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# Statistical Analysis Plan
# AP-recAP-HPP-01-01

**Protocol Title:** **Open-Label Pilot Trial to Evaluate the Effects of Ilofotase Alfa on Biomarkers in Adult Patients with Hypophosphatasia**

**Sponsor code:** **AP-recAP-HPP-01-01**

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|---|---|
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|---|---|---|---|
| N/A | 1.0 | Initial document | 05 June 2023 |
| | | | |

**TABLE OF CONTENTS**

# 1. ABBREVIATIONS

| | |
|---|---|
| ADA | Anti-Drug Antibodies |
| AE | Adverse Event |
| AMP | AM-Pharma |
| AUC | Area Under the Curve |
| CL | Clearance |
| ITT | Intention To Treat Population |
| N/A | Not Applicable |
| PD | Pharmacodynamic(s) |
| PK | Pharmacokinetic(s) |
| PKS | PK Analysis Set |
| PLP | Pyridoxal 5'-phosphate |
| PopPK | Population PK |
| PPi | Pyrophosphate |
| PV | Pharmacovigilance |
| SAE | Serious Adverse Event |
| SAS | Safety Analysis Set |
| SD | Standard Deviation |
| SDV | Source Data Verification |
| SEM | Standard Error of the Mean |
| SOP | Standard Operating Procedure |
| TFL | Table, Figure & Listing |
| TMF | Trial Master File |
| Vd | Volume of distribution |
| VP-Clin Ops | Vice President Clinical Operations |

## 2. SOURCE DOUMENTS

This Statistical Analysis Plan (SAP) was written based on the following documentation:

| Document | Date | Version |
|---|---|---|
| Protocol | 30 March 2023 | Final v1.1 |
| Annotated eCRF (AP-recAP-HPP-01-01_Study Design_V1.1_Annotated_09May2023) | 09 May2023 | Version 1.1 |

# 3. PROTOCOL DETAILS

## 3.1 TRIAL OBJECTIVES

Primary objective:

- The change in Inorganic Pyrophosphate (PPi), and Pyridoxal 5'-phosphate (PLP) levels after low, and high dose ilofotase alfa in adult hypophosphatasia (HPP) patients.

Exploratory objectives:

- To determine the safety and pharmacokinetic (PK) profile of a single iv dose of ilofotase alfa in adult HPP patients.
- To determine the pharmacodynamic (PD) profile of a single iv dose of ilofotase alfa in adult HPP patients.

## 3.2 ENDPOINTS

**Primary Endpoint**

- Change from median baseline PPi to lowest recorded post-baseline value.
- Change from median baseline PLP to lowest recorded post-baseline value.

**Secondary Endpoints**

- Mean area under the curve (AUC) of PPi response over time.
    - 
- Mean AUC of PLP response over time.
    - 

**Further Exploratory Endpoint**

Further exploratory endpoints will be carried out if a notable change is seen in the primary endpoint. Lab readings will be analysed following the same methods as shown in the primary and secondary endpoints. (See section 4.7 for further details)

**Subgroup Analysis**

Both Primary and Secondary endpoints will be investigated by subgroup (dose level) and compared across the subgroups. This will include:

- Change from median baseline PPi to lowest recorded post-baseline values by arm.
    - Comparison of changes between arms.
- Change from median baseline PLP to lowest recorded post-baseline values by arm.
    - Comparison of changes between arms.
- Mean AUC of PPi response over time by arm.
    - Comparison of mean AUC between arms.
- Mean AUC of PLP response over time by arm.
    - Comparison of mean AUC between arms.

Similar subgroup analysis will be carried out for exploratory endpoints if these are performed.

## 3.3 OVERAL TRIAL DESIGN

This is a single-center, open-label, randomized, parallel group clinical trial in adult patients with HPP. Two different dose levels (0.8 mg/kg and 3.2 mg/kg) will be assessed. Up to twelve patients will be randomized, 6 patients to each trial arm. Patients will receive a single dose of 0.8 mg/kg or a single dose of 3.2 mg/kg. Ilofotase alfa will be administered as a 1-hour iv infusion on day 1.

## 3.4 INTERIM ANALYSES

There are no formal interim analyses planned.

## 3.5 FINAL ANALYSIS

The planned final analysis will be performed following last patient's final visit once all required database cleaning activities have been completed and the database has been declared locked by data management.

## 3.6 SAMPLE SIZE AND POWER

No formal sample size calculation is provided as the purpose of this trial is exploratory. Up to twelve patients will be randomized, 6 to each trial arm. If this randomization rate is not achieved in a reasonable timeframe, the Sponsor will review the required sample size.

# 4. STATISTICAL ANALYSIS

## 4.1 GENERAL PRINCIPLES

All data processing, summarization and analyses will be performed using Labcorp's SAS Environment/Version 9.4 (or later) of the SAS® statistical software package.
The following principles will be applied to all Tables, Figures and Listings unless otherwise stated:

| Principle | Value |
|---|---|
| Significant tests | One-sided and use a 2.5% significance level. T-tests will be applied if not otherwise specified |
| Treatment group labels and order presented | ilofotase alfa 0.8 mg/kg<br>ilofotase alfa 3.2 mg/kg |
| Tables | Data in summary tables presented by treatment group, Day and time point (where applicable). |
| Listings | All data collected presented by treatment group, patient number, Day and time point (where applicable), unless otherwise specified. |
| Descriptive summary statistics for continuous variables | Number of patients (n), mean, standard deviation (SD), standard error of the mean (SEM), median, minimum, maximum, Missing |

| Principle | Value |
|---|---|
| Descriptive summary statistics for categorical variables | Frequency counts and percentages [n (%)]. |
| Denominator for percentages | Denominators for percentages will be the number of patients with non-missing data. |
| Include "Missing" as category | Yes, when the number missing is greater than zero for at least one treatment group. |
| Precision for percentages | 1 decimal place (except for 100%) |
| Display to one more decimal place than collected value | Mean<br>Median |
| Display to two more decimal places than collected value | SD, SEM<br>Confidence Interval (CI of the medians) |
| Limit of precision for displays | 3 decimal places |
| Presentation of p-value | Up to 4 decimal places or <0.0001 |
| Date Format | DDMMMYYYY |

## 4.2 ANALYSIS POPULATIONS

Intention to Treat population (ITT)
All randomized patients will be included in the ITT population.

Population for the safety analysis (SAS)
All patients who have received trial medication will be included in the safety analysis set.

Population for the PK analyses (PKS)
All patients who have received ilofotase alfa and for whom sufficient bioanalytical data are available to calculate reliable estimates of the PK parameters.

## 4.3 PROTOCOL DEVIATIONS

A list of protocol deviations will be created and maintained by the study monitor. During the final data review meeting, the list of protocol deviations will be reviewed and finalized. The List of finally agreed Protocol deviations will be added to the Clinical Trial Report.

## 4.4 MISSING DATA

In the case of partial dates used in calculations, where there is only a Year given, the missing month/day will be assumed as January 01; in the case when the day is missing this will be assumed as the first day of the month. Where partial dates are used in listings or for non-calculations, dates will be displayed as given in the database (e.g. 2017, or July 2021). The handling of other missing data is described in further detail within Section 4.6.

## 4.4 PATIENT DISPOSITION

**Trial population and screening Failures**

- Analysis is based on "All enrolled patients set".
- Absolute and relative frequencies will be presented for categorical variables (screen failures, Reason for screening failures, ITT, SAS, PKS) by dose group and overall.
- Derived variables:
    - None.
- Inclusion/Exclusion Criteria information will be listed (Day -2, day 1).

**Disposition of Patients**

- Analysis is based on ITT Set.
- Absolute and relative frequencies will be presented for categorical variables (completed, discontinuation, reasons for discontinuation) by dose group and overall.
- Derived variables:
    - None.
- End of study information will be listed.

## 4.5 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

**Demographics:**

- Analysis is based on ITT Set.
- The median, minimum, maximum, mean, SD and SEM will be presented for continuous variables (Age, Height, Weight, BMI) by dose group and overall.
- Absolute and relative frequencies will be presented for categorical variables (Gender, Childbearing potential, Reasons for non-childbearing potential) by dose group and overall.
- Derived variables:
    - None.
- Demographics data will be listed.

**Medical History:**

- Analysis is based on ITT Set.
- Medical History data will be coded against MedDRA version 26.0.
- Absolute and relative frequencies will be presented (Medical History events, yes/no, System Organ Class, Preferred Term) by dose group and overall.
- Derived variables:
    - None.
- A listing of all medical history events will be generated.

**Physical Examination:**

- Analysis is based on ITT Set.
- Physical examination data will be listed.

**Baseline 12-Lead Electrocardiogram data:**

- Analysis is based on ITT Set.
- 12-Lead Electrocardiogram data will be listed.

## 4.5 PRIOR AND CONCOMITANT MEDICATION

- Analysis is based on ITT Set
- Prior and Concomitant Medications will be coded against WHO-DD version Mar 2023
- Absolute and relative frequencies will be presented (main Anatomical or pharmacological group(ATC level1), Chemical substance (ATC level 5)) by dose group and overall.
- Derived variables:
    - None.
- A listing of Prior and Concomitant Medication will be generated.

## 4.5 STUDY DRUG ADMINISTARTION

**Study Drug Administration:**

- Analysis is based on ITT Set.
- A listing of Study Drug Administration will be generated.

## 4.6 PRIMARY EFFICACY (PPI/PLP)

- Analysis is based on ITT Set.
- The median, minimum, maximum, mean, SD and SEM will be presented for continuous variables (PPi and PLP levels (2nd assessment), Change from Baseline, max change from baseline (absolute and relative), AUC) by dose group and overall.
- For the maximum change of Baseline, 95% Confidence intervals, as well as comparison dosage will be presented in addition.
- For the AUCs, 95% Confidence intervals as well as comparison dosage will be presented in addition.
- Spaghetti plots for the absolute and relative changes from Baseline (PPi and PLP) will be generated by dose group and overall.
- Derived variables:
    - Baseline
        - the baseline value is defined as the median value of the measurements prior to randomization (day -2, day -1, day 1 prior to randomization).
        - In case of missing values, Baseline will be determined from the available data.
        - In case day 1 pre-dose measurement was prior to treatment, but not prior to randomization, this value will not be taken into consideration for the baseline calculation.
    - (absolute) Change from Baseline (difference Visit value - Baseline).
    - Relative Change from Baseline (% change from baseline = Value day/timepoint x / baseline value).
    - Max change from Baseline (is defined as individual maximum (absolute) change from the individual baseline value day 2 to day 10).
    - AUC for change from Baseline values.
- PPi and PLP data will be listed.

## 4.7 EXPLORATORY BIOMARKER

- Analysis is based on ITT Set.
- The median, minimum, maximum, mean, SD and SEM will be presented for continuous variables (and their respective absolute change from Baseline) by dose group and overall.
    - ATP µM
    - PL nmol/L
    - ALP Isoenzymes U/L
    - Osteocalcin ng/mL
    - Adenosine (urine) mmol/mol Creatinine
    - Adenosine (blood) mmol/mol Creatinine
    - PEA mmol/mol Creatinine
    - Creatinine (blood / urine) µmol/L
    - Phosphate (blood / urine) mmol/L
    - Calcium (blood / urine) mmol/L
    - TRP (Tubular Reabsorption of Phosphate) %
    - TmP/GFR (maximum reabsorption rate of Phosphate over Glomerular Filtration Rate) mmol/L
    - ALP activity U/L
    - c-Terminal iFGF-23 pmol/L
    - PTH pg/mL

  - CTX pg/mL
  - PINP ng/ml
  - 25 OH vitamin D ng/ml
- Derived variables:
  - Baseline
    - the baseline value is defined as the median value of the measurements prior to randomization (day -2, day -1, day 1 prior to randomization).
    - In case of missing values, Baseline will be determined from the available data.
    - In case day 1 pre-dose measurement was prior to treatment, but not prior to randomization, this value will not be taken into consideration for the baseline calculation.
- Explorative Biomarker data will be listed.

## 4.8 SAFETY ENDPOINTS

**Adverse Events**

- Analysis is based on SAS Set.
- All AEs reported will be coded and classified according to MedDRA (version 26.0 or higher).
- Summary tables of treatment emergent AEs (TEAEs) will be presented per treatment by system organ class and preferred term based on the MedDRA terminology list:
  - Overall summary of AEs
    - Number of Patients with AEs / number of respective Events.
    - Number of Patients with TEAEs / number of respective Events.
    - Number of Patients with SAEs / number of respective Events.
    - Number of Patients with serious TEAEs / number of respective Events.
    - Number of Patients with AEs leading to discontinuation / number of respective Events.
    - Number of Patients with TEAEs leading to discontinuation / number of respective Events.
    - Number of Patients with fatal AEs / number of respective Events.
    - Number of Patients with TEAEs by intensity / number of respective Events.

  - TEAEs (frequency of occurrence, number and percentage of patients experiencing the event) by MedDRA SOC, PT.
  - Related TEAEs (frequency of occurrence, number and percentage of patients experiencing the event) by MedDRA SOC, PT.
- Derived variables:
  - Study day of AE start date and AE end date (-2, -1, 1, … 10, ...).
- A listing will be given of all individual AEs. (TEAES, non-TEAES).

**Vital Signs**

- Analysis is based on SAS Set
- The median, minimum, maximum, mean, SD and SEM will be presented.
- Derived variables:
  - Change from Baseline (difference Visit value - Baseline value defined as values from day -2).
- Vital signs will be listed.

**Physical examination**

- Analysis is based on SAS Set.
- Absolute and relative frequencies will be presented for the physical examination outcomes.
- Derived variables:
    - None.
- Physical examination data will be listed.

**Safety Laboratory (Clinical Chemistry, Hematology, Urinalysis)**

- Analysis is based on SAS Set.
- The median, minimum, maximum, mean, SD and SEM will be presented for continuous variable by dose group and overall.
- Absolute and relative frequencies will be presented for dichotomous (positive, negative) urinalysis parameter by dose group and overall.
- Spaghetti plots will be created for the continuous laboratory parameters.
- Box Plots will be created for the continuous variables.
- Derived variables:
    - Change from day -2 (difference Visit value - value from day -2) for continuous parameters.
- Safety Laboratory data will be listed.

**Pregnancy Testing**

- Analysis is based on SAS Set.
- Data from Pregnancy tests will be listed.

**ADA**

- Analysis is based on SAS Set.
- Absolute and relative frequencies will be presented by dose group and overall, for:
    - Outcomes at day 1 and day 10 (negative / positive).
    - All combinations of outcomes day 1 and day 10.
- Derived variables:
    - Combinations of outcomes day1/day10 (negative/negative, negative/positive, positive, negative, positive/positive).
- ADA data will be listed.

**PK**

- Analysis is based on PK Set (PKS).
- The median, minimum, maximum, mean, SD and SEM will be presented for PK concentrations by dose group and overall.
- PK concentration plots will be created.
- The PK parameters and their statistical evaluation will be separate from the Clinical Trial Report of this trial. A separate analysis may include data of this trial in the existing population PK (PopPK) models to evaluate clearance (CL) and volume of distribution (Vd), which will be reported separately.
- Derived variables:
    - None.

PK concentration data will be listed.

## 5. LIST OF TABLES, FIGURES AND LISTINGS

| | Output No | Topic | Title | Groups | Population |
|---|---|---|---|---|---|
| 1 | 14.1.1.1 | Patients Disposition | Overview of Trial Populations and Screen Failures<br>All Enrolled Analysis Set | overall | all enrolled |
| 2 | 14.1.1.2 | Patients Disposition | Summary of Disposition of Patients Overall<br>Intent-to-Treat | overall and by Dose | ITT |
| 3 | 14.1.2 | Patients demographics | Summary of Demographics | overall and by Dose | ITT |
| 4 | 14.1.3 | Medical History summary | Summary of Medical History | overall and by Dose | ITT |
| 5 | 14.1.4 | Prior/ Concomitant Medications | Frequencies on WHO-DD ATC 1/ 5/ level | overall and by Dose | ITT |
| | | **Efficacy** | | | ITT |
| 6 | 14.2.1.1 | PPi | Summary of Change from Baseline by Visit on PPi (µM) - | overall and by dose | ITT |
| 7 | 14.2.1.2 | PPi | Maximum Change from Baseline on PPi (µM) - | overall and by dose | ITT |
| 8 | 14.2.1.3 | PPi | Spaghetti Plot for PPi (µM) | overall and by dose | ITT |
| 9 | 14.2.2.1 | PLP | Summary of Change from Baseline by Visit on PLP (nmol/L) | overall and by dose | ITT |
| 10 | 14.2.2.2 | PLP | Maximum Change from Baseline on PLP (nmol/L) | overall and by dose | ITT |
| 11 | 14.2.2.3 | PLP | Spaghetti Plot for PLP (nmol/L) | overall and by dose | ITT |
| 12 | 14.2.3.1 | Exploratory Biomarkers | Summary of Change from Baseline by Visit exploratory Biomarker | overall and by dose | ITT |
| | | **Safety** | | | |
| 13 | 14.3.1.1 | Adverse Events summary | Overall Summary of Adverse Events | overall and by dose | SAS |
| 15 | 14.3.1.2 | Adverse Events | Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term | overall and by dose | SAS |
| 16 | 14.3.1.3 | Adverse Events | Summary of related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term | overall and by dose | SAS |
| 17 | 14.3.2.1 | Vital Signs | Vital Signs | overall and by dose | SAS |
| 18 | 14.3.3.1 | Physical examination | Physical Examination | overall and by dose | SAS |
| 18 | 14.3.4.1 | Laboratory Clinical Chemistry | Safety Laboratory - Clinical Chemistry -Descriptive Analysis | overall and by dose | SAS |

| | | | | | |
|---|---|---|---|---|---|
| 19 | 14.3.4.2 | Laboratory Clinical Chemistry | Spaghetti Plot for Clinical Chemistry Parameters | by patient | SAS |
| 20 | 14.3.4.3 | Laboratory Clinical Chemistry | Box Plots for Clinical Chemistry Parameters | overall and by dose | SAS |
| 21 | 14.3.4.4 | Laboratory Hematology | Safety Laboratory - Clinical Chemistry -Descriptive Analysis | overall and by dose | SAS |
| 22 | 14.3.4.5 | Laboratory Hematology | Spaghetti Plot for Clinical Chemistry Parameters | by patient | SAS |
| 23 | 14.3.4.6 | Laboratory Hematology | Box Plots for Clinical Chemistry Parameters | overall and by dose | SAS |
| 24 | 14.3.4.7 | Laboratory – Urinalysis | Safety Laboratory - Urinalysis -Descriptive Analysis | overall and by dose | SAS |
| 25 | 14.3.4.8 | Laboratory – Urinalysis | Spaghetti Plot for Urinalysis parameters - Urobilinogen | by patient | SAS |
| 26 | 14.3.4.9 | Laboratory - Urinalysis | Box Plot for Urinalysis parameters – Urobilinogen | overall and by dose | SAS |
| 27 | 13.3.4.11 | ADA results | ADA results – descriptive analysis | overall and by dose | ITT |
| 28 | 14.3.4.10 | PK results | PK concentrations – descriptive analysis | overall and by dose | PKS |
| 29 | 13.3.4.11 | PK results | PK Concentration Plots | overall and by dose | PKS |
| | | | Listings | | All |
| 1 | 16.2.1.1 | Disposition | Inclusion and Exclusion Criteria | By dose / patient No. | All enrolled |
| 2 | 16.2.1.2 | Disposition | End of Study | By dose / patient No. | All enrolled |
| 3 | 16.2.4.1 | Demographic data | Demographics | By dose / patient No. | ITT |
| 4 | 16.2.4.2 | Medical History | Medical History | By dose / patient No. | ITT |
| 5 | 16.2.4.3 | Physical Examination | Physical examination | By dose / patient No. | |
| 6 | 16.2.4.4 | Baseline ECG | Baseline ECG | By dose / patient No. | ITT |
| 7 | 16.2.4.5 | Prior and Concomitant Medication | Prior and Concomitant Medications | By dose / patient No. | ITT |
| 8 | 16.2.5.1 | Study Drug | Study Drug Administration | By dose / patient No. | ITT |
| 9 | 16.2.6.1 | Biomarker Listing | Listing Biomarker | By dose / patient No. | ITT |
| 10 | 16.2.7.1 | Adverse Events | Treatment Emergent Adverse Events | By dose / patient No. | SAS |
| 11 | 16.2.7.2 | Adverse Events | Non- Treatment Emergent Adverse Events | By dose / patient No. | SAS |

| | | | | | |
|---|---|---|---|---|---|
| 12 | 16.2.7.3 | Vital Signs | Vital Sign | By dose / patient No. | SAS |
| 13 | 16.2.7.4 | Physical Examination | Physical Examination | By dose / patient No. | SAS |
| 14 | 16.2.8.1 | Laboratory (safety lab) | Safety Laboratory - Clinical Chemistry | By dose / patient No. | SAS |
| 15 | 16.2.8.2 | Laboratory (safety lab) | Safety Laboratory - Hematology | By dose / patient No. | SAS |
| 16 | 16.2.8.3 | Laboratory (safety lab) | Safety Laboratory - Urinalysis | By dose / patient No. | SAS |
| 17 | 16.2.8.4 | Pregnancy Testing | Pregnancy Testing | By dose / patient No. | SAS |
| 18 | 16.2.8.5 | ADA results | ADA results | By dose / patient No. | SAS |
| 19 | 16.2.8.6 | PK Concentrations | PK concentrations | By dose / patient No. | SAS |

# 6. TABLE AND FIGURES SHELLS

The table, figure, and listing (TFL) shells presented in this document are mock-ups and may be subject to minor format modifications once the actual data are used. The data represented in this document are used for example purposes only and do not reflect the actual study data captured. The overall contents in any individual TFL shell will not change, although additional tables may be added if necessary, thus changing the table number scheme. Significant changes will be communicated to the Sponsor.

## 6.1 GENERAL PROGRAMMING SPECIFICATIONS

All TFLs will follow the following rules:

- Paper size will be Letter (8.5" x 11"), with the following margins in Inches:

  Landscape

  | | | | |
  |---|---|---|---|
  | top | 1.5 | left | 1 |
  | bottom | 1.73 | right | 1 |

- Every TFL will have a header containing Sponsor name, Protocol ID.
- Every TFL will have a footnote containing program location, name, run date and run time, and the status of the output: Dry run – Draft – Final Draft – Final (others as needed).
- Further footnotes will be displayed as necessary.
- There will be no page breaks within a section if possible (if a section fits on one page).

The presentation order of the statistics will be:

- N, Mean, SD, SEM, Min, median, max.
- Rules for significant digits in safety data tables are as follows: if the raw value has x decimal places, then the mean and the median will have x+1 decimal places, the standard deviation will have x+2 decimal places.
- N and n will be presented as whole numbers.
- Percentages will always be displayed with 1 decimal place (except for 100%).

Tables Summarizing Categorical Data

- If the number of events is zero, data will be presented as “0”.
- If the categories of a parameter are ordered, all categories between the maximum possible category and the minimum category will be included, even if n=0 for a given category.
- If the categories are not ordered, only those categories for which there is at least one subject represented will be included.
- A “missing” category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

# 6.2 TFLS ACCORDING TO ICH E3 NUMBERING STRUCTURE

# A 14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

## A1 14.1 DEMOGRAPHIC DATA

**Table 14.1.1.1**
**Overview of Trial Populations and Screen Failures**
**All Enrolled Analysis Set**

| | Total | ilofotase alfa 0.8 mg/kg | ilofotase alfa 3.2 mg/kg |
|---|---|---|---|
| All Enrolled Analysis Set [a] | xxx | | |
| Screening Failures [b][c] | xxx ( xx.x%) | | |
| Primary reason | | | |
| Withdrawal of consent | xxx ( xx.x%) | | |
| Failure to meet inclusion and exclusion criteria | xxx ( xx.x%) | | |
| Substantial non-compliance | xxx ( xx.x%) | | |
| Physician decision | xxx ( xx.x%) | | |
| Adverse event | xxx ( xx.x%) | | |
| Lost to Follow up | xxx ( xx.x%) | | |
| Discontinuation by Sponsor | xxx ( xx.x%) | | |
| Other | xxx ( xx.x%) | | |
| Intent-to-Treat Sets [b][d] | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |
| Safety Analysis Set (SAS) [b][e] | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |
| PK Analysis set (PKS) [b] [f] | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |

[a] All patients that have been assigned a patient number regardless of whether they were randomized or received trial drug.
[b] Percentages are calculated based on All Enrolled Analysis Set.
[c] Patients with consent to participate but who will not subsequently be randomly allocated to trial drug.
[d] All patients who are randomly assigned to a trial drug.
[e] All patients who have received trial medication will be included in the safety analysis set..
[f] All patients who have received ilofotase alfa and for whom sufficient bioanalytical data are available to calculate reliable estimates of the PK parameters.

Reference: Listings 16.2.1.1, 16.2.1.2
Program Name: Date/Time Generated: Page x of y

**Table 14.1.1.2**
**Summary of Disposition of Patients Overall**
**Intent-to-Treat**

| | ilofotase alfa 0.8 mg/kg (N = xxx) n (%) | ilofotase alfa 3.2 mg/kg (N = xxx) n (%) | Total (N = xxx) n (%) |
|---|---|---|---|
| ITT Set | xxx | xxx | xxx |
| Completed Trial [a] | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |
| Discontinued Trial [a] | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |
| Primary Reason for Early Trial Discontinuation [a] | | | |
| Withdrawal of consent | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |
| Failure to meet inclusion and exclusion criteria | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |
| Substantial non-compliance | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |
| Physician decision | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |
| Adverse event | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |
| Lost to Follow up | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |
| Discontinuation by Sponsor | xxx ( xx.x%) | xxx ( xx.x%) | xxx ( xx.x%) |
| Other | | | |

[a] Percentages are calculated based on the ITT Set.
Reference: Listing 16.2.1.2
Program Name: Date/Time Generated: Page x of y

**Table 14.1.2**
**Summary of Demographics**
**Intent-to-Treat**

| | ilofotase alfa 0.8 mg/kg (N = xxx) n (%) | ilofotase alfa 3.2 mg/kg (N = xxx) n (%) | Total (N = xxx) n (%) |
|---|---|---|---|
| Age (years) | | | |
| n | xxx | xxx | xxx |
| mean (SD) | xx.x ( xx.xx) | xx.x ( xx.xx) | xx.xx ( xx.xx) |
| SEM | xx.x | xx.x | xx.x |
| median | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| min, max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| missing | | | |
| Height (cm) | | | |
| n | xxx | xxx | xxx |
| mean (SD) | xx.x ( xx.xx) | xx.x ( xx.xx) | xx.xx ( xx.xx) |
| SEM | xx.x | xx.x | xx.x |
| median | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| min, max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Missing | | | |
| Weight (kg) | | | |
| n | xxx | xxx | xxx |
| mean (SD) | xx.x ( xx.xx) | xx.x ( xx.xx) | xx.xx ( xx.xx) |
| SEM | xx.x | xx.x | xx.x |
| median | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| min, max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Missing | | | |
| BMI ($kg/m^2$) | | | |
| n | xxx | xxx | xxx |
| mean (SD) | xx.x ( xx.xx) | xx.x ( xx.xx) | xx.xx ( xx.xx) |
| SEM | xx.x | xx.x | xx.x |
| median | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| min, max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Missing | | | |
| Gender, n (%) | | | |
| Male | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Female | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |

| | | | |
|---|---|---|---|
| Childbearing Potential, n (%)[a] | | | |
| YES | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| NO | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Reason for non-childbearing potential, n (%)[b] | | | |
| 1) >= 1 Year post menopausal (confirmed by FSH level test) | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| 2) < 1 Year post menopausal (confirmed by at least two FSH level tests | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| 3) Hysterectomy | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| 4) Billateral tubal ligation | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |

Note: Percentages are calculated based on the ITT Set.
[a] Percentages are based on female counts.
[b] Percentages are based on female with Childbearing potential "NO".
Reference: Listing 16.2.4.1
Program Name: Date/Time Generated: Page x of y

**Table 14.1.3**
**Summary of Medical History**
**Intent-to-Treat Set**

| | ilofotase alfa 0.8 mg/kg (N = xxx) n (%) | ilofotase alfa 3.2 mg/kg (N = xxx) n (%) | Total (N = xxx) n (%) |
|---|---|---|---|
| Patients with Any Medical History?, n (%) | | | |
| No | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Yes | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Medical History | | | |
| System Organ Class 1 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Preferred Term 1 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Preferred Term 2 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Preferred Term 3 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Preferred Term 4 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| System Organ Class 2 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Preferred Term 1 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Preferred Term 2 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Preferred Term 3 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Preferred Term 4 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| … | | | |

Note: Percentages are calculated based on the ITT Set.
Note: This table contains counts of patients. If a patient had more than one medical history event within a preferred term, the patient is counted only once within a preferred term. If a patient had more than one medical history within a system organ class, the patient is counted once for each preferred term and once for the system organ class.
Note: MedDRA Version 26.0 used for coding.
Reference: Listing 16.2.4.2

Program Name: Date/Time Generated: Page x of y

Programming Notes:
Please sort alphabetically by SOC and in descending order of number in total column for preferred term within SOC.

**Table 14.1.4**
**Summary of Prior / Concomitant Medication**
**Intent-to-Treat Set**

| | ilofotase alfa 0.8 mg/kg (N = xxx) n (%) | ilofotase alfa 3.2 mg/kg (N = xxx) n (%) | Total (N = xxx) n (%) |
|---|---|---|---|
| Patients with Any Prior / Concomitant Medication?, n (%) | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| No | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Yes | | | |
| Prior and Concomitant Medication | | | |
| Main Anatomical or Pharmacological group 1 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Chemical substance 1 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Chemical substance 2 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Chemical substance 3 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Chemical substance 4 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Main Anatomical or Pharmacological group 1 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Chemical substance 1 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Chemical substance 2 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Chemical substance 3 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Chemical substance 4 | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| … | | | |

Note: Percentages are calculated based on the ITT Set.
Note: A patient may have received more than one type of medication. Therefore, the sum of category counts and percentages may not equal the total counts. If a patient received more than one medication in a category, the patient is counted once in that category.
WHO Drug Dictionary (Version B3 MAR 2020) was used for coding.
Reference: Listing 16.2.4.5

Program Name: Date/Time Generated: Page x of y

Programming Notes:
Please sort alphabetically by main Anatomical or Pharmacological group and in descending order of number in total column for Chemical substance.

## A2 14.2 EFFICACY DATA

**Table 14.2.1.1**
**Summary of Change from Baseline by Visit on PPi (µM ) -**
**Intent-to-Treat Set**

| Treatment Group | Visit | Value at Visit | | | | | | Change from Baseline | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | Mean | SD | SEM | Min | Median | Max | n | Mean | SD | SEM | Min | Median | Max |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | relative | | | | | | |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Ilofotase alfaP 3.2 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Ilofotase alfa 3.2 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | relative | | | | | | |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Overall | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| (N = xxx) | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Overall | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | relative | | | | | | |
| (N = xxx) | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |

[a] the baseline value is defined as the median value of the measurements prior to randomization (day -2, day -1, day 1 prior to randomization)
Reference: Listing 16.2.6.1

Program Name: Date Generated: Page x of y

**Table 14.2.1.2**
**Maximum Change from Baseline / AUC on PPi (µM ) -**
**Intent-to-Treat Set**

| Treatment Group | Visit | Maximum Change from Baseline (mCfB) [a] n | Mean | SD | SEM | Min | Median | Max | 95% Confidence intervall | Difference 08 mg/gk – 3.2 mg/kg Estimeate (CI) | p-value[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | |
| (N = xxx) | mCfB absolute | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | [xxxx.x;xxxx.x] | | |
| (N = xxx) | mCfB relative | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | [xxxx.x;xxxx.x] | | |
| (N = xxx) | AUC | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | [xxxx.x;xxxx.x] | | |
| Ilofotase alfa 3.2 mg/kg | | | | | | | | | | | |
| (N = xxx) | mCfB absolute | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | [xxxx.x;xxxx.x] | | |
| (N = xxx) | mCfB relative | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | [xxxx.x;xxxx.x] | | |
| (N = xxx) | AUC | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | [xxxx.x;xxxx.x] | | |
| Comparisons | | | | | | | | | | | |
| (N = xxx) | mCfB absolute | | | | | | | | | xxxx.xx (xxx;xxx) | xxxxx |
| (N = xxx) | mCfB relative | | | | | | | | | xxxx.xx (xxx;xxx) | xxxxx |
| (N = xxx) | AUC | | | | | | | | | xxxx.xx (xxx;xxx) | xxxxx |
| Overall | | | | | | | | | | | |
| (N = xxx) | mCfB absolute | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | [xxxx.x;xxxx.x] | | |
| (N = xxx) | mCfB relative | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | [xxxx.x;xxxx.x] | | |
| (N = xxx) | AUC | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | [xxxx.x;xxxx.x] | | |

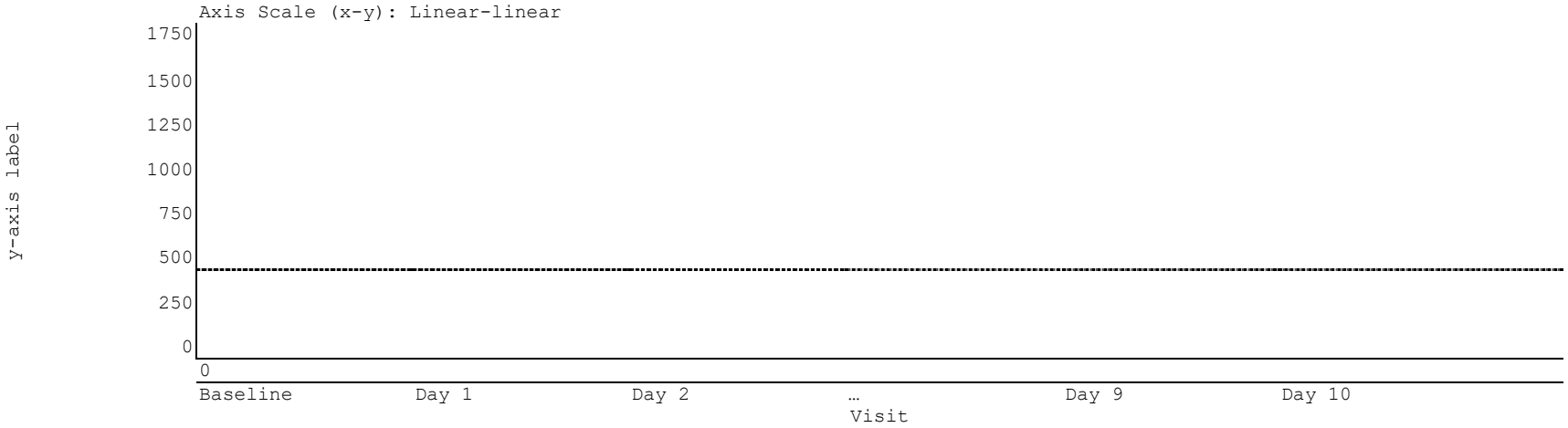
[a] is defined as individual maximum change from the individual baseline value day 2 to day 10
[b] deccription of the test used
Reference: Listing 16.2.6.1

Program Name: Date Generated: Page x of y

**Figure 14.2.1.3**
**Spaghetti Plot for PPi (µM )**
**Intent-to-Treat Set**

Parameter: PPi (µM ) / absolute values

:Ilofotase alfa 0.8 (N = XXX)




N = number of subjects in analysis set.
Reference: Listing 16.2.6.1

Programming Notes:
Repeat for the following parameters:

- ilofotase alfa 0.8 mg/kg absolute values,
- ilofotase alfa 0.8 mg/kg relative changes from baseline
- ilofotase alfa 3.2 mg/kg absolute values
- ilofotase alfa 3.2 mg/kg relative changes from baseline
- overall absolute values
- overall relative changes from baseline

**Table 14.2.2.1**
**Summary of Change from Baseline by Visit on PLP (nmol/L ) -**
**Intent-to-Treat Set**

Analogue 14.2.1.1

**Table 14.2.2.2**
**Maximum Change from Baseline on PLP (nmol/L )-**
**Intent-to-Treat Set**

Analogue 14.2.1.2

**Figure 14.2.2.3**
**Spaghetti Plot for PLP (nmol/L )**
**Intent-to-Treat Set**

Analogue 14.2.1.3

**Table 14.2.3.1**
**Summary of Change from Baseline by Visit exploratory Biomarker - Intent-to-Treat Set**

| Dose group | | Value at Visit | | | | | | | Change from Baseline | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Visit | n | Mean | SD | SEM | Min | Median | Max | n | Mean | SD | SEM | Min | Median | Max |
| ATP µM | | | | | | | | | | | | | | | |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | | absolute | | | | | |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | | relative | | | | | |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Ilofotase alfaP 3.2 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | | absolute | | | | | |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Ilofotase alfa 3.2 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | | relative | | | | | |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |

| Dose group | | Value at Visit | | | | | | | Change from Baseline | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Visit | n | Mean | SD | SEM | Min | Median | Max | n | Mean | SD | SEM | Min | Median | Max |
| | | | | | | ATP µM | | | | | | | | | |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Overall | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| (N = xxx) | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Overall | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | relative | | | | | | |
| (N = xxx) | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | | | | | | PL nmol/L | | | | | | | | | |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Baseline [a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | relative | | | | | | |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | | | | | | Creatinine µmol/L URINE | | | | | | | | | |

| Dose group | | Value at Visit | | | | | | | Change from Baseline | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Visit | n | Mean | SD | SEM | Min | Median | Max | n | Mean | SD | SEM | Min | Median | Max |
| | | | | | | PL nmol/L | | | | | | | | | |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |

……

[a] the baseline value is defined as the median value of the measurements prior to randomization (day -2, day -1, day 1 prior to randomization)
Reference: Listing 16.2.6.1

Program Name: Date Generated: Page x of y

Programming note:

- Extend the table with the following parameters
  - ATP µM
  - PL nmol/L
  - ALP Isoenzymes U/L
  - Osteocalcin ng/mL
  - Adenosine (urine) mmol/mol Creatinine
  - Adenosine (blood) mmol/mol Creatinine
  - PEA mmol/mol Creatinine
  - Creatinine (blood / urine) µmol/L
  - Phosphate (Blood / Urine) mmol/L
  - Calcium (blood / Urine) mmol/L
  - TRP (Tubular Reabsorption of Phosphate) %
  - TmP/GFR (maximum reabsorption rate of Phosphate over Glomerular Filtration Rate) mmol/L
  - ALP activity U/L

- c-Terminal iFGF-23 pmol/L
- PTH pg/mL
- CTX pg/mL
- PINP ng/ml
- 25 OH vitamin D ng/ml

- Repeat the table header as well as the current parameter headline on each page of the table

# A3 14.3 SAFETY DATA

## A31 14.3.1 DISPLAYS OF ADVERSE Events

**Table 14.3.1.1**
**Overall Summary of Adverse Events**
**Safety Set**

| | ilofotase alfa 0.8 mg/kg (N = xxx) n (%)[E] | ilofotase alfa 3.2 mg/kg (N = xxx) n (%)[E] | Total (N = xxx) n (%)[E] |
|---|---|---|---|
| Patients with Adverse Events (AEs) | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| TEAEs | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Patients with serious Adverse Events (AEs) | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| serious TEAEa | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Patients with related Adverse Events(AEs) | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| related TEAEa | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Patients with AEs leading to withdrawal(AEs) | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| TEAEa leading to withdrawal | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Patients with fatal AEs | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Patients with TEAEs by intensity [b] | | | |
| mild | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| moderate | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| severe | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |

MedDRA Version 26.0; TEAE: Treatment-Emergent Adverse Event.
Note: Percentages are calculated based on the Safety Set.
[a] Included are AEs considered possibly or probably related to trial drug and AEs with unknown or missing relationship to study drug
[b] The intensity of an AE is assessed by the investigator as mild, moderate, or severe. Cases with unknown severity are assumed to be severe

Reference: Listing 16.2.7.1, 16.2.7.2

Program Name: Date Generated: Page x of y

**Table 14.3.1.2**
**Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**
**Safety Analysis Set**

| | ilofotase alfa 0.8 mg/kg (N = xxx) n (%)[E] | ilofotase alfa 3.2 mg/kg (N = xxx) n (%)[E] | Total (N = xxx) n (%)[E] |
|---|---|---|---|
| Patients with Any Adverse Events?, n (%) | | | |
| No | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Yes | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Adverse Events | | | |
| System Organ Class 1 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 1 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 2 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 3 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 4 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| System Organ Class 2 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 1 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 2 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 3 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 4 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| etc. … | | | |

MedDRA Version 26.0; TEAE: Treatment-Emergent Adverse Event.
Note: Percentages are calculated based on the Safety Set.

Note: TEAEs are defined as any event not present before exposure to trial drug or any event already present that worsens in either intensity or frequency after exposure to trial drug up to 14 days after last drug exposure.
Note: This table contains counts of patients(n) and number of events (E). If a patient experienced more than one episode of an adverse event, the patient is counted only once within a preferred term. If a patient experienced more than one adverse event within a system organ class, the patient is counted once for each preferred term and once for the system organ class.
Reference: Listing 16.2.7.1

Program Name: Date Generated: Page x of y

Programming Notes:
Please sort by the SOC (descending number of patients overall) and PTs (descending number of patients overall)).

**Table 14.3.1.3**
**Summary of related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**
**Safety Analysis Set**

| | ilofotase alfa 0.8 mg/kg (N = xxx) n (%)[E} | ilofotase alfa 3.2 mg/kg (N = xxx) n (%)[E} | Total (N = xxx) n (%)[E} |
|---|---|---|---|
| Patients with Any related TEAEs?, n (%) [a] | | | |
| No | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Yes | xx ( xx.xx) | xx ( xx.xx) | xx ( xx.xx) |
| Adverse Events | | | |
| System Organ Class 1 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 1 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 2 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 3 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 4 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| System Organ Class 2 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 1 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 2 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 3 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Preferred Term 4 | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| etc. … | | | |

MedDRA Version 26.0; TEAE: Treatment-Emergent Adverse Event.
[a] Included are TEAEs considered possibly or probably related to trial drug and TEAEs with unknown or missing relationship to study drug
Note: Percentages are calculated based on the Safety Set.

Note: TEAEs are defined as any event not present before exposure to trial drug or any event already present that worsens in either intensity or frequency after exposure to trial drug up to 14 days after last drug exposure.
Note: This table contains counts of patients(n) and number of events (E). If a patient experienced more than one episode of an adverse event, the patient is counted only once within a preferred term. If a patient experienced more than one adverse event within a system organ class, the patient is counted once for each preferred term and once for the system organ class.
Reference: Listing 16.2.7.1

Program Name: Date Generated: Page x of y

Programming Notes:
Please sort by the SOC (descending number of patients overall) and PTs (descending number of patients overall)).

**Table 14.3.2.1**
**Vital Signs**
**Safet Analysis Set**

| Treatment Group | Visit | Value at Visit n | Mean | SD | SEM | Min | Median | Max | Change from Day -2 n | Mean | SD | SEM | Min | Median | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Weight (kg)** | | | | | | | | | | | | | | | |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal[a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx. |
| Ilofotase alfa 3.2 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal[a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx. |
| Overall | | | | | | | | | | | | | | | |
| (N = xxx) | Day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal[a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx. |
| **BMI** | | | | | | | | | | | | | | | |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal[a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx. |
| Ilofotase alfa 3.2 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | Day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal[a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx. |
| Overall | | | | | | | | | | | | | | | |
| (N = xxx) | Day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | | | | | | | |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Early Withdrawal[a] | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx. |

[a] Values from Patients who discontinued the trial prior to day 10
Reference: Listing 16.2.7.4

Program Name: Date/Time Generated: Page x of y

Programming Note

- Extend the table with the following parameters
  - Weight (kg)
  - BMI (kg/m2)
  - Temperature (C)
  - Pulse rate - supine (beats/min)
  - Pulse Rate - standing (beats/min)
  - Systolic Blood pressure – supine (mmHg)
  - Systolic Blood pressure – standing (mmHg)
  - Diastolic Blood pressure – supine (mmHg)
  - Diastolic Blood pressure – standing (mmHg)

- Repeat the table header as well as the current parameter headline on each page of the table

**Table 14.3.3.1**
**Physical Examination**
**Safety Analysis Set**

| | ilofotase alfa 0.8 mg/kg (N = xxx) n (%)[E] | ilofotase alfa 3.2 mg/kg (N = xxx) n (%)[E] | Total (N = xxx) n (%)[E] |
|---|---|---|---|
| Physical examination | | | |
| Day -2 | | | |
| Normal | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Abnormal, Not Clinically Significant | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Abnormal, Clinically Significant | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Day 1 | | | |
| Normal | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Abnormal, Not Clinically Significant | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Abnormal, Clinically Significant | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Day 10 | | | |
| Normal | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Abnormal, Not Clinically Significant | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Abnormal, Clinically Significant | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Early Withdrawal | | | |
| Normal | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Abnormal, Not Clinically Significant | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Abnormal, Clinically Significant | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |

Reference: Listing 16.2.4.3

Program Name: Date Generated: Page x of y

### A32 14.3.2 LISTINGS OF DEATHS, OTHER SERIOUS AND SIGNIFICANT ADVERSE EVENTS

If applicable. Listings of Death, other serious and significant AEs will be decided on in the final data Review.

### A33 14.3.3 NARRATIVES OF DEATH, OTHER SERIOUS AND CERTAIN OTHER SIGNIFICANT ADVERSE EVENTS

If applicable. Narratives od Death, other serious and certain other significant AEs will be decided on in the final data Review.

## A34 14.3.4 LABORATORY VALUES

**Table 14.3.4.1**
**Safety Laboratory - Clinical Chemistry -**
**Safety Analysis Set**

| Dose group | | Value at Visit | | | | | | | Change from day -2 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Visit | n | Mean | SD | SEM | Min | Median | Max | n | Mean | SD | SEM | Min | Median | Max |
| Total Bilirubin (µmol/L) | | | | | | | | | | | | | | | |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Ilofotase alfa 3.2 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Overall | | | | | | | | | | | | | | | |
| (N = xxx) | day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Gamma glutamyl transferase (GGT) ( U/L) | | | | | | | | | | | | | | | |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Etc.. | | | | | | | | | | | | | | | |

[a] the baseline value is defined as the median value of the measurements prior to randomization (day -2, day -1, day 1 prior to randomization)
Reference: Listing 16.2.8.1

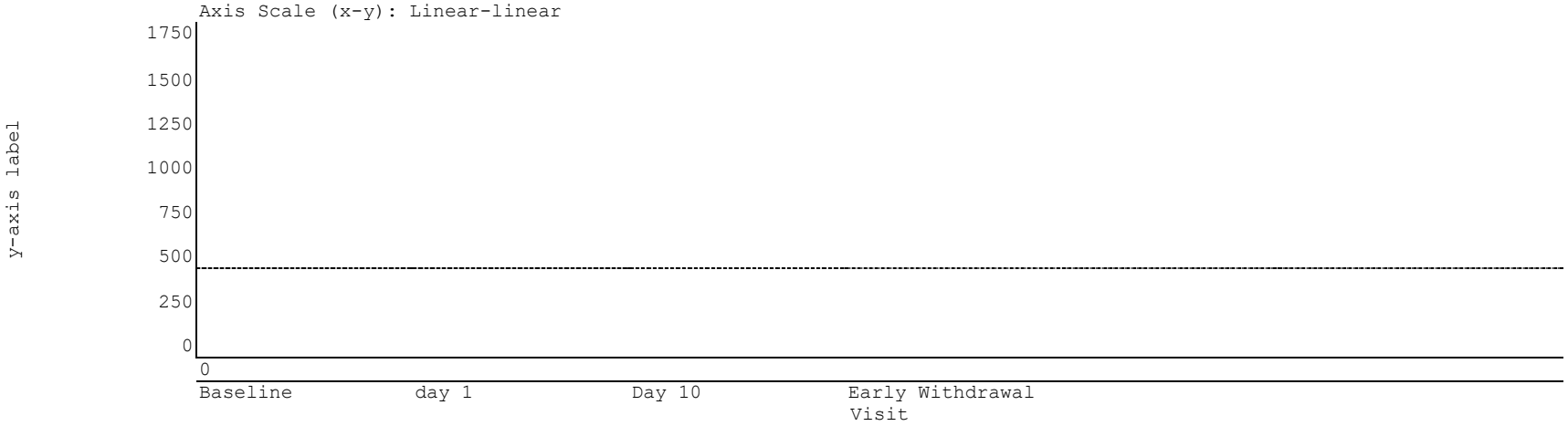
Program Name: Date/Time Generated: Page x of y

Programming note:

- Extend the table with the following parameters
  - Total Bilirubin – µmol/L
  - Gamma glutamyl transferase (GGT - U/L
  - Aspartate Aminotransferase (AST) - U/L
  - Alanine Aminotransferase-(ALT) - U/L
  - Lactate Dehydrogenase (LDH)- U/L
  - Creatinine – µmol/L
  - Blood Urea – mmol/L
  - Total protein – g/L
  - Albumin g/L
  - Inorganic phosphate – mmol/L
  - Sodium – mmol/L
  - Potassium – mmol/L
  - Calcium – mmol/L
  - Glucose – mmol/L
- the table header as well as the current parameter headline on each page of the table

**Figure 14.3.4.2**
**Spaghetti Plot for Clinical Chemistry Parameters**
**safety Analysis Set**

Parameter: Total Bilirubin (µmol/L)




Reference: Listing 16.2.8.1

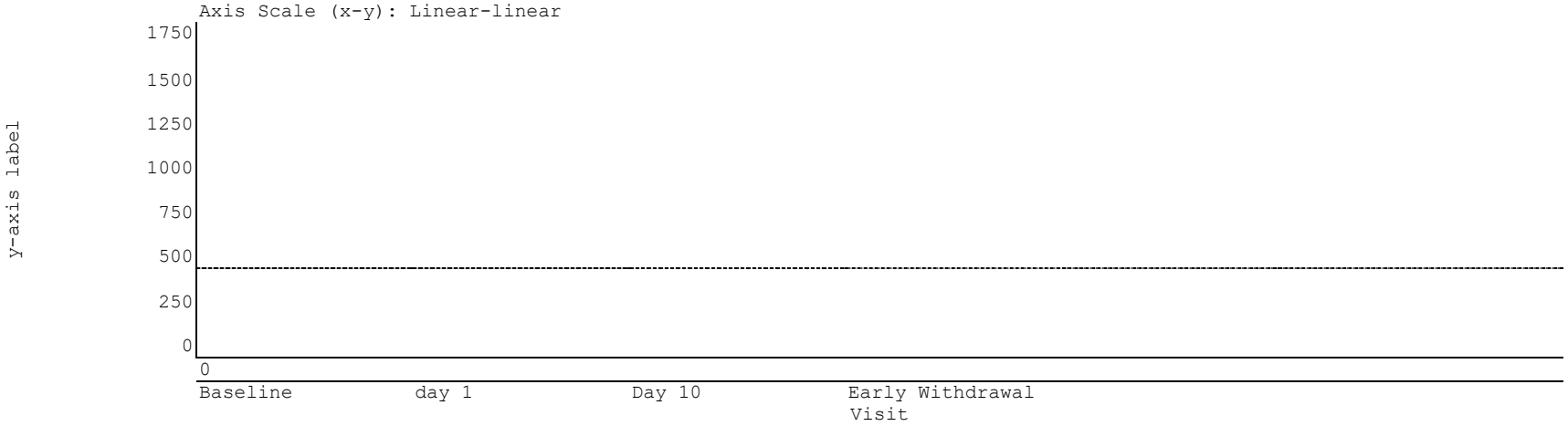
Programming Notes:
Programming note:

- Use different Line types for Patients with 0.8 mg/kg and 32. Mg/kg (explain in legend)
- Extend the graph with the following parameters
  - Total Bilirubin – µmol/L
  - Gamma glutamyl transferase (GGT - U/L
  - Aspartate Aminotransferase (AST) - U/L
  - Alanine Aminotransferase-(ALT) - U/L
  - Lactate Dehydrogenase (LDH)- U/L
  - Creatinine – µmol/L
  - Blood Urea – mmol/L
  - Total protein – g/L

- Albumin g/L
- Inorganic phosphate – mmol/L
- Sodium – mmol/L
- Potassium – mmol/L
- Calcium – mmol/L
- Glucose – mmol/L

**Figure 14.3.4.3**
**Box PLots for Clinical Chemistry Parameters**
**safety Analysis Set**

Parameter: Total Bilirubin (µmol/L)




Reference: Listing 16.2.8.1

Programming Notes:
Programming note:

- Provide three Boxplots per visit day ( ilofotase 0.8 mg/kg, ilofotase 3.2 mg/kg, overall)
- Extend the graphtable with the following parameters
  - Total Bilirubin – µmol/L
  - Gamma glutamyl transferase (GGT - U/L
  - Aspartate Aminotransferase (AST) - U/L
  - Alanine Aminotransferase-(ALT) - U/L
  - Lactate Dehydrogenase (LDH)- U/L
  - Creatinine – µmol/L
  - Blood Urea – mmol/L
  - Total protein – g/L

- Albumin g/L
- Inorganic phosphate – mmol/L
- Sodium – mmol/L
- Potassium – mmol/L
- Calcium – mmol/L
- Glucose – mmol/L

**Table 14.3.4.4**
**Safety Laboratory – Hematology Parameters**
**Safety Analysis Set**

| Dose group | | Value at Visit | | | | | | | Change from day -2 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Visit | n | Mean | SD | SEM | Min | Median | Max | n | Mean | SD | SEM | Min | Median | Max |
| **Total Bilirubin (µmol/L)** | | | | | | | | | | | | | | | |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Ilofotase alfa 3.2 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Overall | | | | | | | | | | | | | | | |
| (N = xxx) | day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| **Gamma glutamyl transferase (GGT) ( U/L)** | | | | | | | | | | | | | | | |
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | | | | | | | |
| (N = xxx) | day -2 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | absolute | | | | | | |
| | Day 1 | xx | xx.x | xx.xx | xx.x. | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| | Early Withdrawal | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x | xx | xx.x | xx.xx | xx.x | xx.x | xx.x | xx.x |
| Etc.. | | | | | | | | | | | | | | | |

[a] the baseline value is defined as the median value of the measurements prior to randomization (day -2, day -1, day 1 prior to randomization)
Reference: Listing 16.2.8.2

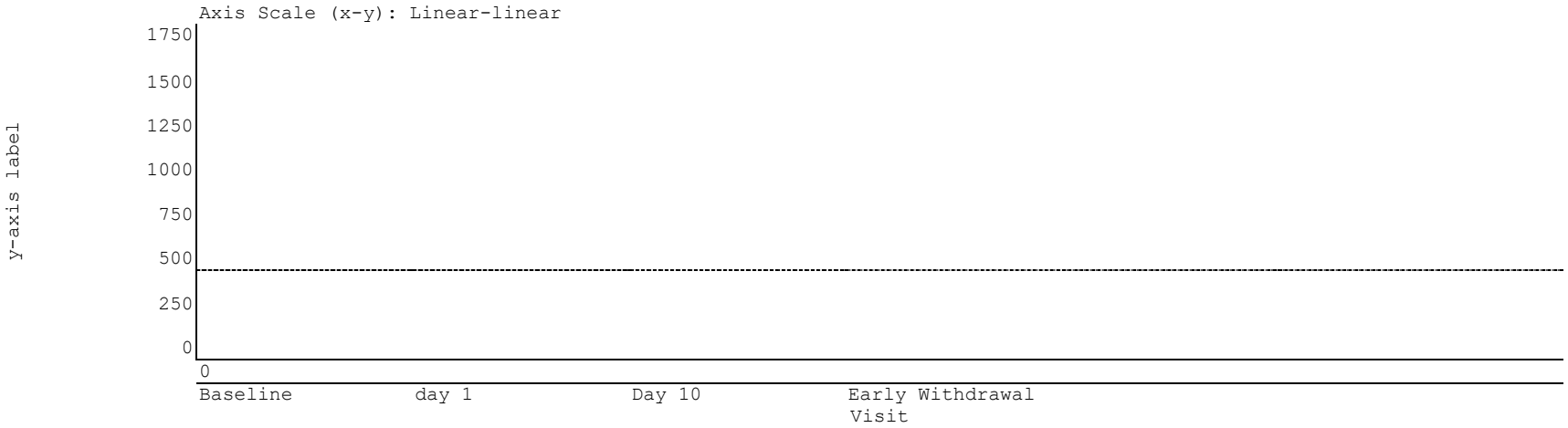
Program Name: Date/Time Generated: Page x of y

Programming note:

- Extend the table with the following parameters
  - Leucocytes (10^3 /µL)
  - Erythrocytes (10^6/µL)
  - Hemoglobin (g/dL)
  - Hematocrit (%)
  - Thrombocytes (10^3/µL)
  - Lymphocytes (10^3/µL)
  - Monocytes (10^3/µL)
  - Eosinophils granulocytes total (10^3/µL)
  - Basophils granulocytes total (10^3/µL)
  - Neutrophils granulocytes total (10^3/µL)
  - Mean corpuscular volume (MCV) (fL)
  - Mean corpuscular hemoglobin (MCH) (pg)
  - Mean corpuscular hemoglobin concentration (MCHC) (g/dL)
- the table header as well as the current parameter headline on each page of the table

**Figure 14.3.4.5**
**Spaghetti Plot for Hematology Parameters**
**safety Analysis Set**

Parameter: Total Bilirubin (µmol/L)




Reference: Listing 16.2.8.2

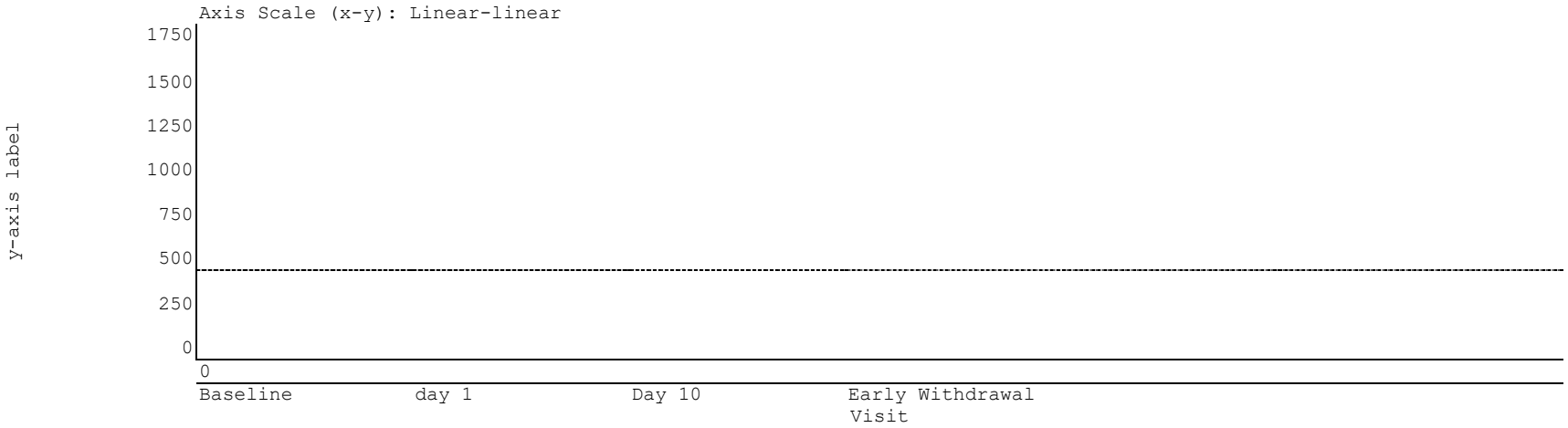
Programming Notes:
Programming note:

- Use different Line types for Patients with 0.8 mg/kg and 32. Mg/kg (explain in legend)
- Extend the graph with the following parameters
  - Leucocytes (10^3 /µL)
  - Erythrocytes (10^6/µL)
  - Hemoglobin (g/dL)
  - Hematocrit (%)
  - Thrombocytes (10^3/µL)
  - Lymphocytes (10^3/µL)
  - Monocytes (10^3/µL)
  - Eosinophils granulocytes total (10^3/µL)

- Basophils granulocytes total (10^3/µL)
- Neutrophils granulocytes total (10^3/µL)
- Mean corpuscular volume (MCV) (fL)
- Mean corpuscular hemoglobin (MCH) (pg)
- Mean corpuscular hemoglobin concentration (MCHC) (g/dL)

**Figure 14.3.4.6**
**Box Plots for Hematology Parameters**
**Safety Analysis Set**

Parameter: Total Bilirubin (µmol/L)




Reference: Listing 16.2.8.2

Programming Notes:
Programming note:

- Provide three Boxplots per visit day ( ilofotase 0.8 mg/kg, ilofotase 3.2 mg/kg, overall)
- Extend the graph with the following parameters
  - Leucocytes (10^3 /µL)
  - Erythrocytes (10^6/µL)
  - Hemoglobin (g/dL)
  - Hematocrit (%)
  - Thrombocytes (10^3/µL)
  - Lymphocytes (10^3/µL)
  - Monocytes (10^3/µL)
  - Eosinophils granulocytes total (10^3/µL)

- Basophils granulocytes total (10^3/µL)
- Neutrophils granulocytes total (10^3/µL)
- Mean corpuscular volume (MCV) (fL)
- Mean corpuscular hemoglobin (MCH) (pg)
- Mean corpuscular hemoglobin concentration (MCHC) (g/dL)

**Table 14.3.4.7**
**Urinalysis Parameters**
**Safety Analysis Set**

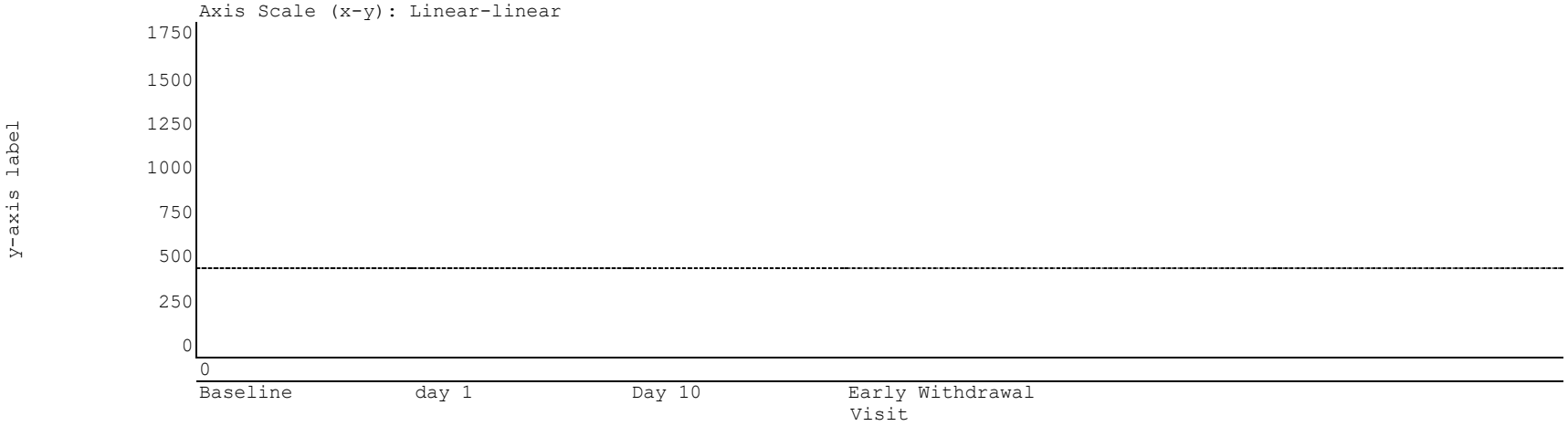
| | ilofotase alfa 0.8 mg/kg (N = xxx) n (%)[E] | ilofotase alfa 3.2 mg/kg (N = xxx) n (%)[E] | Total (N = xxx) n (%)[E] |
|---|---|---|---|
| Hemoglobin | | | |
| Day -2 | | | |
| negative | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| positive | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Day 1 | | | |
| negative | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| positive | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Day 10 | | | |
| negative | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| positive | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Early Withdrawal | | | |
| negative | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| positive | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Ketones | | | |
| see Hemoglobin | | | |
| Glucose | | | |
| see Hemoglobin | | | |
| Urobilinogen | | | |
| Day -2 | | | |
| n | xxx | xxx | xxx |
| mean (SD) | xx.x ( xx.xx) | xx.x ( xx.xx) | xx.xx ( xx.xx) |
| SEM | xx.x | xx.x | xx.x |
| median | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| min, max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Missing | | | |

| | | | |
|---|---|---|---|
| Day 1 | | | |
| n | xxx | xxx | xxx |
| mean (SD) | xx.x ( xx.xx) | xx.x ( xx.xx) | xx.xx ( xx.xx) |
| SEM | xx.x | xx.x | xx.x |
| median | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| min, max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Missing | | | |
| day 10 | | | |
| n | xxx | xxx | xxx |
| mean (SD) | xx.x ( xx.xx) | xx.x ( xx.xx) | xx.xx ( xx.xx) |
| SEM | xx.x | xx.x | xx.x |
| median | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| min, max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Missing | | | |
| Early Withdrawal | | | |
| n | xxx | xxx | xxx |
| n | xx.x ( xx.xx) | xx.x ( xx.xx) | xx.xx ( xx.xx) |
| mean (SD) | xx.x | xx.x | xx.x |
| SEM | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| median | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| min, max | | | |
| Missing | | | |

Reference: Listing 16.2.8.3

**Figure 14.3.4.8**
**Spaghetti Plot for Urinalysis parameters - Urobilinogen**
**Safety Analysis Set**

Parameter: Urobilinogen (mg/dLµmol/L)



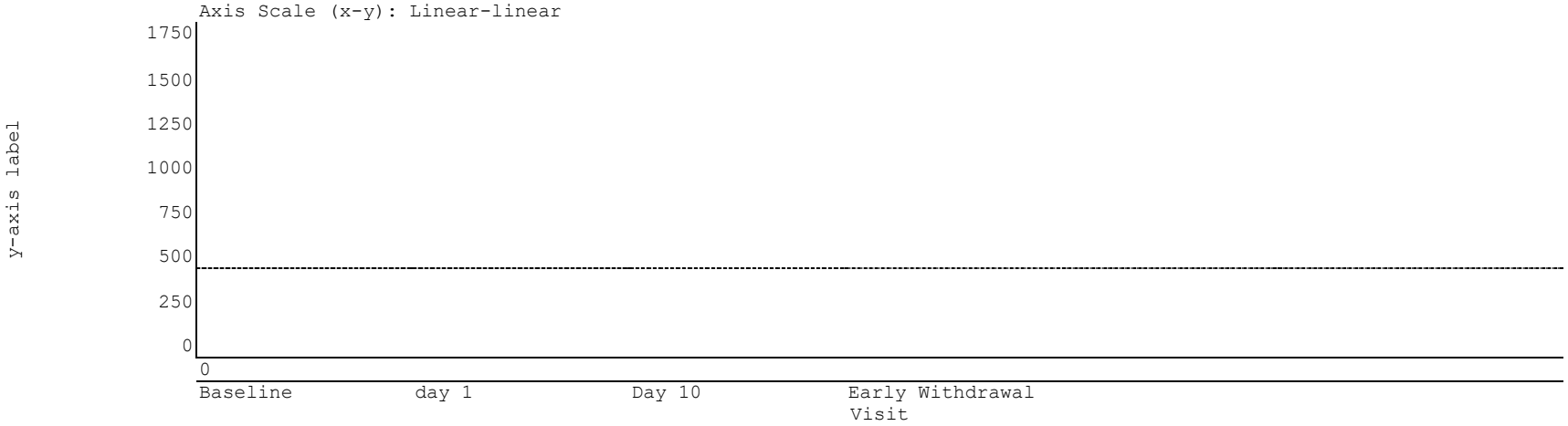

Reference: Listing 16.2.8.3

Programming Notes:
Programming note:

- Use different Line types for Patients with 0.8 mg/kg and 3.2. mg/kg (explain in legend)

**Figure 14.3.4.9**
**Box Plot for Urinalysis parameters - Urobilinogen**
**Safety Analysis Set**

Parameter: Urobilinogen (mg/dL)




Reference: Listing 16.2.8.3

Programming Notes:
Programming note:

- Provide three Boxplots per visit day (ilofotase 0.8 mg/kg, ilofotase 3.2 mg/kg, overall)

**Table 14.3.4.10**
**ADA descriptive Analyses**
**Safety Analysis Set**

| | ilofotase alfa 0.8 mg/kg (N = xxx) n (%) | ilofotase alfa 3.2 mg/kg (N = xxx) n (% | Total (N = xxx) n (%) |
|---|---|---|---|
| Day 1 | | | |
| negative | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| positive | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Day 10 | | | |
| negative | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| positive | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Day 1 negative AND day 10 negative | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Day 1 negative AND day 10 positive | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Day 1 positive AND day 10 negative | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |
| Day 1 positive AND day 10 positive | xx ( xx.xx) [x] | xx ( xx.xx) [x] | xx ( xx.xx) [x] |

Note: Percentages are calculated based on the Safety Set.
Reference: Listing 16.2.8.5

Program Name: Date Generated: Page x of y

**Table 14.3.4.11**
**PK concentrations**
**Population for PK analyses (PKS)**

| Dose group / Group | Visit | Value at Visit n | Mean | SD | SEM | Geometric Mean | Min | Median | Max |
|---|---|---|---|---|---|---|---|---|---|
| Ilofotase alfa 0.8 mg/kg | | | | | | | | | |
| (N = xxx) | day 1 pre-dose | xx | xx.x | xx.xx | xx.x | xxx.x | xx.x | xx.x | xx.x |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| Ilofotase alfa 3.8 mg/kg | | | | | | | | | |
| (N = xxx) | day 1 pre-dose | xx | xx.x | xx.xx | xx.x | xxx.x | xx.x | xx.x | xx.x |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| Overall | | | | | | | | | |
| (N = xxx) | day 1 pre-dose | xx | xx.x | xx.xx | xx.x | xxx.x | xx.x | xx.x | xx.x |
| | Day 1 2h | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 1 4h | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 1 8h | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 2 | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | … | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |
| | Day 10 | xx | xx.x | xx.xx | xx.x. | xxx.x | xx.x | xx.x | xx.x |

Reference: Listing 16.2.8.6

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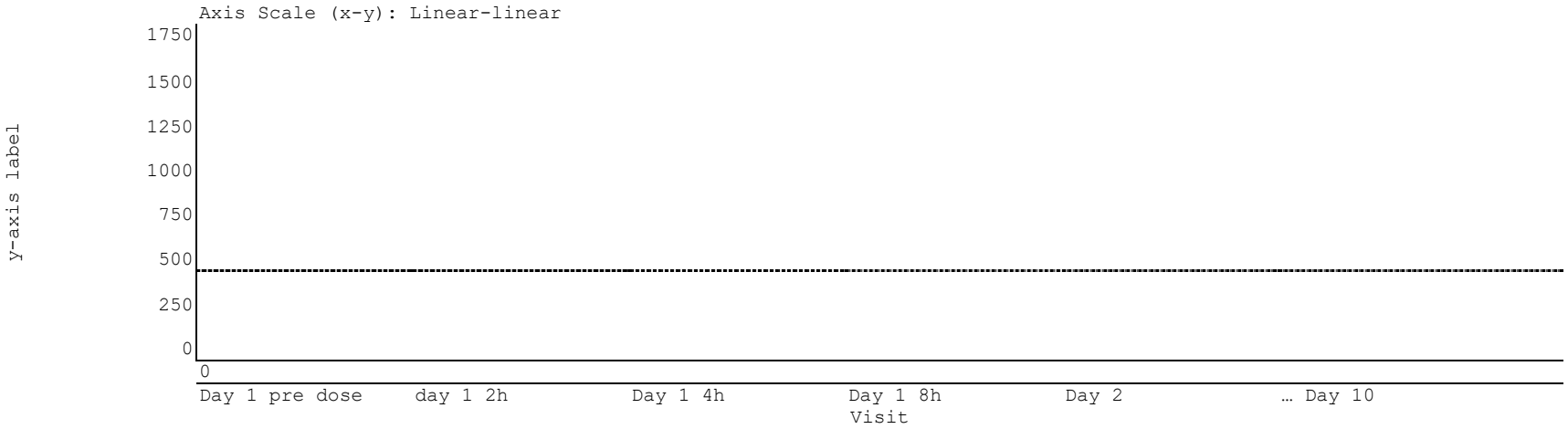
**Figure 14.3.4.12**
**PK Concentration PLots**
**Population for PK analyses (PKS)**

Dose group 1




Reference: Listing 16.2.8.6

Programming Notes:

- Provide graphs for ilofotase 0.8, ilofotase 3.2, overall
- Display : individual graphs, geometric mean graph

# B 16.2 PATIENT DATA LISTINGS

## B1 16.2.1 DISCONTINUED PATIENTS

**Listing 16.2.1.1**
**Inclusion and Exclusion Criteria**
**All enrolled**

| Patient | Age (years)/Sex | Date of Original Informed Consent | Time of Original Informed Consent | Date of eligibility assessment | Did Subject meet all Criteria? | Criterion ID not met |
|---|---|---|---|---|---|---|
| xx | xxx/xx | DDMMMYYYY | HH:MM | <date day -2> | <Yes> | xxxxx |
| | | | | <date day 1> | <NO> | xxxxx |
| xx | xxx/xx | DDMMMYYYY | HH:MM | | | xxxxx |

Program Name: Date/Time Generated: Page x of y

Programming Notes:
Sort by patient

**Listing 16.2.1.2**
**End of Study**
**Intent-to-Treat Set**

| Patient | Age (years)/Sex | Date of Original Informed Consent | Time of Original Informed Consent | Did the subject complete the study ? | date of Last contact | Date of early termination/ screening failure | Primary reason for early termination / screening failure |
|---|---|---|---|---|---|---|---|
| xx | xxx/xx | DDMMMYYYY | HH:MM | | | | |
| xx | xxx/xx | DDMMMYYYY | HH:MM | | | | |

Program Name: Date/Time Generated: Page x of y

Programming Notes:
Sort by patient
In case of other Reason for early discontinuation display “Other (specification)”

### B2 16.2.2 PROTOCOL DEVIATIONS

If applicable. Listing will be created manually based on the results of the final data review meeting

### B3 16.2.3 PATIENTS EXCLUDED FROM THE EFFICACY ANALYSIS

If applicable. Listing will be created manually based on the results of the final data review meeting

## B4 16.2.4 DEMOGRAPHIC DATA

**Listing 16.2.4.1**
**Demographics**
**Intent-to-Treat Set**

Dose Group: Dose

| Patient | Age (years)/ Sex | Date of Informed Consent | Date of Screening | Gender/ Childbearing Potential if Female | Reason for non-childbearing potential | Height (cm) | Weight (kg) [a] | BMI (kg/m²) [a] |
|---|---|---|---|---|---|---|---|---|
| xx | xxx/xx | DDMMMYYYY | DDMMMYYYY | Female/Yes | | xx.xx | Xxx/xxx | xx.xx / xx.xx |
| xx | xxx/xx | DDMMMYYYY | DDMMMYYYY | Male | | xx.xx | Xxx/xxx | xx.xx / xx.xx |
| xx | xxx/xx | DDMMMYYYY | DDMMMYYYY | Female/No | Specification | xx.xx | Xxx/xxx | xx.xx / xx.xx |

Note: BMI = Body Mass Index.
[a] Body weight, BMI day -2 / day 1

Program Name: Date/Time Generated: Page x of y

Programmer Notes: (1) Sort by dose group and patient number

**Listing 16.2.4.2**
**Medical History**
**Intent-to-Treat Set**

Dose Group: Dose

| Patient | Age (years)/ Sex | MH No. | Verbatim Term | System Organ Class | Preferred Term | Start Date/ End Date or Ongoing |
|---|---|---|---|---|---|---|
| xxxx | xxx/xx | 01 | xxxxxxxxxxxxxxx | xxxxxxxxx | xxxxxxxxxxxxxx | DDMMMYYYY/ DDMMMYYYY |
| xxxx | xxx/x | 01 | xxxxxxxxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxxxxxxxx | DDMMMYYY/ Ongoing |
| xxxx | xxx/xx | 01 | xxxxxxxxxxxxxxxxx | xxxxxxxxxxxxx | xxxxxxxxxxxxxx | |

Note: Coded using MedDRA Dictionary (Version 26.0).

Program Name: Date/Time Generated: Page x of y

Programmer Notes: (1) Sort by dose group and patient number

**Listing 16.2.4.3**
**Physical examination**
**Intent-to-Treat Set**

Dose Group: Dose

| Patient | Age (years)/ Sex | Study day | Date/Time of examination | Reason not done | Result | Specification |
|---|---|---|---|---|---|---|
| xxxx | xxx/xx | Day -2 | ddMMMYYY/ HH:MM | | Normal | |
| | | Day 1 | | | Abnormal, NCS | |
| | | Day 10 | | | Abnormal , CS | |
| xxxx | xxx/x | | | | | |
| xxxx | xxx/xx | | | | | |

Note: NCS: Not Clinically Significant, CS: Clinically Significant

Program Name: Date/Time Generated: Page x of y

Programmer Notes:
1) Sort by dose group and patient number
2) Study day ( Day -2, Day1 or Day 10/ day of early withdrawal
3) Date/Time of examination> provide data and time or |Not done" in case of not done

**Listing 16.2.4.4**
**12-Lead Electrocardiogram**
**Intent-to-Treat Set**

Dose Group: Dose

| Patient | Age (years)/ Sex | Date/Time of examination | Reason not done | Heart Rate (beats/min) | PR interval (msec) | QRS duration (msec) | QT interval (msec) | QTc-interval (msec) | Interpretation (finding) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | xxxxx/ finding |
| xxxx | xxx/xx | ddMMMYYY | xxxxx | | | | | | |

Note: NCS: Not Clinically Significant, CS: Clinically Significant

Program Name: Date/Time Generated: Page x of y

Programmer Notes:
1) Sort by dose group and patient number
2) Date/Time of examination> provide date and time or “Not done” in case of not done

**Listing 16.2.4.5**
**Prior and Concomitant Medications**
**Intent-to-Treat Set**

Dose group: Dose 1

| Patient | Age (years)/ Sex | Medication/Therapy (Comment) | Indication | WHO ATC Level 1 WHO ATC Level 5 | Dose | Unit | Frequency | Route | Start Date / End Date or ongoing |
|---|---|---|---|---|---|---|---|---|---|
| xxxxx | xxx/xxx | xxxxxxxxxx (xxxxxxxxx) | xxx | xxxxxxxxxx/ xxxxxxxxxx | xx | xx | xx | xx | DDMMMYYYY / DDMMMYYYY |
| xxxx | xxx/xx | xxxxxxxxxx (xxxxxxxxx) | xxx | xxxxxxxxx/ xxxxxxxxxx | xx | xx | xx | xx | xxxxxxxxx/ xxxxxxxxx |

Note: Coded using WHO Drug Dictionary (Version MAR 2023).

Program Name: Date/Time Generated: Page x of y

Programmer Notes:
1) Sort by dose group and patient number

## B5 16.2.5 COMPLIANCE AND/OR DRUG CONCENTRATION DATA (IF AVAILABLE)

**Listing 16.2.5.1**
**Study Drug Administration**
**Intent to Treat Set**

Dose group: dose *1*

| Patient | Age(years)/ Sex | Study Drug Administered? / Reason | Start Date Time/End Date Time | Total Amount Infused? | Reason if not completely administrated |
|---|---|---|---|---|---|
| xx | xxx/xx | Yes | DDMMMYYYY HH:MM/ DDMMMYYYY HH:MM | Yes | |
| | | Yes<br>No / xxxxxxx | | No | xxxxxxxx |

Program Name: Date/Time Generated: Page x of y

Programmer Notes:
1) Sort by dose group and patient number
2) Date/Time of examination> provide date and time or “Not done” in case of not done

## B6 16.2.6 INDIVIDUAL EFFICACY RESPONSE DATA

**Listing 16.2.6.1**
**Biomarker**
**Intent to treat Set**

Dose group: dose *1*

| Patient | Age (years)/ Gender | Test / Unit | Visit | Collection Date Time (day) | Result | Absolute. difference to BL | Maximum different to BL flag |
|---|---|---|---|---|---|---|---|
| xx | xx/ Male | PPi / muM | Day -2 | DDMMMYYYY HH:MM (xx) | xxx.xx | xxx.xx | - |
| | | PPi | Day -1 | DDMMMYYYY HH:MM (xx) | xxx.xx | xxx.xx | - |
| | | PPi | Day 1 pre-dose | DDMMMYYYY HH:MM (xx) | xxx.xx | xxx.xx | - |
| | | PPi | Baseline [a] | - | xxx.xx | xxx.xx | - |
| | | PPi | Day 1 | DDMMMYYYY HH:MM (xx) | xxx.xx | xxx.xx | |
| | | PPi | … | | xxx.xx | xxx.xx | X |
| | | PPi | Day 10 | DDMMMYYYY HH:MM (xx) | xxx.xx | xxx.xx | |

[a] the baseline value is defined as the median value of the measurements prior to randomization (day -2, day -1, day 1 prior to randomization)
Program Name: Date/Time Generated: Page x of y

Programming Notes:
Repeat for all treatment groups.
Sort by treatment group, patient parameter and visit:

Parameters PPi, PLP, ATP, PL, ALP Isoenzymes, Osteocalcin, Adenosine (urine), Adenosine (blood), PEA, Creatinine (blood / urine), Phosphate (Blood / Urine), Calcium (blood / Urine), TRP (Tubular Reabsorption of Phosphate), TmP/GFR (maximum reabsorption rate of Phosphate over Glomerular Filtration Rate), ALP activity, c-Terminal iFGF-23 , PTH , CTX , PINP, 25 OH vitamin D

# B7 16.2.7 ADVERSE EVENT AND OTHER SAFETY PARAMETER LISTINGS.

**Listing 16.2.7.1**
**Treatment Emergent Adverse Events**
**Safety Set**

Dose group: dose 1

| Patient | AE No. | System Organ Class/ Preferred Term/ Verbatim [a] | Start Date (day) Time Stop Date (day) [b] Time/ Duration (days) | Inten-sity | Relationship to Study Drug | Action Taken[c] | Other Action Taken [d] | Outcome [e] | Serious Yes/No | Serious Criterium [f] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | No | |
| xxxxx | 1 | xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxx/ | DDMMMYYYY (xx) HH:MM DDMMMYYYY (xx) HH:MM /xx | Mild | Unrelated | 2 | 1 | 1 | No | |
| xxxxx | 2 | xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxx/ | DDMMMYYYY (xx)/ DDMMMYYYY (xx)/xx | Moderate | Unlikely | 1 | 2 | 2 | Yes | |

[a] Coded using MedDRA Dictionary (Version 26.0)
[b] Relative to the day of first dose of trial drug. Day is missing for patients who were not treated.
[c] Action Taken with Study Treatment: 1 = Amount not changed, 2 = Product interrupted, 3 = Product Withdrawn, NA = Not applicable.
[d] Other Action Taken: 0 = None, 1 = Medication, 2 = Procedure (therapeutic or diagnostic), 3 = Hospitalization or prolongation of hospitalization, 4 = Discontinuation, 5= Medical visit, 6 = Emergency room visit, OT= other.
[e] Outcome: 1 = Recovered or resolved, 2= Recovering/Resolving, 3 = Recovered/Resolved with Sequelae, 4 = not recovered or not resolved, 5 = Fata; UK = Unknown.
[f] 1= Death, 2= Immediately Life threatening, 3 = Inpatient hospitalization or prolongation of existing hospitalization, 4= Persistent Disability/Incapacity, 5 Congennital Anomaly / Birth defect, 6 Important Medical Event

Program Name: Date/Time Generated: Page x of y

Programming Notes:
Repeat for all dose groups. Sort by dose group, patient, AE No.

**Listing 16.2.7.2**
**Non- Treatment Emergent Adverse Events**
**Safety Analysis Set**

Dose group: dose 1

| Patient | AE No. | System Organ Class/ Preferred Term/ Verbatim [a] | Start Date (day) Time Stop Date (day) [b] Time/ Duration (days) | Intensity | Relationship to Study Drug | Action Taken[c] | Other Action Taken [d] | Outcome [e] | Serious Yes/No | Serious Criterium [f] |
|---|---|---|---|---|---|---|---|---|---|---|
| xxxxx | 1 | xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxx/ | DDMMMYYYY (xx) HH:MM DDMMMYYYY (xx) HH:MM /xx | Mild | Unrelated | 2 | 1 | 1 | No No | |
| xxxxx | 2 | xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxx/ | DDMMMYYYY (xx)/ DDMMMYYYY (xx)/xx | Moderate | Unlikely | 1 | 2 | 2 | Yes | |

[a] Coded using MedDRA Dictionary (Version 26.0)
[b] Relative to the day of first dose of trial drug. Day is missing for patients who were not treated.
[c] Action Taken with Study Treatment: 1 = Amount not changed, 2 = Product interrupted, 3 = Product Withdrawn, NA = Not applicable.
[d] Other Action Taken: 0 = None, 1 = Medication, 2 = Procedure (therapeutic or diagnostic), 3 = Hospitalization or prolongation of hospitalization, 4 = Discontinuation, 5= Medical visit, 6 = Emergency room visit, OT= other.
[e] Outcome: 1 = Recovered or resolved, 2= Recovering/Resolving, 3 = Recovered/Resolved with Sequelae, 4 = not recovered or not resolved, 5 = Fata; UK = Unknown.
[f] 1= Death, 2= Immediately Life threatening, 3 = Inpatient hospitalization or prolongation of existing hospitalization, 4= Persistent Disability/Incapacity, 5 Congennital Anomaly / Birth defect, 6 Important Medical Event

Program Name: Date/Time Generated: Page x of y

Programming Notes:
Repeat for all dose groups. Sort by dose group, patient, AE No.

**Listing 16.2.7.3**
**Vital Sign**
**Safety Analysis Set**

Dose group: dose *1*

| Patient | Age (years)/ Gender | Vital Sign Parameter/ Unit | Visit | Collection Date Time (day) | Result | Unit | Absolute. difference to BL |
|---|---|---|---|---|---|---|---|
| xx | xx/ Male | Height | Day -2 | DDMMMYYYY HH:MM (xx) | xxx.xx | cm | |
| | | Weight | Day -2 | DDMMMYYYY HH:MM (xx) | xxx.xx | kg | xxx.xx |
| | | Weight | Day -1 | DDMMMYYYY HH:MM (xx) | xxx.xx | kg | xxx.xx |
| | | Weight | Day 10 | DDMMMYYYY HH:MM (xx) | xxx.xx | kg | xxx.xx |
| | | Weight | early Withdrawal [a} | DDMMMYYYY HH:MM (xx) | xxx.xx | kg | xxx.xx |
| | | | | - | | | |
| | | BMI | Day -2 | DDMMMYYYY HH:MM (xx) | xxx.xx | kg/m2 | xxx.xx |
| | | BMI | Day -1 | DDMMMYYYY HH:MM (xx) | xxx.xx | kg/m2 | xxx.xx |
| | | BMI | Day 10 | DDMMMYYYY HH:MM (xx) | xxx.xx | kg/m2 | xxx.xx |
| | | BMI | Early Withdrawal | DDMMMYYYY HH:MM (xx) | xxx.xx | kg/m2 | xxx.xx |

[a] In case patient discontinued the trial prior to day 10.
: Date/Time Generated: Page x of y

Programming Notes:
- Repeat for all treatment groups.
- Sort by treatment group, patient parameter and visit:
- Parameters: Height, Weight, BMI, Temperature, Pulse rate – supine, Pulse rate – standing, Systolic blood pressure – supine, Systolic blood pressure – standing, Diastolic blood pressure – supine, Diastolic blood pressure – standing

**Listing 16.2.7.4**
**Physical Examination**
**Safety Analysis Set**

Dose group: dose *1*

| Patient | Age (years)/ Gender | Visit | Collection Date Time (day) | Result | Specification |
|---|---|---|---|---|---|
| xx | xx/ Male | Day -2 | DDMMMYYYY HH:MM (xx) | Normal | |
| | | Day -1 | DDMMMYYYY HH:MM (xx) | CS | xxxxxxx |
| | | Day 10 | DDMMMYYYY HH:MM (xx) | NCS | xxxxxxx |
| | | early Withdrawal [a} | DDMMMYYYY HH:MM (xx) | | |
| xx | xx/ Male | Day -2 | DDMMMYYYY HH:MM (xx) | xxxxx | |
| | | Day -1 | DDMMMYYYY HH:MM (xx) | xxxxx | |
| | | Day 10 | DDMMMYYYY HH:MM (xx) | xxxxx | |
| | | early Withdrawal [a} | DDMMMYYYY HH:MM (xx) | xxxxx | |
| etc | | | | | |

[a] In case patient discontinued the trial prior to day 10.

: Date/Time Generated: Page x of y

Programming Notes:

- Repeat for all treatment groups.
- Sort by treatment group, patient and visit:

## B8 16.2.8 LISTING OF INDIVIDUAL LABORATORY MEASUREMENTS BY PATIENT

**Listing 16.2.8.1**
**Safety Laboratory - Clinical Chemistry**
**Safety Analysis Set**

Dose group: dose *1*

| Patient | Age (years)/ Gender | Test | Visit | Collection Date Time (day) | Result | Unit | Out of range flag |
|---|---|---|---|---|---|---|---|
| xx | xx/ Male | Total Bilirubin – | Day -2 | DDMMMYYYY HH:MM (xx) | xxx.xx | µmol/L | |
| | | Total Bilirubin | Day 1 | DDMMMYYYY HH:MM (xx) | xxx.xx | µmol/L | |
| | | Total Bilirubin | Day 10 | DDMMMYYYY HH:MM (xx) | xxx.xx | µmol/L | |
| | | Total Bilirubin | Early WD [a} | DDMMMYYYY HH:MM (xx) | xxx.xx | µmol/L | |

[a] WD + Withdrawal
Program Name: Date/Time Generated: Page x of y

Programming Notes:
Repeat for all treatment groups.
Sort by treatment group, patient parameter and visit:

Parameters Total Bilirubin, Gamma glutamyl transferase (GGT), Aspartate Aminotransferase (AST), Alanine Aminotransferasec-(ALT), Lactate Dehydrogenase (LDH), Creatinine, Blood Urea, Total protein, Albumin, Inorganic phosphate, Sodium, Potassium, Calcium , Glucose

**Listing 16.2.8.2**
**Safety Laboratory - Hematolgy**
**Safety Analysis Set**

Dose group: dose *1*

| Patient | Age (years)/ Gender | Test | Visit | Collection Date Time (day) | Result | Unit | Out of range flag |
|---|---|---|---|---|---|---|---|
| xx | xx/ Male | Total Leucocytes | Day -2 | DDMMMYYYY HH:MM (xx) | xxx.xx | 10^3 /µL | |
| | | Total Leucocytes | Day 1 | DDMMMYYYY HH:MM (xx) | xxx.xx | 10^3 /µL | |
| | | Total Leucocytes | Day 10 | DDMMMYYYY HH:MM (xx) | xxx.xx | 10^3 /µL | |
| | | Total Leucocytes | Early WD [a} | DDMMMYYYY HH:MM (xx) | xxx.xx | 10^3 /µL | |

[a] WD + Withdrawal
Program Name: Date/Time Generated: Page x of y

Programming Notes:
Repeat for all treatment groups.
Sort by treatment group, patient parameter and visit:

Parameters Total Leucocytes, Erythrocytes, Hemoglobin, Hematocrit, Thrombocytes, Lymphocytes, Monocytes, Eosinophils granulocytes total, Basophils granulocytes total, Neutrophils granulocytes total, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC)

**Listing 16.2.8.3**
**Safety Laboratory - Urinalysis**
**Safety Analysis Set**

Dose group: dose *1*

| Patient | Age (years)/ Gender | Test | Visit | Collection Date Time (day) | Result | Unit | Out of range flag |
|---|---|---|---|---|---|---|---|
| xx | xx/ Male | Hemoglobin | Day -2 | DDMMMYYYY HH:MM (xx) | xxx.xx | | |
| | | Hemoglobin | Day 1 | DDMMMYYYY HH:MM (xx) | xxx.xx | | |
| | | Hemoglobin | Day 10 | DDMMMYYYY HH:MM (xx) | xxx.xx | | |
| | | Hemoglobin | Early WD [a} | DDMMMYYYY HH:MM (xx) | xxx.xx | | |
| | …. | | | | | | |

[a] WD + Withdrawal
Program Name: Date/Time Generated: Page x of y

Programming Notes:
Repeat for all treatment groups.
Sort by treatment group, patient parameter and visit:

Parameters Hemoglobin, Urobilinogen, Ketones, Glucose

**Listing 16.2.8.4**
**Laboratory – Pregnancy Tests**
**Safety Analysis Set**

Dose group: dose *1*

| Patient | Age (years)/ Gender | Test | Visit | Collection Date Time (day) | Result |
|---|---|---|---|---|---|
| xx | xx/ Female | | Day -2 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 1 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 15 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | …. | | | | |

[a] WD + Withdrawal
Program Name: Date/Time Generated: Page x of y

Programming Notes:
Repeat for all treatment groups.
Sort by treatment group, patient and visit:
Report only women of childbearing potential

**Listing 16.2.8.5**
**Laboratory – ADA Results**
**Safety Analysis Set**

Dose group: dose *1*

| Patient | Age (years)/ Gender | Test | Visit | Collection Date Time (day) | Result | Titer |
|---|---|---|---|---|---|---|
| xx | xx/male | | Day 1 | DDMMMYYYY HH:MM (xx) | xxx.xx | |
| | | | Day 10 | DDMMMYYYY HH:MM (xx) | xxx.xx | |
| | …. | | | | | |

Program Name: Date/Time Generated: Page x of y

Programming Notes:
Repeat for all dose groups.
Sort by dose group, patient and visit:

**Listing 16.2.8.6**
**Laboratory – PK Concentrations**
**Safety Analysis Set**

Dose group: dose *1*

| Patient | Age (years)/ Gender | Test | Visit | Collection Date Time (day) | Result |
|---|---|---|---|---|---|
| xx | xx/male | | Day 1 pre dose | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 1 2h | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 1 4h | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 1 8h | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 2 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 3 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 4 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 5 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 6 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 7 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 8 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 9 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | | | Day 10 | DDMMMYYYY HH:MM (xx) | xxx.xx |
| | …. | | | | |

Program Name: Date/Time Generated: Page x of y

Programming Notes:
Repeat for all dose groups.
Sort by dose group, patient and visit:

| | |
|---|---|
| Document Type: | Final Statistical Analysis Plan – Additional Analyses |
| Document Date: | 12 June 2024 |
| Study Title: | Open-Label Pilot Trial to Evaluate the Effects of Ilofotase Alfa on Biomarkers in Adult Patients with Hypophosphatasia |
| Protocol Reference Number: | AP-recAP-HPP-01-01 |
| NCT Number: | NCT05890794 |

# Title: Additional Analyses

**Study:** AP-recAP-HPP-01-01

# Protocol Title: Open Label Pilot Trial to Evaluate the Effects of Ilofotase Alfa on Biomarker in Adult Patients with Hypophosphatasia

**TABLE OF CONTENTS**

# 1. CHANGES IN THE CONDUCT OF THE TRIAL OR PLANNED ANALYSES

(taken from Clinical Study Report, version 1.0 from 12Jun2024, section 9.8)

Changes in the planned analyses were made post hoc, and included:

Biomarkers analysis:

- Osteocalcin, ATP (blood), and ALP isoenzymes were planned but not analyzed.
- Adenosine was analyzed in urine (instead of in blood and urine).

Additional analyses

- Time to return to baseline (first time point in h where the value comes back to baseline ±10%) was added as an extra endpoint for PPi, PLP, PL, PL/PLP, and PEA, and summarized descriptively (n, mean, standard deviation [SD], standard error of the mean [SEM], min, med, max, 95% CI). Additionally, the difference between means and the 95% CI of this difference was presented, including a p-value (2-sided t-test on difference in means between dose groups).
- A mixed model repeated measures (MMRM) analysis was added for PPi, PLP, PL, PL/PLP, and PEA.

  This analysis was performed with SAS proc mixed, and the estimated differences in dose group means per timepoint (including 95% CI and p-value) were calculated with absolute and relative change from baseline as the dependent variables, baseline, dose group,

timepoint and timepoint* dose group as fixed effects, and patient and error as random effects. With 'spatial power' as covariance structure.

- mCFB (absolute and relative) and AUC (relative) were summarized descriptively for all biomarkers (instead of only for the primary biomarkers), including result of two-sided t-test on difference between dose levels.

Changes in definitions

- Relative change from baseline was redefined to:

  (value - baseline value) / baseline value

  And for PL/PLP ratio to fold change from baseline: value / baseline value

Handling of missing values

- For PPi, PLP and PL, the second assessment data was used for analysis purposes (refer to Section 9.5.4 of the CSR ). If the second assessment value was not available, it was replaced by the 1st assessment value.

Presentation of the analyses

- Results for PEA and PL were analyzed and presented with the same methodology as planned for PPi and PLP.
- The PL/PLP ratio was added as an extra endpoint, and results were analyzed and presented with the same methodology as planned for PPi and PLP.
- Graphical presentation (spaghetti plots) of absolute concentrations generated by dose group and overall were presented for all biomarkers (instead of only for the primary biomarkers).

As a result of these changes, the numbering of Section 14.2 tables and figures was updated compared to the SAP.

Additionally, in order to follow the suggested structure for CSRs in ICH E3, Table 14.3.2 'Listings of deaths, other serious and significant adverse events', Table 14.3.3 'Narratives of deaths, other serious and certain other significant adverse events', and Table 14.3.4 'Abnormal laboratory value listing (each patient)' were added, and the numbering of section 14.3 was updated accordingly.