sobi

# Statistical Analysis Plan

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|---|---|
| Protocol number: | SOBI003-001 |
| Title: | **An open, non-controlled, parallel, ascending multiple-dose, multicenter study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of SOBI003 in pediatric MPS IIIA patients** |
| SAP Author: | [redacted] |
| SAP version: | Final version 1.0, dated 24 March 2020 |

[redacted]

# Table of contents

# 1 Abbreviations and definition of terms

| | |
|---|---|
| ADA | Anti-drug antibody |
| AE | Adverse event |
| AEq | Age-equivalence |
| ANOVA | Analysis of variance |
| ATC | Anatomical therapeutic chemical |
| AUC | Area under curve |
| $AUC_{0\text{-}168h}$ | The area under the serum concentration-time curve from time 0 to 168 after dose |
| LLOQ | Below the assay's lower limit of quantification |
| BMI | Body mass index |
| BSID-III | Bayley scales of infant and toddler development®, third edition |
| $C_{End\ of\ inf}$ | The observed serum concentration at the end of infusion of SOBI003 |
| $C_{max}$ | Maximum observed serum concentration |
| $C_{Pre\text{-}dose}$ | The observed serum concentration immediately before the start of infusion of SOBI003 |
| $C_{Trough}$ | The minimum observed serum concentration |
| CI | Confidence interval |
| CL | Clearance |
| CNS | Central nervous system |
| CRIM | Cross reactive immunological material |
| CSF | Cerebrospinal fluid |
| CSHQ | Children´s sleep habits questionnaire |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| CV | Coefficient of variation |
| DMC | Data monitoring committee |
| DQ | Development quotient |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| ERT | Enzyme replacement therapy |

| | |
|---|---|
| ET | Early termination |
| FA | Fractional anisotropy |
| FAS | Full analysis set |
| FDA | Food and drug administration |
| FIH | First time in human |
| HS | Heparan sulfate |
| ICF | Informed consent form |
| ICH | International council for harmonization |
| IMP | Investigational medicinal product |
| IRR | Infusion related reaction |
| i.v. | Intravenous |
| KABC-II | Kaufman assessment battery for children, second edition |
| LSM | Least square means |
| λz | Terminal elimination rate constant |
| MAR | Missing at random |
| MD | Mean diffusivity |
| MedDRA | Medical dictionary for regulatory activities |
| MPS IIIA | Mucopolysaccharidosis type IIIA |
| MRI | Magnetic resonance imaging |
| NAb | Neutralizing antibody |
| NCI CTC | National cancer institute common terminology criteria |
| NH | Natural history |
| NVI | Nonverbal index |
| PD | Pharmacodynamic |
| PedsQL | Pediatric quality of life inventory |
| PI | Principal investigator |
| PK | Pharmacokinetic |
| PKAS | PK analysis set |
| PPS | Per-protocol analysis set |
| PT | Preferred term |

| | |
|---|---|
| Q1 | First quartile |
| Q3 | Third quartile |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SE | Standard error of the mean |
| Sobi | Swedish orphan biovitrum |
| SOC | System organ class |
| SRC | Safety review committee |
| SWI | Susceptibility weighting imaging |
| t | Time |
| $t_{End\ of\ inf}$ | The time of the end of the infusion of SOBI003 |
| $t_{last}$ | The time of the last measurable concentration |
| $t_{max}$ | The time at which the maximum serum concentration is observed |
| $t_{1/2}$ | Half-life |
| TEAE | Treatment emergent adverse event |
| TST | Total sleep time |
| VABS-II | Vineland adaptive behavior scales, second edition |
| WASO | Wake after sleep onset |
| WHO-DD | World health organization drug dictionary |

# 2 Introduction

This statistical analysis plan (SAP) describes the planned analysis and reporting for Swedish Orphan Biovitrum (Sobi) AB (publ), Stockholm, Sweden protocol SOBI003-001 (An open, non-controlled, parallel, ascending multiple-dose, multicenter study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of SOBI003 in pediatric MPS IIIA patients).

This phase I/II study is being performed to assess the safety and tolerability of SOBI003 for the treatment of mucopolysaccharidosis type IIIA (MPS IIIA); Sanfilippo A syndrome in pediatric MPS IIIA patients.

The purpose of this SAP is to outline the planned analyses to be completed to support the clinical study report (CSR) for protocol SOBI003-001. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP will be clearly identified in the respective CSR.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the food and drug administration (FDA) and the International council for harmonization of technical requirements for registration of pharmaceuticals for human use (ICH): guidance on statistical principles in clinical trials (1). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American statistical association and the Royal statistical society, for statistical practice (2).

# 3 Study objectives and endpoints

## 3.1 Primary objective

The primary objective is:

To evaluate the safety and tolerability of SOBI003 at different dose levels.

## 3.2 Secondary objectives

The secondary objectives are the following:

1. To characterize the PK properties of SOBI003 following single and repeated administration by the use of non-compartmental analysis
2. To assess the immunogenicity of SOBI003
3. To assess the PD effect of different dose levels and treatment duration of SOBI003 on HS levels in CSF, serum, and urine
4. To assess the effect of SOBI003 at different dose levels on neurocognition
5. To assess the effect of SOBI003 at different dose levels on adaptive behavior
6. To assess the effect of SOBI003 at different dose levels on gray matter volume

7. To assess the effect of SOBI003 at different dose levels on Quality of life.

## 3.3 Exploratory objectives

The exploratory objectives are to explore the effect of SOBI003 at different dose levels on:

1. Clinical manifestations of MPS IIIA as assessed by endpoints specified in Section 3.4.3.
2. To characterize the PK properties of SOBI003 following single and repeated administration by the use of population PK analysis.
3. To evaluate the PK/PD relationship between SOBI003 concentrations in serum and the effect of SOBI003 on HS levels in CSF, serum, and urine by the use of population modeling analysis.

As local regulations permit, and provided that additional separate caregiver consent is given, the exploratory objectives are also to:

- Collect and store a blood sample for future pharmacogenetic research aimed to explore genetic characteristics that may contribute to and/or modify the disease phenotype and /or with possible impact on safety, tolerability, immunogenicity, PK and PD related to SOBI003 treatment
- Collect and store serum, CSF and urine samples to enable analyses of biomarkers with possible relation to safety, tolerability, immunogenicity, PK and PD of SOBI003, as identified in future

The results of exploratory analyses may not be included in the CSR for this study, but reported separately when analyzed.

## 3.4 Study endpoints

### 3.4.1 Primary safety endpoint

The primary endpoint to evaluate the primary objective of the safety and tolerability of SOBI003 is:

- Treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)

### 3.4.2 Secondary endpoints

The secondary endpoints to evaluate the primary objective of the safety and tolerability of SOBI003 are:

- Vital signs (blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation)
- Laboratory safety variables (hematology, coagulation, clinical chemistry and urine analysis)

The endpoints relating to the 1st secondary objective are:

- Serum SOBI003 PK parameters at Weeks 1, 2, 3, 4, 5, 8, 12, 13, 16, 20, and 24; $t_{End\ of\ inf}$, $C_{End\ of\ inf}$, $C_{max}$, $t_{max}$, $C_{Pre\text{-}dose}$, $C_{Trough}$, CL, $AUC_{0\text{-}168h}$, $t_{1/2}$
- CSF SOBI003 concentration at Weeks 12 and 24

The endpoints relating to the 2nd secondary objective are:

- Occurrence of ADAs against SOBI003 in serum (seroconversion rate, time to seroconversion, transient/persistent). For patients with confirmed ADA positive serum samples, the following additional endpoints apply: ADA titers and IgG subclasses in serum and presence of NAb in serum.
- Occurrence of ADAs against SOBI003 in CSF at baseline, Weeks 12 and 24 (conversion rate, time to occurrence, transient/persistent). For patients with confirmed ADA positive CSF samples, the following additional endpoints apply: ADA titers and presence of NAb in CSF.

The endpoints relating to the 3rd secondary objective are:

- Change from baseline in CSF HS at Weeks 12 and 24
- Change from baseline in serum HS at Weeks 2, 3, 4, 8, 12, 16, 20, and 24
- Change from baseline in urine HS at Weeks 2, 3, 4, 8, 12, 16, 20, and 24

The endpoints relating to the 4th secondary objective are neurocognitive development quotient (DQ) and age-equivalence (AEq) score as assessed by the Bayley scales of infant and toddler development®, third edition (BSID-III) cognitive subtest or the Kaufman assessment battery for children, second edition (KABC™-II); change from baseline at Week 24.

The endpoint relating to the 5th secondary objective is adaptive behavior AEq score as assessed by Vineland™ adaptive behavior scales, expanded interview form, second edition (VABS-II); change from baseline at Week 24.

The endpoint relating to the 6th secondary objective is gray matter volume as assessed by brain volumetric magnetic resonance imaging (MRI); change from baseline at Week 24.

The endpoint relating to the 7th secondary objective is pediatric quality of life inventory (PedsQL™) total score and PedsQL™ family impact module total score; change from baseline at Week 24.

### 3.4.3 Exploratory endpoints

The endpoints related to the 1st exploratory objective are:

- Adaptive behavior composite score as assessed by VABS-II; change from baseline at Week 24
- Neurocognitive composite score as assessed by the BSID-III cognitive subtest or the KABC-II; change from baseline at Week 24
- Expressive and receptive language as assessed by the BSID-III language subtests, or the KABC-II expressive vocabulary subtest, and the VABS-II communication domain; AEq

change from baseline at Week 24Fine and gross motor function as assessed by the BSID-III motor subtests and the VABS-II; AEq change from baseline at Week 24
- Sleep pattern as determined by children´s sleep habits questionnaire (CSHQ) score; change from baseline at Weeks 12 and 24, respectively
- Sleep pattern as determined by actigraphy including total sleep time, total day- and night time sleep duration, sleep latency, sleep efficiency, number of nocturnal awakenings, and wake after sleep onset; change from baseline at Weeks 12 and 24, respectively
- Compound ventricular volume as assessed by brain volumetric MRI; change from baseline at Week 24
- Fractional anisotropy (FA) and mean diffusivity (MD) of corpus callosum as assessed by diffusion tensor imaging MRI; change from baseline at Week 24
- FA and MD of cerebral white matter as assessed by diffusion tensor imaging MRI; change from baseline at Week 24
- Cerebral white matter as assessed by susceptibility weighting imaging (SWI) MRI; change from baseline at Week 24
- Basal ganglia as assessed by SWI MRI; change from baseline at Week 24
- Liver volume as assessed by abdominal MRI; change from baseline at Week 24
- Spleen volume as assessed by abdominal MRI; change from baseline at Week 24

The endpoints related to the 2nd exploratory objective are:

- Population PK model parameter estimates and associated covariates describing intra- and inter-individual variability in respective parameter estimate.

The endpoints related to the 3rd exploratory objective are:

- Population PK/PD model parameter estimates and associated covariates describing intra- and inter-individual variability in respective parameter estimate. The results of these analyses will not be included in the CSR for this study, but reported separately.

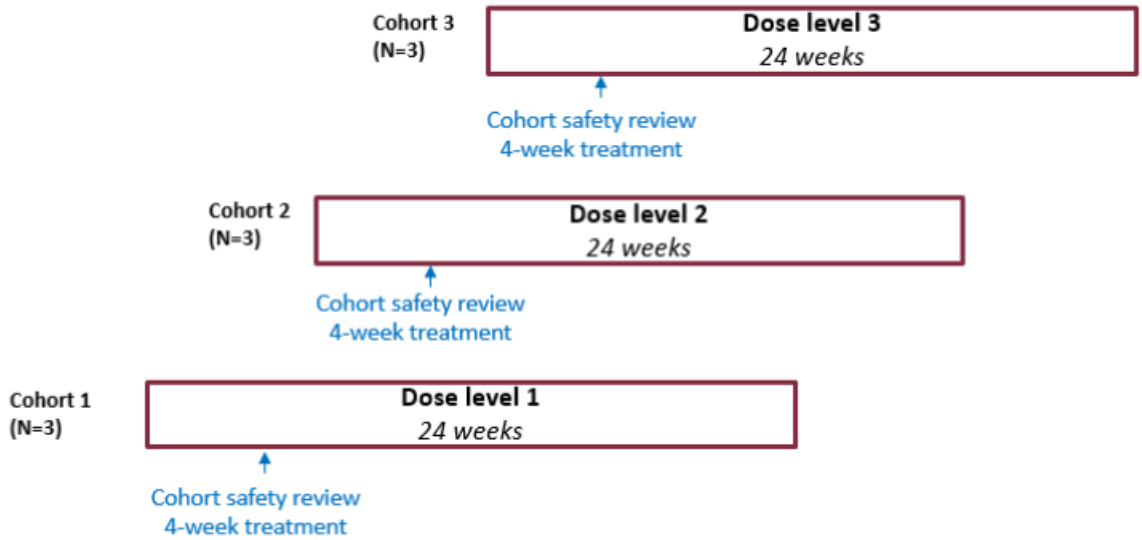
# 4 Study methods

## 4.1 Overall study design and plan

This is an open-label, non-controlled, parallel, sequential ascending multiple-dose, multicenter study to assess the dose related safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of SOBI003 in pediatric MPS IIIA patients. An overview for the study design is presented in Figure 1.

In February 2020, Sobi decided to discontinue the SOBI003 program. At the time of the decision, 3 patients had been included in Cohort 1 and 3 patients in Cohort 2 of the FIH study (SOBI003-001). All patients had been enrolled in the Extension study (SOBI00-002) and will have the possibility to continue their treatment for a total of two years. Thus, Cohort 3 in the FIH study (SOBI003-001) will not be started. Statistical analysis for the FIH study (SOBI003-001) CSR will be done for Cohort 1 and 2.

**Figure 1 Overview for study design for Study SOBI003-001**




SOBI003 is administered as weekly intravenous (i.v.) infusions over a period of time of 4 hours. The study treatment period comprises 24 weekly infusions. Prior to initiation of each infusion, the patients are pre-treated with a single dose of non-sedative antihistamine. If infusion-related reactions occur, then the infusion duration may be expanded up to 24 hours and supportive medication may be administered, at the discretion of the investigator.

The study is planned to consist of 3 dose cohorts, each comprising 3 patients, provided that no significant safety concern arise. An additional cohort comprising 3 patients may be added, if deemed necessary to more accurately characterize the safety, tolerability, PK or PD.

The screening visit can be performed up to 12 weeks prior to the first SOBI003 infusion. At the screening visit, the MPS IIIA diagnosis is verified and the genotype is determined at a central laboratory. Patients are assigned to a dose cohort in consecutive order as the eligibility criteria have been confirmed, with prioritization of the younger patients.

Treatment initiations will be staggered within each cohort in order to be able to observe, interpret and treat possible adverse reactions and to ensure that such reactions can be dealt with promptly. For each cohort, safety review committee (SRC) meetings are scheduled approximately 3 weeks after completion of the 3$^{rd}$ patient's 4$^{th}$ dose administration. Based on the safety, immunogenicity, PK and PD data, the SRC will determine what dose to apply in the next cohort.

A data monitoring committee (DMC), independent from Sobi and the principal investigator PI(s) will monitor safety data.

The DMC will review cumulative data from both the FIH study (SOBI003-001) and the extension study (SOBI003-002). The first DMC review meeting will be held 6 months following first patient visit in the extension study and will occur every 6 months until completion of the extension study (SOBI003-002). If requested by Sobi or DMC, additional ad-hoc meetings may be held.

Upon completion of the 24-week treatment period with satisfactory tolerability, the patient is offered to receive continued SOBI003 treatment by participation in an extension study (SOBI003-002).

The complete schedule of assessments is shown in Table 1 (Screening to Week 24), Table 2 (Weeks 1 to 4) and Table 3 (Weeks 12 and 24).

## Table 1 Schedule of events – Screening to Week 24

| | Screening[a] | Baseline[b] | | Treatment period (24 weeks) | | | | | | | | | | | | | | ET[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **-12 to -7** | **-6 to -1** | **1** | **2** | **3** | **4** | **5** | **6** | **8** | **9** | **12** | **13** | **16** | **17** | **20** | **22** | **24/ END** | |
| Informed consent | X | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | |
| Medical history | X | X | X | | | | | | | | | | | | | | | |
| Eligibility criteria | X | X | X | | | | | | | | | | | | | | | |
| Prior & concomitant therapy[d] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Neurological examination | X | | | | | | | | | | | | | | | | X | X |
| Height & head circumference | | X | | | | | | | | | X | | | | | | X | X |
| Weight[f] | X | X | X | | | | X | | | X | X | | | X | | | X | X |
| Vital signs[g] | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG[h] | X | | X | X | X | X | | X | X | | X | | | | | | X | X |
| Echocardiography | X | | | | | | | | | | | | | | | | X | X |
| Antihistamine[i] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| SOBI003 administration[i] | | | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | |
| Adverse events | X[j] | X[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[j] |
| Anesthesia/sedation[k] for: | | | | | | | | | | | | | | | | | | |
| Venous access port | | X[l] | | | | | | | | | | | | | | | | |
| CSF sampling (PK, ADA, HS, future research[m]) | | X[m] | | | | | | | | | X | | | | | | X[m] | |
| MRI (brain, spleen, liver) | | X | | | | | | | | | | | | | | | X | |

| | Screening[a] | Baseline[b] | | Treatment period (24 weeks) | | | | | | | | | | | | | | ET[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **-12 to -7** | **-6 to -1** | **1** | **2** | **3** | **4** | **5** | **6** | **8** | **9** | **12** | **13** | **16** | **17** | **20** | **22** | **24/ END** | |
| Blood sampling for: | | | | | | | | | | | | | | | | | | |
| Sulfamidase activity[n] | X | | | | | | | | | | | | | | | | | |
| SGSH genotyping | X | | | | | | | | | | | | | | | | | |
| Safety laboratory[o] | X | X[p] | X | X | X | X | X | X | X | | X | | X | | X | X | X | X |
| Immunogenicity | | X | | X | | X | | | X | | X | | X | | X | | X | X |
| HS | | X | | X | X | X | | | X | | X | | X | | X | | X | X |
| PK[q] | X | X | X | X | X | X | X | | X | | X | X | X | | X | | X | X |
| Future research[m] | | X | | | | | | | | | | | | | | X | | X |
| Urine collection for: | | | | | | | | | | | | | | | | | | |
| Safety laboratory (Dipstick)[o] | X | | X | X | X | X | X | X | X | | X | | X | | X | X | X | X |
| HS[u] | X | X | | X | X | X | | | X | | X | | X | | X | | X | X |
| Future research[m] | | X | | | | | | | | | | | | | | X | | X |
| CRIM status (skin fibroblasts) | | X | | | | | | | | | | | | | | | | |
| Actigraphy (sleep pattern)[r] | | X | | | | | | | | | X | | | | | | X | |
| BSID-III/KABC-II (neurocognition, language, motor function)[s] | | X | | | | | | | | | | | | | | | X | |
| Parent/caregiver questionnaires: | | | | | | | | | | | | | | | | | | |
| VABS-II | X | X[t] | | | | | | | | | | | | | | | X | |
| CSHQ[r] | | X | | | | | | | | | X | | | | | | X | |
| PedsQL, incl. Family Impact Module | | X | | | | | | | | | X | | | | | | X | |

a Screening assessments do not need to be performed on the same day, but should be completed to allow baseline assessments to be completed within 6 weeks prior to first SOBI003 infusion.

b Baseline assessments/procedures are not performed on the same day, but should be completed within 6 weeks prior to first SOBI003 infusion. The venous access port should be inserted at least 2 weeks prior to first SOBI003 infusion.
c In case of early termination (ET) of SOBI003 treatment, the assessments should be completed as soon as possible after decision of treatment withdrawal. When possible, all study assessments should continue in accordance with the Schedule of Events until completion of the Week 24 visit. At a minimum, the ET assessments should be repeated 30 to 40 days after the last SOBI003 administration. Patients with ADA-positive samples should continue to be followed in accordance with clinical study protocol (CSP) Section 7.5.5.3.
d Prior and concomitant therapy are recorded continuously from screening until completion of the Week 24 visit.
e General appearance and skin are examined prior to start of each infusion and within 1 hour of completion of each infusion to capture any physical changes during infusion. Any new clinically significant finding or worsening of MPS IIIA related symptoms should be reported as an AE.
f During the treatment period, weight is assessed at approximately 4-week intervals to determine the actual SOBI003 to be administered. Weight is therefore obtained prior to preparation of the SOBI003 infusions solution at Weeks 1, 5, 9, 12, 17, 21 and 24. The weight is obtained either the day prior to the infusion or the day of infusion. The dose may be adjusted on the week after the body weight is obtained, at the discretion of the investigator.
g Vital signs includes blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation. At each infusion, assessments are done pre-infusion, 2 hours after start of infusion and within 1 hour after end of infusion. At Weeks 1 to 8, assessments are also done at 1, 3, 6 to 7, and 8 to 12 hours after start of infusion, and on Days 2 and 3. In addition, at Weeks 1 and 2 assessments are done on Day 5. At Weeks 12 and 24, assessments are also done on Day 3. Continuous pulse oximetry is applied from start of infusion until the completion of each of the 4 first infusions.
h ECGs are obtained on Day 1 at pre-infusion and 4-5 hours after start of infusion (i.e., within an hour after completion of the infusion).
i Within 30 to 60 minutes prior to each SOBI003 infusion, a single dose of a non-sedative antihistamine should be administered. SOBI003 is administered as weekly infusions; +/- 1-day window is applied after the 4$^{th}$ infusion.
j SAE(s) are reported from the time point when the informed consent form (ICF) is signed until 28 days past last SOBI003 infusion. AEs are reported from start of first SOBI003 infusion.
k Use of general anesthesia or sedation is per local hospital routine and anesthesiologist judgement, as well as selection of anesthetic/sedative agents. If all Baseline procedures are not completed in one session, then local hospital routine determines minimum time between consecutive anesthetic/sedation episodes.
l The port should be inserted at least 2 weeks prior to first SOBI003 infusion.
m Only applicable when separate consent has been provided for future research. At Week 22, blood is collected for future genetic research. At Baseline and Week 22, blood and urine are collected for future biomarker research. CSF is collected at Baseline and Week 24 for future biomarker research. In case of ET of SOBI003 treatment, blood and urine is collected for storage for future biomarker and genetic research.
n Central laboratory analyses of sulfamidase activity in leucocytes.
o Sampling time points;
Weeks 1 to 3: pre-infusion (Day 1) and Day 3. For patients <15 kg body weight, blood sampling on Day 3 at Week 3 is NOT applicable.
Weeks 4 to 8: pre-infusion.
Weeks 10 to 22: biweekly pre-infusion, i.e., Weeks 10, 12, 14 etc.
Week 24: Day 3.
p Blood sampling for only hsCRP, IL-1ra, TNFα, IgE, and tryptase. Baseline sample analyzed only in case acute infusion/anaphylactic reaction occur during SOBI003 treatment to facilitate the determination of reaction etiology.
q Frequent PK blood sampling is conducted at Weeks 1, 2, 3, 4, 5, 8, 12, 13, 16, 20, and 24. Samples are also collected before start of infusion and at completion of the infusion at Weeks 2, 3 and 8 and before start of infusion, completion of infusion and at 168 hours (Day 8) at Week 16 and 20. PK blood sampling will be

adjusted based on the patient´s bodyweight in order not to exceed blood draw volume limits. At Baseline, the PK and immunogenicity samples should be taken on the day of CSF sampling for HS analysis. Details on PK blood sampling are given in CSP Table 6.

r Sleep pattern is assessed by actigraph recordings for 7 consecutive days at Baseline and within 2 weeks prior to Week 12 and 24, i.e., Baseline assessment should preferably be completed prior to any anesthetic/sedation is applied and prior to PK and HS blood samplings. The aim should be to have the recordings completed during normal patient sleeping conditions and prior to the SOBI003 infusions on Day 1 at Weeks 12 and 24. A sleep diary is completed during the days of actigraphy. Parents should complete the CSHQ upon completion of each actigraph assessment

s In case both BSID-III and KABC-II are to be administered, there should be at least 2 days between the assessments. Attempts should be made to have the assessment(s) performed at least 5 days after any anesthesia/sedation. The Baseline assessment should be completed within 2 weeks prior to the first SOBI003 infusion.

t The Baseline assessment should be completed within 2 weeks prior to the first SOBI003 infusion.

u Blood samples for immunogenicity and HS and urine sample for HS should be collected pre-infusion.

**Table 2 Detailed schedule of events – Weeks 1 to 4**

| | Weeks 1, 2, 3 and 4 | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **5** | **6** |
| **Time** | **Pre-inf** | **0** | **1:00** | **2:00** | **3:00** | **4:00** | **4:01 - 5:00** | **6:00 – 7:00** | **8:00 - 12:00** | | | | |
| Medical history | X[a] | | | | | | | | | | | | |
| Eligibility criteria | X[a] | | | | | | | | | | | | |
| Prior & concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination[b] | X | | X | X | X | | X | X | X | X | X | X[d] | |
| Weight | X[c] | | | | | | | | | | | | |
| Vital signs[l] | X | | X | X | X | | X | X | X | X | X | X[d] | |
| Continuous pulse-oximetry[e] | → | → | → | → | → | → | ← | | | | | | |
| 12-lead ECG | X | | | | | | X | | | | | | |
| Antihistamine[f] | X | | | | | | | | | | | | |
| SOBI003 administration: | | | | | | | | | | | | | |
| Start of infusion | | X | | | | | | | | | | | |
| Stop of infusion | | | | | | X | | | | | | | |
| Adverse events | X[g] | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood sampling for: | | | | | | | | | | | | | |
| Safety laboratory | X | | | | | | | | | | X[h] | | |
| Immunogenicity | X[i] | | | | | | | | | | | | |
| HS | X[j] | | | | | | | | | | | | |
| PK | X[j] | | | | | | X | X[k] | X[k] | X[k] | X[k] | X[k] | X[k] |
| Urine collection for: | | | | | | | | | | | | | |
| Safety laboratory (Dipstick) | X | | | | | | | | | | X[h] | | |
| HS | X[j] | | | | | | | | | | | | |

a Only applicable at Week 1. Medical conditions present pre-infusion are recorded as medical history. At the time of the 1st infusion, the patient should not have evidence of ongoing infection, as judged by the investigator. In such case, the 1st infusion should be postponed until the infection has resolved.
b General appearance and skin to capture any physical changes during infusion. Any new clinically significant finding or worsening of MPS IIIA related symptoms should be reported as an AE.
c Only applicable at Week 1. Weight obtained pre-infusion at Week 1 determines the actual SOBI003 dose to be administered at Weeks 1 to 4. The dose may be adjusted in the week after the body weight is obtained, at the discretion of the investigator.
d Only applicable at Weeks 1 and 2
e Continuous monitoring up to 24 hours after start of infusion
f Within 30 to 60 minutes prior to each SOBI003 infusion, a single dose of a non-sedative antihistamine should be administered.
g SAE(s) are reported from the time point when ICF is signed until 28 days past last dose of IMP. AEs are reported from start of first SOBI003 infusion.
h NOT applicable at Week 4 and blood sampling is not applicable at Week 3 for patients < 15 kg body weight.
i Only applicable for Weeks 2 and 4.
j NOT applicable for Week 1.
k Only applicable for Weeks 1 and 4. PK sampling time points are pre-dose, 4 hours (end of infusion), 6, 12, 24, 48, 96, 120 and 168 hours after start of infusion. In case SOBI003 infusion is prolonged, applicable adjustments the PK sampling time points are applied (refer to CSP Table 6).
l If the infusion time is reduced or extended, hourly vital signs during infusion should be recorded.

**Table 3 Detailed schedule of events – Weeks 12, 16, 20 and 24; PK at Weeks 5, 8, 12, 13, 16, 20, and 24; ADA, Serum HS, and Urine HS at Weeks 8, 12, 16, 20, and 24**

| | | Weeks 12, 16, 20 and 24<br>PK: Weeks 5, 8, 12, 13, 16, 20, and 24<br>ADA, Serum HS, Urine HS: Weeks 8, 12, 16, 20, and 24 | | | | | | | | | | | | | Week 12 | Week 24 END |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **4** | **5** | **6** | **7 (8[a])** | **7 (8[a])** |
| **Time** | **Pre-inf** | **0** | **1:00** | **2:00** | **3:00** | **4:00** | **4:01 - 5:00** | **6:00 – 7:00** | **8:00 – 12:00** | | | | | | | |
| Prior & concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X |
| Physical examination | X[b] | | | | | | X[b] | | | | | | | | | X |
| Neurological examination | | | | | | | | | | | | | | | | X |
| Height & head circumference | | | | | | | | | | | | | | | X | X |
| Weight | X[k] | | | | | | | | | | | | | | X | X |
| Vital signs | X | | | X | | | X[l] | | | | X | | | | | |
| 12-lead ECG | X[m] | | | | | | X[m] | | | | | | | | | X[c] |
| Echocardiography | | | | | | | | | | | | | | | | X[c] |
| Antihistamine[d] | X | | | | | | | | | | | | | | | |
| SOBI003 administration: | | | | | | | | | | | | | | | | |
| Start of infusion | | X | | | | | | | | | | | | | | |
| Stop of infusion | | | | | | X | | | | | | | | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X |
| Anesthesia for: | | | | | | | | | | | | | | | | |
| CSF sampling (SOBI003, ADA, HS, future research[e]) | | | | | | | | | | X | | | | | | |
| MRI (brain, spleen, liver) | | | | | | | | | | X[f] | | | | | | |

| | | Weeks 12, 16, 20 and 24<br>PK: Weeks 5, 8, 12, 13, 16, 20, and 24<br>ADA, Serum HS, Urine HS: Weeks 8, 12, 16, 20, and 24 | | | | | | | | | | | | | Week 12 | Week 24 END |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **4** | **5** | **6** | **7 (8[a])** | **7 (8[a])** |
| **Time** | **Pre-inf** | **0** | **1:00** | **2:00** | **3:00** | **4:00** | **4:01 - 5:00** | **6:00 – 7:00** | **8:00 – 12:00** | | | | | | | |
| Blood sampling for: | | | | | | | | | | | | | | | | |
| Safety laboratory | X[g] | | | | | | | | | | X[f] | | | | | |
| Immunogenicity | X | | | | | | | | | | | | | | | |
| HS | X | | | | | | | | | X | | | | | | |
| PK | X | | | | | | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] |
| Urine collection for: | | | | | | | | | | | | | | | | |
| Safety laboratory (Dipstick) | X[g] | | | | | | | | | | X[f] | | | | | |
| HS | X | | | | | | | | | X | | | | | | |
| Actigraph device collection | X | | | | | | | | | | | | | | | |
| BSID-III and/or KABC-II (neurocognition, language, motor function)[i] | | | | | | | | | | | | | | | | X |
| Parent/caregiver questionnaires: | | | | | | | | | | | | | | | | |
| VABS-II | | | | | | | | | | | X[f] | | | | | |
| CSHQ[j] | X | | | | | | | | | | | | | | | |
| PedsQL incl. Family Impact Module | | | | | | | | | | | | X | | | | |

a Only PK sampling applicable on Day 8. All other assessments performed on Day 7.
b General appearance and skin at the infusion site are examined prior to start of each infusion and within 1 hour of completion of each infusion to capture any physical changes during infusion. Any new clinically significant finding or worsening of MPS IIIA related symptoms should be reported as an AE.
c If it is not practically feasible to conduct echocardiography and ECG on Day 7, these can be done during Days 3 to 7.
d Within 30 to 60 minutes prior to each SOBI003 infusion, a single dose of a non-sedative antihistamine should be administered.
e Only applicable when separate consent has been provided for future research.

f Only applicable for Week 24
g Only applicable for Week 12
h PK sampling time points are 4 hours (end of infusion), 6, 12, 24, 48, 96, 120 and 168 hours after start of infusion. Samples are also collected at 4 hours (end of infusion) and at 168 hours (Day 8) at Week 5, 8, 12, 13, 16, 20 and 24. The 168-hour sample at Week 12, 16, and 20 is thus taken prior to start of infusion on Day 1 of Week 13, 17, and 21, respectively. The 168-hour sample at Week 24 is thus taken on Day 8 (For patients continuing in the extension study (SOBI003-002), this is prior to start of infusion on Day 1 of the extension study).
i In case both BSID-III and KABC-II are to be administered, there should be at least 2 days between the assessments (i.e., one should then be administered on Days 4 or 5 of Week 24 and the other one on Day 7 of Week 24). A +7-day window is applied for the BSID III/KABC-II assessments.
j CSHQ is completed any time during the infusion days
k Weight is obtained prior to preparation of the SOBI003 infusions solution at Week 12. The weight is obtained either the day prior to the infusion or the day of infusion. The dose may be adjusted on the week after the body weight is obtained, at the discretion of the investigator.
l At each infusion, vital sign assessments are done pre-infusion, mid-infusion and within 1 hour after end of infusion. Timing of assessment to be adjusted in accordance with infusion time.
m Only applicable for Week 12 and 24.

## 4.2 Selection of study population

### 4.2.1 Inclusion criteria

A patient must fulfill the following criteria in order to be included in the study:

1. Informed consent obtained from the patient's legally authorized representative(s)
2. Patients with MPS IIIA, as confirmed by both:
    - A documented deficiency in sulfamidase enzyme activity in concordance with a diagnosis of MPS IIIA*, and
    - Normal enzyme activity level of at least one other sulfatase measured in leukocytes
3. Chronological age of ≥12 and ≤72 months (i.e., 1 to 6 years) at the time of the first SOBI003 infusion and has a developmental age ≥12 months at screening as assessed by the VABS-II
4. Medically stable patient who is expected to be able to comply with study procedures

* as determined by the reference ranges applied by the Greenwood Genetic Center

### 4.2.2 Exclusion criteria

The presence of any of the following will exclude a patient from inclusion in the study:

1. At least one S298P mutation in the N-sulfoglucosamine sulfohydrolase (SGSH) gene
2. Contraindications for anesthetic procedures, surgical procedure (venous access port), MRI scans and/or lumbar punctures
3. History of poorly controlled seizures
4. Patients is currently receiving psychotropic or other medications which in the investigator's opinion, would be likely to substantially confound test results
5. Significant non-MPS IIIA-related central nervous system (CNS) impairment or behavioral disturbances, which in the investigator's opinion, would confound the scientific integrity or interpretation of study assessments
6. Prior administration of stem cell or gene therapy, or enzyme replacement therapy (ERT) for MPS IIIA
7. Concurrent or prior (within 30 days of enrolment into this study) participation in a study involving invasive procedures

## 4.3 Method of treatment assignment and randomization

This is a non-randomized, open-label study; no blinding of treatment assignments is required.

Upon provision of signed informed consent, patients are assigned a site-specific enrolment number in consecutive order. Upon completion of the screening assessments and confirmation of patient eligibility, patients are allocated to a dose cohort in consecutive order, with prioritization

of the younger patients. There is thus no restriction or requirement regarding the site distribution of patients per cohort, i.e., patients within one cohort can be recruited at only one site or at multiple sites.

# 5 Sequence of planned analysis

## 5.1 Safety review committee

Treatment initiations will be staggered within each cohort in order to be able to observe, interpret and treat possible adverse reactions and to ensure that such reactions can be dealt with promptly. For each cohort, SRC meetings are scheduled approximately 3 weeks after completion of the 3rd patient's 4th dose administration. Based on the safety, immunogenicity, PK and PD data, it is the responsibility of the SRC to determine:

- whether dosage of ongoing cohort(s) can continue
- if the infusion time and rate of subsequent administrations at ongoing dose level should be altered
- whether it is safe to continue to the next cohort, i.e., to expose new study patients to SOBI003 treatment
- the SOBI003 dose to be administered in the next cohort and to ongoing patients in the extension study (SOBI003-002).

Additional SRC meetings will be scheduled *ad hoc* as per principal investigator or Sobi SRC member requests. The SRC will review cumulative data from both the FIH study (SOBI003-001) and the extension study (SOBI003-002).

An SRC charter will specify the operating procedures including SRC membership, voting members, responsibilities, data review meeting details, and lines of communication with the study teams at Sobi, Syneos Health, and investigational sites.

The SRC charter will also specify in detail the data and outputs presented in the SRC summary reports, which will be provided to the SRC members for their review.

## 5.2 Data safety monitoring committee

In addition to the SRC, a DMC is assigned to monitor safety, PK, PD, and immunogenicity data. The primary responsibility of the DMC is to provide additional safety oversight of the study conduct in order to further protect study participants.

A DMC charter will specify the operating procedures including DMC membership, responsibilities, data review meeting details, and lines of communication with the study teams at Sobi and Syneos Health.

The DMC charter will also specify in detail the data and outputs presented in the open reports, which will be provided to the voting members of the DMC for their review.

The DMC will review cumulative data from both the FIH study (SOBI003-001) and the extension study (SOBI003-002). The first DMC review meeting will be held 6 months following first patient visit in the extension study and will occur every 6 months until completion of the extension study. If requested by Sobi or DMC, additional ad-hoc meetings may be held.

## 5.3 Interim analyses

No interim analysis is planned for this 24-week study.

## 5.4 Analyses and reporting

All final, planned, analyses identified in the CSP and in this SAP will be performed only after the last patient has completed the study. Tables, listings, and figures to be provided for SRC and DMC review are specified in separate SRC Listing and SRC Table shell documents.

Any post-hoc analyses included in the CSR, which were not identified in this SAP, will be clearly identified as such in the relevant section of the CSR.

# 6 Sample size determination

Given that this is a FIH study with no formal hypothesis tests, no sample size calculation has been performed. Three sequential dose levels with 3 patients in each cohort was considered sufficient to allow assessment of safety and tolerability concerns, as well as characterize a PD dose-response relationship in this rare population with a high unmet medical need.

# 7 Analysis sets

The following analysis sets will be used in the statistical analyses. Analyses will be performed by dose cohort; in addition, summary tables will be presented for all patients.

For PK and PD, analyses will be performed by dose level as described in Section 15 and 16.

## 7.1 Safety analysis set (SAF)

The SAF is the primary analysis set and will consist of all patients who received at least 1 dose of investigational medicinal product (IMP).

The SAF will be used for the safety analyses.

## 7.2 Full analysis set (FAS)

The FAS will consist of all patients who have a baseline and at least 1 post-baseline assessment of any secondary or exploratory assessment.

The FAS will be used for the secondary and explorative efficacy analyses.

## 7.3 PK analysis set (PKAS)

The PKAS will consist of all patients where at least 1 SOBI003 dose has been administered correctly and where SOBI003 serum or CSF concentration data is available without any protocol deviation interfering with these results.

The PKAS will be used for the analysis of PK secondary endpoints relating to the 1st secondary objective.

## 7.4 Immunogenicity analysis set

The immunogenicity set will consist of those patients in the safety analysis set who have sufficient blood samples taken for ADA testing at baseline and at least 1 post-dose time-point.

The immunogenicity set will be used for the immunogenicity analyses.

In case any patient has missing baseline, a second immunogenicity analysis set will be formed including all patients with sufficient blood samples for ADA testing (i.e. including those with missing baseline). All immunogenicity analyses without considering baseline will be performed on that second set.

# 8 General issues for statistical analysis

All statistical tests will be two-sided and performed using a 5 % significance level, if not stated otherwise. Results will be presented as the estimated mean value for each treatment group, the estimated difference between groups, the associated 95 % two-sided confidence interval and P-value. P-values from statistical analyses will be presented to three decimal places with values below 0.001 displayed as <0.001 and confidence intervals will be presented to one more decimal places than the raw data.

Continuous data will be summarized using descriptive statistics: number of patients (n), mean, standard deviation (SD), standard error of the mean (SE), median, minimum and maximum values, unless otherwise indicated. Minimum and maximum values will be presented to the same number of decimal places as the raw data and mean, SD, SE of the mean and median will be presented to one more decimal place than the raw data. Summary tables over all patients will include in addition the first quartile (Q1) and the third quartile (Q3), presented to one more decimal place than the raw data.

Categorical data will be summarized using frequency counts and percentages. Percentages will be suppressed when the count is zero, however the category will still be displayed. The denominator for all percentages will be the number of patients within the treatment group for the population of interest, unless otherwise indicated. Percentages will be presented to one decimal place.

Data for the FIH SOBI003-001 study (up to Week 24) and extension study SOBI003-002 (Week 25 to 104) will be collected in a combined database. All analyses specified in this SAP refer to FIH study SOBI003-001, i.e. for data up to Week 24.

Data obtained up to Week 24 will be summarized in tables by dose cohort, visit, and time point, if applicable. All data obtained up to Week 24 will be listed in individual patient data listings, which will be sorted by dose cohort and patient ID.

If not specified otherwise for the purpose of tabulations, the unscheduled post-baseline values will generally be excluded.

Statistical analyses will be performed using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina, United States).

## 8.1 Handling of missing data and outliers

For all questionnaires and scales, (see Section 13.1 for more details) items that are not answered by the patient will remain as missing. If applicable, specific rules for the calculation of each score are also defined in Section 13.1.

Complete missing or partial dates will be presented in the listings as reported on the electronic case report forms (eCRFs).

If an AE has a completely missing onset date, then the AE will be considered a TEAE, unless the (partial) stop date indicates differently. A medication with a completely missing start date is considered a prior medication. A medication with a completely missing stop date is considered a concomitant medication.

If an AE or a medication has a partial missing start or stop date, the rules presented in Table 4 will be used to impute the date. The imputed date will be used to determine whether it is a TEAE for AE, or a prior or concomitant medication.

**Table 4 Partial date derivation**

| Partial Missing Start or Stop Date | Derived Start Date | Derived Stop Date |
|---|---|---|
| Missing month and day, and the year is present | January 1st of that year or first dose date if the year is the same as the year of first dose date | December 31st of that year |
| Missing day, but year and month are present | First day of that month or first dose date if the year and month are the same as the year and month of first dose date | Last day of that month |
| Missing month, but year and day are present | Missing month derived as January or same as first dose month if the year is the same as the year of first dose | Missing month derived as December |

## 8.2 Multicenter studies

The planned study centers are located in the U.S.A., Turkey, the Netherlands, and Germany. The study will be conducted at up to 5 study centers in total. Analysis will be performed on the combined data from all study centers.

## 8.3 Multiple comparisons and multiplicity

There will be no adjustments for multiplicity.

## 8.4 Derived and computed variables

### 8.4.1 First and last study treatment

Day 1, Week 1 is the day of first study treatment, the day prior to 1st study treatment is Day -1. The last study treatment will be at the latest at Week 24 of the Treatment period.

### 8.4.2 Study treatment exposure

For patients who continued study treatment until end of the study SOBI003-001, study treatment exposure in weeks will be calculated as ([date of last visit attended – date of 1st infusion of study treatment] + 1) / 7, rounded to the nearest decimal.

For patients who stopped study treatment during the course of the study, study treatment exposure in weeks will be calculated as ([date of last infusion + 7 days – date of 1st infusion of study treatment] + 1) / 7, rounded to the nearest decimal.

### 8.4.3 Baseline and change from baseline

Baseline is defined as the last available assessment prior to 1st infusion of study treatment.

Change from baseline = (post-baseline value – baseline value).

### 8.4.4 Age

Age (months) will be derived as date of 1st infusion – birth date. Since only month and year of birth are captured, "15" will be used as day of birth for calculation.

### 8.4.5 Adverse event duration

If times are available and if the duration is less than 24 hours, the duration will be calculated as (end date/time – start date/time) and presented in hh:mm. If at least 1 time is missing or if the duration is at least 24 hours it will be calculated as (end date - start date)+1 and presented in days.

In case of partial/missing start or end date duration will not be calculated.

### 8.4.6 Time since study treatment administration for adverse event

If times are available and if time to onset is less than 24 hours, the time will be calculated as (start date/time – first/last administration date/time) and presented in hh:mm. If at least 1 time is missing or if the time to onset is at least 24 hours then it will be calculated as (start date – first/last administration date) + 1 and presented in days.

In case of partial/missing AE start date the time since study treatment administration will not be calculated.

### 8.4.7 Body mass index (BMI)

Body mass index ($kg/m^2$) will be derived as weight (kg)/(height(cm)/100)$^2$ and rounded to the nearest decimal.

### 8.4.8 Dose received

At each visit from Week 1 onwards, the actual infusion volume administered, including the added SOBI003 volume is reported in the eCRF. Total infusion volume to be administered is 100 mL for patients with a bodyweight < 25 kg and 250 mL for patients with a body weight ≥ 25 kg.

Dose received will be calculated at each visit as (added SOBI003 volume * 20), rounded to the nearest decimal and presented in mg.

Dose received will also be calculated at each visit in mg/kg as (added SOBI003 volume * 20 / bodyweight, rounded to the nearest decimal.

### 8.4.9 Time since diagnosis

Time since diagnosis will be calculated as ([date of 1st infusion – date of diagnosis]+1)/30.4373 and presented in months. In case of partial/missing date of diagnosis, time since diagnosis will not be calculated.

# 9 Patient disposition

An overall summary of patient disposition by dose cohort will be displayed for all screened patients with the numbers and percentage of patients screened, screen failures, treated, and included in the analysis sets. Additionally, the numbers and percentage of patients who completed study and were withdrawn from the study will be summarized, including the reason for study withdrawal. All data, including the reasons for screen failure and reasons for exclusion from each of the analysis sets, will be listed.

All protocol deviations identified will be summarized and listed.

Violated inclusion criteria and fulfilled exclusion criteria will also be listed.

# 10 Demographics and baseline characteristics

Demographic and other baseline characteristics will be summarized by dose cohort with descriptive statistics using the SAF.

## 10.1 Demographics and baseline characteristics

Date of birth, gestational age at birth, gender, ethnicity, race, country of residence and native language will be captured at Screening. In addition, information on the patient's siblings is captured, including age and MPS IIIA diagnostic status (confirmed as nonaffected/ confirmed as affected/under current investigation) (3). For sibling(s) with confirmed diagnosis, the sibling's age at diagnosis and genotype are also captured, when known.

For patient data, the following variables will be summarized: Age at first infusion (derived), gestational age at birth, gender, baseline weight, ethnicity, race, country of residence and native language. The same variables will be also included in listings, as well as date of birth.

For patient's siblings' data, the following variables will be summarized: Age (derived), MPS IIIA diagnostic status, and age at confirmed diagnosis. The same variables will also be included in listings, including also the genotype of siblings with confirmed diagnosis.

## 10.2 Medical history

For all medical history data, a frequency table of the number and percentage of patients will be provided by system organ class (SOC) and preferred term (PT) for each dose cohort. Tables will be sorted alphabetically by SOC and PT.

All medical history data will be coded using the latest version of the medical dictionary for regulatory activities (MedDRA), all data will be listed.

### 10.2.1 MPS IIIA diagnosis

Information on diagnosis date and prior MPS IIIA diagnostic procedures will be captured in the eCRF including assessment date, diagnostic method used and test result. Summary statistics will be presented for diagnostic status and time since diagnosis (defined in 9.4.9). All data will be listed.

# 11 Prior and concomitant medication

Prior medications will be defined as any medications taken prior to the date of 1st study treatment. Concomitant medications will be defined as medications ongoing or with a start date on or after the date of the 1st study treatment or a stop date on or after the date of the 1st study treatment.

All prior and concomitant medication will be coded using the latest version of world health organization drug dictionary (WHO-DD). Data will be listed and summary tables will be presented by anatomical therapeutic chemical classification [ATC] level 4, and WHO-DD preferred term using the SAF.

Prior to each infusion of SOBI003, a single dose of non-sedative antihistamine will be administered. Antihistamine administration including date and time, medication name, dose, unit and route will be listed and summarized per visit.

For patients continuing in the extension study (SOBI003-002), any medications with onset after the 1st dose of study drug in the extension study will not be presented in the tables and listings of the FIH study (SOBI003-001) but in the tables and listings of the extension study.

# 12 Treatment compliance

There will be no measurement of, or analysis of, treatment compliance, nor does it affect population assignment (patients must be exposed to study drug to qualify for the analysis sets).

# 13 Efficacy analyses

Efficacy data will be summarized descriptively by dose cohort, visit, and time point using the FAS.

## 13.1 Questionnaires and scales

The patient's chronological age in combination with the patient's adaptive behavior age equivalent score as established by VABS-II, will determine which neurocognitive test(s) to apply. The algorithm in **Table 5** is applied and the test(s) administered at Baseline should also be used at Week 24.

**Table 5 Selection of neurocognitive assessment method**

| Chronological age at the assessment time point | VABS-II adaptive behavior age-equivalence | Neurocognitive test to apply |
|---|---|---|
| <42 months | Any age-equivalence | BSID-III |
| ≥42 months | <36 months | BSID-III |
| ≥42 months | 36 to 42 months | BSID-III + KABC-II* |
| ≥42 months | >42 months | KABC-II |

* The BSID-III should be administered first, and there should be at least 2 days until the KABC-II assessment in order to reduce KABC-II outcome bias of patient tiredness.

### 13.1.1 VABS-II

For this study, the VABS-II assesses adaptive behavior in 4 competence domains (communication, socialization, daily living skills, and motor skills). The domain scores yield an adaptive behavior composite of the 4 domains (4). The VABS-II is assessed by parent/caregiver interviews performed by child development specialists/ psychologists with prior experience of MPS IIIA patients. A series of age-equivalent questions obtains a decreasing score between "4" and "0" or "DK" (don't know) based on how independently the individual is able to perform the behavior (i.e., 4 = "performs almost always independently", 0 = "never performs/never performs independently") is answered. The developmental age at Screening will be determined as the mean of the subdomain AEq scores including the communication, socialization, daily living skills, and motor skills domains

The adaptive behavior AEq and composite score will be obtained with the mean of the subdomain scores communication, socialization, daily living skills and motor skills for patients aged up to 6 years and 11 months. For patients aged 7 years and above, the adaptive behavior composite score will be obtained with the 3 subdomain scores communication, socialization, and daily living skills.

The VABS-II will be assessed at Screening, Baseline (within 2 weeks prior to 1st SOBI003 infusion) and at Week 24 (see Table 1). Each patient's parent/caregiver should preferably have the same interviewer throughout the study in order to reduce potential variability. Completed

assessment forms will be sent to a central reader (NeuroCog Trials), for data quality assurance of completed assessment forms, calculation of final scores and determination of AEq scores, and data management.

Changes from baseline (as defined in Section 8.4.3) will be calculated at Week 24.

### 13.1.2 BSID-III

The BSID-III is a standard series of measurements used primarily to assess the development of infants and toddlers. Children are assessed in the 5 key developmental subtests of cognitive, language, social-emotional, motor and adaptive behavior (5). For each developmental subtest the patient must respond to a series of questions with a score of "1" or "0" based on the successful completion ("1") of a task. Total raw scores for each subtest can be obtained by adding all scores of the questions in the subtest.

The BSID-II will be assessed at Baseline (within 2 weeks prior to 1st SOBI003 infusion) and at Week 24, if applicable (see Table 1). Each patient should preferably have the same assessor throughout the study in order to reduce potential variability.

Changes from Baseline (as defined in Section 8.4.3) will be calculated at Week 24.

### 13.1.3 KABC-II

The KABC™-II is a standardized test that assesses intelligence and achievement in children. The test is comprised of four global test scores that include: sequential processing, simultaneous processing, achievement and mental processing (6). Each of the global tests contains a number of subtests with several questions. For each question, the patient must respond with a categorical score (mostly between "2"and "0", but between "4" and "0" for some subtests), based on the difficulty that the patient experiences while answering the question (e.g., a difficult task would be scored with "0" and an easy task would be scored with "2" or "4" depending on the subtest).

A cumulative raw score can be obtained then for each subtest by adding the scores for each question in the subtest. Raw scores can be then transformed to adjusted scores and AEq.

The nonverbal index (NVI) of KABC-II is defined by adding certain subtests and based on the age of the patient. For patients between 3-6 years (cognitive age) it includes the subtests: conceptual thinking, face recognition, story completion, triangles, pattern reasoning and hand movements.

The KABC-II will be assessed at Baseline (within 2 weeks prior to 1st SOBI003 infusion) and at Week 24, if applicable (see Table 1). Each patient's parent/caregiver should preferably have the same assessor throughout the study in order to reduce potential variability.

To ensure that the KABC-II assessments are performed in accordance with the study instructions, completed assessment forms will be sent to a central reader (NeuroCog Trials) for data quality assurance, calculation of final scores and determination of AEq and DQ scores.

Changes from Baseline (as defined in Section 8.4.3) will be calculated at Week 24.

### 13.1.4 PedsQL

The PedsQL™ is a modular approach to measuring health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions. PedsQL includes the following scales covering 4 domains: physical, emotional, social and school functioning (7). Questions and scales vary for the different age categories (13 to 24 months, 2 to 4 years, and 5 to 7 years). Also, the PedsQL™ Family Impact Module will be completed with the following 8 domains: physical, emotional, social, and cognitive functioning, as well as communication, worry, daily activities, and family relationships.

For each of the domains, a series of questions will be answered and then rated with a categorical score between "4", "3", "2", "1" or "0" based on how much of a problem the patient has in solving the task described by the question. A summary score is subsequently obtained for each patient so that higher scores indicate better health-related quality of life.

The total score of the PedsQL (for both the assessment of the child's quality of life and of caregiver burden) will be obtained with the following steps:

1. Transform score. Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0
2. Each scale score will be calculated as the sum of the transformed individual score items, divided by the number of non-missing items. Note that a scale score is only calculated if at least 50% of the associated items are non-missing.
3. Total score = sum of all the items over the number of items.

The PedsQL will be assessed at Baseline and at Weeks 12 and 24. Changes from Baseline (as defined in Section 8.4.3) will be calculated at Week 12 and 24. The PedsQL will only be listed.

### 13.1.5 CSHQ

The CSHQ is a psychological questionnaire designed to examine sleep behaviors in children and adolescents. The CSHQ includes items related to a number of key sleep domains that represent typical sleep complaints in this age group (8).

The scores for each of the items are assigned corresponding to the number of times per week that the sleeping behavior occurs, between "3" (usually, 5 to 7 times), "2" (sometimes, 2 to 4 times), or "1" (rarely, 0 to 1 times). A number of items on the questionnaire are reverse-scored, so that higher scores consistently indicate problem behaviors.

Two additional items are added to the original CSHQ questionnaire to further characterize common MPS IIIA specific issues with sleep, i.e., disruptive behavior at night and dangerous behavior at night. This CSHQ will capture the child's sleep habits during the past week.

Items will be combined into 8 subscales. The total sleep disturbance score will be obtained with the sum of the score of all items of the 8 subscales. Note that a subscale score will only be calculated if at least 50% of the associated items are non-missing and the total sleep disturbance score will only be calculated if all subscales have at least 50% non-missing items. For the remaining missing values, each item will be imputed with the mean of the subscale.

The CSHQ will be completed at Baseline and prior to the infusions at Weeks 12 and 24. The CSHQ will be recorded in the eCRF. Changes from Baseline (as defined in 8.4.3) will be calculated at Week 12 and 24.

## 13.2 Secondary efficacy endpoints

### 13.2.1 Neurocognitive developmental age

The neurocognitive developmental age (months) will be derived on the basis of the BSID-III cognitive total score and BSID-III age-normative data.

The neurocognitive developmental age (months) will be derived from the mean AEq scores on the NVI of the KABC-II, where an AEq score is the average score for a particular age.

The DQ is calculated as the AEq for cognitive development divided by the chronological age for the child multiplied by 100, i.e.

$$DQ = 100*AEq / age$$

For patients completing an assessment of both BSID-III and KABC-II, the BSID-III score will be used as a basis for calculating the DQ of neurocognitive development at baseline. A calibration of overlapping AEq scores between BDID-III and KABC-II will be done to assess if a patient outgrows the BSID-III test during the duration of the study. If confirmed, assessments of KABC-II will form the basis for calculating DQ of neurocognitive development for remaining study assessments.

Changes from Baseline (as defined in Section 8.4.3) will be assessed at Week 24.

### 13.2.2 Adaptive behavior

The endpoint relating to the 5$^{th}$ secondary objective will be obtained with the adaptive behavior AEq as assessed by VABS-II (see Section 13.1.2). Change from Baseline (as defined in Section 8.4.3) will also be assessed at Week 24.

### 13.2.3 Magnetic resonance imaging

The endpoint relating to the 6$^{th}$ secondary objective will be obtained with the gray matter volume assessed by brain volumetric MRI. Changes from Baseline (as defined in Section 8.4.3) will be assessed at Week 24.

### 13.2.4 Quality of life and caregiver burden

The endpoint relating to the 7$^{th}$ secondary objective will be obtained with the parent proxy-report format of the PedsQL Version 4.0 used to assess the child's quality of life, and the family impact module of the PedsQL Version 2.0 used to assess the caregiver burden. The PedsQL version (i.e.,

infant/toddler/young children) will be selected on the basis of the chronological age of the patient. Both questionnaires will be recorded in the eCRF.

## 13.3 Exploratory efficacy endpoints

### 13.3.1 Adaptive behavior composite score

This endpoint will be obtained with the adaptive behavior composite score of VABS-II.

Change from Baseline will be assessed at Week 24.

### 13.3.2 Neurocognitive composite score

This endpoint will be obtained with the cognitive subtest score of BSID-III or the mental processing composite score as assessed by KABC-II.

Change from Baseline will be assessed at Week 24.

### 13.3.3 Language

Expressive and receptive language is assessed by the BSID-III language subtest score and the VABS-II communication domain score, respectively.

For patients being assessed with the KABC-II for cognition, language development is assessed by the subtest “Expressive Vocabulary” of the knowledge test.

In addition, written language is assessed by the AEq of subdomain “Written” in the communication domain of VABS-II.

Changes from Baseline will be assessed at Week 24.

### 13.3.4 Motor function

Fine and gross motor skills are assessed by the total scores of the BSID-III corresponding subtests of the motor function module, and by the AEq of the VABS-II motor skills domain.

Changes from Baseline will be assessed at Week 24.

### 13.3.5 Sleep pattern

The patients’ sleep pattern is evaluated using the CSHQ total score and by use of actigraphy.

An actigraph (ActiGraph GT9X Link) will be applied to the non-dominant wrist or ankle (9) and recordings will be made for 7 consecutive days and nights at Baseline and at Weeks 11 and 23. A daily wear time of 20 hours per day will be regarded as a compliant recording. The recording will be supported by an actigraph log, recorded in the eCRF.

The following parameters will be determined on the basis of recordings in the actigraph log:

- Bedtime (Clock time child is put to bed)
- Wake time (Clock time of child is taken out of bed)
- Time in bed (Time between Bedtime and Wake time)

The following variables are derived as obtained from the actigraph software:

- Sleep onset (Clock time for first appearance of a predetermined number of consecutive min of sleep)
- Sleep offset (Clock time for last of a predetermined number of consecutive min of sleep)
- Sleep period (Time between sleep onset and sleep offset)
- Total sleep time (TST, Duration of sleep in sleep period)
- Wake after sleep onset (WASO, number of minutes scored as wake during sleep period)
- Sleep efficiency (Percentage sleep: TST/time in bed)
- Night waking frequency (number of night wakings)
- Night waking duration (Sum of minutes scored as night waking)
- 24 h sleep duration (amount of sleep in a 24-h period)

Sleep onset latency is determined as Time between bedtime (as recorded on the actigraph log) and sleep onset (as captured by the actigraph software).

Changes from Baseline will be assessed at Week 12 and 24.

For more details regarding the methods used by the actigraph software please see the CSP for SOB003-001, Section 7.5.4.5.

### 13.3.6 Magnetic resonance imaging

As listed in Section 3.4.3, the MRI exploratory endpoints refer to compound ventricular volume, FA and MD in corpus callosum, FA and MD of cerebral white matter, SWI in cerebral white matter, and basal ganglia. Also liver and spleen volume are assessed by abdominal MRI.

Changes from Baseline (as defined in Section 8.4.3) will be assessed at Week 24.

## 13.4 Subgroup analyses

No subgroup analyses will be performed for any of the efficacy analyses.

# 14 Safety analyses

Safety data will be summarized descriptively by dose cohort using the SAF.

## 14.1 Drug exposure

Upon provision of signed informed consent, patients are assigned a patient number and allocated to a dose cohort in strict consecutive order. Thus, the first 3 enrolled patients are assigned to Cohort 1 and administrations of SOBI003 at 3 mg/kg/week; for Cohorts 2 and 3, dose levels of 10 mg/kg/week and 20 mg/kg/week are planned.

At the time of the 1st SOBI003 infusion, the patient should not have any clinically significant evidence of an ongoing infection, or an ongoing treatment with antibiotics. In such cases, the 1st infusion should be postponed until the infection has resolved.

SOBI003 is administered as weekly i.v. infusions over a period of time of 4 hours. The study treatment period comprises 24 weekly infusions. For each weekly visit, date and time of administration will be recorded in the eCRF, as well as reasons for infusion stop (if any), dose level, SOBI003 volume, total infusion volume administered, and dosing action taken (e.g., "withdrawn"). All data will be listed.

In addition, actual dose received in mg, actual dose level received in mg/kg (see Section 8.4.8), and study treatment exposure in weeks will be calculated (see Section 8.4.2). These data will be listed and summarized.

## 14.2 Adverse events

The primary endpoints are TEAEs and SAEs.

For the FIH study (SOBI003-001), all AEs (defined in CSP Section 7.5.5.1.1) occurring after the patient has received the 1st dose of investigational medicinal product and up to Day 7 of Week 24 (End of Study) will be recorded on the AE eCRF page.

For the FIH study, SAEs will be reported from the time the ICF is signed until 28 days past the last dose of study drug.

For patients continuing in the extension study (SOBI003-002), the period for recording AEs, including SAEs, on the eCRF begins Day 1 upon signing of the study ICF on Week 25 and ends Day 8 of Week 104 (End of Study) (see CSP Section 7.5.4.1.2). This includes all events observed/diagnosed or reported since the last visit of the FIH study (Week 24 / End of study).

For patients continuing in the extension study (SOBI003-002), any AEs and SAEs with onset after the 1st dose of study drug in the extension study will not be presented in the tables and listings of the FIH study but in the tables and listings of the extension study.

A TEAE is any AE with onset or worsening reported from the time that the 1st dose of study drug is administered until completion of or early termination of the study. In addition to TEAEs, SAEs with an onset date equal to or greater than the informed consent date of the FIH study and earlier than the start date of 1st dose of study drug (non-treatment emergent) will be collected and analyzed.

AEs with missing onset dates will be considered treatment-emergent, unless the stop date indicates otherwise. In the event that only a partial start date (month/year) is available, and

month/year occurs before that of 1st dose of study drug, the AE will be considered as non-treatment-emergent. If month/year occurs on, or after that of 1st dose of study drug, the AE will be considered as treatment emergent. If an AE has a partial missing start or stop date, the rules in Section 8.1 will be used to impute the date.

All AEs will be coded using MedDRA to give a PT and a SOC term for each event. The latest version of MedDRA will be used.

The severity grading is based on the national cancer institute common terminology criteria (NCI CTCAE) (version 4.03), see CSP Section 7.5.5.13.

If the causality assessment (related, not related) of a TEAE is missing, the event will be considered as drug-related following the worst case principle. Non-treatment emergent SAEs with missing causality assessment are considered not related.

An Infusion related reaction (IRR) has been defined as any AE occurring during an infusion or within 24 hours after end of infusion and which is considered related to SOBI003 treatment as judged by the investigator. IRRs may appear as symptoms such as rash, urticaria, erythema, emesis, loose stools, fever, alterations in heart rate, and blood pressure, but could also include other symptoms considered related to the infusion. Such symptoms (by PT and SOC) will be grouped into separate IRRs. There can be one IRR per infusion, in case several IRR symptoms are reported for one infusion they will be counted as one single IRR.

TEAEs will also be classified according to the patients ADA status (positive, negative, boosted, unknown) at the time of the AE occurrence.

All AEs will be summarized by dose cohort. The following analyses will be performed:

- Overall summary of AEs (overall, non-treatment emergent SAEs, TEAEs, drug-related TEAEs, non-serious TEAEs, serious TEAEs, serious drug-related TEAEs, TEAEs leading to study and/or treatment withdrawal, drug-related TEAEs leading to study and/or treatment withdrawal, serious TEAEs leading to study and/or treatment withdrawal, TEAEs leading to death, IRRs)
- Overall summary of IRRs (overall, serious IRRs, IRRs leading to study and/or treatment withdrawal). There can be one IRR per infusion, in case several IRR symptoms are reported for one infusion they will be counted as one single IRR.
- TEAEs by SOC and PT
- TEAEs by SOC and PT and by maximum CTCAE grade
- Drug-related TEAEs by SOC and PT
- Drug-related TEAEs by SOC and PT by maximum CTCAE grade
- Serious TEAEs by SOC and PT
- Serious TEAEs by SOC and PT by maximum CTCAE grade
- Serious drug-related TEAEs by SOC and PT
- Serious drug-related TEAEs by SOC and PT by maximum CTCAE grade
- TEAEs leading to study and/or treatment withdrawal by SOC and PT
- TEAEs leading to study and/or treatment withdrawal by SOC and PT by maximum CTCAE grade

- Drug-related TEAEs leading to study and/or treatment withdrawal by SOC and PT
- Drug-related TEAEs leading to study and/or treatment withdrawal by SOC and PT by maximum CTCAE grade
- TEAEs by SOC and PT and by ADA status
- IRR symptoms by SOC and PT
- IRR symptoms by SOC and PT by maximum CTCAE grade
- Serious IRR symptoms by SOC and PT
- Serious IRR symptoms by SOC and PT by maximum CTCAE grade
- IRR symptoms leading to study and/or treatment withdrawal by SOC and PT
- IRR symptoms leading to study and/or treatment withdrawal by SOC and PT by maximum CTCAE grade
- Frequency of IRR symptoms resolved within 24 hours.

For each SOC and PT, summaries will be made with respect to the proportion of patients having a least one occurrence of that event and the total number of events, with the exception of tables by maximum CTCAE grade (which include only the proportion of patients having at least one occurrence of that event). Tables will be sorted alphabetically, first by SOC and then by PT.

### 14.2.1 Serious adverse events

All serious TEAEs will be presented in a summary table by SOC, PT, and maximum CTCAE grade (see paragraph above). In addition to the summary tables, a detailed listing of all SAEs will be provided in CSR Section 14.3.2.

### 14.2.2 Adverse events leading to withdrawal

All AEs collected with a study medication action taken as “withdrawn” will be presented in a summary table by SOC, PT, and maximum CTCAE grade (see Section 14.2). In addition to the summary tables, a detailed listing of all TEAEs leading to study drug discontinuation will be provided in CSR Section 14.3.2.

### 14.2.3 Deaths

All patient deaths during this study will be presented in a data listing, which will be provided in CSR Section 14.3.2. Data presented will include date of death, date of last visit, date of 1$^{st}$ dose, days from 1$^{st}$ dose until death, date of last dose, number of days from last dose of study drug to death, number of AEs (if applicable), cause of death, and relationship of cause of death to study drug.

### 14.2.4 Infusion related reaction symptoms

For the overall summary of AEs as well as the overall summary of IRRs several IRR symptoms reported for one infusion will be grouped into one single IRR and counted as one event.

All individual IRR symptoms will be presented in a summary table by SOC, PT, and maximum CTCAE grade (see paragraph above). Summary tables by SOC, PT, and maximum CTCAE grade will also be provided for all IRR symptoms leading to study and/or treatment withdrawal and all serious IRR symptoms. Also, the frequency of IRR symptoms resolved within 24 hours will be presented.

In addition to the summary tables, a detailed listing of all IRR symptoms will be provided in CSR Section 14.3.2.

## 14.3 Vital signs

Vital signs (systolic and diastolic blood pressure, heart rate, body temperature, respiratory rate, and oxygen saturation measured with pulse oximetry) are the 1st secondary endpoint related to the primary objective of this study and are measured at the screening visit and at each infusion.

At Weeks 1 to 8, assessments will be performed at pre-infusion, 1 hour (+/- 5 minutes), 2 hours (+/- 5 minutes) and 3 hours (+/- 5 minutes) after start of infusion, within 1 hour after end of infusion, within 6 to 7 hours after start of infusion, within 8 to 12 hours after start of infusion, and on Days 2 and 3. In addition, at Weeks 1 and 2 the assessments are also done on Day 5.

At Weeks 9 to 24, assessments will be performed at pre-infusion, 2 hours (+/- 5 minutes) after start of each infusion and within 1 hour after end of each infusion. At Weeks 12 and 24, the assessments are also done on Day 3.

In case of prolonged SOBI003 infusions (i.e., > 4 hours) and regardless of which Study Week, the assessment schedule should be adjusted so that vital signs are assessed every hour during infusion and within an hour of completion of the infusion. After completed SOBI003 infusion, vital signs are also assessed on Days 2 and 3 (where Day 1 equals the start of the SOBI003 infusion). Depending on the duration of the infusion, the assessment at 8 to 12 hours after start of infusion may also apply. In case of need to prolong infusions (i.e., > 4 hours) at any time during the study, pulse oximetry monitoring will be applied, as judged by the investigator.

Vital signs values will be listed and summarized descriptively by visit and time point including changes from Baseline.

## 14.4 Laboratory data

Laboratory safety variables are the 2nd secondary endpoint related to the primary objective of this study. Clinical chemistry, hematology, coagulation and urine analyses are conducted at a central laboratory (BARC). The time points for sample collection are described in Table 6, together with the analyses performed at each sampling occasion.

**Table 6 Safety laboratory assessment time points**

| Analyses | Study visit | Sampling time point(s) |
|---|---|---|
| **Clinical chemistry (1.5 mL blood):** Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total bilirubin (if >upper limit of normal [ULN] then also direct and indirect bilirubin), Creatinine, Albumin, Potassium (K), Sodium (Na), Calcium (Ca), non-fasting Glucose, and C-reactive protein (CRP).<br>**Hematology (0.5 mL blood):** Hemoglobin (Hb), Erythrocytes, White blood cell count (WBC), Differential blood count and Platelet count.<br>**Coagulation (1.7 mL):** PT/INR, APTT, and Fibrinogen.<br>**Urinalysis** (dip-stick analyses, central laboratory): pH, Glucose, Proteins, and Blood | Screening | |
| | Weeks 1 to 3 | pre-infusion (Day 1) and Day 3 |
| | Weeks 4 to 8 | pre-infusion |
| | Weeks 10, 12, 14, 16, 18, 20, and 22 | pre-infusion |
| | Week 24 | Day 3 |
| C-reactive protein (CRP), IL-1ra, TNFα, IgE, and tryptase (6.4 mL blood) | Baseline | |
| | In case of infusion/anaphylactic reaction | |

Clinical laboratory values will be listed and summarized descriptively by visit and time point including changes from baseline. A separate listing will be provided for abnormal results. Shift tables will be used to evaluate categorical changes from Baseline to End of Study visit by examining the proportion of patients whose test values are outside the normal ranges. Patient plots will illustrate laboratory results for each parameter graphically.

## 14.5 Immunogenicity

Serum samples are collected at Baseline (same time as the CSF sample is collected) and prior to start of SOBI003 infusion at Weeks 2, 4, 8, 12, 16, 20, and 24, and if applicable at Early Termination of SOBI003 treatment, CSF samples (0.5 mL) are collected at Baseline and at Weeks 12 and 24.

The analysis of immunogenicity will in general be based on the immunogenicity analysis set. In case any patient has missing baseline, all immunogenicity analyses without considering baseline will be performed on a second immunogenicity analysis set including all patients with sufficient blood samples for ADA testing (i.e. including those with missing baseline).

The analyses of PK by ADA status at baseline will be based on the PKAS.

The following definitions will apply as defined in the harmonized terminology for immunogenicity (10):

- Evaluable patient: A patients with at least 1 sample taken after study drug administration that is appropriate for ADA testing (with reportable result).
- ADA-positive sample: When ADA is detected in a sample, the sample is considered positive.
- Baseline ADA: Pre-existing antibodies detected at baseline.
- Treatment induced ADA: de novo development following administration of study drug (i.e., formation of ADA any time after the initial study drug administration in a patient without preexisting ADA).
- Treatment boosted ADA: Baseline ADA boosted to higher level following study drug administration (i.e., at any time after the initial study drug administration the ADA titer is greater than the baseline titer by a factor of four).
- ADA-positive patient: A patient with at least 1 treatment-induced or treatment-boosted ADA-positive sample at any time during the treatment or follow-up observation period.
- ADA-negative patient: A patient without a treatment induced or treatment-boosted ADA-positive sample during the treatment or follow-up observation period.
- Baseline ADA positive patient: A patient with ADA at baseline. Such patient can have treatment boosted ADA after dosing.

Note that the requirement for inclusion in the immunogenicity set of at least 1 post-dose ADA assessment means that all patients in the immunogenicity set are “evaluable patients”.

The immunogenicity data will be listed for each patient and individual patient plots of titer measurement over time presented. Titer measurements will be summarized by visit using descriptive statistics by dose cohort and overall. Immunogenicity will be evaluated in regards antibody prevalence (pre-existing antibodies), antibody incidence, titer and boosting following dosing, impact on PK and PD responses.

A summary of ADA positive patients over time will be presented. For each visit this will summarize the number of patients who were ADA positive (treatment induced or treatment boosted ADA). A summary of ADA change from baseline immune response will be presented, summarizing the overall ADA incidence (number of ADA positive patients) as well as the numbers of patients for whom this was treatment induced ADA and treatment boosted ADA, together with summaries of titer.

Figures for each patient will be produced with titer and TEAEs plotted against time with ADA status (positive, negative, boosted) will be marked as well.

## 14.6 CRIM status

At the Baseline visit, a skin biopsy is obtained for isolation of fibroblasts for assessment of cross reactive immunological material (CRIM) status at the central laboratory. The biopsy should preferably be obtained at least 2 weeks prior to the 1$^{st}$ SOBI003 infusion.

CRIM status values will be listed and summarized.

## 14.7 ECG

12-lead Electrocardiograms (ECG) are obtained at Screening and at Weeks 1 to 4, 6, 8, 12, and 24. During the treatment period, ECGs are obtained pre-infusion and within an hour after end of infusion, i.e., 4 to 5 hours after start of the infusion.

ECG values will be listed and number and percentage of patients with normal and abnormal results will be summarized by visit and time point.

## 14.8 Other safety assessments

### 14.8.1 Echocardiography

At screening and Week 24, an echocardiography is performed to determine if there are any cardiac safety concerns that would prevent the patient from participating in the study.

These measurements will be listed and number and percentage of patients with normal and abnormal results will be summarized.

### 14.8.2 Physical examination and anthropometry

The physical examination will be performed at Screening, Baseline and at completion of the Week 24 visit.

At Weeks 1 to 4, general appearance and skin at the infusion site are examined prior to start of each infusion, 1 hour (+/- 5 minutes), 2 hours (+/- 5 minutes) and 3 hours (+/- 5 minutes) after start of infusion, within 1 hour after end of infusion, and 6 to 7 and 8 to 12 hours after start of infusion. At Weeks 1 and 2, the examinations are repeated on Days 2, 3, and 5. At Weeks 3 and 4, the examinations are repeated on Days 2 and 3.

At Weeks 5 to 24, general appearance and skin at the infusion site are examined prior to start of each infusion and within 1 hour after end of infusion.

Physical examination data will be listed and number and percentage of patients with normal and abnormal results will be summarized by visit and time point.

Weight is assessed at Screening, Baseline, every 4 weeks during the treatment period in order to determine the actual SOBI003 dose to be administered, and at completion of the Week 24 visit. Weight is hence obtained prior to start of infusion at Weeks 1, 5, 9, 13, 17, and 21. The body weight is obtained either on the day prior to the infusion or the day of infusion, BMI is calculated (see Section 8.4.7).

Height and head circumference are assessed at Baseline, at Week 12 and at completion of the Week 24 visit (if applicable, also at ET of SOBI003 treatment).

Anthropometric measurements will be listed and summarized by visit, including change from baseline.

### 14.8.3 Neurological examination

At Screening and at completion of the Week 24 visit (if applicable, also at Early Termination of SOBI003 treatment), a pediatric neurologist conducts an applicable age-related neurological examination including:

- Cranial Nerves
- Cerebellar function
- Sensory function
- Reflexes
- Motor function

Normal/abnormal status will be captured, and any abnormalities will be specified. Number and percentage of patients with normal and abnormal status will be summarized; all data will be listed.

# 15 Pharmacokinetic analyses

## 15.1 Secondary pharmacokinetic endpoint analyses

The PKAS will be used for PK analyses including PK parameter calculations, graphical displays of individual and mean data, and the listings and summarization of PK parameters. Patients with missing PK parameters due to unreliable or missing data will be flagged and excluded from summarization.

The SAF will be used for listing of PK concentrations for all patients who received any amount of IMP. The protocol deviations including the deviations leading to patient's exclusion from PKAS will be shown as flags in the listing.

## 15.2 Serum PK sampling schedule

**Table 7 Detailed PK blood sampling schedule**

| Week | Time | BW ≥20 kg No of samples[a] | BW ≥15 kg No of samples[a] | BW ≥10 kg No of samples[a] |
|---|---|---|---|---|
| | **Screening** | 1 | 1 | 1 |
| | **Baseline** | 1 | 1 | 1 |
| **Week 1** | **4h / End of Infusion** | 2 | 2 | 2[c] |
| | **6h** | 2 | | |
| | **12h** | 2 | | |
| | **24h** | 2 | 2 | |
| | **48h** | 1 | | |
| | **72h**[b] | 1 | 1 | |
| | **96h**[b] | 1 | 1 | |
| | **120h** | 1 | 1 | |
| **Week 1 (2)** | **168h/Pre-infusion** | 1 | 1 | 1 |
| | **4h / End of Infusion** | 2 | 2 | |
| **Week 3** | **Pre-infusion** | 1 | 1 | |
| | **4h / End of Infusion** | 2 | 2 | |
| **Week 4** | **Pre-infusion** | 1 | 1 | 1 |
| | **4h / End of Infusion** | 2 | 2 | 2 |
| | **6h** | 2 | 2 | |
| | **12h** | 2 | 2 | |
| | **24h** | 2 | 2 | 2 |
| | **48h** | 1 | 1 | |
| | **72h**[b] | 1 | 1 | 1 |
| | **96h**[b] | 1 | 1 | 1 |
| | **120h** | 1 | 1 | |
| **Week 4 (5)** | **168h/ Pre-infusion** | 1 | 1 | 1 |
| **Week 8** | **Pre-infusion** | 1 | 1 | 1 |
| | **4h / End of Infusion** | 2 | 2 | 2 |
| **Week 12** | **Pre-infusion** | 1 | 1 | 1 |
| | **4h / End of Infusion** | 2 | 2 | 2 |
| | **6h** | 2 | 2 | |
| | **12h** | 2 | 2 | |
| | **24h** | 2 | 2 | 2 |
| | **48h** | 1 | 1 | |

| Week | Time | BW ≥20 kg No of samples[a] | BW ≥15 kg No of samples[a] | BW ≥10 kg No of samples[a] |
|---|---|---|---|---|
| | **72h**[b] | 1 | 1 | 1 |
| | **96h**[b] | 1 | 1 | 1 |
| | **120h** | 1 | 1 | |
| | **168h** | 1 | 1 | 1 |
| **Week 16** | **Pre-infusion** | 1 | 1 | 1 |
| | **4h / End of Infusion** | 1 | 1 | 1 |
| | **168h** | 1 | 1 | 1 |
| **Week 20** | **Pre-infusion** | 1 | 1 | 1 |
| | **4h / End of Infusion** | 1 | 1 | 1 |
| | **168h** | 1 | 1 | 1 |
| **Week 24** | **Pre-infusion** | 1 | 1 | 1 |
| | **4h / End of Infusion** | 2 | 2 | 2 |
| | **6h** | 2 | 2 | |
| | **12h** | 2 | 2 | |
| | **24h** | 2 | 2 | 2 |
| | **48h** | 1 | 1 | |
| | **72h**[b] | 1 | 1 | 1 |
| | **96h**[b] | 1 | 1 | 1 |
| | **120h** | 1 | 1 | |
| | **168h** | 1 | 1 | 1 |

a If Number = 1; PK blood sample is collected from central venous access port. If Number =2; One PK sample will be collected from the central venous access port and one PK sample will be collected from a peripheral venous line. At the Screening visit 1; from peripheral venous line as no central access port has yet been placed.

b If infusion is prolonged, PK samples will be collected 2h and 8h after End of infusion. Thereafter PK sampling will be conducted according to ordinary PK sampling schedule (refer to CSP Section 7.5.6.1).

## 15.3 Serum PK endpoints

The following parameters will be derived:

- Serum SOBI003 PK parameters at Weeks 1, 4, 12, and 24 and as applicable at Weeks 16 and 20; $t_{end\ of\ inf}$, $C_{end\ of\ inf}$, $C_{max}$, $t_{max}$, $C_{pre\text{-}dose}$, $C_{trough}$, CL, $AUC_{0\text{-}168h}$, $t_{1/2}$

Other parameters may be derived such as accumulation ratios $R_{Cmax}$, $R_{Ctrough}$, $R_{AUC0\text{-}168h}$, fluctuation%, etc.

## 15.4 CSF PK endpoints

- CSF SOBI003 concentration at Baseline, Weeks 12 and 24

- Ratio of SOBI003 CSF concentration/SOBI003 serum concentration Week 12 and 24: (SOBI003 concentration CSF / SOBI003 concentration serum)*100 (%)

## 15.5 Presentation of concentration data in serum and CSF

### 15.5.1 Handling of missing data

Missing concentration data for all patients who are administered scheduled study treatment will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the derivation of the area under the curve (AUC) and for the individual serum concentration versus time curves, the following rules will apply:

- Concentration values below the assay's lower limit of quantification (LLOQ) in pre-dose samples and in samples taken before the time of the 1st quantifiable concentration will be treated as zero; except for the log-transformed concentrations for graphs, where concentration values below the assay's LLOQ in pre-dose samples will be set to LLOQ/2;
- The sampling time of pre-dose samples relative to dosing will also be treated as zero;
- In case a concentration value pre-dose is not available, the concentration value collected at screening may be used for derivation of AUC;
- Post-dose below LLOQ values after the 1st quantifiable time point will be set to missing;
- Samples taken outside the sampling windows may be excluded from by-time point summary statistics; this will be determined prior to database lock.

For serum concentration summary, the following rules will apply:

- Serum concentrations below LLOQ in pre-dose samples and in samples taken before the time of the 1st quantifiable value will be set to zero;
- The serum concentrations below LLOQ after quantifiable concentration will set to missing.

For CSF concentration summary, the following rules will apply:

- CSF concentrations below LLOQ in the pre-dose samples taken before the time of the 1st quantifiable value will be set to zero;
- The CSF concentrations below LLOQ after quantifiable concentration will be summarized.

No further imputation will be applied to any missing values.

### 15.5.2 Listing and Presentation of individual PK data

PK concentrations in serum and CSF will be listed for SAF. Flags will be used to show deviations from protocol with the explanation in the footnote.

The actual sampling time of PK blood or CSF sample collection, in relation to start of administration of dose, will be listed for each treatment and will include the deviation in time from the protocol scheduled time, if applicable.

Individual subject serum and CSF concentration data will be listed by subject, time point and SOBI003 dose (mg/kg). Individual subject PK parameters will be listed for the PKAS by subject and will be summarized by treatment group/cohort. Unreliable PK parameters will be listed but flagged and excluded from summary.

The following figures will be produced for individual data for SOBI003:

- Individual serum concentration-time profiles will be presented for each dose level with all patients in the same figure on linear and log-linear scales vs actual time for Weeks 1, 4, 12, and 24. Profiles for patients within the same treatment will be combined.
- Individual trough and end-of-infusion serum concentrations vs dose number for all Weeks combined. Profiles for patients within the same cohort will be combined.
- Scatter plots of CSF concentrations for Weeks 12 and 24 for different treatments.

### 15.5.3 Summary of serum and CSF PK concentrations

PK results, i.e., SOBI003 concentrations in serum and CSF and PK parameters in serum and CSF, will be presented by dose level using descriptive statistics. In addition, results will be presented by demographic characteristics, e.g., age-group and bodyweight, as applicable.

PK serum and CSF concentration data will be summarized by treatment using the following descriptive statistics: n, number and % LLOQ, arithmetic mean, SD, CV%, minimum, median and maximum.

Mean serum concentrations will not be presented if 1 or more out of 3 patients of the actual values at any one time point in the terminal phase are LLOQ or missing.

Samples taken outside the allowed time windows may be excluded from summarization. This will be determined prior to database lock.

Mean ± SD serum concentration-time profiles will be presented, combining the curves for all dose levels within the same figure, on linear and log-linear scales vs nominal time.

Mean ± SD trough and $C_{End\ of\ inf}$ or $C_{max}$ serum concentrations and dose number for all cycles combined. Profiles for cohorts with different dose levels will be combined.

### 15.5.4 PK parameters derivation

The PK parameters will be estimated as follows:

- The apparent $C_{max}$ and the corresponding $T_{max}$ will be read directly from the concentration-time plot (observed data).
- $AUC_{last}$ is calculated using the log-linear trapezoidal interpolation rule for intravenous model.

Terminal elimination parameters, elimination rate constant and $t_{1/2}$, will be derived as below if sufficient data are available.

The terminal elimination rate constant ($\lambda z$) will be determined by log linear regression obtained on at least the 3 last quantifiable concentrations and will not include $C_{max}$;

$t_{1/2}$ is calculated by the program as $\ln 2/\lambda z$;

The $AUC_{0\text{-}inf}$ is calculated by the program as:

$AUC_{0\text{-}inf} = AUC_{last} + AUC_{extrap}$ where last is the sampling time point of the last measurable concentration ($t_{last}$). $AUC_{extrap}$ is calculated by the program as: $C_{last}/\lambda z$, where $C_{last}$ is the observed concentration at time $t_{last}$ and $\lambda z$ is the elimination rate constant during the apparent terminal elimination phase; $AUC_{0\text{-}inf}$ will only be presented for patients with a reliable $\lambda z$;

For single-dose, CL is calculated by program as (dose/$AUC_{0\text{-}inf}$) and for multiple-dose, CL is calculated by program as (dose/$AUC_{0\text{-}168h}$);

V is calculated by the program as (dose/$AUC_{0\text{-}inf}$)/$\lambda z$;

Fluctuation % is calculated by the program as $100\times((C_{max}-C_{min})/C_{avg})$.

The following PK acceptance criteria will be considered to when the reliability of elimination parameters are assessed:

- Number of points to calculate $\lambda z$ is greater than or equal to 3 excluding $C_{max}$ point;
- Interval for calculation of $\lambda z$ is longer than half-life;
- The adjusted square of the correlation coefficient (Rsquare adjusted) for the goodness of fit of the regression line through the data points must be $\geq 0.75$;
- $AUC_{extrap} \leq 30\%$.

However, less strict acceptance criteria may be applied, in exceptional cases, since the number of PK samples are limited. PK parameters may be calculated and reported even if the strict criteria are not fulfilled. When PK parameters are based on less strict criteria, this will be described on an individual level.

Accumulation ratios will be calculated as ratio of PK parameters ($C_{max}$, $C_{min}$, $C_{End\ of\ inf}$, $AUC_{0\text{-}168h}$) for the last vs 1st dose.

### 15.5.5 PK parameters summarization

**Table 8 SOBI003 PK Summary Statistics**

| Variable | Summarized with: |
|---|---|
| $AUC_{0\text{-}168h}$, $C_{max}$, $C_{end\ of\ inf}$, $C_{pre\text{-}dose}$, $C_{trough}$, CL, $R_{Cmax}$, $R_{Ctrough}$, $R_{AUC0\text{-}168h}$, fluctuation% | n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV% |
| $t_{1/2}$, and $\lambda z$ | n, arithmetic mean, SD, CV%, minimum, median, maximum |

| Variable | Summarized with: |
|---|---|
| $t_{max}$, $t_{end\ of\ inf}$, $t_{last}$ (actual time) | n, minimum,Q1, median, Q3 and maximum |

$AUC_{0\text{-}168h}$ = area under the serum concentration-time curve from time 0 to 168 hours after dose; $C_{end\ of\ inf}$ = observed serum concentration at the end of infusion of SOBI003; CL = clearance; $C_{max}$ = maximum observed serum concentration; $C_{pre\text{-}dose}$ = observed serum concentration immediately before the start of infusion of SOBI003; $C_{trough}$ = minimum observed serum concentration; CV = coefficient of variation; $R_{Cmax}$ = $C_{max}$ accumulation ratio; $R_{CTrough}$ = $C_{trough}$ accumulation ratio; $R_{AUC0\text{-}168h}$ = $AUC_{0\text{-}168h}$ accumulation ratio; SD = standard deviation; $t_{end\ of\ inf}$ = time of the end of the infusion of SOBI003; $t_{last}$ = time of the last measurable concentration; $t_{max}$ = time at which the maximum serum concentration is observed; $t_{1/2}$ = half-life; $\lambda z$ = terminal elimination rate constant.

The following conventions will be used for the presentation of the descriptive statistics of PK parameters and of serum concentrations:

**Table 9 PK Reporting Precision**

| Statistics | Degree of Precision |
|---|---|
| Minimum, Maximum | 3 significant digits or as needed based on actual measured values (for example PK concentrations) |
| Mean (arithmetic and geometric), Median | 4 significant digits |
| Standard deviation | 5 significant digits |
| CV and Geometric CV | 1 decimal point |

CV = coefficient of variation

## 15.6 Attainment of steady state for SOBI003

Aggregate assessment of trough concentrations by repeated measures analysis of variance (ANOVA) may be used to evaluate attainment of steady state and determine the dose number to achieve steady state for SOBI003 (11). The approach is based on the comparison of log-transformed trough concentration values for each dose to the mean of the results for all the following doses.

If data are sufficient to support the analysis, repeated measures analysis will be carried out on log-transformed $C_{trough}$ (pre-infusion concentrations) for Week 2 through Week 24 for each infusion where data available. The following SAS code will be used to conduct the repeated measurement analysis:

PROC MIXED

CLASS dose patient;

MODEL log$C_{min}$ = dose;

REPEATED / TYPE=UN SUBJECT=patient;

RUN;

The trough concentrations observed after Week 2 through Week 24 for SOBI003 for each infusion will be compared with the average trough levels for the rest of the period to determine the time at which steady state was achieved. Contrasts will be tested between a time point and the pooled mean over all remaining time points, such as:

Week 2 pre-infusion value vs. the average of Weeks 2 through 24

Week 3 pre-infusion value vs. the average of Weeks 4 through 24

…

Week 8 pre-infusion value vs. the average of Weeks 12 and 24

Week 12 pre-infusion value vs. the Week 24

The first non-significant comparison will be concluded to be the dosing interval at which steady state concentrations are attained. The p-value for difference of least square means (LSM), LSM ratio, and the 90% confidence interval (CI) for the contrasts will be provided.

Additionally, steady state will be assessed using a mixed model (12) with repeated measures performed on $C_{min}$ ss including dosing interval (Week 2 through Week 24 for SOBI003) as a covariate and subject as a random effect. A random slope effect for dosing interval will also be included. The linear effect of dosing interval on the $C_{min}$ ss over time will be used to assess the assumption of steady state.

```
PROC MIXED data=cminDATASET;
CLASS subject ;
MODEL log_Cmin_ss = doseno / ddfm=kr;
RANDOM intercept doseno  /subject= subject;
RUN;
```

The DDFM = KR (KenwardRoger) option performs the degrees-of-freedom calculations detailed by Kenward and Roger (1997) (13). As recommended, the denominator degrees of freedom for the fixed effects will be estimated as the most appropriate method in the mixed-model analysis.

## 15.7 Assessment of Dose Proportionality for SOBI003

Exploratory dose proportionality will be analyzed with the method originally described by Gough et al. (1995) (14) and modified as described by Smith et al. (2000) (15) and further adapted by Hummel et al. (2009) (16).

$C_{end\ of\ inf}$, $AUC_{0\text{-}168h}$ will be analysed, and depending on the results other parameters may be analysed such as $C_{max}$, $C_{min}$ and $AUC_{0\text{-}inf}$ may also be analyzed. The general model log ($C_{max}$, $C_{min}$, $C_{end\ of\ inf}$, $AUC_{0\text{-}168h}$, $AUC_{0\text{-}inf}$ for all doses and cycles where available) = $\mu$+ ß log (dose) will be used to investigate the null hypothesis (H0: ß=1). Dose-proportionality will be rejected if the 90% CI of the estimated slope falls outside the critical interval. Patient's weight or age may be included as covariate.

The critical interval will be calculated as follows:
First the ratio (r) of the highest dose level to the lowest dose level will be calculated.
The lower limit of the critical interval will be calculated as: Log (0.5)/log(r) + 1.
The upper limit of the critical interval will be calculated as: Log (2.0)/log(r) + 1.

r value is based on the ratio between highest and lower dose levels of SOBI003 and equals to 20 / 3 mg/kg = 6.667

Thus, critical interval to declare dose linearity will be 0.63 to 1.37 for 90% CI of the slope estimate.

Additionally, PK parameters $C_{max}$, $C_{min}$, $C_{End\ of\ inf}$, $AUC_{0\text{-}168h}$, $AUC_{0\text{-}inf}$ with total dose and body weight adjusted dose will be investigated using Pearson correlation analysis to estimate which type of dosing has an effect on pharmacokinetics of SOBI003.

The FISHER option in the PROC CORR statement will be used to estimate confidence limits and p-values for Pearson correlation coefficients based on Fisher's z transformation. Alpha value and a null hypothesis value will be specified for 95% two-sided CI.

The formula for sample Pearson product-moment correlation is:

$$r_{xy} = \frac{\sum_i (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_i (x_i - \bar{x})^2 \sum_i (y_i - \bar{y})^2}}$$

Fisher z transformation is calculated as $z = 0.5\log_e\left(\frac{1+r}{1-r}\right)$

CIs in addition to p-value will be calculated to demonstrate the validity of correlation.

Dose proportionality will also be explored graphically with plots of $C_{max}$, $AUC_{last}$ and $AUC_{inf}$ vs body weight adjusted dose (mg/kg) or total dose (mg).

Dose proportionality plots will be presented for SOBI003 $C_{max}$, $C_{min}$, $C_{end\ of\ inf}$, $AUC_{0\text{-}168h}$, $AUC_{0\text{-}inf}$. Regression/scatter plot in log-log and linear scales of PK parameters vs dose levels including body weight normalized and total dose will be presented.

# 16 Pharmacodynamic analyses

## 16.1 Secondary pharmacodynamic endpoint analyses

Serum and urine sampling for HS quantification will be performed at Baseline, Weeks 2, 3, 4, 8, 12, 16, 20, and 24 or at ET. CSF sampling for HS concentrations will be performed at Baseline, Weeks 12 and 24 or at ET.

## 16.2 Presentation of concentration data for HS in serum, urine, and CSF

### 16.2.1 Handling of missing data

Missing concentration data for all patients will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For concentration summary in all matrices, the following rules will apply:

- LLOQ values for HS concentrations in all matrices will be imputed as 0 for all time points where observed.

No further imputation will be applied to any missing values.

### 16.2.2 Listing and Presentation of individual PD data

HS concentrations in serum, urine, and CSF will be listed for SAF. The same listings will also contain change from baseline values for all time points. Baseline will be defined as HS concentration in each matrix before the administration of the 1st dose of SOBI003. Flags will be used to show deviations from protocol with the explanation in the footnote.

The actual sampling time of PD serum, urine or CSF sample collection will be listed for each treatment and will include the deviation in time from the protocol scheduled time, if applicable.

Individual subject serum, urine and CSF concentration data will be listed by subject, age, body weight, gender, time point and treatment (in relevant concentration units). The following figures will be produced for individual data for SOBI003:

- Individual serum and urine HS concentration-time profiles will be presented, for each treatment with all patients in the same figure on linear scale vs Week number. Profiles for patients within the same treatment will be combined.
- Scatter plots of HS concentrations in CSF for Weeks 12 and 24 for different treatments.

### 16.2.3 Summary of HS concentrations in serum, urine, and CSF

HS serum, urine, and CSF concentration data will be summarized by treatment using the following descriptive statistics: n, number and % of LLOQ, arithmetic mean, SD, CV%, minimum, median and maximum, Q1 and Q3. In addition, results will be presented by demographic characteristics, e.g., age group and bodyweight, as applicable.

Samples taken outside the allowed time windows may be excluded from summarization. This will be determined prior to database lock.

Mean ± SD HS concentrations in serum, urine and CSF vs Week number profiles will be presented, combining the curves for all dose levels within the same figure.

The HS levels including change from baseline will also be summarized by visit and time point using descriptive statistics. The HS change from baseline will also be presented as percentages.

The conventions presented in Table 9 for PK parameters will also be used for the presentation of the descriptive statistics of HS serum concentrations.

# 17 Changes from protocol

- Schedule of events tables Table 1, Table 2, Table 3, and Table 7 have been updated according to protocol clarification letters
- According to the protocol linear mixed models were planned to be used to assess the PD effect of different dose levels of SOBI003 on HS levels in CSF, serum, and urine. Because of the discontinuation of the program modelling will be not be performed.

# 18 References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15 Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. CI criteria for assessment of dose proportionality, Pharmaceut. Res. 2000; 17: 1278-1283.

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# 19 Data presentation

Footnotes will be used to clarify ambiguities (e.g., the denominator used to calculate a percentage) and abbreviations. The tables and listings will be presented in A4 landscape, in a fixed font (Courier New) with a size as 8.

## 19.1 Listings Index

The numbering of the listings will be such that they can be easily integrated into the CSR following ICH E3, Section 16.2.

### 16.2 PATIENT DATA LISTINGS

**16.2.1 Patient Disposition**

| | |
|---|---|
| Listing 16.2.1.1 | Patient Disposition (Part 1) – Screened Patients |
| Listing 16.2.1.2 | Patient Disposition (Part 2) – Screened Patients |
| Listing 16.2.1.3 | Patient Disposition – Screen Failures |

**16.2.2 Protocol Deviations**

| | |
|---|---|
| Listing 16.2.2.1 | Protocol Deviations – Safety Analysis Set |

**16.2.3 Patients Excluded from the Analysis Sets**

| | |
|---|---|
| Listing 16.2.3.1 | Violated Inclusion Criteria – Safety Analysis Set |
| Listing 16.2.3.2 | Fulfilled Exclusion Criteria – Safety Analysis Set |
| Listing 16.2.3.3 | Exclusion from Analysis Sets – Safety Analysis Set |

**16.2.4 Demographic Data**

| | |
|---|---|
| Listing 16.2.4.1 | Demographics – Safety Analysis Set |
| Listing 16.2.4.2 | MPS III History of Siblings – Safety Analysis Set |
| Listing 16.2.4.3 | Historical MPS IIIA Diagnostic Procedures – Safety Analysis Set |
| Listing 16.2.4.4 | Central Laboratory Confirmation of MPS IIIA – Safety Analysis Set |
| Listing 16.2.4.5 | Central Laboratory Confirmation of MPS IIIA SGSH – Safety Analysis Set |
| Listing 16.2.4.6 | Medical History – Safety Analysis Set |
| Listing 16.2.4.7 | Prior and Concomitant Medication – Safety Analysis Set |
| Listing 16.2.4.8 | Antihistamine – Safety Analysis Set |
| Listing 16.2.4.9 | Anesthesia/Sedation – Safety Analysis Set |

**16.2.5 Compliance**

| | |
|---|---|
| Listing 16.2.5.1 | Study Drug (SOBI003) Administration – Safety Analysis Set |
| Listing 16.2.5.2 | Study Drug (SOBI003) Administration: Vial Numbers – Safety Analysis Set |

**16.2.6 Individual Efficacy Response Data**

| | |
|---|---|
| Listing 16.2.6.1 | Vineland adaptive behaviour scales, second edition (VABS)-II – Full Analysis Set |
| Listing 16.2.6.2 | Bayley Scales of Infant and Toddler Development, third edition (BSID-III) – Full Analysis Set |
| Listing 16.2.6.3 | Kaufman Assessment Battery for Children (KABC-II) – Full Analysis Set |
| Listing 16.2.6.4 | Magnetic Resonance Imaging (MRI) – Full Analysis Set |
| Listing 16.2.6.5 | Pediatric Quality of Live Inventory (PedsQL) – Full Analysis Set |
| Listing 16.2.6.6 | Children's Sleep Habits Questionnaire (CSHQ) – Full Analysis Set |
| Listing 16.2.6.7 | Actigraphy (sleep pattern) – Full Analysis Set |

**16.2.7 Adverse Events Listings**

| | |
|---|---|
| Listing 16.2.7 | All Adverse Events – Safety Analysis Set |

**16.2.8.1 Listing of individual laboratory measurements by patient**

| | |
|---|---|
| Listing 16.2.8.1.1 | Laboratory Reference Ranges – Safety Analysis Set |
| Listing 16.2.8.1.2 | Clinical Chemistry – Safety Analysis Set |
| Listing 16.2.8.1.3 | Hematology – Safety Analysis Set |
| Listing 16.2.8.1.4 | Coagulation – Safety Analysis Set |
| Listing 16.2.8.1.5 | Urinalysis – Safety Analysis Set |
| Listing 16.2.8.1.6 | Other – Safety Analysis Set |

**16.2.8.2 Other Safety Data**

| | |
|---|---|
| Listing 16.2.8.2.1 | Vital Signs – Safety Analysis Set |
| Listing 16.2.8.2.2 | Antropometry (Height, Weight, Body Mass Index and Head Circumference) – Safety Analysis Set |
| Listing 16.2.8.2.3 | Physical Examination – Safety Analysis Set |
| Listing 16.2.8.2.4 | Neurological Examination – Safety Analysis Set |
| Listing 16.2.8.2.5 | 12-Lead Electrocardiogram (ECG) – Safety Analysis Set |
| Listing 16.2.8.2.6 | Echocardiography – Safety Analysis Set |
| Listing 16.2.8.2.7 | Immunogenicity in Cerebrospinal Fluid (CSF) – Safety Analysis Set |
| Listing 16.2.8.2.8 | Immunogenicity in Serum – Safety Analysis Set |
| Listing 16.2.8.2.9 | PK Sampling and Concentration Data – PK Analysis Set |
| Listing 16.2.8.2.10 | PK Parameters – PK Analysis Set |
| Listing 16.2.8.2.11 | PD assessments Heparan Sulfate (HS) in Cerebrospinal Fluid (CSF) – Safety Analysis Set |
| Listing 16.2.8.2.12 | PD assessments Heparan Sulfate (HS) in Serum – Safety Analysis Set |
| Listing 16.2.8.2.13 | PD assessments Heparan Sulfate (HS) in Urine – Safety Analysis Set |
| Listing 16.2.8.2.14 | PD assessments Heparan Sulfate (HS) Sampling and Concentration Data – Safety Analysis Set |
| Listing 16.2.8.2.15 | Cross Reactive Immunological Material (CRIM) status at Baseline – Safety Analysis Set |

## 19.2 Tables and Figures Index

The numbering of the tables will be such that they can be easily integrated into the CSR following ICH Section 14.

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

### 14.1 DEMOGRAPHIC DATA

#### 14.1.1 Patient Disposition

| | |
|---|---|
| Table 14.1.1.1 | Number of Patients Screened and Study Termination – Screened Patients |

#### 14.1.2 Protocol Deviations

| | |
|---|---|
| Table 14.1.2.1 | Protocol Deviations – Safety Analysis Set |

#### 14.1.3.1 Demographics and Baseline Characteristics

| | |
|---|---|
| Table 14.1.3.1.1 | Demographics – Safety Analysis Set |
| Table 14.1.3.1.2 | MPS III History of Siblings – Safety Analysis Set |

#### 14.1.3.2 Baseline Disease Characteristics

| | |
|---|---|
| Table 14.1.3.2.1 | Duration of Disease – Safety Analysis Set |
| Table 14.1.3.2.2 | MPS IIIA Diagnostic Status – Safety Analysis Set |
| Table 14.1.3.2.3 | Central Laboratory Confirmation of MPS IIIA – Safety Analysis Set |

#### 14.1.3.3 Medical History

| | |
|---|---|
| Table 14.1.3.3.1 | Medical History – Safety Analysis Set |

#### 14.1.4 Medications

| | |
|---|---|
| Table 14.1.4.1 | Prior Medications – Safety Analysis Set |
| Table 14.1.4.2 | Concomitant Medications - Safety Analysis Set |
| Table 14.1.4.3 | Antihistamines - Safety Analysis Set |
| Table 14.1.4.4 | Anesthesia and Sedation - Safety Analysis Set |

### 14.2 EFFICACY DATA

#### 14.2.1 Vineland Adaptive Behaviour Scales (VASB-II)

| | |
|---|---|
| Table 14.2.1.1 | Vineland Adaptive Behaviour Scales (VASB-II) - Communication: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.1.2 | Vineland Adaptive Behaviour Scales (VASB-II) - Daily Living Skills: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.1.3 | Vineland Adaptive Behaviour Scales (VASB-II) - Socialization: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.1.4 | Vineland Adaptive Behaviour Scales (VASB-II) - Motor Skills: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.1.4 | Vineland Adaptive Behaviour Scales (VASB-II) – Adaptive Behaviour Composite Standard Score and Age-equivalent (AEq): Summary by Visit and Change from Baseline – Full Analysis Set |

### 14.2.2 Bayley Scales of Infant and Toddler Development (BSID-III)

| | |
|---|---|
| Table 14.2.2.1 | Bayley Scales of Infant and Toddler Development (BSID-III) - Neurocognitive: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.2.2 | Bayley Scales of Infant and Toddler Development (BSID-III) - Neurocognitive Language: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.2.3 | Bayley Scales of Infant and Toddler Development (BSID-III) - Motor Function: Summary by Visit and Change from Baseline – Full Analysis Set |

### 14.2.3 Kaufman Assessment Battery for Children (KABC-II)

| | |
|---|---|
| Table 14.2.3.1 | Kaufman Assessment Battery for Children (KABC-II) - Neurocognitive Development Quotient (DQ): Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.3.2 | Kaufman Assessment Battery for Children (KABC-II) - Neurocognitive Composite Score: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.3.3 | Kaufman Assessment Battery for Children (KABC-II) - Expressive Vocabulary Subdomain: Summary by Visit and Change from Baseline – Full Analysis Set |

### 14.2.4 Neurocognitive Development Quotient (BSID-III and KABC-II combined)

| | |
|---|---|
| Table 14.2.4.1 | Neurocognitive Development Quotient (DQ): Summary by Visit and Change from Baseline – Full Analysis Set |

### 14.2.5 Magnetic Resonance Imaging (MRI)

| | |
|---|---|
| Table 14.2.5.1 | Brain Volumeric Magnetic Resonance Imaging (MRI) – Gray Matter Volume: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.5.2 | Brain Volumeric Magnetic Resonance Imaging (MRI) – Compound Ventricular Volume: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.5.3 | Diffusion Tensor Imaging Magnetic Resonance Imaging (MRI) – Fractional Anisotropy (FA) and Mean Diffusivity (MD) of Corpus Callosum: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.5.4 | Diffusion Tensor Imaging Magnetic Resonance Imaging (MRI) – Fractional anisotropy (FA) and Mean Diffusivity (MD) of Cerebral White Matter: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.5.5 | Susceptibility Weighting Imaging (SWI) Magnetic Resonance Imaging (MRI) – Cerebral White Matter: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.5.6 | Susceptibility Weighting Imaging (SWI) Magnetic Resonance Imaging (MRI) – Basal Ganglia: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.5.7 | Abdominal Magnetic Resonance Imaging (MRI) – Liver Volume: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.5.8 | Abdominal Magnetic Resonance Imaging (MRI) – Spleen Volume: Summary by Visit and Change from Baseline – Full Analysis Set |

### 14.2.6 Children's Sleep Habits Questionnaire (CSHQ) and Actigraphy

| | |
|---|---|
| Table 14.2.6.1 | Children's Sleep Habits Questionnaire (CSHQ) – Sleep Disturbance Score: Summary by Visit and Change from Baseline – Full Analysis Set |
| Table 14.2.6.2 | Actigraphy: Summary by Visit and Change from Baseline – Safety Analysis Set |

## 14.3 SAFETY DATA

### 14.3.1 Displays of Adverse Events

| | |
|---|---|
| Table 14.3.1.1 | Overall Summary of Adverse Events - Safety Analysis Set |
| Table 14.3.1.2 | Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term – Safety Analysis Set |
| Table 14.3.1.3 | Treatment Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term and maximum CTCAE grade - Safety Analysis Set |
| Table 14.3.1.4 | Drug-related Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term – Safety Analysis Set |
| Table 14.3.1.5 | Drug-related Treatment Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term and maximum CTCAE grade - Safety Analysis Set |
| Table 14.3.1.6 | Serious Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term – Safety Analysis Set |
| Table 14.3.1.7 | Serious Treatment Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term and maximum CTCAE grade - Safety Analysis Set |
| Table 14.3.1.8 | Serious drug-related Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term – Safety Analysis Set |
| Table 14.3.1.9 | Serious drug-related Treatment Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term and maximum CTCAE grade - Safety Analysis Set |
| Table 14.3.1.10 | Treatment Emergent Adverse Events (TEAEs) leading to Study and/or Treatment Withdrawal by System Organ Class and Preferred Term – Safety Analysis Set |
| Table 14.3.1.11 | Treatment Emergent Adverse Events (TEAEs) leading to Study and/or Treatment Withdrawal by System Organ Class, Preferred Term and maximum CTCAE grade - Safety Analysis Set |
| Table 14.3.1.12 | Drug-related Treatment Emergent Adverse Events (TEAEs) leading to Study and/or Treatment Withdrawal by System Organ Class and Preferred Term – Safety Analysis Set |
| Table 14.3.1.13 | Drug-related Treatment Emergent Adverse Events (TEAEs) leading to Study and/or Treatment Withdrawal by System Organ Class, Preferred Term and maximum CTCAE grade - Safety Analysis Set |
| Table 14.3.1.14 | Treatment Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term and Anti-Drug Antibody (ADA) status - Safety Analysis Set |
| Table 14.3.1.15 | Overall Summary of Infusion Related Reactions (IRRs) - Safety Analysis Set |
| Table 14.3.1.16 | Infusion Related Reactions (IRRs) Symptoms by System Organ Class and Preferred Term - Safety Analysis Set |
| Table 14.3.1.17 | Infusion Related Reactions (IRRs) Symptoms by System Organ Class, Preferred Term and maximum CTCAE grade - Safety Analysis Set |
| Table 14.3.1.18 | Serious Infusion Related Reaction (IRRs) Symptoms by System Organ Class and Preferred Term - Safety Analysis Set |
| Table 14.3.1.19 | Serious Infusion Related Reactions (IRRs) Symptoms by System Organ Class, Preferred Term and maximum CTCAE grade - Safety Analysis Set |

| | |
|---|---|
| Table 14.3.1.20 | Infusion Related Reaction (IRRs) leading to Study and/or Treatment Withdrawal by System Organ Class and Preferred Term - Safety Analysis Set |
| Table 14.3.1.21 | Infusion Related Reactions (IRRs) leading to Study and/or Treatment Withdrawal by System Organ Class, Preferred Term and maximum CTCAE grade - Safety Analysis Set |
| Table 14.3.1.22 | Infusion Related Reactions (IRRs) Resolved Within 24 Hours, by System Organ Class and Preferred Term - Safety Analysis Set |

**14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events**

| | |
|---|---|
| Table 14.3.2.1 | Deaths, Listing – Safety Analysis Set |
| Table 14.3.2.2 | Serious Adverse events, Listing – Safety Analysis Set |
| Table 14.3.2.3 | Treatment Emergent Adverse Events (TEAEs) leading to permanent Discontinuation of Study Drug, Listing – Safety Analysis Set |
| Table 14.3.2.4 | Infusion Related Reaction (IRR) Symptoms, Listing – Safety Analysis Set |

**14.3.4.1 Clinical Laboratory Data**

| | |
|---|---|
| Table 14.3.4.1.1.1 | Clinical Chemistry: Summary by Visit, Time point, and Change from Baseline – Safety Analysis Set |
| Table 14.3.4.1.1.2 | Clinical Chemistry: Number (%) of Patients with Values Outside of Normal Range by Visit and Time point – Safety Analysis Set |
| Table 14.3.4.1.1.3 | Clinical Chemistry: Abnormal Results, Listing – Safety Analysis Set |
| Table 14.3.4.1.1.4 | Clinical Chemistry: Shift from Baseline to End of Study Visit – Safety Analysis Set |
| Figure 14.3.4.1.2.1 | Clinical Chemistry: Patient plots over Time by Parameter – Safety Analysis Set |
| | |
| Table 14.3.4.1.3.1 | Hematology: Summary by Visit, Time point, and Change from Baseline – Safety Analysis Set |
| Table 14.3.4.1.3.2 | Hematology: Number (%) of Patients with Values Outside of Normal Range by Visit and Time point – Safety Analysis Set |
| Table 14.3.4.1.3.3 | Hematology: Abnormal Results, Listing – Safety Analysis Set |
| Table 14.3.4.1.3.4 | Hematology: Shift from Baseline to End of Study Visit – Safety Analysis Set |
| Figure 14.3.4.1.4.1 | Hematology: Patient plots over Time by Parameter – Safety Analysis Set |
| | |
| Table 14.3.4.1.5.1 | Urinalysis: Number (%) of Patients with Values Outside of Normal Range by Visit and Time point– Safety Analysis Set |
| Table 14.3.4.1.5.2 | Urinalysis: Abnormal Results, Listing – Safety Analysis Set |
| Table 14.3.4.1.6.1 | Coagulation: Summary by Visit, Time point, and Change from Baseline – Safety Analysis Set |
| Table 14.3.4.1.6.2 | Coagulation: Number (%) of Patients with Values Outside of Normal Range by Visit and Time point – Safety Analysis Set |
| Table 14.3.4.1.6.3 | Coagulation: Abnormal Results, Listing – Safety Analysis Set |
| Table 14.3.4.1.6.4 | Coagulation: Shift from Baseline to End of Study Visit– Safety Analysis Set |
| Figure 14.3.4.1.7.1 | Coagulation: Patient plots over Time by Parameter – Safety Analysis Set |
| | |
| Table 14.3.4.1.8.1 | Other Laboratory Data: Summary by Visit, Time point, and Change from Baseline – Safety Analysis Set |

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| Table 14.3.4.1.8.2 | Other Laboratory Data: Number (%) of Patients with Values Outside of Normal Range by Visit and Time point – Safety Analysis Set |
| Table 14.3.4.1.8.3 | Other Laboratory Data: Abnormal Results, Listing – Safety Analysis Set |
| Table 14.3.4.1.8.4 | Other Laboratory Data: Shift from Baseline to End of Study Visit – Safety Analysis Set |

**14.3.4.2 Vital Signs**

| | |
|---|---|
| Table 14.3.4.2.1 | Vital Signs: Summary by Visit, Time point, and Change from Baseline – Safety Analysis Set |
| Figure 14.3.4.2.2 | Vital Signs: Patient plots over Time by Parameter – Safety Analysis Set |

**14.3.4.3 Anthropometry (Height, weight, BMI, and head circumference)**

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|---|---|
| Table 14.3.4.3.1 | Anthropometry: Summary by Visit and Change from Baseline – Safety Analysis Set |

**14.3.4.4 Physical Examination**

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|---|---|
| Table 14.3.4.4.1 | Physical Examination: Number (%) of Patients with Normal/Abnormal Results by Visit and Time point – Safety Analysis Set |

**14.3.4.5 Neurological Examination**

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|---|---|
| Table 14.3.4.5.1 | Neurological Examination: Number (%) of Patients with Normal/Abnormal Results by Visit – Safety Analysis Set |

**14.3.4.6 12-Lead Electrocardiogram (ECG) and Echocardiography**

| | |
|---|---|
| Table 14.3.4.6.1 | ECG: Number (%) of Patients with Normal/Abnormal Results by Visit and Time point – Safety Analysis Set |
| Table 14.3.4.6.2 | Echocardiography: Number (%) of Patients with Normal/Abnormal Results by Visit – Safety Analysis Set |

**14.3.4.7 Exposure**

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|---|---|
| Table 14.3.4.7.1 | Extent of Exposure – Safety Analysis Set |

**14.3.4.8 Immunogenicity**

| | |
|---|---|
| Table 14.3.4.8.1 | Number (%) of Patients with Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) in Serum by Visit – Immunogenicity Analysis Set |
| Table 14.3.4.8.2 | Number (%) of Patients with Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) in Cerebrospinal Fluid (CSF) by Visit – Immunogenicity Analysis Set |
| Figure 14.3.4.8.3 | Immunogenicity: Patient plots over Time – Immunogenicity Analysis Set |

**14.3.4.9 PK**

| | |
|---|---|
| Table 14.3.4.9.1 | Summary of PK concentrations by Dose, Visit and Time point – PK Analysis Set |
| Table 14.3.4.9.2 | SOBI003 PK parameters by Dose, Visit – PK Analysis Set |
| Table 14.3.4.9.3 | Attainment of Steady State for SOBI003 using Repeated Measures ANOVA – PK Analysis Set |

| | |
|---|---|
| Table 14.3.4.9.4 | Dose Proportionality for SOBI003 PK parameters by Visit using Humel Power Analysis – PK Analysis Set |
| Table 14.3.4.9.5 | Dose Proportionality for SOBI003 PK parameters by Visit using Pearson Correlation Analysis – PK Analysis Set |
| Figure 14.3.4.9.6 | Individual Serum PK Concentration-Time Profiles at Week 1, 4, 12, and 24 by Dose Level in Linear and Log-Linear Scales – PK Analysis Set |
| Figure 14.3.4.9.7 | Mean (SD) Serum PK Concentration-Time Profiles at Week 1, 4, 12, and 24 by Dose Level in Linear and Log-Linear Scales – PK Analysis Set |
| Figure 14.3.4.9.8 | Individual Trough and End of Infusion Serum PK Concentrations by Dose Level in Linear and Log-Linear Scale – PK Analysis Set |
| Figure 14.3.4.9.9 | Mean (SD) Trough and End of Infusion Serum PK Concentrations by Dose Level in Linear and Log-Linear Scale – PK Analysis Set |
| Figure 14.3.4.9.10 | Scatter Plots of Cerebrospinal Fluid PK Concentrations at Week 12 and 24 by Dose Level – PK Analysis Set |
| Figure 14.3.4.9.11 | Regression/Scatter Dose Proportionality for SOBI003 in Log-Log and Linear-Linear Scales – PK Analysis Set |
| Figure 14.3.4.9.12 | Regression/Scatter Dose Proportionality for SOBI003 in Linear-Linear Scales – PK Analysis Set |

**14.3.4.10 PD**

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|---|---|
| Table 14.3.4.10.1 | Heparan Sulphate (HS): Summary by Visit and Change from Baseline – Safety Analysis Set |
| Table 14.3.4.10.2 | Summary of Heparan Sulphate (HS) Concentrations by Visit and Time point - Safety Analysis Set |
| Figure 14.3.4.10.3 | Individual Serum Heparan Sulphate (HS) Concentration-Time Profiles by Dose Level in Linear and Log-Linear Scales – Safety Analysis Set |
| Figure 14.3.4.10.4 | Individual Urine Heparan Sulphate (HS) Concentration-Time Profiles by Dose Level in Linear and Log-Linear Scales – Safety Analysis Set |
| Figure 14.3.4.10.5 | Mean (SD) Serum Heparan Sulphate (HS) Concentration-Time Profiles by Dose Level in Linear and Log-Linear Scales – Safety Analysis Set |
| Figure 14.3.4.10.6 | Mean (SD) Urine Heparan Sulphate (HS) Concentration-Time Profiles by Dose Level in Linear and Log-Linear Scales – Safety Analysis Set |
| Figure 14.3.4.10.7 | Mean (SD) Cerebrospinal Fluid (CSF) Heparan Sulphate (HS) Concentration-Time Profiles by Dose Level in Linear and Log-Linear Scales – Safety Analysis Set |
| Figure 14.3.4.10.8 | Scatter Plots of Cerebrospinal Fluid Heparan Sulphate (HS) Concentrations at Week 12 and 24 by Dose Level – Safety Analysis Set |

**14.3.4.11 Cross Reactive Immunological Material (CRIM) status**

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|---|---|
| Table 14.3.4.11.1 | CRIM: Number (%) of Patients with Negative/Positive Results by Visit – Safety Analysis Set |