An open, single-arm, multicenter extension study to assess the safety, tolerability and efficacy of long-term SOBI003 treatment in pediatric MPS IIIA patients

Final Protocol of the Study
SOBI003-002

IND no. 128889

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

Sponsor's Medical Director

[redacted]

Signature Date

Principal Coordinating Investigator

[redacted]

Signature Date

Sponsor's Study Manager

[redacted]

Signature Date

Sponsor's Statistician

[redacted]

Signature Date

Investigator statement

I have read the protocol entitled "An open, single-arm, multicenter extension study to assess the safety, tolerability and efficacy of long-term SOBI003 treatment 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 1.0, 29 Jun 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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1 Synopsis

STUDY IDENTIFIERS

Title of study:

An open, single-arm, multicenter extension study to assess the safety, tolerability and efficacy of long-term SOBI003 treatment in pediatric MPS IIIA patients

Clinical study number: SOBI003-002

Principal Coordinating Investigator: [redacted]

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 Extension; Therapeutic Exploratory

STUDY OBJECTIVES The efficacy analysis will be based on data 2 years after the start of the FIH study (SOBI003-001), baseline being baseline assessments in the FIH study.

Primary objective: To assess the long-term safety and tolerability of SOBI003.

Secondary objectives: The key secondary objectives are:

- To assess the effect of SOBI003 on neurocognition, as compared to untreated MPS IIIA patients from a natural history (NH) control
- To evaluate the effect of SOBI003 on heparan sulfate (HS) levels in CSF

The secondary objectives are:

1. To assess the effect of SOBI003 on adaptive behavior, as compared to untreated MPS IIIA patients from a NH control
2. To assess the effect of SOBI003 on HS levels in serum and urine
3. To assess the effect of SOBI003 on brain magnetic resonance imaging (MRI) abnormalities
4. To assess the effect of SOBI003 on liver and spleen volume
5. To assess the effect of SOBI003 on Quality of Life
6. To assess the effect of SOBI003 on language
7. To assess the effect of SOBI003 on motor function
8. To assess the effect of SOBI003 on sleep pattern
9. To assess the immunogenicity of SOBI003
10. To characterize steady-state pharmacokinetics (PK) of SOBI003 by the use of non-compartmental analysis (NCA)

Exploratory objectives: The exploratory objectives are:

1. To assess the effect of SOBI003 on adaptive behavior over time.
2. To characterize the PK properties of SOBI003 following 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
4. To evaluate the PK/PD relationship between SOBI003 concentrations in serum and CSF, and the effect of SOBI003 on other biomarkers than HS and neuro-cognitive measures by use of population modelling.

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

5. Collect and store serum and CSF samples to enable analyses of biomarkers with possible relation to safety, tolerability, immunogenicity, PK and PD of SOBI003, as identified in future

STUDY ENDPOINTS

Primary endpoint: Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

Secondary endpoint(s): The secondary endpoints relating to the primary objective 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)

The endpoints relating to the key secondary objective are:

Study efficacy evaluation will primarily be based on:

- Change from baseline at Week 104 in Development Quotient (DQ) 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 104 in CSF HS

Additional key secondary endpoints are:

- Change from baseline at Week 52 in Development Quotient (DQ) 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 Weeks 52 and 104 in Age Equivalent (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 52 in CSF HS

The endpoints relating to the 1st secondary objective are:

- Change from baseline at Weeks 52 and 104 in adaptive behavior age-equivalence score (AEq) as assessed by Vineland Adaptive Behavior Scales, Second edition (VABS-II)

The endpoints relating to the 2nd secondary objective are:

- Change from baseline at Weeks 52 and 104 in serum HS
- Change from baseline at Weeks 52 and 104 in urine HS

The endpoints relating to the 3rd secondary objective are:

- Change from baseline at Weeks 52 and 104 in gray matter volume as assessed by brain volumetric MRI
- Change from baseline at Weeks 52 and 104 in compound ventricular volume as assessed by brain volumetric MRI
- Change from baseline at Weeks 52 and 104 in fractional anisotropy (FA) and mean diffusivity (MD) of corpus callosum as assessed by diffusion tensor imaging MRI
- Change from baseline at Weeks 52 and 104 in FA and MD of cerebral white matter as assessed by diffusion tensor imaging MRI
- Change from baseline at Weeks 52 and 104 in cerebral white matter as assessed by susceptibility weighting imaging (SWI) MRI
- Change from baseline at Weeks 52 and 104 in basal ganglia as assessed by SWI MRI

The endpoints relating to the 4th secondary objective are:

- Change from baseline at Weeks 52 and 104 in liver volume as assessed by abdominal MRI
- Change from baseline at Weeks 52 and 104 in spleen volume as assessed by abdominal MRI

The endpoints relating to the 5th secondary objective are:

- Change from baseline at Weeks 52 and 104 in Pediatric Quality of Life inventory (PedsQL) total score and PedsQL™ Family Impact Module total score

The endpoints relating to the 6th secondary objective are:

- Change from baseline at Weeks 52 and 104 in expressive language AEq score as assessed by the BSID-III language subtests or the KABC-II Expressive Vocabulary subtest, and the VABS-II communication domain
- Change from baseline at Weeks 52 and 104 in receptive language AEq score as assessed by the BSID-III language subtests or the KABC-II Expressive Vocabulary subtest, and the VABS-II communication domain

The endpoints relating to the 7th secondary objective are:

- Change from baseline at Weeks 52 and 104 in gross motor function AEq score as assessed by the BSID-III motor subtests and the VABS-II
- Change from baseline at Weeks 52 and 104 in fine motor function AEq score as assessed by the BSID-III motor subtest and the VABS-II

The endpoints relating to the 8th secondary objective are:

- Change from baseline at Weeks 52 and 104 in sleep pattern as assessed by the Children´s Sleep Habits Questionnaire (CSHQ)

score
- Change from baseline at Weeks 52 and 104 in sleep-related variables as assesses 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)

The endpoints relating to the 9th secondary objective are:

- Occurrence of anti-drug antibodies (ADAs) against SOBI003 in serum at Weeks 38, 52, 78 and 104, and adjacent to dose adjustments (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 at Weeks 52 and 104 (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 10th secondary objective are:

- Serum SOBI003 PK parameters at Weeks 39, 52, 78 and 104, and adjacent to dose adjustments; $t_{End\ of\ inf}$, $C_{End\ of\ inf}$, $C_{Pre\text{-}dose}$, CL, $AUC_{0\text{-}168h}$
- SOBI003 concentrations in CSF at Weeks 52 and 104.

Exploratory endpoint(s):

The endpoints related to the 1st exploratory objective are:

Change from baseline at Weeks 52 and 104 in adaptive behavior composite score as assessed by Vineland Adaptive Behavior Scales, Second edition (VABS-II).
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 results of these analyses will not be included in the Clinical Study Report for this study, but reported separately.

The endpoints related to the 3rd and 4th 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, single-arm, multicenter extension study to assess the safety, tolerability and efficacy of long-term SOBI003 treatment in pediatric MPS IIIA patients. The study is an extension of the First in Human (FIH) SOBI003-001 study, allowing continuous treatment of SOBI003 for up to 2 years. Study patients who complete Week 24 of the FIH study (SOBI003-001) will be invited to continue to Week 25 in the extension study.

As the phase I/II study has a sequential, ascending, multiple-dose design, the first patients will enter the extension study before finalization of the FIH study (SOBI003-001). When entering the extension study, these patients will receive

	the highest dose that has been declared safe in the ongoing FIH study (SOBI003-001). Upon completion of the FIH study, an analysis aimed at selecting the dose for forthcoming studies will take place. Once the dose has been selected, this dose will be applied to all patients enrolled in the extension study. SOBI003 is administered as weekly i.v. infusions over a period of time of 1 to 4 hours. 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 long-term safety, tolerability and immunogenicity of SOBI003 will be assessed throughout the extension study whereas measurements of clinical efficacy and disease-related biomarkers will be performed at Weeks 52 and 104. The potential of SOBI003 to improve the neurocognitive function will be compared to published data from a recent NH study. The independent DMC employed in the FIH study (SOBI003-001) will continue to monitor safety and tolerability data in the SOBI003-002 study at pre-specified intervals. The total duration of the extension study for an individual patient is 80 weeks, resulting in a total of 104 weeks (2 years) of SOBI003 treatment.
Number of subjects planned:	9-12
Diagnosis and main criteria for inclusion:	A patient must fulfill the following criteria in order to be included in the study: 1. Completion of study SOBI003-001 2. Informed consent obtained from the patient's legally authorized representative(s)
Assessments for safety and tolerability evaluation:	AEs are recorded from the time of obtained informed consent until End of Study. Blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation measured by pulse oximetry are assessed prior to each infusion, mid-infusion and within 1 hour of completion of each infusion. Intensified assessments are applied for dose adjustments. Blood and urine samples for central laboratory analyses of hematology, coagulation, and clinical chemistry are collected prior to each infusion at Weeks 38, 52, 78 and 104, as well as during dose adjustment periods and at Early Termination. 12-lead ECGs are obtained Weeks 52 and 104, and at Early Termination. A physical and neurological examination will be performed at Weeks 52 and 104, and at Early Termination. General appearance and skin are examined prior to and within 1 hour of completion of each infusion. Blood samples for central laboratory analyses of ADAs are taken pre-infusion at Weeks 38, 52, 78 and 104, and at Early Termination. For patients discontinuing treatment, ADA is assessed 30 to 40 days after last SOBI003 administration. CSF samples for central laboratory analysis of ADAs are collected at Weeks 52 and 104.

Assessments for pharmacokinetic (PK) and pharmacodynamics (PD) evaluation:	Serum concentration are collected for determination of SOBI003 multiple-dose PK parameters at Weeks 38, 52, 78 and 104 and adjacent to dose-adjustments. In addition, serum PK samples are collected when ADA samples are obtained. SOBI003 concentration in CSF is assessed at Weeks 52 and 104. HS is assessed in urine and serum at Weeks 38, 52, 78 and 104. HS in CSF is assessed at Weeks 52 and 104.
Assessments for efficacy evaluation:	Neurocognition is assessed by the BSID-III and/or KABC-II at Weeks 52 and 104. Adaptive behavior is assessed by the VABS-II at Weeks 52 and 104. Gray matter volume is assessed by MRIs Weeks 52 and 104. The PedsQL is completed by the parent/primary caregiver at Weeks 52 and 104.
Assessments for other efficacy evaluation:	Clinical manifestations, including language, motor function, and sleep pattern are assessed at Weeks 52 and 104. Brain and abdominal MRIs are performed at Weeks 52 and 104 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. When entering the extension study, these patients will receive the highest dose that has been declared safe in the ongoing FIH study (SOBI003-001). Upon completion of the FIH study, an analysis aimed at selecting the dose for forthcoming studies will take place. Once the dose has been selected, this dose will be applied to all patients enrolled in the extension study.
Reference product; dose and mode of administration:	Not applicable.
Duration of treatment(s):	80 weeks (104 weeks total of SOBI003 treatment)
Statistical methods:	Safety tabulations of AE 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. Change from baseline in DQ of neurocognitive development at Week 104 and change from baseline in CSF HS at Week 104 will be evaluated jointly in a hierarchical approach. DQ of neurocognitive development will be evaluated using a repeated measures analysis with the DQ measurements at the individual time points as response, and visit and visit-treatment interaction as fixed factors, baseline age as covariate and an unstructured covariance matrix will be used to estimate the covariance pattern. The control is an untreated group of MPS IIIa patients from a NH trial. The null hypothesis of no treatment effect will be tested with a significance test for the treatment*time-effect in the second step of the multiple testing procedure. The difference between 104 weeks and baseline will be used as the contrast of interest for the test. To assess the PD effect of SOBI003 on HS levels in CSF, serum and urine, linear 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 accumulated dose as covariate and sex as factor. The analyses are conducted for each assessment time point. In addition, linear 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 accumulated dose as covariate and sex as factor will be performed across all assessments, with

assessment as a repeated factor.

For the purpose of the multiple testing procedure, the linear repeated measures analysis with untransformed HS levels will be used, identical to the DQ analysis with the exception of the treatment factors.

The time effect is used to judge the HS level change in CSF. The null hypothesis of no change will be tested with a significance test for the time-effect in the first step of the multiple testing procedure. The difference between 104 weeks and baseline will be used as the contrast of interest for the test.PK results are presented by dose level using descriptive statistics.

Immunogenicity is summarized using frequency counts and percentages by dose level and will be evaluated regarding antibody prevalence (pre-existing antibodies), antibody incidence, titer and boosting following dosing, impact on PK and PD.

Adaptive behavior will be analyzed with the same repeated measures model as DQ, but adapted for one group (i.e. no treatment*visit interaction term).

To assess the PD effect of SOBI003 on MRI, linear models are used to model the change from baseline in MRI as dependent variable for both logged MRI and untransformed MRI, and baseline level and age as continuous covariates, and accumulated dose (including the FIH study) as covariate and sex as factor. The analyses will be conducted for each assessment time point: week 52 and 104.

In addition, linear analyses with MRI levels (both logged MRI levels and untransformed MRI levels), as dependent variable, and baseline level and age as continuous covariates, and accumulated dose as covariate and sex as factor will be performed across all assessments (including the FIH study), with assessment as a repeated factor.

Endpoints relating to other neurocognitive variables, liver and spleen volume, QoL, language, motor function and sleep pattern are summarized using descriptive statistics.

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.

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
$AUC_{0\text{-}168h}$	The area under the serum concentration-time curve from time 0 h to 168 h after dose
BBB	Blood-brain barrier
BSID-III	Bayleys Scales of Infant and Toddler Development®, third edition
CAP	College of American Pathologists
CDISC	Clinical data interchange standards consortium
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
$C_{End\ of\ inf}$	The observed serum concentration at the end of infusion of SOBI003
C_{max}	Maximum observed serum concentration
C_{Trough}	The minimum observed serum concentration
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
FIH	First-in-Human
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 7.5.6.1)
i.v.	Intravenous
ICF	Informed consent form
ICH	International council on harmonisation
IEC	Independent ethics committee
IL	Interleukin
IMP	Investigational medicinal product
IRB	Institutional review board
ITI	Immune Tolerance Induction
KABC-II	Kaufman assessment battery for children, second edition
LSD	Lysosomal storage disease
MABEL	Minimal anticipated biological effect level
MAR	Missing at random
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
NH	Natural history

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 on 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 Swedish Orphan Biovitrum AB (publ) (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/assent form.

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 for notifications to the regulatory authority in USA, where Sobi is responsible. Sobi is responsible for the compilation of Development Safety Update Reports based on data outputs from INC Research. INC Research is responsible for the compilation of Periodic Line Listings, if applicable, and the submission of these reports to the applicable regulatory authorities, and for the distribution to IRB/IEC and investigators, when applicable. Sobi is responsible for the submissions of periodic reports to the regulatory authority in USA.

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.

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

Four central laboratories are used in this study. The analyses of SOBI003, heparan sulfate (HS) and SOBI003 anti-drug-antibodies (ADA) in serum and CSF, including method validation, 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.

Analysis of neutralizing antibodies (NAbs) is assigned to BioAgilytix, Lademannbogen 10, 22339 Hamburg, Germany. This is a GLP compliant 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 College of American Pathologists (CAP) compliant laboratory.

Analysis of the levels of urinary HS is assigned to Greenwood Genetic Center, 106 Gregor Mendel Cir, Greenwood, South Carolina 29646, USA. This is a CAP and Clinical Laboratory Improvement Amendments (CLIA) accredited laboratory.

4.4 Central MRI reading

[redacted] is assigned to develop a study-specific MRI manual applicable for the MRI scans to be used 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 7.5.3.3.

4.5 Data monitoring committee

A data monitoring committee (DMC), independent from Sobi and Principal Investigators, is assigned to monitor all safety and immunogenicity data at intervals specified in Section 7.5.4.8. The primary responsibility of the DMC is to provide safety oversight of the study conduct in order to protect study participants.

The DMC employed in the FIH study (SOBI003-001) will continue to monitor safety and immunogenicity data in this extension study.

The DMC is planned to comprise an independent statistician and 2 clinicians that, collectively, have experience from DMC, management of pediatric patients with lysosomal storage disease (LSD), clinical immunology, and the conduct of clinical studies 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.

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 treatment and relief of symptoms. The unmet medical need is therefore high.

This extension study SOBI003-002 is designed to assess the safety and tolerability of long-term SOBI003 treatment and to evaluate the efficacy of SOBI003 in improving neurocognitive function and other measures indicative of a favorable outcome of SOBI003 treatment as compared to untreated MPS IIIA patients.

Patients completing the 24-week, open-label treatment period of the FIH study (SOBI003-001) with SOBI003 will be offered enrolment into this extension study. The current study will be a direct continuation of the FIH study (SOBI003-001), thus commencing with Week 25 and ending at Week 104, giving a total SOBI003 treatment duration of 2 years.

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) 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 extension 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 passive 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 (27) 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), Sobi encountered hypersensitivity reactions. 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. In the studies performed with anti-histamine pretreatment, including the 3 month toxicity study the ADA response does 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 had 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 (12, 13, 14, 15). 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 this extension study.

5.1.5 Study rationale

SOBI003 is being developed for treatment of MPS IIIA. Scientific advice on the nonclinical and chemistry, manufacturing and control (CMC) development has been obtained from the FDA on 16 February 2016 and from EMA in 28 June 2016. A pre-IND meeting was held with the FDA on 21 June 2017 to obtain agreement on the conduct of the FIH study (SOBI003-001) with SOBI003.

The FIH study (SOBI003-001) 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. Patients completing the 24-week, open-label treatment period of the FIH study will be offered enrolment into the extension study SOBI003-002.

Study SOBI003-002 is designed to assess the safety and tolerability of long-term SOBI003 treatment and to evaluate the efficacy of SOBI003 in improving neurocognitive function and other measures indicative of a favorable outcome of SOBI003 treatment. The follow-up period of the extension study is 80 weeks, giving a total SOBI003 treatment duration of 104 weeks to allow for a comparison with data from a recent NH study (22).

5.2 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 neuro-inflammation and the clinical manifestations of MPS IIIA.

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 foreignness 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 toxicology profile in non-clinical studies, and following patient completion of 24 weeks treatment in the FIH study (SOBI003-001), it is judged that SOBI003 can be given to patients in a carefully monitored extension study. Adherence to study inclusion/exclusion criteria and close clinical monitoring will be applied.

Although SOBI003 has been given for 24 weeks in the 001-study, hypersensitivity reactions/immune-mediated adverse reactions may still occur, 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 (17). Further symptomatic treatment with antipyretics and additional antihistamines may be administered to manage milder hypersensitivity/immune-mediated reactions. Immunosuppressant treatment will be administered in cases of less tolerable reactions. In addition, the availability of cardiopulmonary resuscitation equipment and immediate access to emergency medical services is secured.

Potential delayed hypersensitivity reactions may occur outside the hospital setting (refer to Table 1) for minimum hospitalization periods during study participation). Parents/caregivers will be carefully informed of potential signs and symptoms of delayed hypersensitivity reactions and of the importance to seek immediate medical attention.

SOBI003 has the potential to become the first disease modifying therapy in patients with MPS IIIA. The disease-modifying effect of SOBI003 is believed to be most beneficial if treatment is started in very young patients since they have limited neuronal damage. SOBI003 could possibly stop, or reverse, the progress of the neuronal damage and the neurocognitive decline leading to a normal or a near normal neurocognitive development. In older patients, that have more pronounced neuronal damage, it is likely that already developed neuronal damage is not reversible. However, further disease progression might be prevented or at least slowed down.

The ultimate effect of the disease modifying effect would be to improve the cognition and thereby prolong life, minimize behavioral problems and sleep disturbances, and increase QoL including reduction of caregiver burden. The evaluation of the benefits of SOBI003 treatment in pediatric patients with MPS IIIA is based on the results in the SOBI003 non-clinical studies showing reduced levels of stored HS and its metabolites in brain and CSF, reduction of neuroinflammation in brain, reduction of lysosomal swelling and secondary storage products in brain as well as trends towards a beneficial effect on behavioral impairment. If translated to human these beneficial effects may reduce the devastating clinical manifestations of MPS IIIA.

Potential study procedural risks include the use of sedation/general anesthesia and use of a central venous access port. To minimize study related procedural risks, local hospital routines 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 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. The central venous access port is added as part of the preceding FIH study (SOBI003-001), but there may be occasions when a patient may need to replace an existing port.

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

6 Study objectives and endpoints

The efficacy analysis will be based on data 2 years after the start of the FIH study (SOBI003-001), baseline being baseline assessments in the FIH study.

6.1 Primary objective

The primary objective is:

- To assess the long-term safety and tolerability of SOBI003

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 Key secondary objectives

- To evaluate the efficacy of SOBI003 on neurocognitive function, as compared to untreated MPS IIIA patients from a NH control
- To evaluate the effect of SOBI003 on HS levels in CSF

6.2.1 Key secondary endpoints

The endpoints relating to the key secondary objective are:

Study efficacy evaluation will primarily be based on:

- Change from baseline at Week 104 in Development Quotient (DQ) 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 104 in CSF HS

Additional key secondary endpoints are:

- Change from baseline at Week 52 in Development Quotient (DQ) 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 Weeks 52 and 104 in Age Equivalent (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 52 in CSF HS

6.3 Secondary objectives

The secondary objectives are:

1. To assess the effect of SOBI003 on adaptive behavior, as compared to untreated MPS IIIA patients from a NH control
2. To assess the effect of SOBI003 on HS levels in serum and urine
3. To assess the effect of SOBI003 on brain magnetic resonance imaging (MRI) abnormalities
4. To assess the effect of SOBI003 on liver and spleen volume
5. To assess the effect of SOBI003 on Quality of Life
6. To assess the effect of SOBI003 on language
7. To assess the effect of SOBI003 on motor function
8. To assess the effect of SOBI003 on sleep pattern

9. To assess the immunogenicity of SOBI003
10. To characterize steady-state pharmacokinetics (PK) of SOBI003 by the use of non-compartmental analysis (NCA)

6.3.1 Secondary endpoints

The endpoints relating to the 1st secondary objective are:

- Change from baseline at Weeks 52 and 104 in adaptive behavior age-equivalence score (AEq) as assessed by Vineland Adaptive Behavior Scales, Second edition (VABS-II)

The endpoints relating to the 2nd secondary objective are:

- Change from baseline at Weeks 52 and 104 in serum HS
- Change from baseline at Weeks 52 and 104 in urine HS

The endpoints relating to the 3rd secondary objective are:

- Change from baseline at Weeks 52 and 104 in gray matter volume as assessed by brain volumetric MRI
- Change from baseline at Weeks 52 and 104 in compound ventricular volume as assessed by brain volumetric MRI
- Change from baseline at Weeks 52 and 104 in fractional anisotropy (FA) and mean diffusivity (MD) of corpus callosum as assessed by diffusion tensor imaging MRI
- Change from baseline at Weeks 52 and 104 in FA and MD of cerebral white matter as assessed by diffusion tensor imaging MRI
- Change from baseline at Weeks 52 and 104 in cerebral white matter as assessed by susceptibility weighting imaging (SWI) MRI
- Change from baseline at Weeks 52 and 104 in basal ganglia as assessed by SWI MRI

The endpoints relating to the 4th secondary objective are:

- Change from baseline at Weeks 52 and 104 in liver volume as assessed by abdominal MRI
- Change from baseline at Weeks 52 and 104 in spleen volume as assessed by abdominal MRI

The endpoints relating to the 5th secondary objective are:

- Change from baseline at Weeks 52 and 104 in Pediatric Quality of Life inventory (PedsQL) total score and PedsQL™ Family Impact Module total score

The endpoints relating to the 6th secondary objective are:

- Change from baseline at Weeks 52 and 104 in expressive language AEq score as assessed by the BSID-III language subtests or the KABC-II Expressive Vocabulary subtest, and the VABS-II communication domain

- Change from baseline at Weeks 52 and 104 in receptive language AEq score as assessed by the BSID-III language subtests or the KABC-II Expressive Vocabulary subtest, and the VABS-II communication domain

The endpoints relating to the 7th secondary objective are:

- Change from baseline at Weeks 52 and 104 in gross motor function AEq score as assessed by the BSID-III motor subtests and the VABS-II
- Change from baseline at Weeks 52 and 104 in fine motor function AEq score as assessed by the BSID-III motor subtest and the VABS-II

The endpoints relating to the 8th secondary objective are:

- Change from baseline at Weeks 52 and 104 in sleep pattern as assessed by the Children´s Sleep Habits Questionnaire (CSHQ) score
- Change from baseline at Weeks 52 and 104 in sleep-related variables as assesses 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)

The endpoints relating to the 9th secondary objective are:

- Occurrence of ADAs against SOBI003 in serum at Weeks 38, 52, 78 and 104, and adjacent to dose adjustments (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 at Weeks 52 and 104 (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 10th secondary objective are:

- Serum SOBI003 multiple-dose PK parameters at Weeks 38, 52, 78 and 104, and adjacent to dose adjustments; $t_{End\ of\ inf}$, $C_{End\ of\ inf}$, $C_{Pre\text{-}dose}$, $AUC_{0\text{-}168h}$, CL
- SOBI003 concentrations in CSF at Weeks 52 and 104.

6.4 Exploratory objectives

The exploratory objectives are to explore the effect of SOBI003 on:

1. To assess the effect of SOBI003 on adaptive behavior over time
2. To characterize the PK properties of SOBI003 following 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

4. To evaluate the PK/PD relationship between SOBI003 concentrations in serum and CSF, and the effect of SOBI003 on other biomarkers than HS and neuro-cognitive measures eg. DQ, as well as MRI data, by the use of population modelling

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

- Collect and store serum and CSF samples to enable analyses of biomarkers with possible relation to safety, tolerability, immunogenicity, PK and PD of SOBI003, as identified in future

Serum and CSF samples for potential future 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.

6.4.1 Exploratory endpoints

The endpoints related to the 1st exploratory objective are:

- Change from baseline at Weeks 52 and 104 in adaptive behavior composite score as assessed by Vineland Adaptive Behavior Scales, Second edition (VABS-II)

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 results of these analyses will not be included in the Clinical Study Report for this study, but reported separately.

The endpoints related to the 3rd and 4th 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, single-arm, multicenter extension study to assess the long-term safety, tolerability and efficacy of SOBI003 in pediatric MPS IIIA patients who previously participated in the FIH study (SOBI003-001) study. Patients completing the 24-week treatment of the FIH study will be offered to participate in the continuous 80 week treatment period of the extension study. The extension study starts with enrolment at Week 25, giving a total SOBI003

treatment duration of 104 weeks for each patient. Please refer to Figure 1 for an overview of the study design. A recent NH study is used as external control (22) to enable an evaluation of efficacy. Neurocognitive and adaptive behavior data assessed in the extension study at Week 52 and Week 104 following start of treatment will be compared to available NH data within the target study population. The NH population for comparison consists of 14 patients with a rapid progressive MPS IIIA disease and a baseline age of 12 to 72 months.

As the FIH study (SOBI003-001) has a sequential, ascending, multiple-dose design, the first patients will enter the extension study before the FIH study is completed. When entering the extension study, these patients will receive the highest dose that has been declared safe by the SRC in the ongoing FIH study (SOBI003-001) study. Patients enrolled in Cohort 1 of FIH study may thus be switched to the dose applied in Cohort 2 or Cohort 3, depending on safety clearance by the SRC. If a patient is initially switched to the dose applied in Cohort 2, the patient may subsequently later be switched to the dose applied in Cohort 3. Depending on recruitment rate in the FIH study (SOBI003-001) study, a patient enrolled in Cohort 1 may be directly switched to the dose applied in Cohort 3. Upon completion of the FIH study, an analysis aimed at selecting the dose for forthcoming studies will take place. Once the dose has been selected, this dose will be applied to all patients enrolled in the extension study.

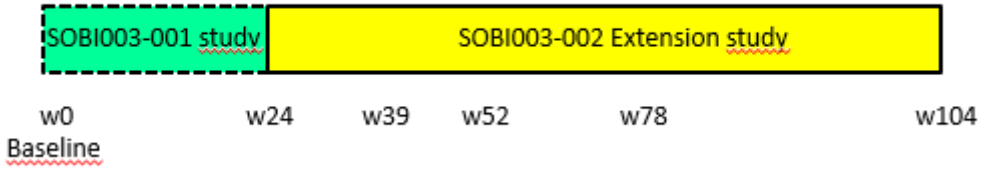
SOBI003 is administered as weekly i.v. infusions over a period of time of 1 to 4 hours. Prior to initiation of each infusion, the patients are pretreated with a single dose of non-sedative antihistamine. If infusion-related reactions occur, then the infusion duration may be expanded up to 24 hours and supportive medication may be administered, at the discretion of the investigator.

The long-term safety, tolerability and immunogenicity of SOBI003 will be assessed throughout the extension study whereas measurements of clinical efficacy and disease-related biomarkers will be performed at Weeks 52 and 104. The potential of SOBI003 to improve the neurocognitive function will be compared to published data from a recent NH study (22).

The independent DMC employed in the FIH study (SOBI003-001) will continue to monitor safety and immunogenicity data in the SOBI003-002 study.

Following completion of the extension study, depending on demonstrated safety, tolerability and benefit-risk evaluation of SOBI003, study patients' continuous access to SOBI003 treatment may be arranged as part of a Sobi-sponsored extension study starting in direct connection to the study, or through an alternative ethically and regulatory accepted approach.

Figure 1 Overview for study design for study SOBI003-002



To secure a close monitoring of the patients and the intensified study assessments at Weeks 52 and 104, and at week(s) of dose adjustments, the minimum hospitalization periods specified in Table 1 are applied:

Table 1 Minimum hospitalization periods

Week	Minimum hospitalization period*
25 to 51, 53 to 103	Admission; day of infusion Discharge; 1 hour or later after the end of each infusion
52 and 104	Admission; day of infusion Discharge; 1 hour or later after the end of infusion
At week(s) of dose adjustments	Admission; day of infusion Discharge; 48 hours after initiation of each of the first 3 infusions**

* Extended as per local routine for admission/discharge and per patient need as determined by the investigator (eg, concurrent illness, travel distance etc)
** If dose adjustment is a decrease in dose as a result of study dose selection for forthcoming studies, and there are no safety concerns, the patient may be discharged 1 hour or later after the end of each infusion.

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. 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 regular weekly infusions of SOBI003 may be administered at home by a trained study nurse or at a geographically closer satellite site, if judged safe by the investigator and Sobi MD. At weeks with scheduled laboratory or efficacy assessments and during 12 weeks following a dose increase or reduction due to safety, SOBI003 infusions will always be performed at the PI site. If the patient receives all infusions at the PI site, they and their parent(s) may be relocated for parts the study or for the full study duration. The families are reimbursed for travel and, if applicable, for accommodation expenses and caregiver meals. Appointed study coordinators will assist the families with travel and accommodation arrangements.

7.2 Discussion of study design

Patients completing the 24-week, open-label treatment period of the FIH study (SOBI003-001) study will be offered enrolment into the 80 week extension study SOBI003-002, giving a total SOBI003 treatment duration of 104 weeks (2 years) for each patient.

Although the SOBI003-002 is designed to primarily assess the safety and tolerability of long-term SOBI003 treatment, the inclusion and exclusion criteria have been selected to allow for an efficacy comparison with data from a recent NH study (22).

In very rare and life-threatening diseases such as MPS IIIA alternative designs to a placebo or untreated control are often needed. A position statement by key experts in the field proposes the

use of natural history data instead of formal comparator groups in clinical studies in MPS diseases (24). In the case of treatment of MPS IIIA, no active comparator exists and Sobi does not consider it ethical to withhold a potentially efficient treatment in patients with a rapidly progressive, and life-shortening condition. Data from a recent NH study (22) will therefore serve as control for the studies in the SOBI003 clinical program.

In order to compare SOBI003 treatment with the NH study, comparable patients will be included and the time points for efficacy evaluations and the neurocognitive and behavioral tools used will be identical. The efficacy endpoints in the SOBI003 clinical development program have been selected based on the recommendations in a position statement by key experts in the field, the clinical relevance (24, 25, 26) as well as on the endpoints in the NH study (22). The efficacy analysis will be based on data 2 years after the start of the FIH study (SOBI003-001), baseline being baseline assessments in the FIH study. The choice of treatment duration is based on advice from key clinical experts in the area and the availability of NH data. It is considered long enough to differentiate efficacy of SOBI003 treatment compared to an untreated control.

The dose in the SOBI003-002 study will primarily be selected on the basis of safety and tolerability results and the magnitude of HS reduction in CSF observed for the dose levels in the FIH study (SOBI003-001). At enrolment into the extension study (SOBI003-002), the individual dose will be adjusted to the highest tolerable dose level in order to optimize treatment duration on an efficacious dose. Upon completion of the FIH study, an analysis aimed at selecting the dose for forthcoming studies will take place. Once the dose has been selected, this dose will be applied to all patients enrolled in the extension study.

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. Completion of the FIH study (SOBI003-001)
2. Informed consent obtained from the patient's legally authorized representative(s)

7.3.2 Exclusion criteria

The presence of the following criterion excludes a patient from inclusion in the study:

1. If, in the opinion of the investigator, there are patient specific safety concerns that contraindicates further treatment with SOBI003

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 AE, the reason for treatment withdrawal should always be stated as 'AE' irrespective of whether this was the investigator's or the patient's primary caregiver(s) decision.

After treatment withdrawal, efficacy, safety, immunogenicity and PK assessments should be completed as soon as possible and repeated 30 to 40 days after the last SOBI003 administration, as specified for "Early Termination" in the Schedule of Events (Table 2).

When possible, study assessments (excluding SOBI003 infusion) of Weeks 38, 52, 78 and 104 should continue in accordance with the Schedule of Events (Table 2) in order to collect continuous immunogenicity, safety and efficacy data for study patients following withdrawn treatment. Additional safety assessments will be performed at the discretion of the investigator, as warranted by the AE(s) leading to treatment withdrawal.

A patient that is withdrawn from study treatment due to an AE, 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. Should the 30 to 40-day post last infusion be ADA-positive, then the ADA titer will be determined and ADA samplings will continue at approximately monthly basis until the ADAs have disappeared or titers have stabilized at a lower level. Every time an ADA sample is taken, a corresponding PK assessment is done.

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. The efficacy, safety, immunogenicity and PK assessments should be completed as soon as possible and repeated 30 to 40 days after the last SOBI003 administration, as specified for "Early Termination" in the Schedule of Events (Table 2). The CRF should be completed to the highest possible extent.

7.3.4 Replacement of withdrawn patients

Withdrawn patients will not be replaced.

7.3.5 Specific restrictions/requirements on patients

The patients are required to visit the site weekly for the SOBI003 infusions and remain at the site for at least 1 hour after the end of the infusion. The hospitalization period may be extended as per local routine for admission/discharge and per patient need as determined by the investigator (e.g., concurrent illness and travel distance).

Following a dose adjustment, patients are hospitalized for at least 48 hours after initiation of each of the first 3 infusions. If dose adjustment is a decrease in dose as a result of study dose selection for forthcoming studies, and there are no safety concerns, the patient may be discharged 1 hour or later after the end of each infusion.

7.4 Treatments

7.4.1 Treatments administered

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

SOBI003 is administered as i.v. infusions given once weekly for a duration of 80 weeks (from Week 25 until Week 104 following the first 24 weeks of IMP administration in the FIH study (SOBI003-001) study.

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.

7.4.2 Identity of investigational medicinal products

SOBI003 is provided as concentrated 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 [redacted]. The drug product is manufactured by [redacted]

[redacted] Secondary packaging of vials and labeling of cartons is done by [redacted]

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

This is a single-arm study.

7.4.4 Selection of doses

Initially, the patients enrolled into the extension study will receive the highest dose that has been declared safe by the Safety Review Committee (SRC) in the at the time ongoing FIH study (SOBI003-001) study. The planned dosage range for the FIH study is 3 to 20 mg/kg.

Patients enrolled in Cohort 1 of the FIH study (SOBI003-001) study may thus be switched to the dose applied in Cohort 2 or Cohort 3, depending on safety clearance by the SRC. If a patient is initially switched to the dose applied in Cohort 2, the patient may subsequently be switched to the dose applied in Cohort 3. Depending on recruitment rate in the FIH study, a patient enrolled in Cohort 1 may be directly switched to the dose applied in Cohort 3.

Upon completion of the FIH study (SOBI003-001) study, an analysis aimed at selecting the dose for forthcoming studies will take place. The analysis is conducted by Sobi and will be based on risk-benefit observed for the doses applied during the FIH study. Once the dose has been selected, this dose will be applied to all patients enrolled in the extension study. This may result in a decrease or increase of all current patient doses in the extension study.

Dose adjustments will be avoided during the 4-week period prior to Week 52 and 104 in order to avoid interference with study efficacy assessments. Any requested dose adjustment during this time should be postponed, if not considered medically justified by the investigator. Patients will be extensively monitored during dose adjustments as described in Section 7.5.1.7.

7.4.5 Selection and timing of doses for each patient

SOBI003 is administered as weekly i.v. infusions. 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 i.e., if the first infusion in study FIH study (SOBI003-001) was administered on a Wednesday, then the infusions in the extension study 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 body weight at 4-week intervals (i.e., the actual dose administered at Weeks 25 to 28 is based on the body weight obtained pre-infusion at Week 25, the actual dose administered at Weeks 29 to 32 is based on the body weight obtained pre-infusion at Week 29, etc.). The body weight is obtained either on the day prior to the infusion or the day of infusion. For a body weight < 25 kg, the targeted total infusion volume is 100 mL. For a body weight ≥ 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.

The SOBI003 infusions are initially given over a period of 4 hours. When no more dose increases are expected, and the intensified study assessments associated with dose adjustments are completed (Section 7.5.1.7), the infusion period in individual patients may step-wise be decreased at the discretion of the investigator. The minimal infusion period is 1 hour.

Infusion rate schedules are provided in a separate IMP manual.

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

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

For individual study patients there may be situations, due to safety or infusion related reactions observed at a higher dose level, where it is judged by investigator that it is in the patient's best interest to reduce the treatment dose. In such situations investigator should discuss with Sobi MD regarding an individual patient dose adjustment.

7.4.6 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 in this study.

As described in Section 7.4.5, a single dose of a 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 (17). Necessary equipment for resuscitation must be available during study drug infusion.

If clinically justified, patients who develop high titer antibodies that affect 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, immune tolerizing approaches used in other LSDs (22) may be applied at the discretion of the investigator after discussion with Sobi Medical Director.

7.4.7 Treatment compliance

Product accountability records will be kept. The pharmacy and investigator must maintain accurate records demonstrating date and amount of IMP received, to whom and by whom administered (patient-by-patient accounting), and accounts of returned IMP and any IMP accidentally or deliberately destroyed.

All unused IMP will be counted. At the end of the study, any remaining IMP will be returned to Almac 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

The following schedule of events provides an overview of extension study assessments (Table 2), as well as the following detailed schedules of events:

Table 3: Detailed Schedule of events – Enrolment and treatment weeks with weight assessment

Table 4: Detailed Schedule of events – Treatment weeks without weight assessment

Table 5: Detailed Schedule of events – Weeks 38 and 78
Table 6: Detailed schedule of events – Weeks 52 and 104 –Day 1
Table 7: Detailed schedule of events – Weeks 52 and 104 – Days 2 to 7
Table 8: Detailed schedule of events – Following a SOBI003 dose adjustment - first 3 weeks
Table 9: Detailed schedule of events – Following a SOBI003 dose adjustment – Weeks 4 and 8

Table 2 Schedule of events – Overview Enrolment to End of Study

	Enrolment and treatment period (Week 25 to 104)					ET[a]
Week	**25**	**38**	**52**	**78**	**104/ END**	
Informed consent	X					
Eligibility criteria	X					
Concomitant therapy	X	→	→	→	→	X
Physical examination[b]	X	→	→	→	→	X
Neurological examination			X		X	X
Height & head circumference			X		X	X
Weight[c]	X	→	→	→	→	X
Vital signs[d]	X	→	→	→	→	X
12-lead ECG			X		X	X
Antihistamine[e]	X	→	→	→	→	
SOBI003 administration[f]	X	→	→	→	→	
Adverse events	X	→	→	→	→	X
Anesthesia/sedation[g] for:						
CSF sampling (PK, ADA, HS)			X		X	
CSF sampling (future research) [h]			X		X	
MRI (brain, liver, spleen)			X		X	
Blood sampling for:						
Safety laboratory		X	X	X	X	X
Immunogenicity		X	X	X	X	X
HS		X	X	X	X	X
PK		X	X	X	X	X
Future research[h]			X		X	
Urine collection for:						
Safety laboratory (Dipstick)		X	X	X	X	X
HS		X	X	X	X	X
Actigraphy (sleep pattern)[i]			X		X	
BSID-III/KABC-II (neurocognition, language, motor function)[j]			X		X	X
Parent/caregiver questionnaires:						
VABS-II			X		X	X
CSHQ [i]			X		X	
PedsQL, incl. Family Impact Module			X		X	X

a In case of Early Termination (ET) of SOBI003 administrations, the assessments should be completed as soon as possible after decision of treatment withdrawal.
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. On Weeks 52 and 104, as well as at Early Termination, a complete physical

examination (general appearance, skin (including potential reactions around the infusion site), eyes, ears, nose, neck, nymph nodes, throat, heart, lungs, abdomen, musculoskeletal system and extremities) is conducted.
c During the treatment period, body weight is assessed at approximately 4-week intervals to determine the actual SOBI003 dose to be administered. Weight is therefore obtained prior to preparation of the SOBI003 infusions solution at Enrolment (Week 25) and every 4th week during the study. The weight is obtained either the day prior to the infusion or the day of infusion.
d Vital signs includes blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation measured by pulse oximetry. At each infusion, assessments are done pre-infusion, mid-infusion and within 1 hour after end of infusion. If dose is adjusted, vital signs are measured according to 7.5.5.4.
e. Within 30 to 60 minutes prior to each SOBI003 infusion, a single dose of a non-sedative antihistamine should be administered.
f. SOBI003 is administered as weekly infusions; +/- 1-day window is applied.
g Use of general anesthesia or sedation as well as selection of anesthetic/sedative agents is per local hospital routine and anesthesiologist judgement.
h Only applicable when separate informed consent has been provided for future research.
i Sleep pattern is assessed by actigraph recordings for 7 consecutive days at Weeks 51-52 and 103-104, i.e., the recordings start Weeks 51 and 103, and will cease in the morning of the Week 52 and 104 infusions. An actigraph log is completed during the days of actigraphy. Parents should complete the CSHQ upon completion of each actigraph assessment (i.e., at Weeks 52 and 104 this will be during the infusion days).
j 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.

Table 3 Detailed Schedule of events – Enrolment and treatment weeks with weight assessment

	Treatment period – Enrolment (Week 25)[a] and Weeks 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 97 and 101				
Time	**Pre-infusion**	**Start of infusion (0:00)**	**Mid-infusion (2:00)[b]**	**Stop of infusion (4:00)[b]**	**Within 1 hour of completing the infusion (4:01 - 5:00)[c]**
Concomitant therapy	X	X	X	X	X
Physical examination (general appearance and skin)	X				X
Weight[d]	X				
Vital signs	X		X[b]		X
Antihistamine[e]	X				
SOBI003 administration:					
Start of infusion		X			
Stop of infusion				X	
Adverse events	X	X	X	X	X

a. Prior to any study assessment the eligibility criteria must be confirmed and the enrolment informed consent obtained.
b. The SOBI003 infusions are initially given over a period of 4 hours. When no more dose increases are expected, and the intensified study assessments associated with dose adjustments are completed, the infusion period in individual patients may step-wise be decreased at the discretion of the investigator. The minimal infusion period is 1 hour. If the infusion period is decreased to <4 hours (see Section 7.4.5), the vital sign assessment is performed in the middle of the infusion period, i.e. if the infusion period is 2 hours, the vital sign assessment is performed 1 hour after start of infusion.
c. The scheduled assessments will be performed within 1 hour after end of infusion, i.e., timing will be dependent on the infusion period.
d. Weight to be obtained prior to preparation of the SOBI003 infusions solution, either the day prior to the infusion or on the day of infusion.
e. Within 30 to 60 minutes prior to each SOBI003 infusion, a single dose of a non-sedative antihistamine should be administered.

Table 4 Detailed Schedule of events – Treatment weeks without weight assessment

	Treatment period - Weeks 26, 27, 28, 30, 31, 32, 34, 35, 36, 39, 40, 42, 43, 44, 46, 47, 48, 50, 51[a], 54, 55, 56, 58, 59, 60, 62, 63, 64, 66, 67, 68, 70, 71, 72, 74, 75, 76, 79, 80, 82, 83, 84, 86, 87, 88, 90, 91, 92, 94, 95, 96, 98, 99, 100, 102 and 103[a]				
Time	**Pre-infusion**	**Start of infusion (0:00)**	**Mid-infusion (2:00)[b]**	**Stop of infusion (4:00)[b]**	**Within 1 hour of completing the infusion (4:01 - 5:00)[c]**
Concomitant therapy	X	X	X	X	X[c]
Physical examination (general appearance and skin)	X				X[c]
Vital signs	X		X[b]		X[c]
Antihistamine[d]	X				
SOBI003 administration:					
Start of infusion		X			
Stop of infusion				X	
Adverse events	X	X	X	X	X

a. Sleep pattern is assessed by actigraph recordings for 7 consecutive days at Weeks 51-52 and 103-104, i.e., the recordings start Weeks 51 and 103, and will cease in the morning of the Week 52 and 104 infusions. An actigraph log is completed during the days of actigraphy.
b. The SOBI003 infusions are initially given over a period of 4 hours. When no more dose increases are expected, and the intensified study assessments associated with dose adjustments are completed, the infusion period in individual patients may be decreased step-wise at the discretion of the investigator. The minimal infusion period is 1 hour. If the infusion period is decreased to <4 hours (see Section 7.4.5), the vital sign assessment is performed in the middle of the infusion period, i.e. if the infusion period is 2 hours, the vital sign assessment is performed 1 hour after start of infusion.
c. The scheduled assessments will be performed within 1 hour after end of infusion, i.e., timing will be dependent on the infusion period.
d. Within 30 to 60 minutes prior to each SOBI003 infusion, a single dose of a non-sedative antihistamine should be administered.

Table 5 Detailed Schedule of events – Weeks 38 and 78

	Weeks 38 and 78					
Time	**Pre-infusion**	**Start of infusion (0:00)**	**Mid-infusion (2:00)[a]**	**Stop of infusion (4:00)[a]**	**Within 1 hour following infusion (4:01 - 5:00)**	**Day 8 (Pre-infusion, 168:00)**
Concomitant therapy	X	X	X	X	X[b]	
Physical examination (general appearance and skin)	X				X[b]	
Vital signs	X		X		X[b]	
Antihistamine[c]	X					
SOBI003 administration:						
Start of infusion		X				
Stop of infusion				X		
Adverse events	X	X	X	X	X	
Blood sampling for:						
Safety laboratory	X					
Immunogenicity	X					
HS	X					
PK	X			X[d]		X[e]
Urine collection for:	X					
Safety laboratory (Dipstick)	X					
HS	X					

a. The SOBI003 infusions are initially given over a period of 4 hours. When no more dose increases are expected, and the intensified study assessments associated with dose adjustments are completed, the infusion period in individual patients may be decreased step-wise at the discretion of the investigator. The minimal infusion period is 1 hour. If the infusion period is decreased to <4 hours (see Section 7.4.5), the vital sign assessment is performed in the middle of the infusion period, i.e. if the infusion period is 2 hours, the vital sign assessment is performed 1 hour after start of infusion.
b. The scheduled assessments will be performed within 1 hour after end of infusion, i.e., timing will be dependent on the infusion period.

c. Within 30 to 60 minutes prior to each SOBI003 infusion, a single dose of a non-sedative antihistamine should be administered.
d. PK sample should be collected as soon as possible following end of infusion.
e. 168 hour PK sample for weeks 38 and 78 is collected pre-infusion on weeks 39 and 79 respectively.

Table 6 Detailed schedule of events – Weeks 52 and 104 –Day 1

	Weeks 52 and 104 – Day 1				
Day	**1**	**1**	**1**	**1**	**1**
Time	**Pre-infusion**	**Start of infusion (0:00)**	**Mid-infusion (2:00)[a]**	**Stop of infusion (4:00)[a]**	**Within 1 hour of completing the infusion (4:01 - 5:00)[b]**
Concomitant therapy	X	X	X	X	X
Physical examination (general appearance and skin)	X				X
Vital signs	X		X		X
Antihistamine[c]	X				
SOBI003 administration:					
Start of infusion		X			
Stop of infusion				X	
Adverse events	X	X	X	X	X
Blood sampling for:					
Safety laboratory	X				
Immunogenicity	X				
HS	X				
PK	X			X[e]	
Future research[d]	X				
Urine collection for:	X				
Safety laboratory (Dipstick)	X				
HS	X				
Actigraphy (sleep pattern)[f]	X				

	Weeks 52 and 104 – Day 1				
Day	**1**	**1**	**1**	**1**	**1**
Time	**Pre-infusion**	**Start of infusion (0:00)**	**Mid-infusion (2:00)[a]**	**Stop of infusion (4:00)[a]**	**Within 1 hour of completing the infusion (4:01 - 5:00)[b]**
Parent/caregiver questionnaires:					
CSHQ[f]	X				

a. The SOBI003 infusions are initially given over a period of 4 hours. When no more dose increases are expected, and the intensified study assessments associated with dose adjustments are completed, the infusion period in individual patients may step-wise be decreased at the discretion of the investigator. The minimal infusion period is 1 hour. If the infusion period is decreased to <4 hours (see Section 7.4.5), the vital sign assessment is performed in the middle of the infusion period, i.e. if the infusion period is 2 hours, the vital sign assessment is performed 1 hour after start of infusion.
b. The scheduled assessments will be performed within 1 hour after end of infusion, i.e., timing will be dependent on the infusion period.
c. Within 30 to 60 minutes prior to each SOBI003 infusion, a single dose of a non-sedative antihistamine should be administered.
d. Only applicable when separate consent has been provided for future research
e. PK sample should be collected as soon as possible following end of infusion.
f. Sleep pattern is assessed by actigraph recordings for 7 consecutive days at Weeks 51-52 and 103-104, i.e., the recordings start Weeks 51 and 103, and will cease in the morning of the Week 52 and 104 infusions. An actigraph log is completed during the days of actigraphy. Parents should complete the CSHQ upon completion of each actigraph assessment (i.e., at Weeks 52 and 104 this will be during the infusion days).

Table 7 Detailed schedule of events – Weeks 52 and 104 – Days 2 to 7

	Weeks 52 and 104 – Days 2 to 7				
Day	**2**	**3**	**4**	**5**	**7 (8[a])**
Concomitant therapy	X	X	X	X	X
12-lead ECG					X
Physical examination (complete)					X
Neurological examination					X
Height, weight & head circumference					X
Adverse events	X	X	X	X	X
Anesthesia/sedation[i] for:					
CSF sampling (PK, ADA, HS, future research[b])	X				
MRI (brain, liver, spleen)	X				
Blood sampling for:					
PK	X				X
BSID-III/KABC-II (neurocognition, language, motor function) [c]			(X)[c]	(X)[c]	X[c]
Parent/caregiver questionnaires:					
VABS-II		X			
PedsQL, incl. Family Impact Module			X		

a. Only PK sampling applicable on Day 8 (168 h after start of infusion). All other assessments are performed on Day 7.
b. Only applicable when separate consent has been provided for future research.

c. In case both BSID-III and KABC-II should be assessed, the BSID-III should be administered first, and there should be at least 2 days between the BSID-III and KABC-II assessments. If only BSID-III or KABC-II is to be assessed this should be done on Day 7.

Table 8 Detailed schedule of events – Following a SOBI003 dose adjustment - first 3 weeks

	Following a SOBI003 dose adjustment – First 3 weeks											
Week	1, 2, 3 (following dose adjustment)											
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**3**	**8**
Time	**Pre-inf**	**0**	**1:00**	**2:00**	**3:00**	**4:00**	**4:01 - 5:00**	**6:00 – 7:00**	**8:00 - 12:00**	**24**	**48**	**168 (pre-inf)**
Concomitant therapy	X		X	X	X		X	X	X	X	X	X
Physical examination (general appearance and skin)	X		X	X	X		X	X	X	X	X	
Vital signs	X		X	X	X		X	X	X	X	X	
Continuous pulse-oximetry	→											
Antihistamine	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
Blood sampling for:												
Safety laboratory	X											
Immunogenicity	X[a]											
HS	X											
PK	X[b]					X[c, d]						X[d]
Urine collection for:												
Safety laboratory (Dipstick)	X											
HS	X											

a. Only on week 3
b. Collected on Weeks 1 and 3 following dose adjustment.

c. PK sample should be collected as soon as possible following end of infusion.
d. Collected on Weeks 1 following dose adjustment.

Table 9 Detailed schedule of events – Following a SOBI003 dose adjustment – Weeks 4 and 8

	Following a SOBI003 dose adjustment – Weeks 4 and 8					
Week	**4, 8 (following dose adjustment)**					
Day	**1**	**1**	**1**	**1**	**1**	**8**
Time	**Pre-infusion**	**Start of infusion (0:00)**	**Mid-infusion (2:00)[a]**	**Stop of infusion (4:00)[a]**	**Within 1 hour of completing the infusion (4:01 - 5:00)[b]**	**Pre-infusion next week (168:00)**
Concomitant therapy	X		X		X	X
Physical examination (general appearance and skin)	X				X	
Vital signs	X		X		X	
Antihistamine[c]	X					
SOBI003 administration						
Start of infusion		X				
Stop of infusion				X		
Adverse events	X	X	X	X	X	X
Blood sampling for:						
PK	X			X[d]		X

a. The SOBI003 infusions are initially given over a period of 4 hours. When no more dose increases are expected, and the intensified study assessments associated with dose adjustments are completed, the infusion period in individual patients may step-wise be decreased at the discretion of the investigator. The minimal infusion period is 1 hour. If the infusion period is decreased to <4 hours (see Section 7.4.5), the vital sign assessment is performed in the middle of the infusion period, i.e. if the infusion period is 2 hours, the vital sign assessment is performed 1 hour after start of infusion.
b. The scheduled assessments will be performed within 1 hour after end of infusion, i.e., timing will be dependent on the infusion period.
c. Within 30 to 60 minutes prior to each SOBI003 infusion, a single dose of a non-sedative antihistamine should be administered.
d. PK sample should be collected as soon as possible following end of infusion.

Table 10 Detailed PK blood sampling schedule

Week	Time	No of samples[a]
Week 38	**Pre-infusion**	1
	4h / End of Infusion	2
	168h	1
Week 52	**Pre-infusion**	1
	4h / End of Infusion	2
	Day 2[c]	1
	168h	1
Week 78	**Pre-infusion**	1
	4h / End of Infusion	2
	168h	1
Week 104	**Pre-infusion**	1
	4h / End of Infusion	2
	Day 2[c]	1
	168h	1
At week of dose adjustment[b]	**Pre-infusion**	1
	4h / End of Infusion	2
	168h	1
3 weeks after dose adjustment	**Pre-infusion**	1
4 weeks after dose adjustment[b]	**Pre-infusion**	1
	4h / End of Infusion	2
	168h	1
8 weeks after dose adjustment[b]	**Pre-infusion**	1
	4h / End of Infusion	2
	168h	1
At early treatment/study termination	**Early Termination visit – time point same as immunology sample**	1
	30-40 days post Early Termination visit - time point same as immunology sample	1
	If additional immunogenicity samples as part of follow-up- number of samples per time point	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. The PK samples from a peripheral venous line for the End of infusion sample can be excluded if it has been confirmed in the FIH study (SOBI003-001) that the SOBI003 i.v. infusion does not interfere with the PK blood sampling..
b If the dose of SOBI003 is adjusted in a patient, PK blood samples will be collected before infusion, at the end of infusion and 168 hours after start of the infusion at the week of dose adjustment and 4 and 8 weeks after the dose adjustment.
c At the time of CSF sample collection Day 2, a PK blood sample will also be collected. In case the time point for the CSF sample is deviating from the planned time point, the blood samples should be adjusted accordingly.

7.5.1.2 Week 25 / Enrolment

The patient is admitted to the hospital the day prior to or on the day of the SOBI003 infusion. This week will be continue directly following last study visit (Week 24) in the FIH study (SOBI003-001) without any break in treatment. Baseline information collected during the first study will be used for the extension study. Patient demography information will only be collected at Week 25 if there are any changes to the already collected data.

The informed consent process, including the provision of signed consent for study participation, is completed and the patient eligibility is confirmed.

AEs and concomitant medications are captured continuously from Day 1 of Week 25 until study completion. This includes all events observed/diagnosed or reported since the last visit of the FIH study (SOBI003-001) study (Week 24 / End of study).

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
- General appearance and skin are assessed (part of physical examination)
- Vital signs are assessed

Within 30 to 60 minutes prior to start of the SOBI003 infusion, a single dose of a non-sedative antihistamine is administered. SOBI003 is administered in accordance with Section 7.4.5.

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

The patient may be discharged from the hospital 1 hour or more after the end of the infusion.

7.5.1.3 Weeks 26 to 37, Weeks 39 to 51, Weeks 53 to 77 and Weeks 79 to 103

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. AEs and use of concomitant medications during non-hospital stay are captured.

Prior to start of each infusion, weekly vital signs and general appearance and skin are assessed.

At Weeks 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 97 and 101, body weight is also assessed to determine the SOBI003 dose to be administered during a forthcoming 4-week interval, respectively. The body weight is obtained either on the day prior to the infusion or the day of infusion.

At Weeks 39 and 79, a pre-infusion PK sample with be collected as part of the PK collection from previous visits (Weeks 38 and 78 respectively).

Within 30 to 60 minutes prior to start of each SOBI003 infusion, a single dose of a non-sedative antihistamine is administered. SOBI003 is administered in accordance with Section 7.4.5.

Vital signs are assessed approximately mid-infusion as described in Section 7.5.5.4. Within an hour of completion of the infusion, vital signs and general appearance and skin are assessed.

Prior to discharge at Weeks 51 and 103, the parent/caregiver is given the actigraph and the accompanying actigraph log. The parent/caregiver is instructed to start the sleep assessment 7 days prior to attendance for the 52th and 104th infusion.

The patient may be discharged from the hospital 1 hour or more after the end of each infusion.

7.5.1.4 Weeks 38 and 78

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. AEs 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. Blood and urine are collected for safety laboratory and HS assessments, and blood samples are also collected for assessment of immunogenicity and PK.

Within 30 to 60 minutes prior to start of each SOBI003 infusion, a single dose of a non-sedative antihistamine is administered. SOBI003 is administered in accordance with Section 7.4.5.

Vital signs are assessed approximately mid-infusion as described in Section 7.5.4.4. As soon as possible following end of infusion a blood sample is collected for PK evaluation. Vital signs and general appearance and skin are assessed within an hour of completing the infusion.

The patient may be discharged from the hospital 1 hour or later after the end of each infusion.

On Day 7, prior to the next weekly infusion, a blood sample is collected for PK evaluation.

7.5.1.5 Week 52

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. AEs and use of concomitant medications during non-hospital stay are captured. The actigraph and accompanying actigraph log are collected.

7.5.1.5.1 Week 52, Day 1 Assessments

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

- Vital signs are assessed
- General appearance and skin are assessed
- Blood and urine is obtained for safety laboratory
- Blood and urine is obtained for HS assessment
- Blood is obtained for immunogenicity and PK assessments
- When separate consent for future research has been provided, serum samples will also be collected for storage at the central laboratory.

Within 30 to 60 minutes prior to start of each SOBI003 infusion, a single dose of a non-sedative antihistamine is administered. SOBI003 is administered in accordance with Section 7.4.5.

Vital signs are assessed approximately mid-infusion as described in Section 7.5.4.4. As soon as possible following end of infusion, a blood sample is collected for PK evaluation. Vital signs and general appearance and skin are assessed within an hour of completing the infusion.

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

7.5.1.5.2 Week 52, Day 2 to 7 Assessments

On day 2, general anesthesia is applied in accordance with local routines at the study site. CSF sampling 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 in the FIH study (SOBI003-001). When separate consent for future research has been provided, CSF will also be collected for storage at the central laboratory.

At the time of CSF sample collection Day 2, a PK blood sample will also be collected. In case the time point for the CSF sample is deviating from the planned time point, the blood samples should be adjusted accordingly.

On Day 3, the VABS-II is assessed by parent/caregiver (refer to Section 7.5.3.2).

The parent/caregiver completes the PedsQL questionnaire, preferably during Day 4.

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 7.5.3.1, 7.5.3.2, and 7.5.3.6, 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 complete physical examination are performed, an ECG is conducted and height, weight and head circumference are obtained. In addition, blood is collected on Day 8 (approximately 168h after start of SOBI003 infusion) for PK analyses as specified in Section 7.5.5.1.

The patient may be discharged from the hospital 1 hour or later after start of the infusion. The patient will then return to the hospital for study assessments as detailed in Schedule of Events (Table 7).

7.5.1.6 Week 104 / End of Study

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. AEs and use of concomitant medications during non-hospital stay are captured. The actigraph and accompanying actigraph log are collected.

7.5.1.6.1 Week 104, Day 1 Assessments

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

- Vital signs are assessed

- General appearance and skin are assessed
- Blood and urine is obtained for safety laboratory
- Blood and urine is obtained for HS assessment
- Blood is obtained for immunogenicity and PK assessments
- When separate consent for future research has been provided, serum samples will also be collected for storage at the central laboratory.

Within 30 to 60 minutes prior to start of each SOBI003 infusion, a single dose of a non-sedative antihistamine is administered. SOBI003 is administered in accordance with Section 7.4.5.

Vital signs are assessed approximately mid-infusion as described in Section 7.5.5.4. As soon as possible following end of infusion, a blood sample is collected for PK evaluation. Vital signs and general appearance and skin are assessed within an hour of completing the infusion.

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

7.5.1.6.2 Week 104, Day 2 to 7 Assessments

General anesthesia is applied in accordance with local routines at the study site. CSF sampling 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 in the FIH study (SOBI003-001). When separate consent for future research has been provided, CSF will also be collected for storage at the central laboratory.

At the time of CSF sample collection Day 2, a PK blood sample will also be collected. In case the time point for the CSF sample is deviating from the planned time point, the blood samples should be adjusted accordingly.

On Day 3, the VABS-II is assessed by parent/caregiver (refer to Section 7.5.3.2).

The parent/caregiver completes the PedsQL questionnaire, preferably during Day 4.

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 7.5.3.1, 7.5.3.2, and 7.5.3.6, 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 complete physical examination are performed, an ECG is conducted and height, weight and head circumference are obtained. In addition, blood is collected on Day 8 (approximately 168h after start of SOBI003 infusion) for PK analyses as specified in Section 7.5.5.1.

The patient may be discharged from the hospital 1 hour or later after start of the infusion. The patient will then return to the hospital for study assessments as detailed in Schedule of Events (Table 7).

For patients that are permanently discontinuing SOBI003 treatment, 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 7.5.4.3 and 7.5.5.1.

7.5.1.7 Weeks of dose adjustments

During the study there may be situations where individual patients or all study patients will increase or reduce their treatment dose, please refer to 7.4.4 and 7.4.5 for more details. In such situations, a more extensive initial schedule of assessments will follow.

Dose adjustments will be avoided during Weeks 48 to 52 and 100 to 104, in order not to interfere with study efficacy assessments on Week 52 and 104, respectively. Any requested dose adjustment during this time should be postponed until after these assessments have been completed, if not considered medically justified by the investigator.

7.5.1.7.1 First 3 weeks following a SOBI003 dose adjustment

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. AEs and use of concomitant medications during non-hospital stay are captured.

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

- Vital signs are assessed
- General appearance and skin are assessed
- Blood and urine is obtained for safety laboratory
- Blood and urine is obtained for HS assessment
- Blood is obtained for immunogenicity (only on week 3) and PK assessments (on weeks 1 and 3)
- A pulse-oximeter is applied

Within 30 to 60 minutes prior to start of each SOBI003 infusion, a single dose of a non-sedative antihistamine is administered. SOBI003 is administered in accordance with Section 7.4.5.

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. As soon as possible following end of infusion, a blood sample is collected for PK evaluation (only on week 1). Vital signs and general appearance and skin are assessed within an hour of completing the infusion, and the continuous pulse oximetry is discontinued.

Vital signs, general appearance and skin are assessed within 6-7 hours after start of infusion, and also within 8 to 12 hours after start of infusion, as well as on Day 2 and 3.

On Day 8 (only on week 1) a blood sample for PK evaluation is collected (pre-infusion the following weekly dose).

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 3 and 8.

If dose adjustment is a decrease in dose as a result of study dose selection for forthcoming studies, and there are no safety concerns, the patient may be discharged 1 hour or more after the end of each infusion. In such situations the assessments should follow the schedule with the exemption that the vital signs, general appearance and skin assessments within 6-7 hours after start of infusion, and also within 8 to 12 hours after start of infusion, as well as on Day 2 and 3 may be excluded as per investigator decision.

7.5.1.7.2 On Weeks 4 and 8 following a SOBI003 dose adjustment

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. AEs and use of concomitant medications during non-hospital stay are captured.

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

- Vital signs are assessed
- General appearance and skin are assessed
- Blood is obtained for PK assessments

Within 30 to 60 minutes prior to start of each SOBI003 infusion, a single dose of a non-sedative antihistamine is administered. SOBI003 is administered in accordance with Section 7.4.5.

Vital signs are assessed approximately mid-infusion as described in Section 7.5.4.4. As soon as possible following end of infusion, a blood sample is collected for PK evaluation. Vital signs and general appearance and skin are assessed within an hour of completing the infusion.

On Day 8 a blood sample for PK evaluation is collected (pre-infusion the following weekly dose).

The patient may be discharged from the hospital 1 hour or more after the end of each infusion.

7.5.1.8 Early withdrawal from treatment/study

If the patient is withdrawn from study treatment, the patient should be examined as soon as possible after making the withdrawal decision. AEs and use of concomitant medications are captured. Blood is collected for safety laboratory, HS, immunogenicity and PK assessments. Urine is collected for safety laboratory and HS assessments.

Vital signs are assessed, and a neurological and a physical examination are performed. An ECG is conducted, and height, weight and head circumference are obtained.

The VABS-II is assessed by parent/caregiver (refer to Section 7.5.3.2). The parent/caregiver completes the PedsQL questionnaire.

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 7.5.3.1, 7.5.3.2, and 7.5.3.6, respectively). If *both* BSID-III and KABC-II should be assessed, then the BSID-III should be administered 2 days prior to the completion of KABC-II.

When possible, study assessments (excluding SOBI003 infusion) of Weeks 38, 52, 78 and 104 should continue in accordance with the Schedule of Events. 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 7.5.4.3 and 7.5.5.1.

7.5.1.9 Estimated blood sampling volumes and sampling priority list

Applying the European Commission guidance (18), 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.

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 central laboratory manual. The total blood volume will not exceed 8 mL at a single time.

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. Serum collection for future biomarker analyses

7.5.2 Demography

The following demographic data are captured in the FIH study (SOBI003-001); date of birth (month and year), gestational age at birth, gender, ethnicity, race, country of residence and native language. In addition, information on the patient's sibling(s) 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.

Any changes to the patient´s demographic data (i.e., country of residence) or information on the patient´s siblings are recorded at Week 25 / Enrolment.

7.5.3 Efficacy assessments

7.5.3.1 Neurocognition

Neurocognition is assessed at Weeks 52 and 104, and during Early Termination, by use of the neurocognition domain of the BSID-III and/or the KABC-II Nonverbal Index (NVI).

The selection of neurocognitive assessment method is done at the baseline assessment of the FIH study (SOBI003-001) based on the algorithm presented in Table 11. The neurocognitive test(s) applied in the FIH study should also be used in the extension study.

Table 11 Selection of neurocognitive assessment method

Chronological age at the assessment time point	Development age-equivalence as established by VABS-II adaptive behavior composite	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, where an AEq scores is the average score for a particular age.

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

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

Neurocognition assessments are performed by child development specialists/psychologists with prior experience of MPS IIIA patients. Each patient should preferably have the same assessor throughout the study in order to reduce potential variability. 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.

7.5.3.2 Adaptive behavior

Adaptive behavior is assessed at Weeks 52 and 104, and during Early Termination.

The patients' ability to cope with changes, to demonstrate independence and to learn new skills are assessed by use of the Parent/Caregiver Rating 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. Every effort will be made to have the same parent/caregiver completing the form at each assessment time point.

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 domain).

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.

7.5.3.3 Magnetic resonance imaging

Brain and abdominal MRI are performed under general anesthesia at Weeks 52 and 104.

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. 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.

7.5.3.4 Quality of life and caregiver burden

The parent proxy-report format of the PedsQL questionnaire (Version 4.0) (29) 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 52 and 104 and at early termination. Every effort should be made to have the same parent/caregiver responding to the PedsQL questions at each assessment time point.

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

7.5.3.5 Language

Expressive and receptive language are assessed at Weeks 52 and 104, and during Early Termination, 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 is applied to assess language development.

7.5.3.6 Motor function

Fine and gross motor skills are assessed at Weeks 52 and 104, and during Early Termination, by the BSID-III motor function module and the VABS-II motor skills domain.

7.5.3.7 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 prior to the infusions at Weeks 52 and 104. 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 will be applied to the non-dominant wrist and recordings will be made for 7 consecutive days and nights before the Weeks 52 and 104 assessments.

The wrist or ankle placement should be used consistently throughout the study period and be the same as used during the FIH (SOBI003-001) study. 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 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-hour 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 (28) 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 Safety assessments

7.5.4.1 Adverse events

7.5.4.1.1 Definitions

Adverse event

An 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.

AEs 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 AEs:

- 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 AE 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 AE reporting period started and noted on the pretreatment medical history/physical examination form of the FIH study (SOBI003-001) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

Procedures

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

Serious adverse event (SAE)

An AE 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 AE 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 AE 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 early termination from the study.

7.5.4.1.2 Adverse event reporting period

The period for recording AE, including SAEs, on the CRF begins Day 1 upon signing of the study ICF on Week 25 and ends at Day 8 of Week 104 (End of Study). This includes all events observed/diagnosed or reported since the last visit of the FIH study (SOBI003-001) (Week 24 / End of study).

In addition, SAEs should be reported, from the time the ICF is signed until 28 days past the last dose of IMP, unless the patient will continue SOBI003 treatment in a Sobi-sponsored extension study starting in direct connection to the study, collecting these events.

7.5.4.1.3 Eliciting and recording adverse event information

The investigator is to record all directly observed AE, and all AEs 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 AE.

Severity assessment

For the purpose of consistency, the investigator will use the grading provided in Table 12 to describe the maximum intensity of the AE. The grading is based on the NCI CTCAE (version 4.03).

Table 12 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 AE. **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 AE, 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 AE. The AE 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).

7.5.4.1.4 Serious adverse event reporting

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

7.5.4.1.5 Follow-up of unresolved adverse events

All AEs 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 Day 7 of Week 104 (End of Study). How to report changes in an ongoing AE during a patient's participation in the study is described in the CRF instructions.

In addition, all serious and non-serious AEs 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.

7.5.4.2 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 13 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 (taken at an AE grade III or greater but may also include grade II at the discretion of the investigator, central laboratory analyses): C-reactive protein (hsCRP), IL-1ra, TNFα, IgE, and tryptase.

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 AEs (see Section 7.5.4.1.1 for details).

Sampling details are provided separately in the Study laboratory manual.

Table 13 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	Weeks 38, 52, 78 and 104	Pre-infusion (Day 1)
	In case of SOBI003 dose adjustment	For the first 3 infusions following dose adjustment: Pre-infusion (Day 1)
C-reactive protein (hsCRP), IL-1ra, TNFα, IgE, and tryptase (6.4 mL blood)	In case of infusion/anaphylactic reaction	

7.5.4.3 Immunogenicity

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

Serum samples are collected prior to start of SOBI003 infusion at Weeks 38, 52, 78 and 104, and during Early Termination. Triplicate aliquots are required for each sampling time point.

CSF samples (0.5 mL) are collected at Weeks 52 and 104.

If the dose of SOBI003 is adjusted in a patient, serum samples are collected prior to start of the first adjusted infusion and then prior to the 3rd adjusted infusion i.e., at 2 occasions per dose adjustment.

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, then a serum sample will be collected 30 to 40 days after the last SOBI003 administration for ADA assessment. Should the sample be ADA-positive, then the ADA titer will be determined and 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 laboratory manual.

7.5.4.4 Vital signs

Vital signs (blood pressure, heart rate, body temperature, respiratory rate, and oxygen saturation) are measured at each SOBI003 infusion.

At Weeks 25 to 104, vital signs are measured pre-infusion, mid- infusion and within 1 hour after end of each infusion. Vital signs are also measured at Early Termination.

If the dose of SOBI003 is adjusted in a patient, vital signs are measured pre-infusion, 1, 2 and 3 hours after start of infusion, within 1 hour after end of infusion, within 6-7 hours after start of infusion, within 8-12 hours after start of infusion, 24 hours after start of infusion and 48 hours following infusion for the first 3 infusions. During these weeks, continuous pulse oximetry is assessed from pre-infusion until completion of SOBI003 infusion.

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). 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.

Clinically significant abnormal vital signs values should be reported as AEs (see Section 7.5.4.1.1 for details).

7.5.4.5 Electrocardiograms

12-lead ECGs are obtained at Weeks 52 and 104, and during Early Termination. ECG machines Mortara ELI 250c with VERITAS^{TM} 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 health care 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 patients are awake during the ECG recording.

Paper printouts of 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 ECG findings should be reported as AEs (see Section 7.5.4.1.1 for details).

7.5.4.6 Other safety assessments

7.5.4.6.1 Physical examination and anthropometry

The complete physical examination performed on Day 7 of Weeks 52 and 104, as well as during Early Termination, includes an assessment of the following: general appearance, skin (including potential reactions around the infusion site), eyes, ears, nose, neck, nymph nodes, throat, heart, lungs, abdomen, musculoskeletal system and extremities.

At Weeks 25 to 104, general appearance and skin at the infusion site are examined prior to start of each infusion and within 1 hour after end of infusion.

Height and head circumference are assessed at Weeks 52 and 104.

Weight is assessed every 4 weeks during the treatment period in order to determine the actual SOBI003 dose to be administered (Section 7.4.5). The body weight is obtained either on the day prior to the infusion or the day of infusion.

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.

7.5.4.6.2 Neurological examination

At Weeks 52 and 104, and during Early Termination, 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.

7.5.4.7 Appropriateness of measurements

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

7.5.4.8 Data safety monitoring board

A DMC is assigned to monitor safety and immunogenicity data. In addition, selected PD and efficacy data will be provider in order to facilitate a risk benefit review of study 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 2 scheduled DMC review meetings, one upon all patients' completion of Week 52 and one upon all patients' completion of Week 104.

7.5.5 Pharmacokinetic assessments

7.5.5.1 Sampling procedures

The sampling procedures are briefly described below and are described in more detail in the Study laboratory manual. Blood samples are obtained through the central venous access port to characterize SOBI003 PK in serum. For the PK samples collected at the end of infusion a PK sample will also be collected from a peripheral venous line, as described in more details below. 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, as applicable.

PK blood samples will be collected before start of infusion, at the end of infusion and 168h after start of infusion at Weeks 38, 52, 78 and 104.

If the dose is adjusted in a patient, PK blood samples will also be collected before, at the end of infusion and 168 h after start of the infusion for the adjusted dose. In addition, PK blood samples will be collected before, at the end of infusion and 168 h after start of the infusion 4 weeks and 8 weeks after adjusting the dose. A PK blood sample will also be collected before the 3rd adjusted dose, as reference for ADA (see Section 7.5.4.3 for more details).

Acceptable deviations from these planned sampling time points are the following: 4 h (end of infusion) (+0.5h), and 168h (- 1h).

Details on PK blood sampling are presented in Section 7.5.1.1. and ~~y~~summarized in Table 10.

Duplicate aliquots are required for each sampling time point. Separate blood samples from a peripheral venous line are collected in parallel for samples collected at the end of infusion 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. The PK samples from a peripheral venous line for the End of infusion sample can be excluded if it has been confirmed in the FIH study (SOBI003-001) that the SOBI003 i.v. infusion does not interfere with the PK blood sampling.

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. Therefore, in case the SOBI003 treatment is terminated prior to Week 104, then a PK and immunogenicity sample should be obtained as soon as possible after the decision of early treatment termination, as well as 30 to 40 days after the final SOBI003 infusion.

For patients with confirmed ADA levels, blood samples for PK and immunogenicity analysis should continue in accordance with Section 7.5.4.3.

CSF samples (0.5 mL) are collected during general anesthesia at Day 2 on Weeks 52 and 104 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 samples should be adjusted accordingly.

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 laboratory manual.

7.5.5.2 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

7.5.5.3 Non-compartmental pharmacokinetic analysis

PK calculations, based on serum concentrations, are performed in Phoenix WinNonlin by means of NCA. Individual serum concentration data from each patient and the exact time points for blood sampling will be used throughout the analyses. The following multiple-dose PK parameters will be determined for SOBI003 at Weeks 39, 52, 78 and 104, and during dose-adjustments:

- 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, $C_{End\ of\ inf}$
- The observed serum concentration immediately before the start of infusion of SOBI003, $C_{Pre\text{-}dose}$
- The area under the plasma concentration-time curve from time 0 to last sample, AUC_{168h}Clearance, CL

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.

7.5.5.4 Population PK analysis

All SOBI003 serum concentration data will be included in the population PK analysis. The objective is to explore the PK and the impact of covariates (e.g. body weight, age and dose level) on the PK of SOBI003.

7.5.5.5 Population PK/PD analysis

SOBI003 serum concentration data and SOBI003 CSF concentration data are planned to be included in the population PK/PD analysis. The objective of this analysis is to explore the relationship between SOBI003 exposure and selected biomarkers e.g. HS in serum and CSF.

7.5.6 Pharmacodynamic assessments

7.5.6.1 Heparan sulfate

Serum and urine are collected pre-infusion at Weeks 38, 52, 78 and 104 for analyses of HS. The blood sampling volume is a 0.3 mL at each sampling occasion.

CSF samples (200 μL) are collected at Weeks 52 and 104 for analyses of HS.

The serum and CSF HS analyses are performed at a central laboratory (York Bioanalytical Solutions Limited, York YO26 6QR, United Kingdom). Urine HS analysis is performed at another laboratory (Greenwood Genetic Center, 106 Gregor Mendel Cir, Greenwood, South Carolina 29646, USA).

HS storage in serum and CSF is assessed using liquid chromatography tandem mass spectrometry (LC-MS/MS). The HS polymer itself is highly heterogeneous and therefore it is not possible to analyze at the intact molecule level. Therefore, the total level of HS is measured by analyzing selected disaccharides derived from enzymatic digestion (adaptation of method described in Naimy et al. 2016) (20).

Sampling, storage and shipment details are provided separately in the Study laboratory manual.

7.5.6.2 Future bioanalytical research

As local regulations permit and provided that additional separate caregiver consent is given, blood (2 mL) and CSF (1 mL) samples are collected for future biomarker analyses at Weeks 52 and 104.

The samples will be stored at a central laboratory (York Bioanalytical Solutions Limited) 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:

- Biomarkers in serum 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 laboratory manual.

7.5.6.3 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 (21). 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 (22). 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

All patients completing the FIH study (SOBI003-001) will be offered to continue into this extension study and the number of patients in the extension study is thus not based on statistical grounds.

However, the 14 patients in the NH study that will be used as an external control group had a mean baseline DQ of 58.9 points and declined with a mean of 30.4 (SD=12.1) DQ points during 24 months. Therefore, assuming very high likelihood of showing significant decrease in HS (with baseline mean of 5.2, std 1.8, correlation of 0.1 and a decrease of 80% the power is 99%), with 9 patients treated with SOBI003, the power to demonstrate an improvement in cognitive function is at least 80% if the decline is 9.8 DQ points for patients treated with SOBI003 as compared to a decline of 30.4 DQ points for untreated control patients (SD=13.0) and the reduction is homogeneous across age.

9.2 Definition of study populations

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

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

The full-analysis set (FAS) is the efficacy analysis set which will consist of all patients enrolled in this extension study, and all patients in the NH study with a rapid progressive disease having a baseline age of 12-72 months (in the DQ analyses).

PK analysis set (PK): The PK set will consist of all 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.

Immunogenicity analysis set (IAS): The IAS will consist of those subjects in the safety analysis set who have sufficient blood samples taken for ADA testing at baseline (screening visit) and at least one post-dose time-point

The SAF is used for the safety analysis, the FAS is used for the secondary and explorative efficacy variables.

A subpopulation of the FAS patients who are up to 30 months of age and in the FIH (SOBI003-001) study was initially assigned a dose at least as high as the dose selected for a planned phase III study will be included in future primary analysis population for demonstrating efficacy using combined data from the FIH study and the extension study, the Phase III trial and the corresponding patients in the NH study (control patients), consisting of the 14 patients with a rapid progressive MPS IIIA disease and a baseline age of 12 to 72 months.

9.3 Estimands

There will be a de facto estimand in the study, which is the primary estimand for the evaluation of efficacy. The estimand is the change in

- cognitive decline in all the patients from the population captured by the inclusion and exclusion criteria (see Sections 4.2.1 and Section 4.2.2) and the part of the NH population with a rapid progressive disease having a baseline age of 12-72 months, irrespectively of other medications used and adherence to treatment, and estimated by a repeated measures model of the change from baseline in DQ as described in Section 14.1.
- decline in HS levels in CSF in all the patients from the population captured by the inclusion and exclusion criteria (see Sections 4.2.1 and Section 4.2.2) irrespectively of other medications used and adherence to treatment, and estimated by a repeated measures model of the change from baseline in HS as described in Section 14.1.

To address foreseeable inter-current events, such as drop-outs, all missing values will be imputed (see Section 9.4.4) in accordance with the treatment policy principle. A sensitivity analysis will be performed where no imputations are performed, but all values are used: If a patient has a missing value in any assessment, then the same patient's non-missing scores will be used in the repeated measures model. The repeated measures model (see Section 9.4.4) handles missing values based on the missing at random (MAR) assumption. One further sensitivity analysis for DQ will address this assumption based on zero imputations, the rational being that the patients not assessed are those expected to have a severe DQ decline. Other sensitivity analyses for this purpose will be tipping point analyses.

9.4 Overall statistical and analytical plan

9.4.1 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.

9.4.2 Demographics and baseline characteristics

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

9.4.3 Analysis related to primary objective

Safety tabulations of AE 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.

9.4.4 Analysis related to secondary objectives

9.4.4.1 Key secondary endpoints at Week 104

The first key efficacy endpoint related to the first key secondary objective is the change from baseline in Development Quotient (DQ) of neurocognitive development at Week 104 after start of SOBI003 treatment in the FIH study (SOBI003-001). Since this is a single-arm study without an internal control group, efficacy relating to neurocognition will be evaluated through a comparison to an external historical control group consisting of the available natural history data within the target study population, i.e. 14 patients with a rapid progressive disease and a baseline age of 12 to 72 months followed for 24 months (22).

The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) or the Kaufman Assessment Battery for Children, Second Edition (KABC-II) will be used to assess neurodevelopment using the same approach as in the NH study (22). For each patient, an age-equivalent score (AEq) is determined using published normative data for the US population. An AEq score is the average score for a particular age. The Development Quotient is calculated as the AEq divided by the chronological age of the child multiplied with 100, i.e. DQ = 100*AEq / Age.

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

DQ of neurocognitive development will be evaluated using a repeated measures analysis with the DQ measurements at baseline, Week 52, and Week 104 as response, and visit and visit-

treatment interaction as fixed factors, baseline age as covariate and an unstructured covariance matrix will be used to estimate the covariance pattern. The primary efficacy analysis set will thus consist of all patients included in this extension study (patients treated with SOBI003) and 14 patients from the NH study (untreated patients). The null hypothesis of no treatment effect will be tested with a significance test for the treatment*time-effect, in the second step of the multiple testing procedure (see Section 9.4.5) The difference between 104 weeks and baseline will be used as the contrast of interest for the test.

All missing DQ values will be imputed. For a patient who stops treatment, let *tp* denote the turning point, i.e. the time point when the patient stops treatment. The patient's assessments as well as the time points for prediction are classified as being on either side of the turning point or at the turning point: prior to *tp*, at *tp*, or after *tp*. For patients who does not stop treatment, let $tp = \infty$, i.e. every time point is considered as prior to the *tp*. Let v denote a missing value to be imputed for a patient. The imputations will be based on two categories of predictions.

1) If the patient has two or more observations on the same side of *tp* as v (including a possible observation at *tp*), then v is considered as *exclusively patient-predictable* (p_1), i.e. it can be predicted by simple linear regression based only on the patient's data (intra -or extra-polation). On the other hand, if only one or zero observations exists on the same side of *tp* (from the particular patient) as v (including a possible observation at *tp*), then it is considered as *non-predictable exclusively* from the patient's data.

2) The other type of prediction (p_2), will be calculated by the use of a population derived slope, estimated based on the repeated measures model in Section 9.4.4 (without imputations), and a patient observation. There will be two cases; If the patient has one or more observations on the same side of *tp* as v (including a possible observation at *tp*), then the nearest observation will be used together with a slope, which is based on the population (treated or untreated) of the same status as the side of *tp* where the prediction time point is situated, as well as the interval relative the visits which contain the prediction time point. The other case is when there is no observation on the same side of *tp* as v (and no observation at *tp*). In this case, a prediction at *tp* will first be calculated, based on the same method as described above (under 2) but on the other side of *tp*, i.e. the nearest observation relative *tp* on the other side of *tp* will be used together with a slope based on the population (treated or untreated) of the same status as the side of *tp* where this nearest observation time point is situated, as well as the interval relative the visits which contain the *tp*. This prediction at the *tp* is in then used to predict v as described under the first case (under 2).

For each missing value v, the following algorithm is used to impute v by *i*:

If p_1 does not exists, then p_2 is used, i.e., $i = p_2$.

Otherwise, a weighted average will be used for the imputation: $i = w_1 p_1 + w_2 p_2$, where $w_1 = exp(-\lambda ln(2)/3)$ and $w_2 = 1 - exp(-\lambda ln(2)/3)$ and λ is the distance in months between the time point for prediction and the nearest available non-missing patient assessment time point. The exponential function is motivated by an exponential decrease of relevance of individual patient data relative to population data with increasing time, and the coefficient $ln(2)/3$ is chosen such that population data reach the same weight as individual patient data after 75 % of the distance between 2 visits, i.e. 3 months. When individual patient data is available near a missed visit, the patient data weight is near 100 %, and when the distance is near one year on the other hand, the individual patient data weight has decreased to nearly 6 %.

The second key efficacy endpoint related to the second key secondary objective is the change from baseline in HS levels in CSF at Week 104 after start of SOBI003 treatment in the FIH study (SOBI003-001).

For the purpose of the multiple testing procedure (see Section 14.3), the linear repeated measures analysis with untransformed HS levels in CSF will be used, identical to the DQ analysis with the exception of the treatment factors.

The time effect is used to judge the HS level change in CSF. The null hypothesis of no change will be tested with a significance test for the time-effect in the first step of the multiple testing procedure (see Section 9.4.5). The difference between 104 weeks and baseline will be used as the contrast of interest for the test. Missing HS values will be imputed according to the same methodology as for the missing DQ values.

9.4.4.2 Secondary endpoints and additional key secondary endpoints

To assess the PD effect of SOBI003 on HS levels in CSF, serum and urine, linear 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 accumulated dose as covariate and sex as factor. The analyses are conducted for each assessment time point. In addition, linear 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.

Adaptive behavior will be analyzed with the same repeated measures model as DQ, but adapted for one group (i.e. no treatment*visit interaction term), the SOBI003 group.

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 SOBI003 on MRI, linear models are used to model the change from baseline in MRI as dependent variable, for both logged MRI and untransformed MRI, and baseline level and age as continuous covariates, and accumulated dose (including the FIH study) as covariate and sex as factor. The analyses are conducted for each assessment time point i.e. Weeks 52 and 104.

In addition, linear analyses with MRI levels, both logged MRI levels and untransformed MRI levels, as dependent variable, and baseline level and age as continuous covariates, and accumulated dose as covariate and sex as factor will be performed across all assessments (including the FIH study), with assessment as a repeated factor.

Endpoints relating to the neurocognition, adaptive behavior, liver and spleen volume, QoL, language, motor function and sleep pattern are summarized using descriptive statistics.

9.4.5 Multiple comparison procedure

A hierarchical approach will be used for the key secondary co-endpoints.

The primary analysis will be based on a 2-sided test using a significance level of 0.05. A stepwise sequential testing procedure will be used to ensure a multiple level of significance of 0.05.

- 1st step: The null hypothesis of no difference between the treatments with respect to the reduction from baseline HS in CSF at 24 months will be tested using a significance level of 0.05. If the null hypothesis is rejected, then it will be concluded that SOBI003 reduces HS. Furthermore, the 2nd step of the sequential testing procedure will be performed.
- 2nd step: The null hypothesis of no difference between the treatments with respect to the change in DQ score at 24 months will be tested using a significance level of 0.05. If the null hypothesis is rejected, it will be concluded that SOBI003 improves cognitive function as compared to untreated patients.

This multiple comparison procedure controls that the multiple level of significance is no more than 5%.

Formally, the second confirmatory step will only be valid after the 1st step has been successfully met.

9.4.6 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.

9.4.7 Analysis of safety and tolerability data

9.4.7.1 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 AEs leading to discontinuation are also presented.

9.4.7.2 Physical examination

All physical examination records will be listed.

9.4.7.3 Neurological examination

All neurological examination records will be listed.

9.4.7.4 Laboratory variables

Laboratory test results will be compared to laboratory reference ranges, and values outside of the applicable range will be flagged as high (H) or low (L). The laboratory test results will be listed for each subject and summarized by descriptive statistics.

9.4.7.5 Vital signs

Vital sign results will be compared to reference ranges, and values outside the applicable range (including clinically important change and orthostatic change values) will be flagged as high (H) or low (L). The vital sign results will be listed for each subject and summarized by descriptive statistics.

9.4.7.6 ECG

12-lead ECGs are obtained at Weeks 52 and 104, and during Early Termination. ECG machines Mortara ELI 250c with VERITASTM resting ECG interpretation algorithm will be provided to the sites. The ECGs will be listed for each subject.

9.4.8 Interim analysis

No interim analysis is planned for this study.

9.4.9 Multiple comparison/multiplicity

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

9.4.10 Handling of missing data

All missing DQ values will be imputed. A sensitivity analysis will be performed where no imputations are performed, but all values are used: If a patient has a missing DQ score in any assessment, then the same patient's non-missing scores will be used in the repeated measures model (see Section 9.4.4). The repeated measures model handles missing values based on the MAR assumption. One further sensitivity analysis will address this assumption based on zero imputations. Another sensitivity analysis for this purpose will be a tipping point analysis.

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. For the MRIs and actigraph assessments, the digital files are the source. For ECG the print-outs 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.

Sobi follows the principles of the International committee of medical journal editor's recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals (23). After completion of this 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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