applicable.

6.1.2 Analysis Approach for Continuous Variables

See Section 6.1 above.

6.1.3 Analysis Approach for Binary Variables

See Section 6.1 above.

6.1.4 Analysis Approach for Time-to-Event Variables

Not applicable.

6.2 Disposition of Subjects

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

Protocol deviations will be summarized for the ITT set, as well as listed for each subject.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Baseline and demographic variables will be descriptively summarized by age groups for the ITT Set.

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

The following baseline demographics will be summarized:

- age (years) at Informed Consent
- weight (kg) and height (cm)
- BMI (kg/m^2)
- Sex
- Hemoglobin (g/dL)
- Platelet count ($x10^9/L$)
- Normalized liver size (as %BW)
- Normalized spleen size (as %BW)

6.3.2 Medical History and Concurrent Medical Conditions

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

6.3.3 Baseline Characteristics

Refer to Section 6.3.1.

6.4 Medication History and Concomitant Medications

6.4.1 Prior Medications

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

Prior treatment (medication or procedure) refers to all treatments (medications or procedures) received and discontinued prior to signing the ICF.

Prior medication will be listed by subject for the Safety Set.

6.4.2 Concomitant Medications

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

The number and percentage of subjects 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 most recent WHO-Drug Dictionary version).

Concomitant medication will be summarized and listed by subject for the Safety Set.

Prior and concomitant treatment (medication or procedure) refers to all treatments (medications or procedures) received prior to signing the ICF, and continued to be taken during the study period, that is, after signing the ICF.

6.5 Efficacy Analysis

6.5.1 Primary Endpoint(s) Analysis

6.5.1.1 Derivation of Endpoint(s)

The primary analysis will be the incidence of serious TEAEs and is discussed in Section 6.6 below.

6.5.1.2 Main Analytical Approach

Not applicable.

6.5.1.3 Sensitivity Analysis

Not applicable.

6.5.1.4 Supplementary Analyses

Not applicable.

6.5.2 Secondary Endpoint(s) Analysis

Efficacy analysis

The observed values, the change from baseline, the change over time, and the percentage change from baseline for the efficacy measurements (hemoglobin, platelet count, liver and spleen size), will be summarized by visit and sex for the ITT set.

Additionally, the observed values, the change from baseline and the percentage change from baseline in multiples of normal (MN) for liver and spleen volume will be summarized by visit and sex for the ITT set.

If applicable, mean (±SE) efficacy measurements (hemoglobin, platelet count, liver and spleen size) will be plotted by visit for the ITT set.

6.5.2.1 Key Secondary Endpoint(s) Analysis (if applicable)

No secondary endpoint has been identified as key.

6.5.2.2 Derivation of Endpoint(s)

BMI will be derived as follows:

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)} / [\text{height (m)}]^2.$$

Normalized liver and spleen volumes (as percentage of body weight) will be derived as follows:

$$\text{Normalized liver/spleen volume (\%BW)} = [\text{liver/spleen size (mL)} / \text{body weight (g)}] * 100.$$

The multiples of normal for spleen volume is given by

$$\text{Spleen volume (MN)} = \text{spleen volume (cm}^3\text{)} / [2* \text{subject's weight (kg)}].$$

The multiples of normal for liver volume is given by

$$\text{Liver volume (MN)} = \text{liver volume (cm}^3\text{)} / [25* \text{subject's weight (kg)}].$$

6.5.2.3 Main Analytical Approach

Not applicable.

6.5.2.4 Sensitivity Analysis

Not applicable.

6.5.2.5 Supplementary Analyses

Not applicable.

6.5.3 Other Secondary Endpoints Analysis (if applicable)

Not applicable.

6.5.4 Subgroup Analyses (if applicable)

Efficacy analyses will be analyzed by age group (<18 [<12 / ≥12 to <18] / ≥18 years at informed consent) and sex. Treatment naïve subjects (at enrolment) and subjects who switched from Imiglucerase will also be summarized separately.

6.6 Safety Analysis

The primary analysis will be the incidence of serious TEAEs.

A TEAE is defined as any event emerging or manifesting at or after the initiation of the investigational product or any existing event that worsens in either intensity or frequency following exposure to the investigational product.
Serious adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Serious treatment-emergent adverse events (TEAEs) will be summarized for overall and by system organ class (SOC) and preferred term (PT). Furthermore, serious TEAEs will be summarized by maximum severity, by age groups and by relationship to investigational product.

Analysis of AEs will be performed at both subject level and AE level.

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

The Safety Set will be used.

6.6.1 Adverse Events

Secondary safety analysis

The secondary safety analyses will be based on the Safety Set.

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Treatment-emergent adverse events (TEAEs) will be summarized for overall and by system organ class (SOC) and preferred term (PT). Analysis of AEs will be performed at both subject level and AE level, i.e., summarized by number (%) of subjects who reported at least one AE, as well as the number of AEs reported. Similar displays will be provided for IRRs.

An IRR will be defined as an AE that

1) begins either during or within 12 hours after the start of the infusion, and
2) is judged as related to study drug.

The AEs will be summarized by severity, seriousness, age groups, and relation to investigational product.

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

All fatal AEs will be listed by subject.

6.6.2 Adverse Events of Special Interest (if applicable)

Infusion-related reactions (IRRs) will be summarized in a similar fashion than overall TEAEs – see Section 6.6.1 above. An additional summary table will be provided for the potential relationship between IRRs and anti-VPRIV antibody status. This summary table will include the specific IRR, the outcome of the IRR, and the antibody status (positive / negative). This summary will be done at a visit level (i.e., at Week 13, 25 and 37) where infusions and antibody samples collected are done at the same visit.

6.6.3 Other Safety Analysis (if applicable)

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

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

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

Laboratory data will be listed by subject. Subjects with newly occurring abnormalities outside the normal range will be flagged, listed separately, and summarized. The mean change from baseline in laboratory values or a shift table will be provided for each visit. The change from baseline will be calculated by subtracting the baseline value from the postbaseline value. If needed, the white blood cell differential count will be calculated by multiplying the white blood cell count by the percentage of each type of white cell.

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

Normal ranges for each vital sign parameter are provided below.

	≥ 12 years old	≥ 6 but <12 years old	⩾ 2 but < 6 years old
Body temperature (˚C)	36.5 to 37.2	36.5 to 37.2	36.5 to 37.2
Respiration rate (breaths/min)	12-24	12-22	20-30
Pulse (bpm)	40-100	55-95	65-110

		≥ 18 years old	< 18 years old
Systolic BP (mm Hg)	HIGH	≥ 140	≥ 20+ 80+ 2*age
	LOW	< 90	< -20+ 80+ 2*age
Diastolic BP (mm Hg)	HIGH	≥ 90	≥ 20+ (80+2*age)*(2/3)
	LOW	< 50	< -20+ (80+2*age)*(2/3)

Antibody data, including neutralizing antibody status, will also be presented in the form of summary tables by age groups and individual subject listings.

The 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.

Antibody status will be defined as follows:

- treatment-induced positive: pretreatment is negative, post treatment become positive
- treatment-boosted positive: pretreatment is positive, post treatment Ab titer increases >= 4 folds compared to pretreatment
- persistent positive: at least positive two times (>16 weeks), including last time point tested, or only positive at last timepoint tested
- transient positive: at least tested positive once, last time point tested is negative

Below are more details regarding the definitions provided above:

- Treatment-induced positive: baseline negative and at least one post-baseline positive
- Treatment-boosted positive: at least one post-treatment positive with Ab titer increases >= 4 folds compared to pre-treatment
- Persistent and transient positive: baseline not necessarily negative

- Persistent positive: the duration between first and last post-treatment positive > 16 weeks. The last post-treatment will be the last time point tested and the result of last time point tested should be positive.
- Persistent positive: This also include only if the last time point tested positive, regardless of outcome of previous tests.
- Transient positive: at least one post-treatment positive, but last time point tested is negative
- Transient positive: exclude the subjects that fulfilled the condition of persistent positive.

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

Immunology data will be listed for each subject, using the Safety Set.

6.6.4 Extent of Exposure and Compliance

Treatment compliance and exposure summaries will be presented. For each subject, the subject's percent of compliance, reflecting the subject's willingness to accept the intravenous infusion at each infusion visit, will be calculated as follows for up to 51 weeks:

$$\text{Compliance} = [(\text{Number of Complete Infusions Received}) / (\text{Expected Number of Infusions})]*100$$

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

The number and percentage of subjects 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 number of subjects with missed infusions will also be summarized.

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

$$\text{Exposure (weeks)} = [(\text{Date of the last dose} - \text{Date of first dose}) + 1]/7$$

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 measurement on or prior to each infusion date. The per-protocol dose amount for naïve subjects is 60 U/kg. The actual and per protocol dose amounts (U/kg) and durations of infusion (minutes) will be

averaged across the non-missing infusions for each subject and then summarized by the descriptive statistics across all subjects. All exposure data will be presented in a by-subject listing.

For subjects who received Imiglucerase ERT within the 12 months prior to screening, the initial dose will be determined by the investigator after discussing with the sponsor and recording in appropriate document based on the subject's specific treatment and the situation at the time of enrollment, according to the subject's benefit and risk assessment.

Duration of infusion (minutes) will be derived as follows:

Duration (min) = infusion stop time – infusion start time.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

Individual pharmacokinetic concentrations will be listed and summarized for the PK Analysis Set by age (e.g., ⩾18 years vs 12 through 17 years vs 4 through 11 years), visit and scheduled time points for naive subjects with PK assessments with descriptive statistics (number, arithmetic mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, and CV [95% CI] of the geometric mean). Individual concentration-time profiles of VPRIV will be generated based on actual time, and mean (± SD) concentration-time profiles of VPRIV will be generated based on scheduled time.

Pharmacokinetic parameter estimates will be computed with Phoenix® WinNonlin® software Version 8.3 using noncompartmental methods from individual serum-concentration time data and actual times and dosing, where appropriate.

PK parameters include, but are not limited to, the following:

- C_{max}: Maximum concentration observed
- T_{max} (min): Time of maximum observed concentration sampled post-dose
- AUC_{inf} (ng•min/mL): Area under the concentration-time curve from time zero extrapolated to infinity
- $T_{1/2}$ (min): Terminal elimination half-life, defined as the natural log of 2 divided by the terminal rate constant (λ_z)
- CL (mL/min/kg): Total body clearance of the drug from serum, normalized for body weight
- Vss (mL/kg): Volume of distribution at steady state, normalized for body weight

Individual PK parameters of VPRIV at Week 1 will be listed and summarized for the PK Analysis Set by treatment as well as by age group, with descriptive statistics (number, arithmetic

mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, and CV and 95% CI of the geometric mean).

6.7.2 Pharmacodynamic Analysis

Not applicable.

6.7.3 Biomarker Analysis

The observed values, the change from baseline, the change over time, and the percentage change from baseline for biomarkers will be summarized by visit. Furthermore, the percentage change from baseline for biomarker will be summarized by anti-VPRIV antibody status at Week 13, 25, 37 and 53. These will be shown for the ITT set. A by-subject listing will also be provided for the ITT set.

If applicable, individual biomarker measurements and the percentage change from baseline will be plotted by visit for the ITT set.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

6.8.1 PRO Analysis

The change over time in subject rating of QoL will be analyzed using the SF-36v2 for subjects ≥18 years of age and CHQ-PF50 for subjects ≥5 and <18 years of age. Quality of life assessments are not applicable for subjects <5 years of age.

The SF-36v2 comprises 36 items across eight domains (subscales). The eight SF-36v2 subscales will be aggregated using weight to calculate Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. The CHQ-PF50 consists of 50 items on 14 unique concepts to measure physical vs. psychosocial aspects of general health. The domains can be further combined to derive overall physical and psychosocial scores: the Physical Component Summary and Psychosocial Component Summary scores.

Following the scoring instructions of the instruments, the scale item scores for the SF-36v2 and CHQ-PF50 will be summed and directly transformed into a 0-100 scale, with a mean of 50 and SD of 10, on the assumption that each item carries equal weight. The higher the scale score, the better the health state (i.e., a score of 0 is equivalent to worst possible health state and a score of 100 is equivalent to best possible health). Some specific items will be re-coded to ensure that all items are positively scored and that higher scores indicate better health.

Descriptive summary statistics will be produced for the overall component summary scores and (if available) any subscale score of SF-36v2 and CHQ-PF50, respectively, by presenting the mean, SD, median, Q1, Q3, minimum, and maximum at each time point and also the score change from baseline to Week 53. All available QoL assessments will be used in summary.

6.8.2 Health Care Utilization Analysis

Not applicable.

6.9 Other Analyses

Further by-subject listings will be provided for pregnancy tests (female subjects), and electroencephalogram, using the Safety Set.

6.10 Interim Analyses

Not applicable.

6.11 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
6.5.2 Secondary Endpoint(s) Analysis		Add multiples of normal (MN) for hepatomegaly and splenomegaly summary.	Update.
6.5.2.2 Derivation of Endpoint(s)		Add the multiples of normal calculation formula.	Update.
6.6.1 Adverse Events	begins either during or within **24** hours after the start of the infusion, and	Update IRR definition.	Keep consistent with protocol.
6.6.3 Other Safety Analysis		Update vital sign parameter normal ranges.	Update.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Means and medians (and Q1/Q3) will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. CIs intervals will be presented using the same number of decimal places as the parameter estimate.

For categorical variables, the count (n) and percent (%) will be displayed. Unless otherwise stated in table shells, the denominator for percentages is N (the number of subjects in the treatment group within that analysis set). For any summary by subgroups (e.g. by sex), the denominator is the number of subjects in that subgroup/treatment group within that analysis set.

Percentages will be reported to 1 decimal place, except when the percentage equals exactly 100 where it will be displayed as an integer (100). For zero, only count and no percentage will be displayed.

For summaries of categorical variables percentages are usually based on N as stated above. However, if missing is not a category then the denominator is the number of subjects with non-missing values. Any exceptions to the denominator should be explained in the footnotes.

9.2.2 Imputation of missing dates

Any date that is collected only as MONTH / YEAR, e.g, date of birth, the 15th of the month will be imputed.

If AE start date is partial, the following imputation will be done:

- If day is missing, impute 1st of the month
- If day and month are missing, impute 01 July. However, this should be checked not to be later than the AE stop date. If AE stop date is available, the 1st of the month of the AE stop month should be imputed.

If AE stop date is partial, the following imputation will be done:

- If day is missing, impute end of the month (30th or 31st)
- If day and month are missing, impute 31 Dec.

The same rules above (for AE date imputation) will be followed for medical history and prior / concomitant medications.

9.2.3 Definition of Baseline

Baseline will be defined as the data collected prior to or on the first administration of study drug (for measurements on the same day as first dose, but with no time collected, it will be assumed as

prior to first dose). If the value prior to first administration is not available, the screening value will be used.

9.2.4 Definition of Visit Windows

For the efficacy analysis, we will take the closest scheduled visit 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 both unscheduled and scheduled visits exist for the same visit, then the scheduled visit will be used.

9.3 Analysis Software

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