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

Version 2.0, Amended Protocol of the Study
Including Amendment 1

SOBI003-001
IND no. 128889

Type of Study: **Phase I/II, Human Pharmacology, Therapeutic Exploratory**

Sponsor's Medical Director

Anders Bröijersén, MD, PhD
Medical Director Clinical Development
Swedish Orphan Biovitrum AB (publ)
[redacted]

Signature Date

Principal Coordinating Investigator

Paul Harmatz, MD
Associate Director in Gastroenterology
UCSF Benioff Children's Hospital Oakland
[redacted]

Signature Date

Sponsor's Study Manager

[redacted]

Signature Date

Sponsor's Statistician

[redacted]

Signature Date

Investigator statement

I have read the amended protocol entitled "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" and the accompanying current investigator's brochure. I agree to conduct the clinical investigation in compliance with the Final Protocol, Version 2.0, 06 Jul 2018, the International Council on Harmonisation (ICH) harmonised tripartite guideline E6(R2): Guideline for Good Clinical Practice, applicable regulatory/government regulations, and in accordance with the latest revision of the Ethical Principles for Medical Research Involving Human Subjects (the Declaration of Helsinki). I will not implement any changes to study procedures or conduct without prior approval from the sponsor and, when applicable, the Independent Ethics Committee/Institutional Review Board and Regulatory Authority.

I agree to maintain the confidentiality of this study protocol, as described on the title page. Further, I will not publish results of the study without authorization from Swedish Orphan Biovitrum AB (publ).

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

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Protocol Amendment History and Reasons for Amendment

Version	Date	Reason for Amendment
Version 1.0	08 Dec 2017	Original Protocol
Version 2.0 Non-substantial amendment 1	06 Jul 2018	All changes are administrative and updates are minor. The amendment is considered as non-substantial. • Two additional countries, the Netherlands and Germany, are added to the study. Total number of study clinics are updated accordingly. • Information added that the white blood cell isolation for sulfamidase activity and purification of fibroblasts from skin biopsy will, for non-US-samples, be assigned to Histalim in France. • Description of the overall study design is slightly amended to clarify that patients are assigned to a dose cohort in consecutive order as the eligibility criteria have been confirmed, with prioritization of the younger patients. • Storage temperature details have been removed from the section “Identity of investigational medicinal products” as this and further details are specified in the pharmacy manual for the study. • There have been some updates for clarification to the Schedules of Events and in the text describing the visit assessments. • The Detailed PK blood sampling schedule has been updated to clarify that PK sample will be taken peripherally during the Screening visit as no central access port is yet applied. • Specified that blood for HS analysis should be collected at the same time as the CSF sampling and urine collected for HS analysis should be taken as close as possible to the CSF sampling. • Clarified that for patients entering the extension study, all AEs and SAEs occurring after Week 24 visit, should be noted in the extension study SOBI003-002

1 Synopsis

STUDY IDENTIFIERS	
Title of study:	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
Clinical study number:	SOBI003-001
Investigator(s):	The coordinating investigator is: Paul Harmatz, MD, Associate Director in Gastroenterology UCSF Benioff Children's Hospital Oakland 52nd Street, Oakland, CA 94609, U.S.A. There will be up to 4 additional investigators.
Study center(s):	The planned study centers are in the U.S.A., Turkey, Netherlands and Germany. The study will be conducted at up to 5 study centers.
Type of study:	Phase I/II; Human pharmacology and Therapeutic exploratory
STUDY OBJECTIVES	
Primary objective:	To evaluate the safety and tolerability of SOBI003 at different dose levels.
Secondary objectives:	1. To characterize the pharmacokinetic (PK) properties of SOBI003 following single and repeated administration by the use of non-compartmental analysis (NCA) 2. To assess the immunogenicity of SOBI003 3. To assess the pharmacodynamic (PD) effect of different dose levels and treatment duration of SOBI003 on heparan sulfate (HS) levels in cerebrospinal fluid (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
Exploratory objectives:	To explore the effect of SOBI003 at different dose levels on: 1. Clinical manifestations of MPS IIIA as assessed by endpoints specified in exploratory endpoint section below 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 effect of SOBI003 on HS levels in CSF, serum and urine by the use of population modelling analysis

Exploratory objectives continued:	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 Serum, CSF, and urine samples for potential future pharmacogenetic and biomarker analyses will be stored for a maximum of 10 years following study completion. The results of any such analyses will not be included in the Clinical Study Report for this study, but reported separately when analyzed, thus enabling exploration of any emerging novel disease-related discoveries of e.g., previously unknown alleles, inflammatory cytokines, other HS biomarkers (e.g. HS metabolites), components of the complement system, and neurodegeneration.
STUDY ENDPOINTS	
Primary endpoint:	Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs).
Secondary endpoint(s):	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, 4, 12, 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 anti-drug antibodies (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 neutralizing antibodies (NAb) in serum.
- Occurrence of ADAs against SOBI003 in CSF (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 and 24
- Change from baseline in urine HS at Weeks 2, 3, 4, 8, 12 and 24

The endpoints relating to the 4th secondary objective are neurocognitive Development Quotient (DQ) and age-equivalence score (AEq) 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 age-equivalence score (AEq) 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.

Exploratory endpoint(s):

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 24
- Fine 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
- 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 in 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 susceptibility weighting imaging (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 Clinical Study Report for this study, but reported separately.

STUDY DESIGN AND METHODS

Study design:	This is an open-label, non-controlled, parallel, sequential ascending multiple-dose, multicenter study to assess the dose related safety, tolerability, PK and PD of SOBI003 in pediatric MPS IIIA patients. SOBI003 is administered as weekly 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 pretreated 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 strict consecutive order as the eligibility criteria have been confirmed. 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 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, the SRC will determine what dose to apply in the next cohort. An independent Data Monitoring Committee will monitor safety data at pre-specified intervals. 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.
Number of subjects planned:	9 In case of an additional 4th cohort and replacements of prematurely withdrawn patients, the number of patients will not exceed 15.
Diagnosis and main criteria for inclusion:	MPS IIIA patients, 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, that are ≥12 to ≤72 months of age and that have a developmental age ≥12 months. Patients with at least one S298P mutation in the SGSH gene are excluded, as well as patients that have received prior stem cell or gene therapy, or enzyme replacement therapy for MPS IIIA.

Assessments for safety and tolerability evaluation:	Adverse events are recorded from the time of first investigational product administration until last study visit (Week 24). Blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation are assessed at Screening, prior to each infusion, 2 hours after start of infusion and within 1 hour of completion of each infusion. Intensified assessments are applied for Weeks 1 to 8. The last assessments are done 3 days after last infusion. Blood and urine samples for central laboratory analyses of hematology, clinical chemistry and coagulation are collected at Screening and prior to each infusion at Weeks 1 to 8. Pre-infusion sampling also applies biweekly from Week 10 to 22. After each of the 3 first infusions, post-infusion samples are also collected 2 days after the infusions (Day 3). At Week 24, a post-infusion sample is obtained on Day 3. 12-lead ECGs are obtained at Screening and prior to and post the infusions on Weeks 1 to 4, 6, 8, 12 and 24. A physical examination will be performed at Screening, Baseline and at Week 24. General appearance and skin are examined prior to and within 1 hour of completion of each infusion. A neurological examination will be performed at Screening and Week 24. Blood samples for central laboratory analyses of ADAs are collected at Baseline and pre-infusion at Weeks 2, 4, 8, 12 and 24. For patients not continuing in the extension study, immunogenicity and PK are assessed 30 to 40 days after last SOBI003 administration. CSF samples for central laboratory analysis of ADAs are collected at Baseline and at Weeks 12 and 24. For the determination of cross reactive immunological material (CRIM) status of the patients in fibroblasts, a skin biopsy is taken at Baseline.
Assessments for pharmacokinetic (PK) and pharmacodynamics (PD) evaluation:	Serum concentration vs time profiles are obtained for determination of SOBI003 PK variables at Weeks 1, 4, 12 and 24. In addition, serum samples are collected when ADA samples are obtained. SOBI003 concentration in CSF is assessed at Weeks 12 and 24. HS is assessed in CSF at Baseline and Weeks 12 and 24. HS in serum is assessed at Baseline and at Weeks 2 to 4, 8, 12 and 24. HS in urine are assessed at Screening, Baseline, and at Weeks 2 to 4, 8, 12, and 24.
Assessments for efficacy evaluation:	Neurocognition is assessed by the BSID-III and/or KABC-II at Baseline and at Week 24. Adaptive behavior is assessed by the VABS-II at Baseline and at Week 24. Gray matter volume is assessed by MRIs at Baseline and at Week 24. The PedsQL is completed by the parent/primary caregiver at Baseline and at Weeks 12 and 24.
Assessments for exploratory PD evaluation:	Clinical manifestations, including language, motor function, and sleep pattern are assessed at Baseline and at Week 24. Sleep pattern is also assessed at Week 12. Brain and abdominal MRIs are performed at Baseline and at Week 24 to assess ventricles, white matter, basal ganglia, and liver and spleen volumes.
Test product; dose and mode of administration:	SOBI003, 20 mg/mL, concentrate for solution for i.v. infusion 3 dose levels are planned. The dose level for Cohort 1 is 3 mg/kg. The planned mid and maximum dose levels for Cohorts 2 and 3 are 10 mg/kg and 20 mg/kg, respectively. The dose levels for Cohorts 2 and 3 will be determined by the Safety Review Committee and will be based on review of pre-specified safety, tolerability, immunogenicity, PK and PD data

Reference product; dose and mode of administration:	Not applicable
Duration of treatment(s):	24 weeks
Statistical methods:	Safety tabulations of adverse event data and laboratory data are performed. Continuous variables are summarized using the number of patients, the mean, the standard deviation, the median, the minimum value, and the maximum value. Categorical variables are summarized using frequency counts and percentages. PK results are presented by dose level using descriptive statistics. In addition, results are presented by demographic characteristics e.g. age-group and body-weight, as applicable. Immunogenicity is summarized using frequency counts and percentages by dose level. To assess the PD effect of different dose levels of SOBI003 on HS levels in CSF serum, and urine, linear mixed models are used to model the change from baseline in HS levels as dependent variable, for both logged HS levels and untransformed HS levels, and baseline level and age as continuous covariates, and dose and sex as factors. The analyses are conducted for each assessment time point: Weeks 12 and 24 for CSF, and Weeks 4, 8, 12 and 24 for serum and urine. In addition, linear mixed analyses with HS levels, both logged HS levels and untransformed HS levels, in CSF, serum, and urine, as dependent variable, and baseline level and age as continuous covariates, and dose and sex as factors will be performed across all assessments, with assessment as a repeated factor in a accumulating pattern: across weeks 12 and 24 for HS in CSF, and across Weeks 4 and 8, across Weeks 4, 8 and 12, and across Weeks 4, 8, 12 and 24 for HS in serum. Endpoints relating to the neurocognition, adaptive behavior, gray matter volume and Quality of Life are summarized using descriptive statistics.

2 Abbreviations and definition of terms

ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AEq	Age-equivalence
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under curve
$AUC_{\tau,ss}$	Area under the plasma concentration-time curve during a dosage interval (τ)
AUC_{168h}	The area under the serum concentration-time curve from time 0 to 168 after dose
BBB	Blood-brain barrier
BSID-III	Bayleys Scales of Infant and Toddler Development®, third edition
CDISC	Clinical data interchange standards consortium
CL	Clearance
$C_{End\ of\ inf}$	The observed serum concentration at the end of infusion of SOBI003
C_{max}	Maximum observed serum concentration
C_{Trough}	The minimum observed serum concentration
C_{max}	Maximum (peak) serum drug concentration
CNS	Central nervous system
$C_{Pre\text{-}dose}$	The observed serum concentration immediately before the start of infusion of SOBI003
CRF	Case report form
CRIM	Cross reactive immunological material
CRO	Contract research organization
CSF	Cerebrospinal fluid
CSHQ	Children´s sleep habits questionnaire
DMC	Data monitoring committee

DQ	Development quotient
ECG	Electrocardiogram
ERT	Enzyme replacement therapy
FAS	Full-analysis set
GCP	Good clinical practice
GLP	Good laboratory practice
HS	Heparan sulfate; throughout this protocol, the term “HS” is also used for the disaccharide levels detected in the bioanalytical assay (refer to Section 7.5.7.1)
i.v.	Intravenous
ICF	Informed consent form
ICH	International council for harmonisation
IEC	Independent ethics committee
IL	Interleukin
IMP	Investigational medicinal product
IRB	Institutional review board
KABC-II	Kaufman assessment battery for children, second edition
LSD	Lysosomal storage disease
MABEL	Minimal anticipated biological effect level
MPS IIIA	Mucopolysaccharidosis type IIIA
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NAb	Neutralizing antibody
NCA	Non-compartmental analysis
NCI CTC	National cancer institute common terminology criteria
NOAEL	No observed adverse effect level
NVI	Nonverbal index
PAD	Pharmacologically Active Dose
PD	Pharmacodynamic
PedsQL	Pediatric quality of life inventory

PK	Pharmacokinetic
PT/INR	Prothrombine time/international normalized ratio
SAE	Serious adverse event
SAF	Safety analysis set
SGSH	N-Sulfoglucosamine sulfohydrolase
Sobi	Swedish Orphan Biovitrum AB (publ)
SRC	Safety review committee
t	Time
$t_{End\ of\ inf}$	The time of the end of the infusion of SOBI003
t_{max}	The time at which the maximum serum concentration is observed
$t_{1/2}$	Half-life
TBV	Total blood volume
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VABS-II	Vineland adaptive behavior scales, second edition
Vd	Volume of distribution

3 Ethics

3.1 Independent ethics committee

It is the responsibility of the investigator to obtain approval of the study protocol, possible amendments and the written patient information and informed consent form (ICF) from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The investigator should file all correspondence with the IRB/IEC. Copies of IRB/IEC correspondence and approvals should be forwarded to the contract research organization (CRO) INC Research.

3.2 Ethical conduct of the study

This study will be conducted in compliance with this protocol, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) [1], applicable regulatory requirements, and in accordance with the latest revision of the Ethical Principles for Medical Research Involving Human Subjects (the Declaration of Helsinki) [2].

3.3 Patient information and consent

It is the responsibility of the investigator to give each patient's legally authorized representative(s), prior to any study related activities, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patient's legally authorized representative(s) must be informed about their right to withdraw from the study at any time. The written patient information and/or consent form must not be changed without prior discussion with Sobi. Before any revisions are implemented, the revised written patient information and/or consent form must be approved by the IRB/IEC.

It is the responsibility of the investigator to obtain signed informed consent (or witnessed verbal consent according to applicable regulations) from the patient's legally authorized representative(s) prior to any study related activities. The local regulations will be followed in the definition of legally authorized representative. Even where not legally required, if it is considered desirable by the investigator or IRB, informed consent can be obtained from both legally authorized representatives.

The patient's legally authorized representative(s) should receive a copy of the written information and signed ICF.

Once the ICF has been signed, the patient will be assigned an Enrollment Number.

4 Study administrative structure

4.1 Sponsor

The sponsor of the study is Swedish Orphan Biovitrum AB (publ), Stockholm, Sweden (Sobi).

4.2 Clinical research organizations

4.2.1 Study management

The following study-related duties are transferred to INC Research LLC, with its principal place of business at 3201 Beachleaf Court, Raleigh, NC 27604-1547, U.S.A.: monitoring, development of master written patient information and ICF, pharmacokinetics (PK), data management, biostatistics, submission of Clinical Trial Application to applicable regulatory authorities, and investigational product management (including secondary packaging, labeling and distribution).

Handling of serious adverse event (SAE) reporting is a shared responsibility between Sobi and INC Research. Upon receipt of an SAE report from a study site, INC Research will process the report and forward it to the Drug Safety Department at Sobi. Requests for complementary follow-up information are sent to investigators through INC Research. Notification of expedited SAEs to regulatory authorities is a shared responsibility of Sobi and INC Research. INC Research is responsible for notifications to IRB/IEC, investigators and the regulatory authorities

except notifications to the regulatory authority in U.S.A., which are managed by Sobi. Sobi is responsible for the compilation of Development Safety Update Reports based on data outputs from INC Research and INC Research is responsible for the compilation of Periodic Line Listings, if applicable, and the submission of these periodic reports to applicable regulatory authorities, as well as distribution to IRB/IEC and investigators, when applicable. Sobi is responsible for the submissions of periodic reports to the regulatory authority in U.S.A.

Contact relating to project management and monitoring are to be directed to INC Research.

4.2.2 Neurodevelopment assessments

For the neurodevelopment assessments, the following study related duties are assigned to NeuroCog Trials Holdings, Inc., 3211 Shannon Road, Suite 300, Durham, NC 27707, U.S.A.: development of a study-specific assessment manual, study-specific training and certification of local child-development assessors, central data quality assurance of completed assessment forms, calculation of final scores and determination of Age Equivalence scores, and data management of adaptive behavior and neurocognition assessments.

The development of the study-specific manual will be in collaboration with Shapiro Neuropsychology Consulting LLC, 820 NW 12 Ave. Apt. 304, Portland, OR 97209, U.S.A.

4.3 Central laboratories

Five central laboratories are used in this study. The analyses of SOBI003, heparan sulfate (HS), and SOBI003 anti-drug-antibodies (ADA) in serum and cerebrospinal fluid, including method validations, are assigned to York Bioanalytical Solutions Limited, Cedar House, Northminster Business Park, Upper Poppleton, York YO26 6QR, United Kingdom. This is a Good Laboratory Practice (GLP) compliant laboratory. Storage of samples for future bioanalytical research is also assigned to York Bioanalytical Solutions Limited.

The SGSH genotyping, assessment of potential cellular sulfamidase activity and levels of urine HS are assigned to Greenwood Genetic Center, 106 Gregor Mendel Cir, Greenwood, South Carolina 29646, U.S.A. This is a College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) accredited laboratory.

The safety laboratory analyses are assigned to BARC USA Inc., 5 Delaware Drive, Lake Success NY 11042-1114, U.S.A. This is a GLP and CAP compliant laboratory.

Analyses of neutralizing antibodies (NAbs) is assigned to BioAgilytix, Lademannbogen 10, 22339 Hamburg, Germany. This is a GLP compliant laboratory.

The determination of cross reactive immunological material (CRIM) status will be performed at Biochemical Genetics Laboratory, Duke University Health System, 801 Capitola drive, Suite 6, Durham, NC 27713, U.S.A.

The white blood cell isolation for sulfamidase activity and purification of fibroblasts from skin biopsy will, for non-US-samples, be assigned to Histalim, 126, rue Emile Baudot, Le Millénaire, 34000 Montpellier, France.

4.4 Central MRI reading

Dr Igor Nestrasil, at Quantims LLC, 3749 Foss Road, Saint Anthony, MN 55421, U.S.A., is assigned to develop a study-specific MRI manual specifying the MRI settings to be applied at study sites, validation of test-data from each site, quality assurance of completed MRI scans, and determination of the brain and abdominal variables from completed MRI assessments, as specified in Section 7.5.4.6.

4.5 Data monitoring committee

A data monitoring committee (DMC), independent from Sobi and principal investigators (PIs), is assigned to monitor all safety and immunogenicity data at intervals specified in Section 7.5.5.10. The primary responsibility of the DMC is to provide safety oversight of the study conduct in order to protect study participants. The DMC is planned to comprise an independent statistician and two clinicians that, collectively, have experience from DMC, management of pediatric patients with lysosomal storage disease (LSD), clinical immunology, and the conduct of clinical trials with enzyme replacement therapy (ERT). A DMC charter will outline DMC membership, responsibilities, data review meeting details, and lines of communication with the study teams at Sobi and INC Research.

4.6 Safety review committee

The appointed SRC will comprise the principal investigators and relevant Sobi staff, including the Safety Physician, Clinical Pharmacologist, Study Statistician, Principal Scientist of Immunology, Toxicologist, Medical Director Clinical Development, and VP Head of Clinical Development. The primary responsibility of the SRC is to review emerging safety, PK and PD data during the dose-escalation phase in order to determine the continuation to the next cohort. Refer to Section 7.5.5.9 for further details.

5 Introduction

Sobi is developing SOBI003, a chemically modified recombinant human sulfamidase, for enzyme replacement in patients with Mucopolysaccharidosis type IIIA (MPS IIIA); Sanfilippo A syndrome. MPS IIIA is a rare disease with rapid progression from early childhood, often resulting in death during the 2nd or 3rd decade of life. Currently there is no approved treatment and to date, therapy is limited to symptomatic treatment and relief of symptoms. The unmet medical need is therefore high.

This first-in-human Phase I/II study is designed to determine the safety, tolerability, PK and pharmacodynamics (PD) of SOBI003 in pediatric MPS IIIA patients. Healthy volunteers with normal enzyme levels are not a suitable population as they are not a representative population for assessment of safety, tolerability, immunogenicity and PD.

5.1 Background

5.1.1 MPS IIIA

MPS IIIA or Sanfilippo A, is an inherited LSD that is progressive, life-shortening and rare. MPS IIIA is one of 4 distinct subtypes of MPS III (denoted IIIA, IIIB, IIIC and IIID) (3).

MPS IIIA is an autosomal recessive disorder caused by mutations in the SGSH gene that result in absence of or a deficiency in the enzyme sulfamidase (N-sulfoglucosamine sulfohydrolase). Lack of sulfamidase activity leads to insufficient degradation of HS and lysosomal accumulation of HS and its metabolites in lysosomes throughout the body (4). As of today, 142 mutations have been described in the SGSH gene coding for sulfamidase (5). Data suggest a geno- and phenotype correlation and that patients homozygous or compound heterozygous for the S298P mutation have a slower progression of the disease (6).

Depending on disease severity, patients have a median life-expectancy of about 15 years. The clinical course of MPS IIIA can be divided into 3 phases (7). In the first phase, which usually starts between 1 and 4 years of age, a developmental delay becomes apparent after an initial normal development during the first 1 to 2 years of life. The most prominent finding in this phase is speech delay (6,7,8).

The diagnosis of MPS IIIA is usually established during the second phase, which generally starts around 3 to 4 years of age. This phase is characterized by increasing behavioral problems with hyperactivity, aggressive and destructive behavior as well as reduced attention span (7), which responds poorly to standard medications and behavioral-based interventions (9). A pronounced and rapid decline in cognitive skills becomes evident and the sleeping pattern is disturbed with extreme difficulty in falling asleep and with frequent awakening (10).

In the third and final “quiet” phase, behavioral symptoms diminish while motor retardation emerges with walking and swallowing difficulties sometimes requiring percutaneous endoscopic gastrostomy (PEG) feeding. The progressive neurodegeneration causes spasticity, seizures, loss of speech, and severe dementia, which ultimately results in a vegetative state (9).

Patients usually die from respiratory infections in the end of the second or beginning of the third decade of life (11,12) although patients with a slowly progressing phenotype may live longer (6).

5.1.2 SOBI003

SOBI003 is a chemically modified variant of recombinant human sulfamidase. SOBI003 is a sterile solution for i.v. infusion after dilution. In this Phase I/II study, SOBI003 is administered once weekly.

By modification of the sulfamidase glycans, the uptake of SOBI003 systemically is strongly reduced. This translates into a reduced serum clearance as demonstrated in mice. SOBI003 passes the blood-brain barrier (BBB) presumably by adsorptive mediated transcytosis, whereby the increased plasma exposure facilitates generation of pharmacological relevant levels of SOBI003 in the central nervous system (CNS) compartment. Once SOBI003 enters the target cells and reaches the lysosomal compartment, it shows enzymatic activity and stability comparable to that of unmodified sulfamidase, as demonstrated in fibroblasts of MPS IIIA patients.

5.1.3 SOBI003 nonclinical development

In a MPS IIIA mouse model with a spontaneous missense mutation of the SGSH gene, disease manifestations similar to the human conditions are obtained, including lysosomal storage of HS and neurological pathology. In these mice, repeated i.v. administration of SOBI003 resulted in a dose and time dependent clearance of HS in brain. The reduction in HS translated into improvements in terms of lysosomal size and neuroinflammation as well as beneficial effects on behavioral impairments.

HS reduction in cerebrospinal fluid (CSF) correlated with reduction of HS in whole brain of MPS IIIA mice following repeated i.v. administration of SOBI003, thus supporting the use of HS reduction in CSF as a biomarker of disease modification.

In MPS IIIA mice, a relationship between treatment effect and SOBI003 dose level and treatment duration was observed. The reduction of HS in brain was related to the accumulated active SOBI003 dose. The return to baseline HS biomarker levels after discontinuation of treatment was also a gradual process in this mouse model. To quantify and understand the dose, time, concentration and effect relationship in MPS IIIA mice, a semi-mechanistic in silico model was developed based on mouse PK, distribution of SOBI003 to the brain, SOBI003 entering target cells, the intracellular retention of SOBI003 and an intracellular SOBI003 concentration-effect relationship on HS reduction. Human fibroblasts of an MPS IIIA patient (GM00879, Coriell Institute) were used for in vitro determination of SOBI003 cell entry rate, cell retention, and intracellular concentration-effect relationship. Allometric scaling from rat and cynomolgus monkey to human was applied to predict clearance and volume of distribution in patients (body weight 20 kg). Translating the mouse in silico model to human repeated weekly administration of 3 mg/kg, SOBI003 is predicted to gradually achieve a brain HS reduction of ~ 35 % after 3 months and ~ 45 % after 6 months treatment. Thus, according to model-based simulations using the in silico model, the 3 mg/kg dose level is expected to gradually elicit a pharmacological effect in CNS in humans. Repeated weekly administration of 10 and 20 mg/kg SOBI003 is predicted to achieve a brain HS reduction of ~ 75 % and ~ 80 % after 3 months and ~ 80 % and ~ 85 % respectively after 6 months treatment relative to baseline.

Nonclinical safety assessments have been performed to support the SOBI003 development program. The nonclinical safety studies were performed in accordance to international standards for drug development and OECD Principles of GLP. A 3-month toxicity study was performed in MPS IIIA mice, a disease model to evaluate any potential interactions of the drug and the

disease. A 1-month toxicity study in healthy non-human primates (cynomolgus monkey) was also performed. In addition, to support the clinical development in pediatric patients, juvenile rats were treated for one month from 10 days up to 5 weeks of age, which corresponds to a life-span in humans ranging from neonates up to the age of 6 years. Throughout the nonclinical safety program SOBI003 was administered by i.v. infusion every third day following pre-treatment with anti-histamine to appropriately resemble the clinical treatment regimen.

In the species tested, the treated animals did not show any signs of adverse effects. Thus, the safety evaluation of SOBI003 has shown that it is well-tolerated. In favor of SOBI003 treatment was also improvements in the disease state in MPS IIIA mice, such as lower incidences and/or severity of microscopic findings and with lower kidney, liver and spleen weights. However, the histopathological examinations revealed that the treatment of all three species at higher doses were associated with an accumulation of eosinophilic material in the cytoplasm of macrophages of various origin; liver, lymph nodes and the heart. The observations were clearly dose dependent and did not cause any detected harmful effects or other negative consequences to the animals. The observations were partially reversible after 4 weeks withdrawal of treatment. The anomalies were judged to be a result of a normal physiological function of tissue macrophages to scavenge proteins and the observed accumulation may be due to the high protein load. Thus, since these findings were not considered as adverse the NOAEL was set to the highest dose administered in the three species tested, i.e., 300 mg/kg in the mice and rats and 150 mg/kg in the cynomolgus monkeys.

The lowest SOBI003 serum exposures at the NOAEL dose levels in these species were observed in the mice following the 300 mg/kg dose, where mean $C_{max,ss}$ was 86.3 and 163 µmol/L and mean $AUC_{\tau,ss}$ was 718 and 934 µmol*h/L in in male and female mice, respectively. Based on predicted steady state PK in patients ($C_{max,ss}$ 0.89, 3.0, and 5.9 µmol/L; $AUC_{\tau,ss}$ 11.5, 38.5, and 77.0 h·µmol/L at dose levels 3, 10 and 20 mg/kg), the margins to SOBI003 exposure in the pivotal toxicity studies are thus at least 100-fold for a starting dose of 3 mg/kg and at least 10-fold for a dose of 20 mg/kg. Further details are presented in the SOBI003 investigator brochure.

5.1.4 SOBI003 immune mediated reactions

In an initial explorative study in MPS IIIA mice, where the efficacy of 3 different sulfamidase derivatives was assessed (whereof SOBI003 was one), hypersensitivity reactions were encountered following treatment with SOBI003. Mice were given the test articles at 30 mg/kg every other day as a bolus injection without antihistamine pretreatment. The study was terminated due to hypersensitivity reactions in connection with the fifth i.v. dose. A second study was performed, where the mice were pretreated with the antihistamine chlorpheniramine, and the injection rate was extended to approximately 5 to 10 seconds per injection. The same test articles, doses, and dose frequencies were applied as in the initial study, and the second study could be finalized as planned without any abnormal observations (a 25-day treatment period with a total of 13 injections). Subsequently, antihistamine pretreatment was included in the chronic efficacy studies.

The nonclinical studies in MPS IIIA mice show that ADAs are generated against SOBI003. The ADA response did not compromise safety or alter the exposure, as assessed at 24 hours after last dose administration. A number of chronic efficacy studies have been performed with antihistamine pretreatment in MPS IIIA mice without observing any obvious toxicities or lack of efficacy. In cynomolgus monkey a repeated dose paradigm with doses once every third day indicated that ADAs have an impact on SOBI003 exposure. ADAs did not appear to impact the C_{max} in plasma, but possibly the AUC. Apart from these deviations, exposure after the last dose was similar to that observed after the first dose. No ADA development was seen in the pivotal juvenile rat toxicity study.

Development of ADAs is a common finding in ERTs and correlates to the degree of endogenous enzyme expression (14, 15, 16, 17). Nonclinical assessments of immunogenicity of human proteins, applying in silico, in vitro, or animal models have, so far, shown only limited or no translatability to the clinical situation.

The polypeptide sequence of SOBI003 is identical to human sulfamidase. However, as a result of use of the CHO expression system and the glycan modifications, through which some peripheral carbohydrate ring structures in the glycans are linearized, the overall structure of SOBI003 is not identical to human sulfamidase. Therefore, an immune reaction to SOBI003 may be expected in analogy to what occurs with other ERTs. ADAs and their impact on safety, PK and PD are monitored closely in the Phase I/II study.

5.2 Study rationale

SOBI003 is being developed for treatment of MPS IIIA. Scientific advice on the nonclinical and chemistry, manufacturing and control (CMC) development was obtained from the FDA on 16 February 2016 and from EMA on 28 June 2016. A pre-IND meeting was held with the FDA on 21 June 2017 to obtain agreement on the conduct of this first-in-human study with SOBI003.

This first-in-human study is designed to assess the safety, tolerability, PK, PD and immunogenicity of SOBI003 at 3 dose levels to provide knowledge needed to optimize the further evaluation of SOBI003 in patients with MPS IIIA.

Given the above and that for ERTs, healthy volunteers are not a representative population for assessment of tolerability, immunogenicity or PD, the SOBI003 first-in-human study is conducted in MPS IIIA patients. The severity of disease and the limited number of patients with an acceptable level of mental and physical stability to allow study assessments warrant a condensed clinical development program. This integrated Phase I/II study will therefore also include the establishment of a clinically relevant PD dose-response relationship for SOBI003.

5.3 Potential risks and benefits

MPS IIIA is an irreversible, progressive, life-shortening disease with no existing effective therapeutic alternative. SOBI003 provides a potential clinical benefit by reducing the levels of

stored HS and its metabolites and thereby reducing neuroinflammation which potentially could reduce the clinical manifestations.

Apart from ADA development in two species (MPS IIIA mouse and cynomolgus monkey) out of the three included in the pivotal toxicity program, which is an expected finding considering the foreign nature of a human protein to animal species, the nonclinical safety evaluation of SOBI003 did not show any signs of adverse effects, thus SOBI003 was well-tolerated.

Given the observed pharmacological and toxicological profile in the non-clinical studies, it is judged that SOBI003 can be given to man in a carefully monitored First-In-Human study. Adherence to study inclusion/exclusion criteria, staggered dose escalation, close clinical monitoring, and stopping rules will be applied.

Hypersensitivity reactions/immune-mediated adverse reactions, including anaphylaxis and infusion reactions, are commonly reported for lysosomal ERTs. To reduce the incidence and severity of these adverse reactions, slow infusion rates, prolonged infusion duration and pretreatment with antihistamines will be applied. Severe and potentially life-threatening adverse hypersensitivity/immune-mediated reactions may however still occur.

Close clinical supervision by medical staff that are experienced with ERT treatment will be applied during and after the infusions. This will ensure early detection and adequate treatment of potential adverse reactions. Potential hypersensitivity reactions including anaphylactic events and infusion related reactions will be treated in accordance with the current anaphylactic algorithm (19) including treatment with antipyretics and additional antihistamines to manage milder hypersensitivity/immune-mediated reactions. Availability of cardiopulmonary resuscitation equipment and immediate access to emergency medical services will be secured.

Potential delayed hypersensitivity reactions may occur outside the hospital setting (refer to Section 7.1. for minimum hospitalization periods during study participation). Parents/caregivers will be carefully informed of potential signs and symptoms of hypersensitivity reactions and of the importance to seek immediate medical attention.

The potential clinical benefit of the 24-week treatment period of this study is expected to be limited as the need of ERT is expected to be life-long. Therefore, patients that complete the 24-week treatment period will be offered to receive continued SOBI003 treatment by participation in an extension study. Furthermore, the dose-levels applied in this study are expected to be sufficiently pharmacologically active to result in peripheral and central reduction of HS, potentially also reducing or stabilizing neuroinflammation, and neurodegeneration with potential effect on clinical manifestations including amelioration of neurocognitive dysfunction in these patients with MPS IIIA. These predictions are based on current nonclinical data, and are thus to be confirmed in clinical studies.

Potential study procedural risks include the use of sedation/general anesthesia, the surgical procedure and use of a central venous access port. To minimize study related risks, local hospital procedures will be applied for the procedures. The selection of anesthetic method will be in accordance with local hospital routines and as judged by pediatric anesthesiologist with prior experience from MPS patients. The local surgeon will make the decision on which vein to be used for the central venous access port for each individual patient. The parents/caregivers will be

trained in management of the port, in accordance with local hospital routines. This includes the actions to take in case an infection is suspected. SAEs are captured from the time the ICF is signed and adverse events are captured from the start of the first SOBI003 infusion.

In summary, the potential benefits of SOBI003 treatment are considered to outweigh the foreseeable risks.

6 Study objectives and endpoints

6.1 Primary objective

The primary objective is:

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

6.1.1 Primary endpoint

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

- Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

6.1.2 Secondary endpoints related to the primary objective

The secondary endpoints to evaluate 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)

6.2 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 (NCA)
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

6.2.1 Secondary endpoints

The endpoints relating to the 1st secondary objective are:

- Serum SOBI003 PK parameters at Weeks 1, 4, 12, 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 neutralizing antibodies (NAb) in serum.
- Occurrence of ADAs against SOBI003 in CSF (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 and 24
- Change from baseline in urine HS at Weeks 2, 3, 4, 8, 12 and 24

The endpoint relating to the 4th secondary objective are neurocognitive Development Quotient (DQ) ad age-equivalence score (AEq) 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 age-equivalence score (AEq) 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 endpoints 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.

6.3 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 6.3.1
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 effect of SOBI003 on HS levels in CSF, serum and urine by the use of population modelling 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

Serum, CSF, and urine samples for potential future pharmacogenetic and biomarker analyses will be stored for a maximum of 10 years following study completion. The results of any such analyses will not be included in the Clinical Study Report for this study, but reported separately when analyzed, thus enabling exploration of any emerging novel disease-related discoveries of e.g., previously unknown alleles, inflammatory cytokines, other HS biomarkers (e.g. HS metabolites), components of the complement system, and neurodegeneration.

6.3.1 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 24
- Fine 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
- 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 in from baseline at Week 24
- FA and MD of cerebral white matter as assessed by diffusion tensor imaging MRI; change in from baseline at Week 24

- Cerebral white matter as assessed by susceptibility weighting imaging (SWI) MRI; change in from baseline at Week 24
- Basal ganglia as assessed by susceptibility weighting imaging (SWI) MRI; change in 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 endpoint 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 Clinical Study Report for this study, but reported separately.

7 Investigational plan

7.1 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, PK and PD of SOBI003 in pediatric MPS IIIA patients.

SOBI003 is administered as weekly 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 pretreated 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. The principal investigator and Sobi may decide to replace patients withdrawn prematurely, when applicable. An additional cohort comprising 3 patients may be added, if deemed necessary to more accurately characterize the safety, tolerability, PK or PD. The total number of patients to be exposed to SOBI003 is not to exceed 15.

The study population is MPS IIIA patients that are 1 to 6 years of age, excluding patients with the S298P genotype. The study is planned to be conducted in the U.S.A., Turkey, Netherlands and Germany, at up to five study sites in total.

A central venous access port is used for SOBI003 infusions and for PK, PD and safety laboratory blood samplings. Blood sampling from additional peripheral line is applied in accordance with local hospital routine and also to verify PK analyses from the central line (Section 7.5.6.1). Refer to Section 7.5.1.3 for details on insertion of the port.

At the start of screening, i.e., when the ICF is signed, the majority of patients are expected to already have a confirmed MPS IIIA diagnosis, either by genotyping or verification of reduced sulfamidase enzyme activity. The anticipated number of screen failures is therefore expected to be low, i.e., 10 to 20% or up to 2 patients.

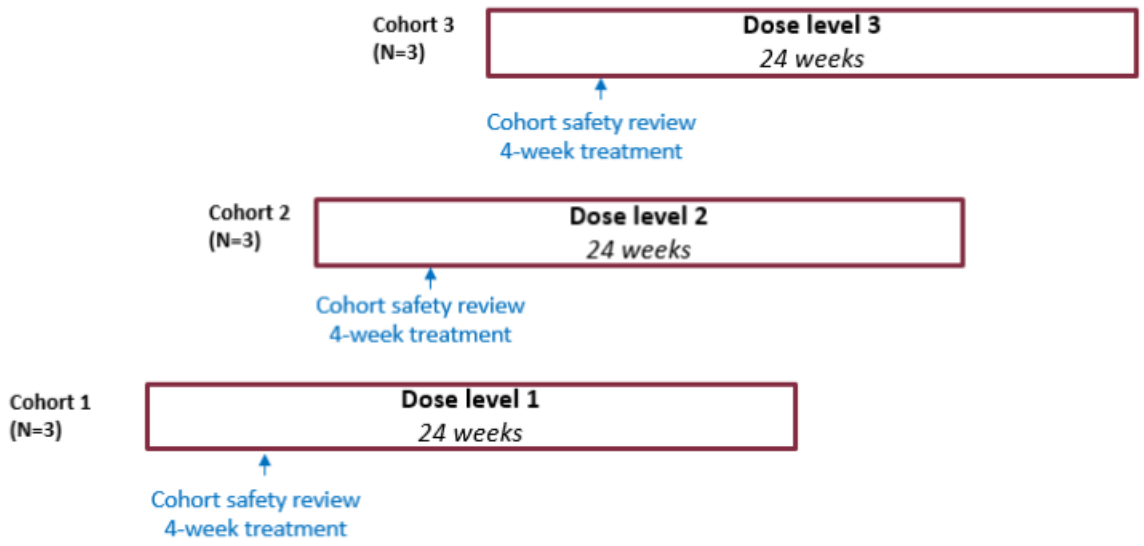
The screening visit can be performed up to 12 weeks prior to the first SOBI003 infusion. At the screening visit, the MPS IIIA diagnosis is verified and the genotype is determined at a central laboratory (see Section 7.5.2.1). To determine the patient's developmental age, the VABS-II is assessed by interviewing the patient's parent/caregiver and the mean of the subdomain age-equivalence scores is determined. Once the patient eligibility has been confirmed, visits are scheduled for baseline assessments and insertion of a central venous access port (see Section 7.5.1.3). The baseline assessments and procedures should be performed within 6 weeks prior to the first SOBI003 infusion. There should however be at least 2 weeks between the insertion of the venous access port and the first SOBI003 infusion, and the VABS-II and BSID-III/KABC-II should be assessed within 2 weeks prior to the first SOBI003 infusion. The total study duration for an individual patient will range from 31 to 36 weeks.

Patients are assigned to a dose cohort in consecutive order as the eligibility criteria have been confirmed, 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.

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 the first patient within each dose cohort, the investigator will review safety data, including the safety laboratory results, and signs and symptoms captured up to Day 6 of the dosed patient and notify Sobi in writing of his conclusion of adequate safety for exposing a new patient to the same SOBI003 dose level. Once the adequate safety has been concluded for the first patient, invasive baseline assessments of the next patients in the cohort can be initiated. There will be a minimum of 3 days between treatment initiations in the 2nd and 3rd patient within the cohort. Before the 3rd patient within the same dose cohort is exposed to SOBI003, the investigator will review available safety data and signs and symptoms of the dosed patient(s) at his/her site and notify Sobi in writing of his conclusion of adequate safety for exposing a new patient to the same SOBI003 dose level. Sobi will then confirm whether a new patient can be dosed. Should the investigator or Sobi have any safety concerns, then an *ad hoc* SRC meeting will be summoned to determine dosing of additional patients.

For each cohort, SRC meetings are scheduled approximately 3 weeks after completion of the 3rd patient's 4th dose administration. Prior to commencing invasive baseline assessments of patients for the next cohort, the SRC will review pre-specified safety, immunogenicity, and PK data to confirm that continued dosing is safe. In addition, PD data in terms of HS in serum and urine, as well as any available HS levels in CSF, will be reviewed. Based on the safety, immunogenicity, PK and PD data, the SRC will determine what dose to apply in the next cohort (see Section 7.5.5.9).

Figure 1 Overview for study design for Study SOBI003-001



Study-specific stopping criteria, both at individual patient level and at cohort(s) level are presented in Section 7.5.5.9.1.

The dose level for Cohort 1 is selected on the basis of nonclinical data, the PK/PD *in silico* model and the emerging toxicology data (see Section 7.4.5.1).

Close clinical monitoring of patients will be required during and after SOBI003 administration for any symptoms of anaphylaxis, hypersensitivity reactions, circulatory and/or respiratory changes, urticaria, or other signs of related reactions. Anaphylactic reactions will be treated in accordance with current anaphylaxis algorithm "Hypersensitivity to Biological Agents - Updated Diagnosis, Management, and Treatment" issued by the American Academy of Allergy, Asthma & Immunology (AAAI) (19).

To secure the close monitoring of the patients and the intensified study assessments following the 4th, 12th and 24th infusions, the minimum hospitalization periods specified in Table 1 are applied:

Table 1 Minimum hospitalization periods

Infusion No.	Minimum hospitalization period*
1 to 3	Admission; day prior to 1st infusion for pre-dose assessments Discharge; 48 hours after initiation of 3rd infusion
4 to 8, 12, and 24	Admission; day of infusion Discharge; 48 hours after initiation of each infusion
9 to 11, 13 to 23	Admission; day of infusion Discharge; 12 hours after initiation of each infusion

* Extended as per local routine for admission/discharge and per patient need as determined by the investigator (e.g., concurrent illness, travel distance etc.)

Prior to discharge following the third infusion, the parents/caregivers will be carefully informed of potential signs and symptoms of hypersensitivity reactions including rash, itching, sweating, swelling of lips/tongue/face, vomiting, noisy breathing, dizziness, fainting as well as late reactions such as dermatological events/skin reactions such as contact dermatitis, maculopapular rash/eruptions, bullous eruptions/dermatitis/exanthemas, pustular exanthemas, and of the importance to seek immediate medical attention. An emergency card containing details on how to seek medical help will be provided to each parent/caregiver and they will be instructed to always carry the emergency card with them. The card will also contain brief details on the study treatment and contact details to site staff in order to secure appropriate medical management of any emergency situation that has to be managed outside the study site.

Depending on the distance and any travelling difficulties, the patient and parent(s) may be relocated for the full study duration. The families are reimbursed for travel and accommodation expenses and, if applicable, for caregiver meals during the hospitalization periods. Appointed study coordinators will assist the families with travel and accommodation arrangements.

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.

A DMC will monitor safety data at pre-specified intervals throughout the 24-week and the extension studies.

7.2 Discussion of study design

Regulatory advice on the design of the Phase I/II study was obtained from the FDA on 21 June 2017.

The non-controlled design of the FIH study is justified by the MPS IIIA disease severity, rapid progression, lack of available treatment and the limited number of potential patients for study participation.

Three sequential dose levels with 3 patients in each cohort will enable assessment of safety and tolerability, as well as characterize a pharmacodynamic dose-response relationship.

A study duration of 24 weeks has been chosen to enable establishment of a dose-response relation in terms of reduction of HS in CSF.

Patients between 1 and 6 years of age who have not received previous treatment for MPS IIIA with an ERT, gene- or stem cell therapy will be eligible to participate in this study. Patients carrying the S298P mutation, a mutation that is associated with a slower progression of disease, will be excluded to reduce the variability in HS levels in CSF.

Patients below 1 year are considered more vulnerable and it would be preferable to initiate inclusion of such patients after the safety of SOBI003 has been established in older patients. In addition, the lower age limit of 1 year has been selected to reduce the potential variability in SOBI003 PK and to ensure that the blood sampling volumes needed for the Phase I/II study can be collected. Applying the European Commission guidance (20), the study-related blood loss should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time. In an average 1 year-old child with a bodyweight of 10 kg, it is thus considered acceptable to draw blood volumes of 8 mL as a single draw and 24 mL over a 4-week period, assuming an estimated blood volume of 80 mL/kg. These volumes are considered appropriate to adequately monitor safety and to generate data enabling conclusions on PK and PD. The upper age limit of 6 years has been selected to exclude patients that are close to progressing or who have progressed to a more severe state of disease which might interfere with protocol compliance.

As a precautionary measure, staggered dosing is applied. For the first patient within each dose cohort, the investigator will review safety data, including the safety laboratory results, and signs and symptoms captured up to Day 6 of the dosed patient and notify Sobi in writing of his conclusion of adequate safety for exposing a new patient to the same SOBI003 dose level. There will be a minimum of 3 days between treatment initiations in the 2nd and 3rd patient within the cohort. This staggered treatment initiation is expected to be sufficient to monitor for acute and subacute adverse events prior to treating additional patients at the same dose level.

For each cohort, SRC meetings are scheduled approximately 3 weeks after completion of the 3rd patient's 4th dose administration. The 4-week treatment period prior to dose escalation is chosen to enable a detection of an early immunogenicity response following limited number of repeated doses. In addition, based on current data, steady-state of SOBI003 in serum is expected to have been approached at this time point.

7.3 Selection of study population

7.3.1 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 Vineland Adaptive Behavior Scales, Second Edition (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

7.3.2 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 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 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 ERT for MPS IIIA
7. Concurrent or prior (within 30 days of enrolment into this study) participation in a study involving invasive procedures

7.3.3 Withdrawal of patients from treatment or study

7.3.3.1 Withdrawal from treatment

A patient should be withdrawn from the study treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient's primary caregiver(s). During the informed consent process, the investigator will clarify that it is essential for the patient's safety to be willing to comply with the study protocol requirements, including study safety and immunogenicity assessments following a potential withdrawal of study treatment.

When a patient is withdrawn from study treatment, the date and time of the last SOBI003 infusion and the date and reason for treatment withdrawal should be clearly described in the relevant sections of the case report form (CRF). If a patient is removed from treatment because of an adverse event (AE), the reason for treatment withdrawal should always be stated as 'adverse event' irrespective of whether this was the investigator's or the patient's primary caregiver(s) decision. The study assessments as specified in Section 7.5.1.13 should be completed as soon as possible after making the treatment withdrawal decision. If study treatment is withdrawn due to AE(s), additional safety assessments will be performed at the discretion of the investigator, as warranted by the AE(s) leading to treatment withdrawal.

When possible, non-infusion-related study assessments should continue in accordance with the Schedule of Events (refer to Table 3) until completion of the Week 24 visit.

7.3.3.2 Withdrawal from study

The patient's legally authorized representative is free to withdraw the patient from the study at any time. A patient that is withdrawn from the study should be examined as soon as possible, whenever possible, irrespective of the reason for withdrawal.

Refer to Sections 7.3.3.1and 7.5.1.13 for guidance on applicable study assessments to be completed when the decision to withdraw from the study coincides with the decision to withdraw study treatment.

For any patient that is found to be ADA-positive after completion of the repeated Early Termination assessments (as specified in Sections 7.5.1.13 and Table 3), every effort should be made to continue ADA samplings at approximately monthly basis until the ADA has disappeared or titers have stabilized at a lower level (refer to Sections 7.5.5.3 and 7.5.6.1).

Irrespective of the study assessments to be performed in case of treatment and/or study withdrawal, a patient that is withdrawn from study treatment due to an adverse event, should be followed up until the AE(s) leading to treatment withdrawal are either resolved or have stabilized even after the patient's participation in the study is over. Each clinically significant abnormal laboratory value or other clinically meaningful abnormality should be followed until the abnormality resolves or until a decision is made that it is not likely to resolve.

7.3.4 Replacement of withdrawn patients

The principal investigator and Sobi may decide to replace patients that are withdrawn prematurely from treatment, when applicable. Any new patient will be assigned to the same study cohort as the withdrawn patient.

7.3.5 Specific restrictions/requirements on patients

The patients are required to remain hospitalized from the time of first SOBI003 infusion until at least 48 hours after initiation of the 3rd SOBI003 infusion. After discharge following the 3rd infusion and until admission for the 9th infusion, the patients are requested to stay within a reasonable distance from the site to allow timely follow-up of applicable AEs. For patients living far away from the study site, temporary accommodation may be provided. Following the 9th infusion, the patients may move back to their homes to attend the site weekly for the infusions at the site. All patients will however be required to be hospitalized up to 48 hours after initiation of the 12th and 24th infusions, due to the schedule of study assessments, including anesthesia.

7.4 Treatments

7.4.1 Treatments administered

In this open-label non-controlled study, the investigational medicinal product (IMP) is SOBI003.

SOBI003 is administered as 4-hour i.v. infusions given once weekly for a duration of 24 weeks. In case of occurrence of infusion reactions, the infusion duration may be prolonged up to 24 hours at the discretion of the investigator.

Three dose levels of SOBI003 will be assessed, provided that the SRC concludes that the safety profile is acceptable. The planned lowest dose level is 3 mg/kg (cohort 1). For cohorts 2 and 3, the dose levels will be selected on basis of at least 4-week safety, PK, immunogenicity, and PD data of prior dose cohort(s) as well as applicable toxicology data (refer to Section 7.4.5). An additional cohort comprising 3 patients may be added, if deemed necessary for safety, tolerability, PK or PD evaluation.

SOBI003 solution, 20 mg/mL, is mixed with NaCl 0.9% infusion solution prior to administration. For a bodyweight < 25 kg, the total infusion volume is 100 mL. For a bodyweight ≥ 25 kg, the total infusion volume is 250 mL.

Actual materials to be used for mixing SOBI003 solution with NaCl infusion solution (i.e., infusion solutions, syringes and needles) and for administering the infusions (i.e., infusion lines, syringes, manifolds, venous access ports) must be preapproved by Sobi to secure that all materials are compatible with SOBI003.

Detailed IMP preparation instructions are provided in a separate IMP manual.

Table 2 Investigational medicinal products

Cohort	Investigational product	Dosage form	Route	Weekly dose	Dosage regimen
1	SOBI003	Solution for infusion	i.v.	3 mg/kg	4-hour infusion given once weekly
2	SOBI003	Solution for infusion	i.v.	X mg/kg[1]	4-hour infusion given once weekly
3	SOBI003	Solution for infusion	i.v.	Y mg/kg[1]	4-hour infusion given once weekly

[1] Actual dose levels are determined by SRC (refer to Section 7.4.5).

7.4.2 Identity of investigational medicinal products

SOBI003 is provided as concentrate for solution for i.v. infusion, 20 mg/mL, in 5-mL injection vials. Each vial contains 4 mL. Ten vials are packed in one box/outer carton. Vial and outer carton labeling will comply with national regulatory requirements. To facilitate accurate drug accountability, vial-specific numbers are printed on the vial labels.

The drug substance is manufactured by Swedish Orphan Biovitrum AB (publ), SE-112 76 Stockholm, Sweden. The drug product is manufactured by Rechon Life Science AB, SE-216 13 Limhamn, Sweden. Secondary packaging of vials and labeling of cartons is done by Almac Group, 4204 Technology Drive, Durham NC 27704, U.S.A.

SOBI003 is shipped and stored at frozen conditions.

Possible deficiencies related to the handling, storage and quality of the IMPs should be reported to the study monitor and also directly to complaints@sobi.com.

7.4.3 Method of assigning patients to a treatment group

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

The terminology of "enrolled patients" refer to patients that have been assigned an enrolment number. The terminology of "included patients" refer to patients that have been assigned a subject number (and hence, assigned to a specific cohort).

The first 3 included patients are thus assigned to Cohort 1 and administrations of SOBI003 at 3 mg/kg/week.

7.4.4 Selection of doses

7.4.5 Selection of dose levels

7.4.5.1 Dose level for Cohort 1

The starting dose of 3 mg/kg has been selected based on the Maximum Recommended Starting Dose (MRSD) which is derived from the NOAEL defined in the pivotal toxicology studies and an estimation of the pharmacologically active dose (PAD).

The nonclinical safety evaluation of SOBI003 did not show any signs of adverse effects. Thus, the safety evaluation of SOBI003 has shown that it is well-tolerated. Also, improvements in the disease state in MPS IIIA mice were shown. A dose dependent, partially reversible accumulation of eosinophilic material in the cytoplasm of macrophages of various origin was observed in all three species, but these were considered to be a result of a normal physiological function of tissue macrophages and were therefore not considered to be adverse. Consequently, the NOAEL was set to the highest dose administered in the three species tested, i.e., 300 mg/kg in the rodents and 150 mg/kg in the cynomolgus monkeys. Based on predicted steady state PK in patients (C_{max} 0.89 µmol/L; $AUC_{\tau,ss}$ 11.5 h·µmol/L for the dose level 3 mg/kg), the margins to SOBI003 exposure in the pivotal toxicity studies are at least 100-fold for a starting dose of 3 mg/kg. Further details are presented in Section 5.3.13 of the investigator brochure.

The MRSD is estimated to 2.4 mg/kg and has been based on the NOAEL derived from the pivotal toxicology studies in MPSIII A mice. The lowest HED when calculated from the NOAELs was obtained from the MPS IIIA mice constituting the most sensitive species in the toxicology studies. The highest dose in this study, 300 mg/kg did not cause any adverse effects. The NOAEL can therefore be determined to be at least 300 mg/kg. The body weight-adjusted human equivalent dose (HED) can thus be calculated to be 24 mg/kg, and by using a 10-fold-safety margin the MRSD will be 2.4 mg/kg.

The PAD has been estimated to 3 mg/kg. This is based on model-based simulations using an in silico model where the 3 mg/kg dose level is expected to elicit a potential pharmacological effect in CNS. A repeated dose of 3 mg/kg SOBI003 in humans will gradually result in a HS reduction in the brain of ~35% after 3 months and ~45% after 6 months treatment, whereas only negligible effect is expected after a single dose of 3 mg/kg.

The Minimal Anticipated Biological Effect Level (MABEL) for SOBI003 is based on peripheral HS reduction in liver, spleen, heart, and lung following single dose administration in MPS IIIA mice, and has been set to 0.1 mg/kg. The SOBI003 dose levels that are expected to produce a pharmacological effect in the CNS are much higher, and the SOBI003 exposure in the CNS is much lower than peripherally according to nonclinical distribution studies.

A starting dose of 3 mg/kg is based on PAD and the estimated MRSD (2.4 mg/kg), which however is higher than the MABEL for peripheral effects (0.1 mg/kg). Sobi considers a starting dose of 3 mg/kg justified given the nature of the target, the low risk for off-target toxicities with biologics like SOBI003, that acute toxicities related to on-target sulfamidase enzyme activity are not expected and that SOBI003 does not possess any agonistic properties. Furthermore, the MPS IIIA mouse is considered a relevant pharmacology and toxicology species for SOBI003 (21). Finally, MPS IIIA is a chronically debilitating, progressive, irreversible, life-shortening disease with no effective curative treatment available where the favorable benefit/risk ratio for SOBI003 supports the use of a PAD for the selection of the starting dose.

7.4.5.2 Dose levels for Cohort 2 and 3

With a starting dose of 3 mg/kg and given adequate safety, the planned mid and maximum dose levels are 10 mg/kg and 20 mg/kg, respectively. The SRC will review pre-specified safety, tolerability, immunogenicity, pharmacokinetic and pharmacodynamic data to confirm that continued/escalating dosing is safe (see Section 7.5.5.9). SRC can also decide to await further safety data, apply the same or a lower dose level for the next cohort, halt or discontinue the study. The highest expected target dose of 20 mg/kg will be guided by emerging safety and tolerability data in this study. Predicted serum concentrations of SOBI003 at 20 mg/kg in humans are 5.9 µmol/L for $C_{max,SS}$ and 77.0 h*µmol/L for $AUC_{\tau,SS}$. This provides a 15-fold margin between predicted exposure at 20 mg/kg and the NOAEL in the most sensitive species (MPS IIIA mice) (for details, refer to Section 5.3.13 of the SOBI003 investigator brochure). Based on the preclinical PK/PD model translated to patients, the effect on HS reduction is predicted to be both time and exposure dependent. Repeated weekly administration of 10 and 20 mg/kg SOBI003 is predicted to achieve a brain HS reduction of ~ 75 % and ~ 80 % after 3

months and ~ 80 % and ~ 85 % respectively after 6 months treatment relative to baseline (refer to Section 7.1 of the SOBI003 investigator brochure)

Dose escalations will continue until the maximum tolerated dose (MTD) is achieved (refer to Section 7.5.5.9.1) or expected target dose is reached.

7.4.6 Selection and timing of doses for each patient

Upon completion of the screening assessments and confirmation of patient eligibility, including confirmation of sulfamidase enzymatic activity, patients are assigned a subject number and allocated to a dose cohort in strict consecutive order.

At the time of the first SOBI003 infusion, the patient should not have clinically significant evidence of ongoing infection, as judged by the investigator, or ongoing treatment with antibiotics. In such cases, the first infusion should be postponed until the infection has resolved.

SOBI003 is administered as 4-hour i.v. infusions given once weekly for a duration of 24 weeks. The infusions are administered by qualified health care professionals. Every effort should be made to have the infusions administered every 7th day. A +/- 1-day window is applied after the 4th infusion. Therefore, if the first infusion was administered for instance on a Wednesday, then the 5th to the 24th infusions can be administered on Tuesdays, Wednesdays or Thursdays.

In case of signs and/or symptoms of ongoing infection at subsequent infusion occasions, infusion may be postponed, as judged by the investigator. If the infusion needs to be postponed more than 3 days, then the investigator should discuss with the Sponsor's MD to determine the timing of the next infusion (i.e., whether to await the next scheduled infusion).

Within 30 to 60 minutes prior to each infusion, a single dose of a non-sedative antihistamine should be administered. The antihistamine can either be e.g., cetirizine, levo-cetirizine, loratadine, des-loratadine or fexofenadine, and the administered doses will be in compliance with locally approved labeling. The antihistamine agent is selected at the discretion of the investigator. Antipyretic medication may also be administered, at the discretion of the investigator.

The actual doses of SOBI003 to be administered should be based on the patient's bodyweight at 4-week intervals (i.e., the actual dose administered at Weeks 1 to 4 is based on the bodyweight obtained pre-infusion at Week 1, the actual dose administered at Weeks 5 to 8 is based on the bodyweight obtained pre-infusion at Week 5, etc.). The body weight is obtained either on the day prior to the infusion or the day of infusion.

SOBI003 concentrated solution is diluted with NaCl 0.9% infusion solution prior to administration. For a bodyweight < 25 kg, the targeted total infusion volume is 100 mL. For a bodyweight ≥ 25 kg, the targeted total infusion volume is 250 mL. If the infusion bag contains an overfill volume, the infusion should continue until the infusion bag is emptied.

The final concentration of SOBI003 in the infusion bag will be calculated based on the added volume of SOBI003 to the infusion bag, and the total volume in the infusion bag.

A slower infusion rate is applied for the initial hour for all dose cohorts, targeting the delivery of 3% of the total dose/infusion volume. The infusion rate will be set to deliver the remaining 97% of the dose/infusion volume over the next 3 hours. Infusion rate schedules are provided in a separate IMP manual.

In case of occurrence of infusion reactions, the infusion duration may be prolonged up to 24 hours at the discretion of the investigator.

The drug accountability records will capture sufficient details to verify the amount of SOBI003 administered at each infusion occasion.

7.4.7 Prior and concomitant therapy

Other therapies considered necessary for the patient's welfare including melatonin for sleep disorder may be given at the discretion of the investigator. Patients on low dose genistein (<10 mg/kg/day) may continue treatment on the same dose throughout the study. All such therapy that is administered or used from the time of enrolment until completion of the study must be recorded in the CRF. This includes prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications and the anesthetic drugs administered during study procedures (oxygen is not captured). Preferably, the treatment regimen should be unaltered during the study and thus only adjusting dose or medication(s) when medically warranted.

No other medicinal product under investigation may be used concomitantly with the IMP(s) in this study. In addition, prior exposure to stem cell or gene therapy and ERT for MPS IIIA will not be allowed.

As described in Section 7.4.6, a single dose of an oral non-sedative antihistamine should be administered prior to start of each SOBI003 infusion. Each administration is recorded in the CRF.

In case of identified infusion-related reactions, immediate treatment is given at the discretion of the investigator. Depending on symptoms, this may e.g., be antipyretics such as acetaminophen (paracetamol), corticosteroids or additional antihistamines. Anaphylactic reactions will be treated in accordance with current anaphylaxis algorithm "Hypersensitivity to Biological Agents - Updated Diagnosis, Management, and Treatment" issued by the AAAI (19). Necessary equipment for resuscitation must be available during study drug infusion.

If clinically justified, patients who develop high titer antibodies that affects PK/PD and/or safety may benefit from the use of an immune tolerizing regimen. As there is no proven immune tolerizing approach established for ERTs in MPS IIIA, approaches used in other LSDs (24) may be applied at the discretion of the investigator after discussion with Sobi Medical Director.

7.4.8 Treatment compliance

Product accountability records will be kept. The pharmacy and investigator must maintain accurate records demonstrating date and amount of IMP(s) received, to whom and by whom

administered (patient-by-patient accounting), and accounts of returned IMP(s) and any IMP accidentally or deliberately destroyed.

All unused IMP will be counted. At the end of the study, any remaining IMP(s) will be returned to Sobi for destruction, or destroyed locally. In either case, a certificate of destruction must be issued.

7.5 Efficacy, safety, pharmacokinetic, and pharmacodynamic assessments

7.5.1 Study schedule

7.5.1.1 Schedule of events

Table 3 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**	**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
Physical examination[e]	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
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	
SOBI003 administration[i]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X[j]	X[j]	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**	**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
Immunogenicity		X		X		X			X		X					X	X
HS		X		X	X	X			X		X					X	X
PK[q]	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
HS	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 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 Early Termination 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 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 at the infusion site are examined prior to start of each infusion and within 1 hour of completion of each infusion.

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.

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 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 Early Termination 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, 4, 12, and 24. Samples are also collected before start of infusion and at completion of the infusion at weeks 2, 3 and 8. 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 Table 6.

r Sleep pattern is assessed by actigraph recordings for 7 consecutive days at Baseline and at Weeks 11-12 and 23-24, i.e., Baseline assessment should preferably be completed prior to any anesthetic/sedation is applied and prior to PK and HS blood samplings. . At Weeks 11 and 23, the aim should be to have the recordings completed 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 (i.e., at Weeks 12 and 24 this will be during the infusion days).

s In case both BSID-III and KABC-II are to be administered, the BSID-III should be administered first, and there should be at least 2 days between the BSID-III and KABC-II 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.

Table 4 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	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

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.
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, 4h (end of infusion), 6, 12, 24, 48, 96, 120 and 168 h after start of infusion. In case SOBI003 infusion is prolonged, applicable adjustments the PK sampling time points are applied (refer to Table 6).

Table 5 Detailed schedule of events – Weeks 12 and 24

		Weeks 12 and 24												Week 12	Week 24 END
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**3**	**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
Physical examination	X[b]						X[b]								X
Neurological examination															X
Height & head circumference														X	X
Weight	X[k]														X
Vital signs	X			X			X				X				
12-lead ECG	X						X								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
Anesthesia for:															
CSF sampling (PK, ADA, HS, future research[e])										X					
MRI (brain, spleen, liver)										X[f]					
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]

		Weeks 12 and 24												Week 12	Week 24 END
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**3**	**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**						
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
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 h (end of infusion), 6, 12, 24, 48, 96, 120 and 168 h after start of infusion. The 168h sample at Week 12 is thus taken prior to start of infusion on Day 1 of Week 13. The 168h sample at Week 24 is thus taken on Day 8 (For patients continuing in the Extension study, 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, the BSID-III should be administered first, and there should be at least 2 days between the BSID-III and KABC-II assessments (i.e., the BSID-III should then be administered on Days 4 or 5 of Week 24 and the KABC-II 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.

Table 6 Detailed PK blood sampling schedule

Week	Time	BW ≥20 kg No of samples[a]	BW 15 to <20 kg No of samples[a]	BW 10 to <15 kg No of samples[a]
	Screening	1	1	1
	Baseline	1	1	1
Week 1	**4h / End of Infusion [b] (Day 1)**	2	2	2
	6h [b] (Day 1)	2		
	12h[b] (Day 1)	2		
	24h (Day 2)	2	2	
	48h (Day 3)	1		
	96h (Day 5)	1	1	
	120h (Day 6)	1	1	
Week 1 (2)	**168h/Pre-infusion (Day 8)**	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[b](Day 1)	2	2	2
	6h[b] (Day 1)	2	2	
	12h[b] (Day 1)	2	2	
	24h (Day 2)	2	2	2
	48h (Day 3)	1	1	
	96h (Day 5)	1	1	1
	120h (Day 6)	1	1	
Week 4 (5)	**168h/ Pre-infusion (Day 8)**	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[c] (Day 1)	2	2	2
	6h[c] (Day 1)	2	2	
	12h[c] (Day 1)	2	2	
	24h (Day 2)	2	2	2
	48h (Day 3)	1	1	
	96h (Day 5)	1	1	1
	120h (Day 6)	1	1	
Week 12 (13)	**168h/ Pre-infusion (Day 8)**	1	1	1
Week 24	**Pre-infusion**	1	1	1
	4h / End of Infusion[b] (Day 1)	2	2	2
	6h[b] (Day 1)	2	2	

	12h[b] (Day 1)	2	2	
	24h (Day 2)	2	2	2
	48h (Day 3)	1	1	
	96h (Day 5)	1	1	1
	120h (Day 6)	1	1	
	168h (Day 8)	1	1	1
If Early Termination	**Eerly termination of SOBI003 treatment**	1	1	1
After final infusion (If additional Immunogenicity samples)	**Day 30-40 after final infusion**	1	1	1
	Additional time-point 1	1	1	1
	Additional time-point 2	1	1	1
	Additional time-point 3	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 Section 7.5.6.1).

7.5.1.2 Screening

The screening assessments are initiated after completion of the informed consent process, including the provision of signed consent for study participation. The patient is assigned a site-specific enrollment number once the informed consent has been signed.

SAEs are reported from the time point when the ICF has been signed.

Information on medical history, demography and prior and concomitant medications are obtained. Neurological and physical examinations are performed. Vital signs, 12-lead ECG and echocardiography are performed. Weight is assessed. Blood and urine samples are obtained for central laboratory analyses of safety laboratory variables (see Section 7.5.5.2). Screening assessment results are used to confirm medical stability and exclusion of contraindications for anesthesia, lumbar puncture, and MRI.

Leucocytes are obtained for central laboratory analyses of sulfamidase enzyme activity (Section 7.5.2.1). Blood is obtained for central laboratory SGSH genotyping and PK analysis (Sections 7.5.2.1 and 7.5.6.1). Urine is collected for central laboratory analyses of HS (Section 7.5.7.1.2).

The VABS-II is assessed by interviewing the parent/caregiver (see Section 7.5.4.1).

All Screening assessments do not have to be completed on the same day, but should be completed to allow Baseline assessments to be completed within 6 weeks prior to first SOBI003 infusion.

If SAEs have occurred since the informed consent was signed, these are reported in accordance with Section 7.5.5.1.4.

7.5.1.3 Baseline

Once patient eligibility is confirmed, including the central laboratory results of the patient's sulfamidase activity and SGSH genotype, the baseline procedures are initiated. Applicable

hospital visits and/or hospitalizations are scheduled to have the baseline assessments and procedures completed within 6 weeks prior to first planned SOBI003 administration.

Information on medical history and prior and concomitant medications are obtained. This includes events observed/diagnosed during the baseline period. If SAEs have occurred since the informed consent was signed, these are reported in accordance with Section 7.5.5.1.4.

Height, head circumference and weight are obtained. A physical examination is performed.

The parent/caregiver is given an actigraph together with the actigraph log and is instructed on how to apply and use the device and how to complete the log (see Section 7.5.4.5). Written instructions are also provided, including on when to make the 7-day baseline assessment of sleep pattern. The aim should be to have the recording completed prior to any anesthesia/sedation is applied.

Blood is collected to have a baseline assessment of hsCRP, IL-1ra, TNFα, IgE and tryptase in case of occurrence of an acute reaction or anaphylactic reaction during the study treatment period. For patients for whom separate informed consent has been provided for future research, whole blood, serum and urine (for biomarker analyses) is collected and sent for storage at the central laboratory. When possible, these baseline blood samples should be collected at least 4 weeks prior to the planned start of SOBI003 infusion in order to minimize the total blood volume drawn within one-month timeframes.

A central venous access port is inserted. The surgical procedure is performed in accordance with local hospital routines, including the applicable anesthetic procedure to apply, the selection of central vein, and confirmation of subsequent venous access by X-ray. The brand and type of port must however be preapproved by Sobi (see Section 7.4.1). The parents/caregivers will be trained in the management of the port in accordance with local hospital routines. This includes the actions to take in case an infection is suspected. There should be at least 2 weeks between the insertion of the venous access port and the first SOBI003 infusion.

A skin biopsy is taken for assessment of CRIM status in fibroblasts. The biopsy should preferably be obtained at least 2 weeks prior to the first SOBI003 infusion.

General anesthesia/sedation is applied in accordance with local hospital routines and as determined by the anesthesiologist. CSF sampling (a total of 0.9 mL) for PK, ADA and HS assessments and MRI scanning of brain, liver and spleen are completed while the patient is anesthetized. The order of the procedures should preferably be as stated. Should this not be feasible, then effort should be made to have the assessments performed in the same order at each assessment time point (i.e., at Baseline and Week 24) for an individual patient. When separate consent for future research has been provided, then CSF (1.0 mL) will also be collected for storage at the central laboratory.

At the day of CSF sampling, serum samples are collected for PK, HS and immunogenicity analysis and a urine sample is collected for analysis of HS.

The VABS-II is assessed by interviewing the parent/caregiver (see Section 7.5.4.1). The VABS-II should be completed within 2 weeks prior to first SOBI003 infusion. Based on the patient's chronological age and the adaptive behavior age-equivalent score, as determined by the VABS-II, the BSID-III and/or KABC-II tests are conducted for assessment of neurocognition, language and motor function (see Sections 7.5.4.2, 7.5.4.3, and 7.5.4.4, respectively). The BSID-III/KABC-II should be completed within 2 weeks prior to first SOBI003 infusion. Attempts

should be made to have the neurocognition, language, and motor skills assessed at least 5 days after any anesthesia/sedation.

Any SAEs should be reported in accordance with Section 7.5.5.1.4.

The parent/caregiver completes the CSHQ and PedsQL questionnaires. The completion of the questionnaires should be distributed over the Baseline visit in order to avoid that the parent/caregiver spends more than one hour at a time for questionnaire completion.

7.5.1.4 Week 1

The patient is admitted to the hospital the day prior to the first SOBI003 infusion.

Prior to start of the infusion, the following is performed:

- Body weight is obtained either the day prior to the infusion or the day of infusion
- Medical history and prior and concomitant medication are obtained
- General appearance and skin are assessed
- Vital signs are assessed and a 12-lead ECG is obtained
- Blood and urine is collected for safety laboratory assessments

The results of the above assessments will constitute the patient's baseline.

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. Antibiotic treatment should also be completed, when applicable, prior to start of SOBI003 treatment.

Within 30 to 60 minutes prior to start of the SOBI003 infusion, a single dose of an oral non-sedative antihistamine is administered. A pulse-oximeter is applied and SOBI003 infusion is initiated. Refer to Section 7.4.6 for infusion details. Day 1 of Week 1 constitutes the day of the first SOBI003 infusion.

Adverse events and concomitant medications are captured continuously from the start of the first infusion until study completion.

At hourly intervals during the infusion, (i.e., at approximately 1, 2 and 3 hours after start of infusion) vital signs, general appearance and skin are assessed.

Upon completion of the 4-hour infusion, and as soon as practically possible, a PK blood sample is obtained. Within an hour of completion of the infusion, vital signs, general appearance and skin are assessed. In addition, a 12-lead ECG is obtained and the continuous pulse oximetry is discontinued.

Vital signs (including oxygen saturation), general appearance and skin are assessed on Day 1 (within 6 to 7 hours after start of infusion, and also within 8 to 12 hours after start of infusion) and on Days 2, 3 and 5.

Blood and urine is collected for safety laboratory analyses on Day 3. Blood is collected for PK analyses at Days 1, 2, 3, 5, and 6 at time points specified in Section 7.5.6.1.

Well in advance of discharge at Week 3, the parents/caregivers will be trained on signs and symptoms of acute and delayed hypersensitivity reactions (both verbally and in writing), and informed on the importance to seek immediate medical attention if hypersensitivity reactions occurs. Acute hypersensitivity reactions include rash, itching, sweating, swelling of lips/tongue/face, vomiting, noisy breathing, dizziness, fainting, and delayed reactions includes dermatological events/skin reactions such as contact dermatitis, maculopapular rash/eruptions,

bullous eruptions/dermatitis/exanthemas and pustular exanthema. They will be instructed on whom to contact in such cases and these details will also be specified on an emergency card that the parent/caregiver is provided. The parent/caregiver will be instructed to always carry the emergency card with them. The card will also contain brief details on the study treatment and contact details to site staff in order to secure appropriate medical management of any emergency situation that has to be managed outside the study site.

7.5.1.5 Week 2

Prior to start of the second infusion (Day 1 of Week 2), the following is performed:

- General appearance and skin are assessed
- Vital signs are assessed and a 12-lead ECG is obtained
- Blood is obtained for safety laboratory assessments, immunogenicity, HS and PK assessments
- Urine is collected for safety laboratory assessments and HS analysis
- Within 30 to 60 minutes prior to start of the SOBI003 infusion, a single dose of an oral non-sedative antihistamine is administered
- A pulse-oximeter is applied

SOBI003 is administered in accordance with Section 7.4.6.

At hourly intervals during the infusion, (i.e., at approximately 1, 2 and 3 hours after start of infusion) vital signs, general appearance and skin are assessed.

Upon completion of the 4-hour infusion, and as soon as practically possible, a PK blood sample is obtained. Within an hour of completion of the infusion, vital signs, general appearance and skin are assessed. In addition, a 12-lead ECG is obtained and the continuous pulse oximetry is discontinued.

Vital signs (including oxygen saturation), general appearance and skin are assessed on Day 1 (within 6 to 7 hours after start of infusion, and also within 8 to 12 hours after start of infusion) and on Days 2, 3 and 5.

Blood and urine is collected for safety laboratory analyses on Day 3.

Concomitant medications and adverse events (including any clinically significant findings from the vital signs, ECG and physical examinations) are recorded continuously.

7.5.1.6 Week 3

Prior to start of the third infusion (Day 1 of Week 3), the following is performed:

- General appearance and skin are assessed
- Vital signs are assessed and a 12-lead ECG is obtained
- Blood is obtained for safety laboratory, HS and PK assessments.
- Urine is collected for safety laboratory assessments and HS analysis
- Within 30 to 60 minutes prior to start of the SOBI003 infusion, a single dose of an oral non-sedative antihistamine is administered
- A pulse-oximeter is applied

SOBI003 is administered in accordance with Section 7.4.6.

At hourly intervals during the infusion, (i.e., at approximately 1, 2 and 3 hours after start of infusion) vital signs, general appearance and skin are assessed.

Upon completion of the 4-hour infusion, and as soon as practically possible, a PK blood sample is obtained. Within an hour of completion of the infusion, vital signs, general appearance and skin are assessed. In addition, a 12-lead ECG is obtained and the continuous pulse oximetry is discontinued.

Vital signs, general appearance and skin are assessed Day 1 (within 6 to 7 hours after start of infusion, and also within 8 to 12 hours after start of infusion) and on Days 2 and 3.

Blood is collected for safety laboratory analyses on Day 3 except for patients <15 kg body weight and urine is collected for safety laboratory analyses on Day 3.

Concomitant medications and adverse events (including any clinically significant findings from the vital signs, ECG and physical examinations) are recorded continuously,

The patient may be discharged from the hospital 48 hours after start of the 3rd infusion. Based on investigator judgement of social and medical circumstances (e.g., distance between hospital and home/relocation accommodation, patient's family situation, patient's general medical condition etc.) the patient may however continue to remain hospitalized.

Prior to discharge, the parent/caregiver will be reminded to always carry the emergency card.

7.5.1.7 Week 4

Patients being discharged during Week 3 will return to the hospital the day prior to or on Day 1 of Week 4. Adverse events and use of concomitant medications during non-hospital stay are captured.

Prior to start of the fourth infusion (Day 1 of Week 4), the following is performed:

- General appearance and skin are assessed
- Vital signs are assessed and a 12-lead ECG is obtained
- Blood is obtained for safety laboratory assessments, immunogenicity, HS and PK assessments
- Urine is collected for safety laboratory assessments and HS analysis
- Within 30 to 60 minutes prior to start of the SOBI003 infusion, a single dose of an oral non-sedative antihistamine is administered
- A pulse-oximeter is applied

SOBI003 is administered in accordance with Section 7.4.6.

At hourly intervals during the infusion, (i.e., at approximately 1, 2 and 3 hours after start of infusion) vital signs, general appearance and skin are assessed.

Upon completion of the 4-hour infusion, and as soon as practically possible, a PK blood sample is obtained. Within an hour of completion of the infusion, vital signs, general appearance and skin are assessed. In addition, a 12-lead ECG is obtained and the continuous pulse oximetry is discontinued.

Vital signs (including oxygen saturation), general appearance and skin are assessed on Day 1 (within 6 to 7 hours after start of infusion, and also within 8 to 12 hours after start of infusion) and on Days 2 and 3.

Blood is collected for PK analyses on Days 1, 2, 3, 5, and 6 at time points specified in Section 7.5.6.1.

The patient may be discharged from the hospital 48 hours after start of the 4th infusion. The patient will then return to the hospital for PK samplings on Days 5 and 6.

7.5.1.8 Weeks 5 to 8

SOBI003 is administered as weekly infusions; a +/- 1-day window is applied. The patients will return to the hospital the day prior to or on the day of each infusion. Adverse events and use of concomitant medications during non-hospital stay are captured.

Prior to start of infusion blood and urine is collected for safety laboratory analyses.

Prior to start of each infusion, vital signs and general appearance and skin are assessed. At Week 5, body weight is also assessed to determine the SOBI003 dose to be administered at Weeks 5 to 8. The body weight is obtained either on the day prior to the infusion or the day of infusion. At Weeks 6 and 8, 12-lead ECGs are obtained. Within 30 to 60 minutes prior to start of each SOBI003 infusion, a single dose of an oral non-sedative antihistamine is administered.

SOBI003 is administered in accordance with Section 7.4.6.

At hourly intervals during the infusion, (i.e., at approximately 1, 2 and 3 hours after start of infusion) vital signs (including oxygen saturation) are assessed. Assessments are also done within an hour of completion of the infusion and within 6 to 7 hours and within 8 to 12 hours after start of infusion, as well as on Days 2 and 3.

Within an hour of completion of the 4-hour infusion, general appearance and skin are assessed.

On Day 1 of Weeks 5 and 8, PK blood samples are collected prior to start of infusion. At Week 8, upon completion of the 4-hour infusion, and as soon as practically possible, another PK sample is obtained.

On Day 1 (prior to start of infusion) of Week 8, blood is collected for immunogenicity and HS assessments and urine is collected for analysis of HS.

On Day 1 of Weeks 6 and 8, 12-lead ECGs are obtained within an hour of completion of the 4-hour infusion.

The patient may be discharged from the hospital 48 hours after start of each infusion.

7.5.1.9 Weeks 9 to 11

SOBI003 is administered as weekly infusions; a +/- 1-day window is applied. The patients will return to the hospital the day prior to or on the day of each infusion. Adverse events and use of concomitant medications during non-hospital stay are captured. Prior to start of each infusion, vital signs and general appearance and skin are assessed. At Week 9, body weight is also assessed to determine the SOBI003 dose to be administered at Weeks 9 to 12. The body weight is obtained either on the day prior to the infusion or the day of infusion. Within 30 to 60 minutes prior to start of each SOBI003 infusion, a single dose of an oral non-sedative antihistamine is administered.

Prior to start of infusion at Week 10, blood and urine is collected for safety laboratory analyses.

SOBI003 is administered in accordance with Section 7.4.6.

Vital signs (including oxygen saturation) are assessed at approximately 2 hours after start of infusion as well as within an hour of completion of the infusion.

Within an hour of completion of the 4-hour infusion, general appearance and skin are assessed.

Prior to discharge at Week 10, the parent/caregiver is given the actigraph and the accompanying diary. The parent/caregiver is instructed to start the sleep assessment 7 days prior to attendance for the 12th infusion.

The patient may be discharged from the hospital 12 hours after start of each infusion.

7.5.1.10 Week 12

SOBI003 is administered as weekly infusions; a +/- 1-day window is applied. The patients will return to the hospital the day prior to or on the day of each infusion. Adverse events and use of concomitant medications during non-hospital stay are captured. The actigraph and accompanying diary are collected.

Prior to start of the infusion, the following is performed:

- Vital signs and a 12-lead ECG is obtained
- General appearance and skin are assessed
- Blood is obtained for immunogenicity, HS and PK assessments
- Urine is collected for HS analysis
- Blood and urine is collected for safety laboratory analyses
- Body weight is assessed to determine the SOBI003 dose to be administered at Weeks 12 to 16. The body weight is obtained either on the day prior to the infusion or the day of infusion.

Within 30 to 60 minutes prior to start of SOBI003 infusion, a single dose of an oral non-sedative antihistamine is administered. SOBI003 is administered in accordance with Section 7.4.6.

Vital signs are assessed approximately 2 hours after start of infusion. Upon completion of the 4-hour infusion, and as soon as practically possible, a PK blood sample is obtained. Within an hour of completion of the infusion, vital signs and general appearance and skin are assessed, and a 12-lead ECG is obtained.

The parent/caregiver completes the CSHQ questionnaires, preferably during Day 1.

On Day 2, CSF sampling (a total of 0.9 mL) is performed for PK, ADA, and HS analysis under general anesthesia/sedation in accordance with local hospital routines. When separate consent for future research has been provided, then CSF (1.0 mL) will also be collected for storage at the central laboratory. Blood for HS analysis should be collected at the same time as the CSF sampling and urine collected for HS analysis should be taken as close as possible to the CSF sampling.

On Day 3, vital signs are obtained. The VABS-II is assessed by interviewing the parent/caregiver (refer to Section 7.5.4.1).

On Days 1, 2, 3, 5 and 6, and 8 blood samples are collected for PK assessments at time points specified in Section 7.5.6.1. On Day 7, height and head circumference are assessed. The body weight is also obtained either on Day 7 of Week 12 OR pre-infusion on Day 1 of Week 13 in order to determine the SOBI003 dose to be administered at Weeks 13 to 16.

The parent/caregiver completes the PedsQL questionnaire, preferably during Day 6.

The patient may be discharged from the hospital 48 hours after start of the 12th infusion. The patient will then return daily to the hospital for study assessments on Days 2 to 4, and on Day 6.

7.5.1.11 Weeks 13 to 23

SOBI003 is administered as weekly infusions; a +/- 1-day window is applied. The patients will return to the hospital the day prior to or on the day of each infusion. Adverse events and use of concomitant medications during non-hospital stay are captured.

Prior to start of each infusion, vital signs and general appearance and skin are assessed. At Weeks 17 and 21, body weight is also assessed to determine the SOBI003 dose to be administered at Weeks 17 to 20 and 21 to 24, respectively. The body weight is obtained either on the day prior to the infusion or the day of infusion. Within 30 to 60 minutes prior to start of each SOBI003 infusion, a single dose of an oral non-sedative antihistamine is administered.

Biweekly, prior to start of each infusion (i.e., at Weeks 14, 16, 18, 20, and 22), blood and urine is collected for safety laboratory analyses. At Week 22, for patients for whom separate informed consent has been provided for future research, blood and urine is collected and sent for storage at the central laboratory.

On Day 1 of Week 13, a PK blood sample is collected prior to start of infusion. SOBI003 is administered in accordance with Section 7.4.6.

Vital signs are assessed approximately 2 hours after start of infusion. Within an hour of completion of the 4-hour infusion, vital signs and general appearance and skin are assessed.

Prior to discharge at Week 22, the parent/caregiver is given the actigraph and the accompanying diary. The parent/caregiver is instructed to start the sleep assessment 7 days prior to attendance for the 24th infusion.

The patient may be discharged from the hospital 12 hours after start of each infusion.

7.5.1.12 Week 24 / last study visit

SOBI003 is administered as weekly infusions; a +/- 1-day window is applied. The patients will return to the hospital the day prior to or on the day of the last infusion. Adverse events and use of concomitant medications during non-hospital stay are captured. The actigraph and accompanying diary are collected.

Prior to start of the infusion, the following is performed:

- Vital signs and a 12-lead ECG is obtained
- General appearance and skin are assessed
- Blood is obtained for immunogenicity, HS and PK assessments
- Urine is collected for HS analysis

Within 30 to 60 minutes prior to start of each SOBI003 infusion, a single dose of an oral non-sedative antihistamine is administered. SOBI003 is administered in accordance with Section 7.4.6.

Vital signs are assessed approximately 2 hours after start of infusion. Upon completion of the 4-hour infusion, and as soon as practically possible, a PK blood sample is obtained. Within an hour of completion of the infusion, vital signs and general appearance and skin are assessed, and a 12-lead ECG is obtained.

The parent/caregiver completes the CSHQ questionnaires, preferably during Day 1.

On Day 2, blood is collected for HS and PK assessment at the same time point as CSF sampling is performed. Urine is collected for HS analyses as close as possible to the CSF sampling. General anesthesia is applied in accordance with local routines at the study site. CSF sampling (a total of 0,9 mL) for PK, ADA, and HS assessments and MRI scanning of brain, liver and spleen are completed while the patient is anesthetized. The order of the procedures should preferably be as stated. Should this not be feasible for an individual patient, then effort should be made to have the assessments performed in the same order as they were performed at Baseline. When separate consent for future research has been provided, CSF (1.0 mL) will also be collected for storage at the central laboratory.

On Day 3, blood and urine are collected for safety laboratory analyses. Blood is also collected for PK analysis. Vital signs are obtained. The VABS-II is assessed by interviewing the parent/caregiver (refer to Section 7.5.4.1).

In addition, PK blood samples are collected on Days 5, 6 and 8 (approximately 168h after start of SOBI003 infusion) at time points specified in Section 7.5.6.1.

The parent/caregiver completes the PedsQL questionnaire, preferably during Day 6.

Based on the patient's developmental age, as determined by the VABS-II score, the BSID-III and/or KABC-II tests are conducted for assessment of neurocognition, language and motor function (see Sections 7.5.4.2, 7.5.4.3, and 7.5.4.4, respectively). If *only* BSID-III or *only* KABC-II is to be assessed, then this should be done on Day 7. If *both* BSID-III and KABC-II should be assessed, then the BSID-III should be administered on Day 4 or 5 and the KABC-II on Day 7.

On Day 7, a neurological and a physical examination are performed and height, weight and head circumference are obtained. A 12-lead ECG and echocardiography are performed. Should Day 7 not be practically feasible, then the ECG and echocardiography can be performed during Days 3 to 7.

The patient may be discharged from the hospital 48 hours after start of the infusion. The patient will then return to the hospital for study assessments on Days 4, 5, 6 and 7.

On Day 7, height, weight and head circumference are assessed and the investigator will assess patient eligibility for enrolment in the extension study SOBI003-002.

For patients that are permanently discontinuing SOBI003 treatment, i.e., not continuing in the extension study, serum samples for PK and ADA analyses should be obtained 30 to 40 days after last SOBI003 infusion. Patients with ADA-positive samples should continue to be followed in accordance with Sections 7.5.5.3 and 7.5.6.1.

7.5.1.13 Treatment Withdrawal

If the patient is withdrawn from study treatment, the patient should be examined as soon as possible after making the withdrawal decision. Adverse events and use of concomitant medications are captured. Blood and urine are collected for safety laboratory, immunogenicity, HS and PK assessments. When separate consent for future research has been provided, blood and urine are also collected for storage at the central laboratory for future biomarker research, and if the patient is also withdrawn from the study blood is collected for future genetic research. Vital signs are assessed and a neurological and a physical examination are performed. A 12-lead ECG is obtained and an echocardiography is performed. Height, weight and head circumference are obtained. Additional safety assessments will be performed at the discretion of the investigator, as warranted by any AE(s) leading to treatment withdrawal.

When possible, non-infusion-related study assessments should continue in accordance with the Schedule of Events (refer to Table 3) until completion of the Week 24 visit. At minimum, the Early Termination 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 Sections 7.5.5.3 and 7.5.6.1.

7.5.1.14 Estimated blood sampling volumes and sampling priority list

Applying the European Commission guidance (20), the study-related blood loss should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time. Examples of recommended blood draw volume limits per the European Commission guidance are provided in Table 7.

Local and/or regional guidelines regarding blood draw volumes may also apply.

Information of blood volumes per assessment type and sampling occasion are provided in a separate study-specific Laboratory Manual. An overview is presented in Appendix 1.

Blood sampling necessary for the clinical management of the patient will prevail over any study specific sampling.

Should the blood volume be restricted at any of the sampling time points, then the analyses should be prioritized in the following order:

1. Immunogenicity (ADA)
2. Coagulation
3. PK
4. Hematology
5. Blood chemistry
6. HS
7. Blood sample collection for future pharmacogenetics research
8. Serum collection for future biomarker analyses

Table 7 Examples of recommended blood draw volume limits

Patient Weight (kg)	Blood Draw Limits (mL)[a]	
	Single Occasion[b]	4 weeks [c]
10.0	8.0	24.0
15.0	12.0	36.0
20.0	16.0	48.0
25.0	20.0	60.0

a European Commission guidance (20)
b Representing 1% of total blood volume, where total blood volume is estimated to 80 ml/kg body weight
c Representing 3% of total blood volume, where total blood volume is estimated to 80 ml/kg body weight

7.5.2 Medical history

7.5.2.1 MPS IIIA diagnosis

Information on diagnosis date and prior MPS IIIA diagnostic procedures are captured, including assessment date, diagnostic method used, and test result (positive/negative). The following diagnostic methods are of particular interest; urinary glycosaminoglycan (GAG), serum HS, sulfamidase enzyme activity in leucocytes or fibroblasts, and SGSH genotyping. Moreover, information is collected regarding MPS IIIA disease in older siblings and if prenatal diagnosis has been conducted.

At Screening, blood (5 mL) is obtained for SGSH genotyping and extraction of leucocytes for assessments of sulfamidase enzyme activity at a central laboratory (Greenwood Genetic Center). Blood sampling details are provided separately in the Study laboratory manual. The central laboratory results are used for confirmation of the eligibility criteria.

7.5.2.2 Other diagnoses

Information on prior and current other diagnoses obtained within 6 years prior to study enrolment are captured (diagnosis and date of diagnosis), with emphasis on conditions that are frequent in the MPS IIIA population. This includes inguinal and umbilical hernias, cardiac valve disease, epilepsy/seizures, spasticity, congenital joint stiffness, hip dysplasia, scoliosis, kyphosis, lumbar lordosis, carpal tunnel syndrome, trigger digits, joint contractions, autism, hyperactivity or attention deficit disorder (ADD).

7.5.2.3 Other medical conditions

Information on prior and current other medical conditions within 1 year prior to study enrolment are captured (symptom, frequency when applicable and month of onset of most recent episode), with emphasis on conditions that are frequent in the MPS IIIA population. This includes hepato- and/or splenomegaly, ear-nose-throat (ENT) infections, diarrhea, sleep disorder, swallowing/eating difficulties, hearing loss and/or visual acuity problems.

The definition of prior medical conditions includes signs, symptoms, and diagnoses made prior to the informed consent is signed.

The definition of current medical conditions includes all signs, symptoms, and diagnoses made from the time informed consent is signed until completion of the Baseline assessments, i.e., until the first SOBI003 infusion is about to be initiated on Day 1 at Week 1.

7.5.2.4 Prior medical procedures

Information on prior medical procedures performed within 6 years prior to study enrolment are captured (procedure and month/year conducted), with emphasis on conditions that are frequent in the MPS IIIA population. This includes tonsillectomy, adenoidectomy, myringotomy, gastrostomy, and jujenostomy.

7.5.3 Demography

The following demographic data are captured at Screening; date of birth, gestational age at birth, gender, ethnicity, race, country of residence and native language. In addition, information on the patient's siblings is captured, including age and MPS IIIA diagnostic status (confirmed as non-affected/confirmed as affected/under current investigation). For sibling(s) with confirmed diagnosis, the sibling's age at diagnosis and genotype are also captured, when known.

7.5.4 Efficacy assessments

7.5.4.1 Adaptive behavior

The VABS-II is assessed at Screening, Baseline (within 2 weeks prior to first SOBI003 infusion) and at Week 24. The screening assessment is used to determine patient eligibility in terms of developmental age.

The patients' ability to cope with changes, to demonstrate independence and to learn new skills are assessed by use of the Expanded Interview Form of the VABS-II. This measures five competence domains: communication, socialization, daily living skills, motor skills and an adaptive behavior composite of the first four domains.

The VABS-II is assessed by parent/caregiver interviews performed by child development specialists/psychologists with prior experience of MPS IIIA patients. Prior to study initiation, additional study-specific assessment training is provided in order to reduce between-site variability. Every effort will be made to have the same parent/caregiver interviewed at each assessment time point (i.e., at Screening, Baseline and Week 24). In addition, each patient's parent/caregiver should preferably have the same interviewer throughout the study in order to reduce potential variability.

The developmental age at Screening is determined as the mean of the subdomain age-equivalent scores including the communication, socialization, daily living skills, and motor skills domains.

The adaptive behavior age-equivalent score is determined as the mean of the subdomain age-equivalent scores including the communication, socialization, and daily living skills (thus, excluding the motor skills domains).

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 Age Equivalence scores, and data management.

7.5.4.2 Neurocognition

Neurocognition is assessed at Baseline (within 2 weeks prior to first SOBI003 infusion) and at Week 24, by use of the neurocognition domain of the BSID-III and/or the KABC-II Nonverbal Index (NVI).

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 8 is applied and the test(s) administered at Baseline should also be used at Week 24.

Table 8 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.

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

The neurocognitive developmental age (months) is derived from the mean AEq scores on the NVI of the KABC-II.

The Development Quotient (DQ) is obtained by dividing the neurocognitive developmental age with chronological age.

Neurocognition assessments are performed by child development specialists/psychologists with prior experience of MPS IIIA patients. Prior to study initiation, additional study-specific assessment training is provided in order to reduce between-site variability.

Each patient should preferably have the same assessor throughout the study in order to reduce within-patient variability. Attempts should be made to have the assessments made at least 5 days after any anesthesia/sedation. When practically feasible, the aim should be to have the assessments performed in rested children early during the day, i.e., prior to 1 pm. The aim should also be to roughly keep the same assessment time point for an individual child, i.e., morning/afternoon.

To ensure that the BSID-III and 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 Age Equivalence scores.

7.5.4.3 Language

Language is assessed at Baseline and at Week 24.

Expressive and receptive language are assessed by the BSID-III language module and the VABS-II communication domain. In addition, written language is assessed by the VABS-II communication domain.

For those patients taking the KABC-II for cognitive assessment, the Expressive Vocabulary from the KABC-II will be applied to assess language development.

7.5.4.4 Motor function

Motor function is assessed at Baseline and at Week 24.

Fine and gross motor skills are assessed by the BSID-III motor function module and the VABS-II motor skills domain.

7.5.4.5 Sleep pattern

The patients' sleep pattern is evaluated using the CSHQ and by use of actigraphy.

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. The CSHQ is completed by the primary caregiver at Baseline and prior to the infusions at Weeks 12 and 24. This CSHQ will capture the child's sleep habits during the past week. Every effort will be made to have the same caregiver completing the CSHQ at each assessment time point.

An actigraph (ActiGraph GT9X Link) will be applied to the non-dominant wrist or ankle and recordings will be made for 7 consecutive days and nights at Baseline and at Weeks 11 and 23. The wrist or ankle placement should be used consistently throughout the study. At Baseline, the aim should be to have the recording completed prior to any anesthesia/sedation is applied and prior to blood samplings. At Weeks 11 and 23, the aim should be to have the recordings completed prior to the SOBI003 infusions on Day 1 at Weeks 12 and 24.

The device will be worn constantly during the recording periods only allowing removal for washing and bathing. The aim is to ensure that at least 5 days of evaluable recordings are obtained on each occasion. 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 actigraph data will be evaluated using the accompanying software developed by the manufacturer. A subset of the actigraphy data is coded to be analyzed in a subsequent separate blinded analysis of the manually edited dataset.

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)

The Sadeh algorithm (25) is used for determining which epochs (1-minute recordings) are marked as “sleep” versus which are marked as “awake”. The Tudor-Locke method is applied to determine sleep periods, where 5 consecutive minutes of recorded “sleep” defines Sleep onset and where 10 consecutive minutes of “awake” time defines Sleep offset.

7.5.4.6 Magnetic resonance imaging

MRI scanning protocols including details on sequence parameters and scanning guidelines are provided to the clinical sites under the coordination of the central MRI reader. MRI field strength should be a minimum of 1.5, preferable, 3.0 tesla.

Preferably, the same MRI technician should perform all study related scans. The separate MRI assessment protocol provided prior to the study start should be followed for each scan. Study specific training is provided and test scans will be reviewed by the central MRI reader prior to initiation of any study assessments at the site.

Brain and abdominal MRI are performed under general anesthesia at Baseline and Week 24. MRI data are sent to the central reader for quantitative analyses.

The brain MRI assessment protocol includes:

1. 3D T1-weighted MPRAGE (~6 min) for volumetric analysis
2. DTI and gre fieldmap (~10 min) for white matter analysis
3. 3D FLAIR and T2 (~8 min) for volumetric analysis
4. 4.SWI (~10 min) for iron content analysis

The abdominal MRI assessment protocol includes:

1. T1 3D VIBE (~2 min.)
2. T2 HASTE (~2 min.)

Liver /spleen volumes are evaluated by MRI using a standard MRI protocol.

7.5.4.7 Quality of life and caregiver burden

The parent proxy-report format of the PedsQL questionnaire (Version 4.0 [26]) will be used to assess the child’s quality of life. The Family impact Module of the PedsQL (Version 2.0) will be used to assess the caregiver burden. The PedsQL will be completed at Baseline and at Weeks 12 and 24. Every effort should be made to have the same parent/caregiver responding to the PedsQL questions at each assessment time point (i.e., at Baseline and Weeks 12 and 24).

The PedsQL version (i.e., infant/toddler/young children) will be selected on the basis of the chronological age of the patient.

7.5.5 Safety assessments

7.5.5.1 Adverse events

7.5.5.1.1 Definitions

Adverse event

An Adverse event (AE) is any untoward medical occurrence in a patient or trial subject administered a pharmaceutical product; the event does not necessarily have a causal relationship with the treatment or usage.

Adverse events include the following:

- Abnormal test findings, as specified below.
- Clinically significant signs and symptoms.
- Changes in physical examination findings.
- Unexpected progression/worsening of underlying disease.

In addition, signs and symptoms resulting from the following should also be handled according to the same principles as Adverse Events:

- Overdose.
- Withdrawal of treatment.
- Interactions.
- Abuse.
- Misuse.

Abnormal test findings

An abnormal test finding, e.g. abnormal laboratory analysis results, vital signs or ECG, should be recorded as an Adverse Event in any of the following situations:

- The test is associated with accompanying symptoms. Note, that the symptom, not the test result, should be recorded as an AE.
- The test result leads to a medical/surgical intervention including withdrawal of IMP(s) or discontinuation from the study. Repeat/confirmatory testing is not considered a medical intervention.
- The investigator considers the test result to be clinically significant.

Preexisting conditions

A preexisting condition (i.e., a disorder present before the adverse event reporting period started and noted on the pretreatment medical history/physical examination form) should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period.

Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy entered in the comments section of the CRF.

Serious adverse event (SAE)

An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death.
- Is life-threatening (i.e., at immediate risk of death).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect (i.e., in an offspring to the study subject).

Other medically important adverse events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Serious also includes any other event that the investigator or company judges to be serious. Any suspected transmission of an infectious agent via IMP shall also be considered serious.

Hospitalization

Hospitalization includes transfers within a hospital (e.g. from the hospital ward to the intensive care unit) and also includes admissions less than 24 hours. The following situations are not considered hospitalizations (although other SAE criteria may still apply):

- Outpatient procedures / ambulatory care.
- Emergency department visits.

Hospitalization in the absence of an adverse event occurring during the study should not be considered an SAE. This includes:

- Hospitalization due to a pre-existing condition not associated with a worsening of the pre-existing condition.
- Protocol specified admission.
- Elective admission, e.g. due to cosmetic surgery.
- Pre-planned admission for a condition specified at Baseline for the patient.

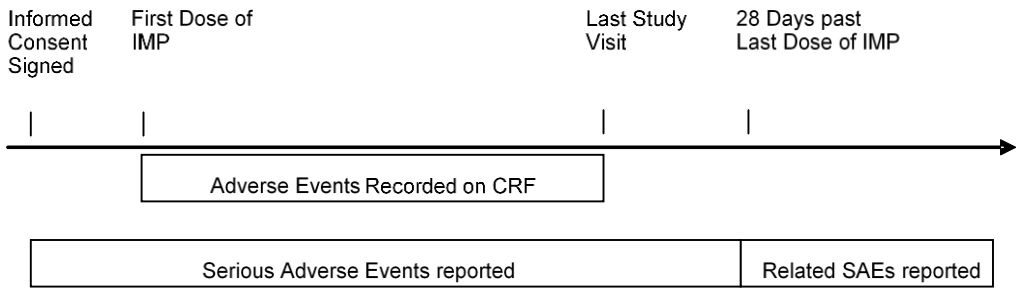
Treatment-emergent adverse event (TEAE)

TEAE is any AE with onset or worsening reported from the time that the first dose of IMP is administered until completion of or withdrawal from the study.

7.5.5.1.2 Adverse event reporting period

The period for recording adverse events, including SAEs, on the CRF begins upon receiving the first dose of investigational medication and ends at completion of the Week 24 visit.

In addition, SAEs should be reported, from the time the ICF is signed until 28 days past the last dose of IMP. Furthermore, any SAE should be reported to Sobi irrespective of the time of occurrence if a causal relationship between the event and the IMP(s) is suspected.



7.5.5.1.3 Eliciting and recording adverse event information

The investigator is to record all directly observed adverse events, and all adverse events spontaneously reported by the parent/patient, in the CRF using concise medical terminology.

When possible and appropriate, a diagnosis rather than individual signs and symptoms shall be recorded. The investigator is responsible for obtaining sufficient information to determine seriousness, causality and outcome of each adverse event.

Severity assessment

For the purpose of consistency, the investigator will use the grading provided in Table 9 to describe the maximum intensity of the adverse event. The grading is based on the NCI CTCAE (version 4.03).

Table 9 Severity grade definitions according to NCI CTCAE (version 4.03)

Grade I	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade II	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
Grade III	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade IV	Life-threatening consequences; urgent intervention indicated

Note the distinction between the seriousness (serious/non-serious) and the intensity (severity) of an adverse event. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

Causality assessment

For each adverse event, the investigator or sub-investigator must make a causality assessment on the basis of his/her clinical judgment to determine if there is a reasonable possibility that the IMP(s) caused the adverse event. The adverse event is assessed as related or not related to the IMP(s) with the following definitions:

Related
The AE follows a reasonable temporal sequence from the study product administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications).

Not Related
The AE does not follow a reasonable temporal sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

7.5.5.1.4 Serious adverse event reporting

Both serious and non-serious adverse events are to be reported on the adverse event page of the CRF as specified in the CRF instructions. The form for collection of SAE information is not the same as the general adverse event CRF page. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms.

Any SAE must be reported by the investigator if it occurs during the clinical study whether or not the SAE is considered to be related to the investigational product. An SAE report consists of the SAE form including medical history and concomitant medications. A copy of these forms must be emailed or faxed **within 24 hours** at:

- SAE reporting email address: INCDrugsafety@INCResearch.com
- SAE reporting toll fax number: +1 877 464 7787
- SAE reporting country specific toll-free fax numbers

In addition, to the SAE reporting to INC, the investigator must via email notify the Sobi Medical Director and Drugsafety@sobi.com.

The investigator shall provide INC Research with sufficient information to enable a complete medical assessment of the reported event. Best efforts shall be made by the investigator to provide INC Research with additional information related to any SAE as requested.

The investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained. All new information obtained, relevant to an SAE report, should be forwarded to INC Research within the same timeframe as the initial information.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

Sobi and/or INC Research will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the independent ethics committee (IEC)/institutional review board (IRB) approval/favorable opinion of the study. In addition, INC Research, on behalf of Sobi, will expedite the reporting to all concerned investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected. The expedited reporting to the regulatory authority in the U.S.A. will however be managed by Sobi.

7.5.5.1.5 Follow-up of unresolved adverse events

All adverse events should be followed until they are resolved or the investigator assesses them as chronic or stable, or the patient's participation in the study ends, i.e., until completion of the Week 24 visit. For patients entering the extension study, all AEs and SAEs occurring after Week 24 visit, should be noted in the extension study SOBI003-002. How to report changes in an ongoing adverse event during a patient's participation in the study is described in the CRF instructions.

In addition, all serious and non-serious adverse events assessed by the investigator as related to SOBI003 should continue to be followed until they resolve or until the investigator assesses them as "chronic" or "stable", even after the patient's participation in the study is over.

7.5.5.2 Laboratory safety assessments

Biochemistry, hematology, coagulation and urine analyses are conducted at a central laboratory (BARC). The time points for sample collection are summarized in Table 10 as well as the analyses performed at each sampling occasion.

At the discretion of site personnel, urine collection bags will be used as needed.

In case of acute infusion reaction or anaphylactic reaction (AE grade III or greater but may also include grade II at the discretion of the investigator), blood is collected for central laboratory analyses of C-reactive protein (hsCRP), IL-1ra, TNFα, IgE, and tryptase. To facilitate interpretation of the analyses results, blood is also collected at Baseline to enable comparison. When possible, the Baseline blood sample should be collected at least 4 weeks prior to the planned start of SOBI003 infusion in order to minimize the total blood volume drawn within one-month timeframes.

Depending on the severity of the reaction and at the discretion of the investigator additional analyses may be performed at local laboratory to better understand the mechanism of the reaction.

Clinically significant laboratory values should be reported as adverse events (see Section 7.5.5.1.1 for details).

Sampling details are provided separately in the study-specific Laboratory Manual.

Table 10 Safety laboratory assessment time points

Analyses	Study visit	Sampling time point(s)
Biochemistry (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). **Hematology (0.5 mL blood):** Hemoglobin (Hb), Erythrocytes, White blood cell count (WBC), Differential blood count and Platelet count. **Coagulation (1.7 mL):** PT/INR, APTT, and Fibrinogen. **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 (hsCRP), IL-1ra, TNFα, IgE, and tryptase (6.4 mL blood)	Baseline	
	In case of infusion/anaphylactic reaction	

7.5.5.3 Immunogenicity

Serum and CSF samples are collected for central laboratory analysis (York Bioanalytical Solutions Limited, York YO26 6QR, United Kingdom) of SOBI003 ADAs by a validated immunoassay method. Assays are being developed for assessment of neutralizing antibodies, both for antibodies inhibiting cellular uptake and for enzyme activity inhibiting antibodies (BioAgilytix, Lademannbogen 10, 22339 Hamburg, Germany). At each sampling occasion, a blood volume of 1.5 mL will be collected.

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, and 24, and if applicable at Early Termination of SOBI003 treatment. Triplicate aliquots are required for each sampling time point.

CSF samples (0.5 mL) are collected at Baseline and at Weeks 12 and 24.

For patients with an ADA-positive serum sample, the following will also be determined in serum: ADA titer, IgG subclasses, and presence of NAb.

For patients with an ADA-positive CSF sample, the following will also be determined in CSF: ADA titer and presence of NAb.

Should any patient permanently discontinue SOBI003 treatment prior to Week 24, then serum samples for ADA assessments should be obtained as soon as possible after the decision of Early Termination of SOBI003 treatment as well as 30 to 40 days after the last SOBI003 administration. Should the latter sample be ADA-positive, then ADA samplings will continue at approximately monthly basis until the ADA has disappeared or titers have stabilized at a lower level.

The impact of ADAs on the safety, tolerability, and PK of SOBI003 will be explored, as well as the potential impact on HS levels in CSF, serum and urine.

Sampling details are provided separately in the study-specific Laboratory Manual.

7.5.5.4 CRIM status

At the Baseline visit, a skin biopsy is obtained for isolation of fibroblasts for assessment of CRIM status at the central laboratory (Biochemical Genetics Laboratory, Duke University Health System, 801 Capitola drive, Suite 6, Durham, NC 27713, U.S.A). The biopsy should preferably be obtained at least 2 weeks prior to the first SOBI003 infusion.

7.5.5.5 Vital signs

Vital signs (blood pressure, heart rate, body temperature, respiratory rate, and oxygen saturation) are measured at the screening visit and at each infusion.

At Weeks 1 to 4, continuous pulse oximetry is applied to assess oxygen saturation from pre-infusion until completion of SOBI003 infusion. Blood pressure, heart rate, body temperature and respiratory rate are assessed pre-infusion, 1 hour (+/- 5 minutes), 2 hours (+/- 5 minutes) and 3 hours (+/- 5 minutes) after start of infusion, and within 1 hour after end of infusion. Blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation are assessed within 8 to 12 hours after start of infusion, as well as on Days 2 and 4. In addition, at Weeks 1 and 2 the assessments are also done on Day 5.

At Weeks 5 to 8, blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation are assessed 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 8 to 12 hours after start of infusion, as well as on Days 2 and 4.

At Weeks 9 to 24, blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation are assessed 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.

Blood pressure and heart rate are measured in accordance to each clinic´s standard procedures. When the clinical situation allows, the assessments should preferably be done in supine position after the patient has rested comfortably for at least 5 minutes. Body temperature is measured in degrees Celsius using a tympanic thermometer according to each clinic´s standard procedures. The pulse oximetry sensor device is placed on a fingertip or earlobe (according to standard routines at the study site).

Clinically significant abnormal vital signs values should be reported as adverse events (see Section 7.5.5.1.1 for details).

7.5.5.6 Electrocardiograms

12-lead ECGs 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 machines Mortara ELI 250c with VERITAS™ resting ECG interpretation algorithm will be provided to the sites.

Any ECG that is auto-interpreted as abnormal should be assessed for clinical significance by a healthcare professional with sufficient competence and experience of interpreting pediatric ECGs. If a patient shows an abnormal ECG, additional safety recordings may be made and the abnormality followed to resolution if required.

If the clinical situation allows, attempts should be made to have the 12-lead ECG recordings obtained after the patients have been resting in a supine position for at least 5 minutes. The patients should preferably avoid any postural changes during the ECG recordings and clinical staff will ensure that patients are awake during the ECG recording.

Paper printouts of the ECGs are to be stored as source documents to allow the possibility of retrospectively analyzing the ECGs. A Study ECG manual will be provided.

Clinically significant abnormal ECG findings should be reported as adverse events (see Section 7.5.5.1.1 for details).

7.5.5.7 Other safety assessments

7.5.5.7.1 Echocardiography

At screening, an echocardiography is performed in accordance with local hospital routines. The investigator and the pediatric cardiologist should determine if there are any cardiac safety concerns that would prevent the patient to participate in the study.

The echocardiography should be repeated at Week 24.

7.5.5.7.2 Physical examination and anthropometry

The physical examination performed at Screening, Baseline and at completion of the Week 24 visit will include an assessment of the following: general appearance, skin (including any potential reaction around the infusion site), eyes, ears, nose, neck, lymph nodes, throat, heart, lungs, abdomen, musculo-skeletal system and extremities.

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.

Weight is assessed at Screening, Baseline, approximately every 4 weeks during the treatment period in order to determine the actual SOBI003 dose to be administered (Section 7.4.6), and at completion of the Week 24 visit. Weight is hence obtained prior to start of infusion at Weeks 1, 5, 9, 12, 17, and 21. The body weight is obtained either on the day prior to the infusion or the day of infusion.

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

Anthropometric measurements should be performed according to standard routines at the study site. Shoes must however be taken off during height and weight assessments.

Height and head circumference are recorded in centimeters and weight in kilograms. For all weight assessments, a scale with at least 100-g accuracy should be used.

7.5.5.7.3 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.

7.5.5.8 Appropriateness of measurements

The safety assessments in this study are widely used and generally recognized as reliable, accurate, and relevant.

7.5.5.9 Safety review committee

The appointed SRC will comprise the principal investigators and relevant Sobi staff, including the Safety Physician, Clinical Pharmacologist, Study Statistician, Principal Scientist of Immunology, Toxicologist, Medical Director and VP Head of Clinical Development. It is the responsibility of the SRC to determine:

- whether dosage of ongoing cohort(s) can continue
- if the infusion rate of subsequent administrations in ongoing cohort(s) 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

The SRC will adhere to the pre-defined stopping criteria that are specified in Section 7.5.5.9.1.

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, INC Research, and investigational sites.

For each cohort, SRC meetings are scheduled approximately 3 weeks after completion of the 3rd patient's 4th dose administration. The SRC will review pre-specified safety, PK, immunogenicity and PD data (HS in serum and urine, HS in CSF will also be included when analysis results are available) of the current cohort, as well as for previous cohort(s). It should be recognized that based on patient enrolment rate, each individual patient's total treatment duration will vary at the time points of the SRC meetings. Hence, at the time of the SRC meeting for cohort 1, there will be more than 4-week data available for the 1st included patient.

The safety data made available for the SRC reviews will comprise the adverse events, safety laboratory analyses, physical examination, vital signs and ECG data obtained up to at least 3 days after start of the 4th infusion. It should be noted that the data summaries will only be made available for the SRC and for the INC Research staff compiling the data. Other staff at Sobi and INC Research, or study sites, will not have access to the data summaries.

Additional SRC meetings will be scheduled *ad hoc* as per principal investigator or Sobi SRC member requests.

7.5.5.9.1 Stopping rules

In the context of this study, the term toxicity means clinically significant drug related adverse reaction(s). In case of serious toxicity defined as a Grade III-V SAE, an *ad hoc* SRC meeting will be held within 24 hours after Sobi awareness of the adverse event. SRC will decide on the impact on an individual, cohort or entire study level, continue trial unchanged, continue trial with modifications, or to put the trial on hold.

Standard toxicity grading according to the NCI CTCAE are used to grade AEs and to decide on suspension level.

- The study will be halted if a patient develops a Grade IV-V SAE suspected to be IMP related.
- The treatment arm will be halted if at least 2 out of 3 patients in the same cohort experience a similar drug-related Grade III SAE.
- Study treatment will be discontinued on an individual level if assessment by an *ad hoc* SRC or the investigator conclude significant risk to the subject's safety.

If at least 2 out of 3 patients in the same cohort experience a drug-related Grade III AE in different organ systems, the SRC will base the dose level selection for the next cohort(s) on the nature of the adverse events observed. An *ad hoc* DMC meeting may be held to provide recommendation if requested by the SRC.

Table 11 Toxicity grade definitions according to NCI CTCAE (version 4.03)

Grade I	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade II	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
Grade III	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade IV	Life-threatening consequences; urgent intervention indicated
Grade V	Death related to AE

7.5.5.10 Data safety monitoring board

In addition to the SRC, a DMC is assigned to monitor safety 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.

The DMC is planned to comprise an independent statistician and two clinicians that, collectively, have experience from DMC, management of pediatric patients with LSD, clinical immunology,

and the conduct of clinical trials with ERT. The DMC members must not be investigators in the study or otherwise associated with the sponsor.

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 INC Research. There are two scheduled DMC review meetings, one upon all patients' completion of Week 12 and one upon all patients' completion of Week 24. If requested by the SRC, additional *ad hoc* meetings may be held to provide recommendations to the SRC.

7.5.6 Pharmacokinetic assessments

7.5.6.1 Sampling procedures

The sampling procedures are briefly described below and are described in more detail in the study-specific Laboratory Manual. Blood samples are obtained through the central venous access port from the Baseline visit onwards to characterize SOBI003 PK in serum. Separate blood samples from a peripheral venous line are collected in parallel for samples (marked with * below) in order to compare serum SOBI003 concentrations in samples collected from a peripheral line with samples from the central venous access port line, which is used also for the i.v. administration of SOBI003. The purpose of these parallel samples is to confirm that the SOBI003 i.v. infusion does not interfere with the blood sampling. A blood volume of 0.3 mL will be collected from the central venous access port and an additional 0.3 mL blood will be collected from the peripheral venous line when applicable. Duplicate serum aliquots will be prepared at all sampling time points to allow for re-analysis if needed.

Serum samples are collected at Screening and Baseline. Thereafter, frequent sampling is conducted at Weeks 1, 4, 12, and 24 at the following time points: 4 h* (end of infusion), 6*, 12*, 24*, 48, 96, 120 and 168 h after start of infusion. In addition, samples are collected before start of infusion and at completion of the infusion at Weeks 2, 3 and 8. In case SOBI003 infusion is prolonged, PK sampling time points will be adjusted. PK samples will be collected 2 h and 8 h after end of infusion and thereafter 24 h after start of infusion, and thereafter as for the ordinary PK-sampling schedule for the 4 h infusion. A reduced PK blood sampling schedule is applied for patients with low bodyweight to avoid exceeding blood draw volume limits. Details on PK blood sampling are given in Table 6. Acceptable deviations from these planned sampling time points are: 4 h (end of infusion) (+0.5h), 6 (± 0.5h), 12 (± 0.5h), 24 (± 0.5h), 48 (± 0.5h), 96 (±1h), 120 (± 1h) and 168 (- 1h).

CSF samples (0.5 mL) are collected during general anesthesia at Baseline and at Weeks 12 and 24 for determination of SOBI003. Triplicate aliquots are required for each sampling time-point. At the time of CSF sample collection, a blood sample will also be collected for determination of SOBI003 in serum. In case the time point for the CSF sample is deviating from the planned time-point, the blood sampling should be adjusted accordingly.

In addition, at each time point a sample is collected for immunogenicity, a blood sample is obtained for determination of SOBI003 in serum. In case of a time deviation for the immunogenicity sample, the time for the PK sample should be adjusted accordingly, or an additional PK sample may have to be collected.

Should any patient permanently discontinue SOBI003 treatment prior to Week 24, then a PK and an immunogenicity sample should be obtained as soon as possible after the decision of early treatment withdrawal, as well as 30 to 40 days after the last SOBI003 administration. For

patients with confirmed ADA levels, blood samples for PK and immunogenicity analysis should continue in accordance with Section 7.5.5.3.

The exact time of the SOBI003 infusion start and completion as well as of each PK sampling are recorded in the CRF for each patient.

Sampling, storage and shipment details are provided separately in the study-specific Laboratory Manual.

7.5.6.2 Bioanalytical method

SOBI003 concentrations in serum and CSF are determined at a central laboratory (York Bioanalytical Solutions Limited, York YO26 6QR, United Kingdom) by the use of a validated immunoassay. The bioanalytical method may not be specific for SOBI003 and may cross-react with endogenous sulphamidase. Potential endogenous pre-dose sulphamidase concentrations are taken into consideration in the PK analysis e.g. by subtracting these levels from post-dose SOBI003 concentrations

7.5.6.3 Pharmacokinetic calculations

PK calculations, based on serum concentrations, are performed in Phoenix WinNonlin by means of NCA. Results on PK parameters calculated by NCA will be available continuously during the study in order to support dose escalation decisions at SRC meetings.

Individual serum concentration data from each patient and the exact time points for blood sampling are used throughout the analyses. Samples with serum concentrations below the lower limit of quantification (LLOQ) appearing in the terminal samples will be omitted from the analysis. The following PK parameters are determined for SOBI003:

At Weeks 1, 2, 3, 4, 8, 12, 24:

- The observed serum concentration immediately before the start of infusion of SOBI003, $C_{Pre\text{-}dose}$

At Weeks 1, 2, 3, 4, 8, 12, 24:

- The time of the end of the infusion of SOBI003, $t_{End\ of\ inf}$
- The observed serum concentration at the end of infusion of SOBI003, $C_{End\ of\ inf}$

At Weeks 1, 4, 12 and 24:

- The minimum observed serum concentration, C_{Trough}
- The maximum observed serum concentration, C_{max}
- The time at which the maximum serum concentration is observed, t_{max}
- Clearance, CL
- The area under the plasma concentration-time curve from time 0 to last sample, AUC_{168h}
- The half-life, $t_{½}$

The area under the plasma concentration-time curve from time 0 to last sample, AUC_{168h} calculated according to the linear log trapezoidal method. Other PK parameters may be calculated as applicable.

7.5.7 Pharmacodynamic assessments

7.5.7.1 Heparan sulfate

7.5.7.1.1 Heparan sulfate in serum and CSF

Blood (0.3 mL) is collected at Baseline and pre-infusion at Weeks 2 to 4, 8, 12, and 24, and if applicable at Early Termination of SOBI003 treatment, for analysis of HS in serum. In addition, serum is also collected on Day 2 at Weeks 12 and 24.

CSF (0.2 mL) is collected at Baseline and at Weeks 12 and 24 for analyses of HS.

The HS analyses are performed at a central laboratory (York Bioanalytical Solutions Limited, York YO26 6QR, United Kingdom). The HS polymer itself is highly heterogeneous and therefore it is not possible to analyze at the intact molecule level. The detection of HS levels is initiated by depolymerization of the polymer mixture enzymatically, followed by analysis of the constituent disaccharides (22). The polymer mixture includes the HS polymer as well as accumulated intermediate HS degradation products. Throughout this protocol, the term “HS” is used for the assessed disaccharide levels.

Effects of SOBI003 on HS storage in affected cells are assessed by measuring HS in serum and CSF using liquid chromatography tandem mass spectrometry (LC-MS/MS). The total level of HS is measured by analyzing selected disaccharides derived from enzymatic digestion (adaptation of method described in Naimy et al. 2016 [22).

Sampling, storage and shipment details are provided separately in the study-specific Laboratory Manual.

7.5.7.1.2 Heparan sulfate in urine

Urine (3 mL) samples are collected at Screening, Baseline, and pre-infusion at Weeks 2 to 4, 8, 12 and 24, and if applicable, at Early Termination of SOBI003 treatment, for analysis of HS. In addition, urine is also collected on Day 2 at Weeks 12 and 24.

The urine HS analyses are performed at a central laboratory (Greenwood Genetic Center, 106 Gregor Mendel Cir, Greenwood, South Carolina 29646, U.S.A.). HS is quantified using stable isotope dilution-tandem mass spectrometry. The urine sample is treated with methanol to produce HS polymer dimers that are separated by ultra-performance liquid chromatography (UPLC) and analyzed by electrospray ionization tandem mass spectrometry (MS/MS). The assay reports the concentration of HS relative to the creatinine concentration in the urine.

Sampling, storage and shipment details are provided separately in the study-specific Laboratory Manual.

7.5.7.2 Future bioanalytical research

As local regulations permit and provided that additional separate caregiver consent is given, blood, urine and CSF samples are collected for future analyses. At Baseline, blood (2 mL), urine (2 mL) and CSF (1 mL) samples are collected for future biomarker analyses. At Week 22, blood and urine are collected for future biomarker analyses and additional blood (2 mL) is collected for future genetic research. At Week 24, CSF is collected for future biomarker analyses.

When possible, the baseline blood sample should be collected at least 4 weeks prior to the planned start of SOBI003 infusion in order to minimize the total blood volume drawn within one-month timeframes.

The samples will be stored at a central laboratory (York Bioanalytical Solutions Limited, York YO26 6QR, United Kingdom) for a maximum of 10 years following study completion (i.e., last patient's last visit in this study).

MPS IIIA is a very rare and severe disease for which there is a lot of research ongoing to further increase the understanding of disease pathology as well as diagnosis. The purpose of the sample storage is to allow future exploration/confirmation of new research findings. This includes:

- SGSH genotypes
- Geno- and/or phenotype associated correlations with possible impact on safety, tolerability, immunogenicity, PK and PD related to SOBI003 treatment
- Biomarkers in serum, urine and/or CSF with possible relation to the safety, tolerability, immunogenicity, PK and PD of SOBI003

The results of any such analyses will not be included in the Clinical Study Report for this study, but reported separately when analyzed, thus enabling exploration of any emerging novel disease-related discoveries of e.g., previously unknown disease alleles, inflammatory cytokines (e.g., IL1Ra, TNFα, calprotectin, neopterin), other HS biomarkers (e.g. HS metabolites), components of the complement system, and neurodegeneration (e.g., T-tau, hepatocyte growth factor, calbindin D).

Sampling details are provided separately in the study-specific Laboratory Manual.

7.5.7.3 Appropriateness of measurements

Storage of HS in brain lysosomes causes pathological changes such as neuroinflammation and inhibition of autophagy in the MPS IIIA mouse model (23). As demonstrated in nonclinical studies, SOBI003 treatment reduces blood and brain HS levels, has favorable effects on pathophysiological parameters such as neuroinflammation and lysosomal size and shows trends towards normalization of behavior in mice. Furthermore, the levels of HS derivatives in brain homogenate and CSF are strongly correlated, and the HS reduction at different dose levels of SOBI003 is paralleled in these two compartments.

Patients with MPS IIIA have elevated CSF HS levels in CSF as compared to healthy individuals (24). Also in humans, a reduction of HS in CSF is expected to mirror the reduction in brain and thus be a useful PD tool for dose selection.

8 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study specific procedures, INC Research SOPs, the ICH Guideline for Good Clinical Practice, and applicable regulatory requirements.

Monitoring visits to the study site are performed periodically during the study, to help ensure compliance with the protocol, study specific procedures and applicable regulatory requirements. Source documents are reviewed for verification of agreement with data in CRFs. All patient informed consent forms are reviewed. The investigator or institution guarantees access to source documents by Sobi, its representatives, and appropriate regulatory agencies.

The study site may be subject to a quality assurance audit by Sobi or its representatives, as well as inspection by appropriate regulatory agencies.

It is important that the investigator(s) and the(ir) relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

9 Statistical plan

9.1 Determination of sample size

Given that this is a first-in-human study and with no formal hypothesis tests, no sample size calculation has been performed. Three sequential dose levels with 3 patients in each cohort has been evaluated to be 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.

9.2 Definition of study populations

The following analysis sets will be used in the statistical analyses.

Safety set (SAF): The SAF will consist of all patients who received at least 1 dose of IMP.

Full-analysis set (FAS): The FAS is the efficacy analysis set and will consist of all patients who have a baseline and at least 1 post baseline assessment of any secondary or exploratory assessment.

PK analysis set (PK): This PK set will comprise patients where at least one 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 SAF is used for the safety analysis, the FAS is used for the secondary and explorative efficacy variables.

Patients in this study who are up to 30 months of age and was initially assigned a dose at least as high as the dose selected for a planned phase III study will be included in a future primary analysis population for demonstrating efficacy. Efficacy will be evaluated using combined data from the FIH study and the extension study, a planned Phase III trial and the corresponding patients in a recent NH study (24), the latter serving as control patients and consisting of the 5 patients with a rapid progressive MPS IIIA disease and a baseline age of 12 to 30 months.

9.3 Overall statistical and analytical plan

9.3.1 General statistical issues

A detailed description of the statistical analyses to be performed will be documented in a statistical analysis plan to be completed prior to database lock.

9.3.2 Demographics and baseline characteristics

Demographic and other baseline characteristics are listed and summarized with descriptive statistics.

9.3.3 Analysis related to primary objective

Safety tabulations of adverse event data, vital signs data, and laboratory data are performed. Continuous variables are summarized using the number of patients, the mean, the standard deviation, the median, the minimum value, and the maximum value. Categorical variables are summarized using frequency counts and percentages.

9.3.4 Analysis related to secondary objective

PK results are presented by dose level using descriptive statistics. In addition, results are presented by demographic characteristics, e.g., age-group and bodyweight, as applicable.

Immunogenicity is summarized using frequency counts and percentages by dose level.

To assess the PD effect of different dose levels of SOBI003 on HS levels in CSF, serum, and urine, linear mixed models are used to model the change from baseline in HS levels as dependent variable, for both logged HS levels and untransformed HS levels, and baseline level and age as continuous covariates, and dose and sex as factors. The analyses are conducted for each assessment time point: Weeks 12 and 24 for CSF, and Weeks 4, 8, 12 and 24 for serum and urine.

In addition, linear mixed analyses with HS levels, both logged HS levels and untransformed HS levels, in CSF serum, and urine, as dependent variable, and baseline level and age as continuous covariates, and dose and sex as factors will be performed across all assessments, with assessment as a repeated factor in a accumulating pattern: across weeks 12 and 24 for HS in CSF, and across Weeks 4 and 8, across Weeks 4, 8 and 12, and across Weeks 4, 8, 12 and 24 for HS in serum.

Endpoints relating to the neurocognition, adaptive behavior, gray matter volume and Quality of Life are summarized using descriptive statistics.

9.3.5 Analysis related to exploratory objectives

Continuous variables are summarized using the number of patients, the mean, the standard deviation, the median, the minimum value, and the maximum value. Categorical variables are summarized using frequency counts and percentages.

9.3.6 Analysis of safety and tolerability data

9.3.6.1 Adverse events

Reported AE(s) during the study are coded using MedDRA and severity of AEs is graded using NCI CTCAE v.03. The number of patients with any AE are is summarized in frequency tables by treatment dose level, body system, preferred term, relation to IMP and maximum severity. Listings of AE subgroups such as SAE(s) and adverse events leading to discontinuation are also presented.

9.3.7 Interim analysis

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

9.3.8 Multiple comparison/multiplicity

Since no hypothesis tests will be performed, there will be no adjustments for multiplicity.

9.3.9 Handling of missing data

No imputation for missing data will be used.

10 Data collection, handling and record keeping

10.1 Data standards

Collection of data should be performed in the Clinical Data Acquisition Standards Harmonization (CDASH) format, according to the Clinical Data Interchange Standards Consortium (CDISC). The standards should be used to the extent possible and/or required for the specific study/project. The minimum requirement of the CDISC standard is to collect all core variables specified as 'Required' in the Study Data Tabulation Model (SDTM) format.

10.2 Case report form

A CRF is required and should be completed for each included patient. In this study an electronic CRF will be used. The completed original CRFs are the sole property of Sobi and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from Sobi.

It is the responsibility of the investigator to ensure completion and to review and approve all CRFs. CRFs must be signed electronically by the investigator. These signatures serve to attest that the information contained on these CRFs is correct. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

10.3 Source data

Patient source documents are the physician's patient records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. In those cases, the information collected on the CRFs must match those charts. In addition to the physician's patient records, the printed 12-lead ECGs are source. For the MRIs and actigraph assessments, the digital files are the source. For the VABS-II, BSID-III and the KABC-II, the completed test forms and the central reader's confirmation of total scores and age-equivalence scores are the source.

10.4 Database closure

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The study database must be locked before generation of any final results. The database lock will be approved by relevant study personnel and all edit accesses will be removed. The study database can only be unlocked in case critical errors, affecting the main conclusions of the study, are discovered.

10.5 Record retention

To enable evaluations and/or audits from Health Authorities and/or Sobi (or delegates), the investigator agrees to keep records in accordance with the essential documents defined in the ICH GCP Guidelines [1], including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all paper CRFs (i.e., completed paper questionnaires and BSID-III/KABC-II assessments forms), an archival copy on compact disc of the electronic CRFs provided by INC Research and detailed records of IMP accountability. The records should be retained by the investigator according to local regulations or as specified in the Clinical Trial Agreement.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to Sobi. The investigator must obtain Sobi's written permission before disposing of any records.

11 End of study

The end of this study is defined as the date of last patient out, i.e., the last patient's last visit.

12 Sponsor's discontinuation criteria

Sobi reserves the right to discontinue the study prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating patients within 2 weeks. All study materials must be collected and all the CRFs completed to the greatest extent possible.

13 Dissemination and publication of results

Sobi will register the study and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations, e.g. on www.clinicaltrials.gov and EudraCT.

For this rare indication, patients enrolled in this Phase I/II study may form part of the pivotal efficacy population by continuation into the extension study. Cognition is the primary efficacy outcome in MPS IIIA, therefore the cognition and adaptive behavior results at Week 24 of this

Phase I/II study may be withheld from publishing in order to prevent the risk of inadvertent bias of cognition and adaptive behavior assessments in the extension study.

Sobi follows the principals of the International committee of medical journal editors recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals [27]. After completion of this Phase I/II study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will be responsible for these activities and will work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues. The results of the study, or any part thereof, shall not be published without the prior written consent and approval of Sobi, such consent and approval not to be unreasonably withheld.

14 References

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Appendix 1 Blood sampling volume overview

Table 12 Blood sampling volumes (mL) per study visit

Sample	SA, SGSH genotype	Acute reactions	Safety	Immuno-genicity	HS	Pharmacokinetics[a]			Future research	Total blood volume (mL)		
Week						BW ≥20 kg	BW 15 to <20 kg	BW 10 to <15 kg		BW ≥20 kg	BW 15 to <20 kg	BW 10 to <15 kg
-12 to -7	5,0		3,7			0,3	0,3	0,3		9,0	9	9
-6 to -2		6,4							2	8,4	8,4	8,4
-1				1,5	0,3	0,3	0,3	0,3		2,1	2,1	2,1
1			7,4			3,3	1,8	0,6		10,7	9,2	8
2			7,4	1,5	0,3	0,9	0,9	0,3		10,1	10,1	9,5
3			7,4[b]		0,3	0,9	0,9	0		8,6	8,6	4
4			3,7	1,5	0,3	3,6	3,6	1,8		9,1	9,1	7,3
5			3,7			0,3	0,3	0,3		4	4	4
6			3,7							3,7	3,7	3,7
7			3,7							3,7	3,7	3,7
8			3,7	1,5	0,3	0,9	0,9	0,9		6,4	6,4	6,4
10			3,7							3,7	3,7	3,7
12			3,7	1,5	0,6	3,6	3,6	1,8		9,4	9,4	7,6
13						0,3	0,3	0,3		0,3	0,3	0,3
14			3,7							3,7	3,7	3,7
16			3,7							3,7	3,7	3,7
18			3,7							3,7	3,7	3,7
20			3,7							3,7	3,7	3,7
22			3,7						4,0	7,7	7,7	7,7
24			3,7	1,5	0,6	3,9	3,9	2,1		9,7	9,7	7,9

a 168 h samples are counted to the following week, except for week 24

b In children with a body weight < 15 kg, the volume will be 3,7 mL, since no safety sample will be collected on Day 3 of Week 3

Table 13 Blood sampling volumes (mL) per 4-week study periods

Sample	SA, SGSH genotype	Acute reactions	Safety	Immuno-genicity	HS	Pharmacokinetics[a]			Future research	Total blood volume (mL)		
Week						BW ≥20 kg	BW 15 to <20 kg	BW 10 to <15 kg		BW ≥20 kg	BW 15 to <20 kg	BW 10 to <15 kg
-1 to 3			22,2[b]	3	0,9	5,4	3,9	1,2	0	31,5	30	23,6
4 to 7			14,8	1,5	0,3	3,9	3,9	2,1	0	20,5	20,5	18,7
8 to 11			7,4	1,5	0,3	0,9	0,9	0,9	0	10,1	10,1	10,1
12 to 15			7,4	1,5	0,6	3,9	3,9	2,1	0	13,4	13,4	11,6
16 to 19			7,4	0	0	0	0	0	0	7,4	7,4	7,4
20 to 23			7,4	0	0	0	0	0	4	11,4	11,4	11,4
Total			**66,6[c]**	**7,5[c]**	**2,1[c]**	**14,1[c]**	**12,6[c]**	**6,3[c]**	**4[c]**	**121,4[d]**	**119,9 [d]**	**108,1 [d]**

a 168 h samples are counted to the following week, except for week 24
b In children with a body weight < 15 kg, the volume will be 18,5 mL, since no safety sample will be collected on Day 3 of Week 3
c From -1 to Week 23
d Total study = Week -12 to Week 24