Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator:	Sabrina Paganoni, MD, PhD
Project Title:	An Expanded Access Protocol of Intravenous Trehalose Injection 90.5 mg/mL Treatment of Patients with Amyotrophic Lateral Sclerosis
Version Date:	July 29, 2024
Version Name/Number:	Version 4.0

SPONSOR APPROVAL

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol complies with International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines.

Warren W. Wasiewski, MD, FAAP
Senior Consulting Neurologist
Seelos Therapeutics, Inc.

Date

INVESTIGATOR'S AGREEMENT

I have read the EAP protocol and agree to conduct the EAP in accordance with all applicable government regulations. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

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Printed Name and Signature of Site investigator Date

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LIST OF ABBREVIATIONS

AEs	Adverse Events
ALS	Amyotrophic Lateral Sclerosis
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire-40
ALSFRS-R	ALS Functional Rating Scale – Revised
CDC	Centers for Disease Control and Prevention
EAP	Expanded Access Protocol
EDC	Electronic Data Capture
EHR	Electronic Health Record
FALS	Familial Amyotrophic Lateral Sclerosis
IB	Investigator's Brochure
IP	Investigational Product
IRB	Institutional Review Board
LPLV	Last Patient Last Visit
mg	Milligram
NfL	Neurofilament Light
PAV	Permanent assisted ventilation
SAE	Serious Adverse Event
SALS	Sporadic Amyotrophic Lateral Sclerosis
SI	Site Investigator
SOA	Schedule of Activities
SOD1	Superoxide Dismutase
TESAE	Treatment Emergent Serious Adverse Event
WOCBP	Women Of Child-Bearing Potential

SCHEDULE OF ACTIVITIES

- Participants receive a weekly infusion of SLS-005 for up to 24 weeks. Participants who join from the HEALEY ALS Platform Trial Regimen E OLE may do all infusions at home. Participants who join from the HEALEY ALS Platform Trial Regimen E RCT and/or have not previously received SLS-005 in the HEALEY ALS Platform Trial will complete the first four infusion visits in-clinic, then these participants may be permitted, based on safety and tolerability assessments, to have infusions administered at home. There are 25 infusions over 24 weeks (first infusion occurs at the Screening/Baseline Visit).
- In addition to infusion visits, participants will have three scheduled in-clinic visits at Screening/Baseline, Week 3, and Week 24, and 2 phone call or telemedicine visits at Week 12 and approximately 28 days following the last dose of the investigational medical product.

Schedule of Activities – Cohort 1 (Trehalose Naïve Participants)

Activity	**Screening/ Baseline Combined[7]**	**Week 1, Week 2**	**Week 3**	**Week 12**	**Week 24 or Early Term.**	**Follow-up Safety Call**
	Clinic	In-clinic infusion-only[5]	Clinic	Telemed/ Phone	Clinic	Telemed/ Phone
	Day -21 to 0	Day 7 ±3, Day 14 ±3	Day 21 ±3	Day 84 ±7	Day 168 ±14	28±7 days after last dose
Written Informed Consent	X					
Inclusion/Exclusion Review	X					
ALS & Medical History	X					
Demographics	X					
Physical Examination	X					
Neurological Exam	X					
Vital Signs[1]	X Weekly documentation of infusion-associated vital signs					
Slow Vital Capacity (SVC)	X				X	
ALSFRS-R	X		X	X	X	
ALSAQ-40	X				X	
Clinical Safety Labs[2]	X		X		X	
Biomarker Collection (Serum)	X				X	
Concomitant Medication Review	X		X	X	X	
Adverse Event Review	X		X	X	X	X
Document infusion-related adverse events[3]	X Weekly documentation of infusion-related adverse events.					
Columbia-Suicide Severity Rating Scale	X		X		X	
Adjust Dose as Needed[4]			X			
Administer/Dispense Study Drug[5]	X Weekly infusions will continue through Week 24. Based on safety and tolerability assessments, infusions may be administered at home after the first 4 in-clinic infusions at Screening/Baseline, Week 1, Week 2, and Week 3.					
Drug Accountability/Compliance[6]	X Weekly infusions will continue through Week 24. Refer to the Pharmacy Manual, site policy, and GCP guidelines on drug accountability, compliance, and source documentation.					
Vital Status Determination[8]					X	X

1 Vital signs are collected at the Screening/Baseline, Week 3, and Week 24 visits and weekly in conjunction with study drug administration from Baseline through Week 24. Vital signs collected at in-clinic visits (Screening/Baseline, Week 3, Week 24) include systolic and diastolic pressure, respiratory rate, heart rate, temperature, and weight. Height is measured at Screening/Baseline Visit only. If significant weight change is reported or suspected at any point during the study, the SI may choose to collect an additional in-clinic weight at their discretion. During each weekly infusion, vital signs associated with the infusion (systolic and diastolic pressure, respiratory rate, and heart rate) are to be measured pre-infusion, 30 minutes (± 5 mins) after the start of infusion (SOI), 60 minutes after the SOI (± 10 mins), and 90 minutes (± 10 mins) after the SOI. If a participant requires a 90-minute infusion duration due to receiving more than 2 bags of study drug, an additional vital signs measurement is to be completed approximately 30 minutes (± 10 mins) after the end of the 90-minute infusion.

2 Clinical safety labs include hematology (CBC with differential), complete chemistry panel and urinalysis at Screening/Baseline, Week 3, and Week 24. Hb A1C will be included in labs at Screening/Baseline and Week 24. If labs are abnormal at Week 3, they may need to be repeated per investigator judgement. Serum pregnancy testing will occur in women of child-bearing potential at the Screening Visit and as necessary during the study. Pregnancy testing is only repeated as applicable if there is a concern for pregnancy. All urine samples must be collected prior to IP administration. Clinical safety labs may be drawn at the study site or obtained at a local site convenient for the participant. Clinical safety lab results obtained locally may be used to assess participant eligibility.

3 Infusion-related AEs are documented weekly in conjunction with study drug administration from Screening/Baseline through week 24

4 The weight collected at the Screening/ Baseline clinic visit will be used to calculate the participant's initial dose. The participant will remain on a stable dose until the next in-person visit when weight be collected, at which point the dose may be adjusted if the participant's weight has increased or decreased by 2kg. Additional information on dose adjustments is included in section 6.7.4 Dosing Changes.

5 Administer first dose of study drug only after Screening/Baseline Visit procedures are completed. For participants in cohort 1, infusions occur in-person at clinic at the Screening/Baseline study visit, Week 1, Week 2, and the Week 3 study visits. Weekly infusions will continue through Week 24. An in-clinic infusion and clinic visit may occur on the same day, provided both visits are conducted in-person and within window. There should be no fewer than 4 days (96 hours) between study drug infusions.

6 Refer to the Pharmacy Manual, site policy, and GCP guidelines on site investigator responsibilities, drug accountability, compliance, and source documentation. Any and all accountability records may be requested by sponsor for review at any time.

7 The combined Screening/ Baseline visit may be split into a Screening and a Baseline visit as needed. If baseline infusion occurs on the same day as screening, it must occur after obtaining written informed consent, completing all screening procedures, and confirming participant eligibility.

8 Vital status, defined as a determination of date of death or death equivalent or date last known alive, will be determined for each enrolled participant at the end of their EAP participation (generally the Week 24 visit, as indicated). If at that time the participant is alive, his or her vital status should be determined again at the time of the last patient last visit (LPLV) of the EAP. We may also ascertain vital status at later time points by using publicly available data sources as described in section 6.6.10 of this protocol.

Schedule of Activities – Cohort 2 (Platform Trial RGE Roll-over Participants)[10]

Activity	Screening/ Baseline Combined[1,8]	Week 3	Week 12	Week 24 or Early Term.	Follow-up Safety Call
	Clinic	Clinic	Telemed/ Phone	Clinic	Telemed/ Phone
	Day -21 to 0	Day 21 ±3	Day 84 ±7	Day 168 ±14	28 ±7 days after last doses
Written Informed Consent	X				
Inclusion/Exclusion Review	X				
ALS & Medical History	X				
Demographics	X				
Physical Examination[10]	X				
Neurological Exam[10]	X				
Vital Signs[2]	X[1,10]	X Weekly documentation of infusion-associated vital signs			
Slow Vital Capacity (SVC)[10]	X[1]			X	
ALSFRS-R	X[1]	X	X	X	
ALSAQ-40[10]	X[1]			X	
Clinical Safety Labs[3]	X[1]	X		X	
Biomarker Collection (Serum)[10]	X			X	
Concomitant Medication Review	X[1]	X	X	X	
Adverse Event Review	X[1]	X	X	X	X
Document infusion-related adverse events[4]	X[1]	X Weekly documentation of infusion-related adverse events.			
Columbia-Suicide Severity Rating Scale	X[1]	X		X	
Adjust Dose as Needed[5]		X			
Administer/Dispense Study Drug[6]	X Weekly infusions will continue through Week 24. Participants who join from OLE may do all infusions at home.				
Drug Accountability/Compliance[7]	X Weekly infusions will continue through Week 24. Refer to the Pharmacy Manual, site policy, and GCP guidelines on drug accountability, compliance, and source documentation.				
Vital Status Determination[9]				X	X

1 Participants who join from HEALEY ALS Platform Trial Regimen E RCT and/or OLE may leverage assessments completed during the last Platform Trial visit if the last Platform Trial visit is completed on the same day as EAP Screening visit. Only those assessments collected after obtaining written informed consent for the EAP may be used in such cases.

2 Vital signs are collected at Screening/Baseline, Week 3, and Week 24 visits and weekly in conjunction with study drug administration from Baseline through Week 24. Vital signs collected at in-clinic visits (Screening/ Baseline, Week 3, Week 24) include weight, systolic and diastolic pressure, respiratory rate, heart rate, and temperature. Height is measured at Screening/Baseline Visit only. If significant weight change is reported or suspected at any point during the study, the SI may choose to collect an additional in-clinic weight at their discretion. During each weekly infusion, vital signs associated with the infusion (systolic and diastolic pressure, respiratory rate, and heart rate) are to be measured pre-infusion, 30 minutes (± 5 mins) after the start of infusion (SOI), 60 minutes after the SOI (± 10 mins), and 90 minutes (± 10 mins) after the SOI. If a participant requires a 90-minute infusion duration due to receiving more than 2 bags of study drug an additional vital signs measurement is to be completed approximately 30 minutes (± 10 mins) after the end of the 90-minute infusion.

3 Clinical safety labs include hematology (CBC with differential), complete chemistry panel and urinalysis at Screening/Baseline, Week 3, and Week 24. Hb A1C will be included in labs at Screening/Baseline and Week 24. If labs are abnormal at Week 3, they may need to be repeated per investigator judgement. Serum pregnancy testing will occur in women of child-bearing potential at the Screening Visit and as necessary during the study. Pregnancy testing is only repeated as applicable if there is a concern for pregnancy. All urine samples must be collected prior to IP administration. Clinical safety labs may be drawn at the study site or obtained at a local site convenient for the participant. Clinical safety lab results obtained locally may be used to assess participant eligibility.

4 Infusion-related AEs are documented weekly in conjunction with study drug administration from Screening/Baseline through week 24

5 The weight collected at the Screening/ Baseline clinic visit will be used to calculate the participant's initial dose. The participant will remain on a stable dose until the next in-person visit when weight be collected, at which point the dose may be adjusted if the participant's weight has increased or decreased by 2kg. Additional information on dose adjustments is included in section 6.7.4 Dosing Changes.

6 Administer first dose of study drug only after Screening/Baseline Visit procedures are completed. For participants in cohort 2 who join from HEALEY ALS Platform Trial Regimen E OLE, all infusions may occur at-home. For participants in cohort 2 who join from HEALEY ALS Platform Trial Regimen E RCT, infusions occur in-person at clinic at the Screening/Baseline study visit, Week 1, Week 2, and the Week 3 study visits. Weekly infusions will continue through Week 24. An in-clinic infusion and clinic visit may occur on the same day, provided both visits are conducted in-person and within window. There should be no fewer than 4 days (96 hours) between study drug infusions.

7 Refer to the Pharmacy Manual, site policy, and GCP guidelines on site investigator responsibilities, drug accountability, compliance, and source documentation. Any and all accountability records may be requested by sponsor for review at any time.

8 The combined Screening/ Baseline visit may be split into a Screening and a Baseline visit as needed. If baseline infusion occurs on the same day as screening, it must occur after obtaining written informed consent, completing all screening procedures, and confirming participant eligibility.

9 Vital status, defined as a determination of date of death or death equivalent or date last known alive, will be determined for each enrolled participant at the end of their EAP participation (generally the Week 24 visit, as indicated). If at that time the participant is alive, his or her vital status should be determined again at the time of the last patient last visit (LPLV) of the EAP. We may also ascertain vital status at later time points by using publicly available data sources as described in section 6.6.10 of this protocol.

10 Complete remote participation may be considered for select participants who join from HEALEY ALS Platform Trial Regimen E OLE on a case-by-case basis with permission from the Healey Coordination Center and Sponsor. Refer to section 6.2.1.

1.0 BACKGROUND AND SIGNIFICANCE

1.1 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a serious, life-threatening, rare degenerative disorder of large motor neurons of the cerebral cortex, brain stem and spinal cord that results in progressive wasting and paralysis of voluntary muscles [1]. The incidence of ALS is currently approximately 2/100,000/year [2,3] and may be increasing [4]. The lifetime ALS risk is 1 in 600 to 1 in 1000. Even though the incidence of ALS is similar to that of multiple sclerosis [5], the prevalence is only 4- 6/100,000 (about 25,000 patients in the United States), due to the higher mortality rate. Fifty percent of people with ALS die within three years of onset of symptoms and 90% die within five years [5]. The median age of onset is 55 years. The cause in most cases is unknown. Age and gender are the only risk factors repeatedly documented in epidemiological studies [6]. There is a slight male predominance (3:2 male to female ratio) in sporadic ALS.

No treatment prevents, halts or reverses the disease, although riluzole use is associated with a 10% prolongation of survival [7, 8], and edaravone, an antioxidant, slows illness by approximately 33% in some people [9].

The majority of people with ALS have sporadic (SALS) disease; 10% are familial (FALS). More than 100-point mutations in the gene encoding cytosolic copper-zinc superoxide dismutase (SOD1) have been demonstrated to cause typical FALS [10]. Essential features of ALS are progressive signs and symptoms of lower motor neuron dysfunction (atrophy, cramps, and fasciculations) associated with corticospinal tract signs (spasticity, enhanced and pathological reflexes) in the absence of sensory findings [3]. There is relative sparing of muscles of eye movement and the urinary sphincters. The course is relentless with decline in strength, respiratory function and overall function with time during the active phase of the disease [11]. Natural history studies have determined that age at onset, site of onset, delay from first symptom to entering ALS clinic, and rate of change in respiratory function are significant covariates of survival [12,13,14,15].

1.2 SLS-005, Trehalose Injection 90.5 mL for Intravenous Infusion, Background Information

Trehalose is a disaccharide that is well known for its protein-stabilizing properties [16,17] and its ability to activate autophagy [18]. Because of its known ability to reduce abnormal protein aggregations, trehalose was studied in several cellular and animal models of hereditary neurologic and muscular disorders, especially those associated with CAG repeat expansion and polyalanine/polyglutamine accumulation [19,20]. This was the basis for human trials of intravenous (IV) trehalose in oculopharyngeal muscular dystrophy (OPMD) and spinocerebellar ataxia type 3 (SCA3 or Machado Joseph disease).

Trehalose has been shown to penetrate both muscle and brain. In recent years it became clear that trehalose exposure results in the activation of cellular pathways that are relevant to its use as a potential treatment of ALS. Trehalose activates lysosomal and autophagic activity by various pathways and increases expression of biomarkers of autophagy such as microtubule-associated protein 1A/1B-light chain 3 (LC-3 II). It was shown that the basis of activation of these pathways is cellular glucose starvation [21]. However, the mechanism of lysosomal-autophagic activation by trehalose cannot be only glucose starvation. Trehalose also activates autophagy through the activation of Transcription Factor EB (TFEB), and relocation to the nucleus, a key factor in lysosomal and autophagy gene expression [18]. Activation of TFEB is an emerging therapeutic target for a number of diseases with pathologic accumulation of storage material.

Trehalose is not absorbed well in the human gut because of trehalase enzymes in the brush border that cleave the molecule into two glucose molecules. Oral ingestion of trehalose results in <0.5% absorption of trehalose. Seelos Therapeutics has developed an IV formulation to circumvent the breakdown of trehalose in the gut. In Study BBCO-001, an open-label Phase 2a study of 25 OPMD patients with dysphagia, weeklySLS-005 treatments at a dose of 27 grams (g) for 6 months was well tolerated. A single ascending dose study identified that clearance of SLS-005 is weight dependent and that the maximum tolerated dose (MTD) as 0.75 g/kg. This is the dose to be employed in this study.

1.3 Nonclinical and Clinical Data

1.3.1 Nonclinical Experience

The safety and tolerability of SLS-005 has been extensively investigated. A detailed review of safety in animals is presented in the SLS-005 Investigator's Brochure (IB).

Three-month IV Good Laboratory Practice (GLP) toxicology studies in rats and dogs at a dose of 3.6 g/kg administered twice weekly showed no organ toxicity. A 6-month GLP toxicology study in rats with doses of 2.7, 5.4, and 10.8 g/kg demonstrated no organ toxicity. An inflammatory response at the end of the indwelling catheter was noted in a dose-dependent manner. Although there were an increasing number of observations with the increasing dose it was not a linear increase and thus it was considered by the reporting pathologist to a procedural related change due to manipulation of the catheter and not drug related. There was no systemic inflammatory response noted. A 9-month chronic toxicity study in dogs using the same doses of 2.7, 5.4, and 10.8 g/kg did not demonstrate any organ toxicity.

1.3.2 Nonclinical Literature

Three in vivo studies demonstrated that trehalose is a potential protective agent in ALS. These studies were performed using the SOD1 'classical' mouse model with the G93T mutation or the G86R mutation. In mice trehalose can be used orally because they lack intestinal trehalase.
In the work of Castillo et al (2013) [22], trehalose was administered to animals with a G86R SOD1 mutation from age 35 days onward. The dose used was 3 weekly IP injections of 2 g/kg plus 3% trehalose in free drinking water. It was found that in female mice trehalose increased survival from a mean of 139 days in untreated animals to 154 days in trehalose treated animals. Male mice survival increased from 145 to 177 days. The level of SOD1 accumulation in the brain was lower when tested postmortem. In addition, there was preservation of motor neurons noted in the ventral horn of the spinal cord in trehalose treated animals.

In a similar study, Zhang et al (2014) [23] administered trehalose to animals with the G93A SOD 1 mutation in the drinking water only (2% concentration) starting on day 60. Trehalose delayed mean onset of disease from day 95 to 112 (based on clinical observation in the animals). Mean survival was prolonged from 124 to 145 days of age; however, disease duration was unchanged.

The number of preserved motor neurons in the spinal cord was assessed on day 120. Trehalose-treated animals had increased numbers of preserved motor neurons compared with untreated control animals. Neuronal SOD1 aggregates and p62 accumulation were decreased with trehalose treatment. Furthermore, histologic studies of muscle showed an increase in mean fiber size and evidence of preserved neuromuscular junctions, indicating reduced denervation of muscle tissue.

Li Y et al (2015) [24] evaluated 2 protocols for the study of trehalose in the SOD1-G93A mouse model (given in 2% solution in the drinking water). A short-term therapy protocol evaluated the effects after 30 days of treatment. Long-term therapy monitored the effects from onset to death. In both protocols, trehalose therapy was started on day 60. Disease onset, defined as the time when the animal dragged 1 leg, was significantly delayed by trehalose. Similarly, the time to reach grade 2 (2 affected limbs) was prolonged. Survival (defined as animal sacrifice time when it reached grade 4 of the disease) was delayed by 7 days, but this change did not reach statistical significance. In the short-term protocol motor function was improved as assessed by rotarod and hanging functional tests. There was a clear change in autophagy activation (levels of p62) in the spinal cord during the short-term protocol.

1.3.3 Clinical Experience

Previous clinical trials evaluating SLS-005 in healthy subjects and patients with OMPD and SCA3 are summarized below. Overall, administration of SLS-005 to adults appears safe and well tolerated. Sixty-two (62) subjects have been exposed to SLS-005: 18 healthy subjects, 25 OPMD patients, 15 SCA3 patients, 1 patient with Sanfilippo syndrome type B, 1 patient with Sanfilippo syndrome type A, and 2 patients with ALS. Out of the 62, 12 patients received SLS-005 in the under expanded access use programs (10 subjects with OPMD, 1 with Sanfilippo syndrome type B and 1 with Sanfilippo syndrome type A). In completed studies; The healthy subjects received a single dose of 27, 54, or 81 g (6 subjects each dose), the OPMD patients received repeated weekly doses of 27 g SLS-005 for a duration of 5 to 18 months, the SCA3 patients received repeated weekly doses of 13.5 or 27 g for a duration of 6 to 12 months. In the ongoing studies/treatment as of 15Mar2022; The Sanfilippo syndrome type B patient is receiving 0.75 g/kg weekly for a duration of 12 months. The patient with Sanfilippo syndrome type A received 4 weekly treatments of 0.25 g/kg of SLS-005 and 2 weekly 0.5 g/kg doses of SLS-005. The ALS patients are receiving weekly doses of 0.75g/kg of SLS-005 or placebo. Exposure is described below
Study BB-TRE-101 studied the safety, tolerability, and pharmacokinetics (PK) of single ascending doses of SLS-005 in healthy subjects. The study demonstrated proportional linear kinetics for increasing doses of SLS-005 from 27 g to 81 g. In addition, it demonstrated a need for weight-based dosing since clearance increased with increasing weight. One (1) treatment-emergent adverse event was assessed as possibly related elevated liver enzymes in 1 subject in the 81 g treatment group and was reported as a suspected unexpected serious adverse reaction (SUSAR). Based on the data from this study, along with supportive data from animal studies, the MTD was established as 0.75 g/kg.

Study BBCO-001, an open-label study in patients with OPMD, assessed the safety, tolerability, PK, and efficacy of SLS-005 in patients treated for 6 months with weekly infusions of 27 grams. SLS-005 was generally safe and well tolerated. The most common adverse event (AE) was elevated urine glucose that occurred in 52% of patients. The AE of glycosuria was only reported from 1 site and, although the patients were asymptomatic, the investigator assessed the laboratory result as clinically significant. Increased glucose in urine is an anticipated result because trehalose is metabolized to glucose, however serum glucose did not exceed normal range There were 3 serious adverse events (SAEs) occurring in 2 patients: urinary tract infection, aspiration pneumonia, and aspiration leading to death. None of the SAEs were considered related to study drug.

The subsequent Study BB-OPMD-301 was an open-label extension protocol to BBCO 001 that continued treatment of patients for more than 1 year. The safety profile in this study was similar to the initial study.

Study BB-MJD-201, a Phase 2 double-blind, dose-controlled study in SCA3 patients, was an open-label study of 15 patients with SCA3 that evaluated the safety and tolerability of 2 different IV doses of SLS-005, 13.5 and 27 g, administered weekly. All AEs were considered mild in severity. The most common AE was transient glucosuria occurring in 20% (n=3) of patients. SLS-005 treatment was generally safe and well tolerated in this patient population.

1.4 SLS-005 Therapeutic Rationale

1.4.1 Rationale for the study

The nonclinical data generated to date for trehalose support its potential to be used as an effective treatment for ALS. Through its effects on reducing proteinaceous aggregates/inclusions promoting autophagy and lysosomal pathways and reducing cell death, trehalose improved muscle strength and

overall motor skills in animal models of OPMD, SCA3, and ALS. The clinical safety profile of trehalose and the nonclinical toxicology data support the investigation of SLS-005 as a potential treatment of ALS.

1.4.2 Rationale for the Dose, Dosing Regimen, and Route of Administration
If administered orally < 0.5% of ingested trehalose is absorbed into the blood stream. Therefore, to achieve therapeutic blood levels of trehalose, it is necessary to circumvent the metabolism in the human gastrointestinal tract. As such, Seelos has developed SLS-005 an IV formulation of trehalose for injection, 90.5 mg/mL to be used in this study.

In the single ascending dose study of SLS-005 in healthy subjects, the mean weight in the 54 g dose cohort was 74.5 kg. At the dose of 54 g, subjects received 0.72 g/kg. The area under the curve to time infinity (AUC_{inf}) at that dose was 8,595±2,575 hour × µg/mL. Since clearance is dependent on body weight (i.e., clearance increases with increasing body weight), in order to achieve a consistent exposure in, at, or near the exposure at the MTD, 54 g/1 hour, a weight-based dose of 0.75 g/kg should achieve an exposure within the clinically acceptable safety range.

One of the proposed mechanisms of action of SLS-005 is to activate autophagy, the blockade of glucose receptors results in a starvation scenario within the cell [25]. Therefore, the MTD will be used to ensure significant exposure. Weekly dosing of SLS-005 is the only regimen to be evaluated in clinical trials to date (patients with OPMD and SCA3) and will be used in this trial.

1.4.3 Rationale for the Patient Population
The pathologic hallmark of the disease is aggregation of proteinaceous inclusions in motor neurons. The main composite of these inclusions is misfolded TDP43 (especially the phosphorylated form), which accumulates in the cytoplasm and is depleted in the nucleus. Patients with either sporadic or familial ALS accumulate TDP43 and patients with the SOD mutation accumulate SOD aggregates and thus have the potential to benefit from treatment with SLS-005 through activation of autophagy.

2.0 SPECIFIC AIMS AND OBJECTIVES

The primary objective of this intermediate expanded access protocol (EAP) is to provide access to the investigational product, SLS-005, to about seventy (70) participants with ALS who are not eligible to participate in clinical trials.

Additional objectives include:

1. Assessment of long-term safety of SLS-005 in a broad population of participants diagnosed with ALS who are not eligible to participate in clinical trials.
2. Assessment of disease progression in a broad population as measured by changes in ALS disease specific measures [ALS Functional Rating Scale-Revised (ALSFRS-R) scores, Slow Vital Capacity (SVC) and ALSAQ-40], and survival.
3. Assessment of markers of neurodegeneration as measured by changes in levels of serum neurofilaments.

3.0 GENERAL DESCRIPTION OF STUDY DESIGN

Planned enrolment is approximately 70 people living with ALS at up to 25 sites in the US. Participants will receive weekly 60- or 90-minute IV infusions of trehalose, 90.5 mg/mL, at a dose of 0.75g/kg at the

study center or at home. This is the same treatment dosage and dosing interval used in regimen E of the HEALEY ALS Platform Trial.

This EAP will enroll two cohorts of participants:

- Cohort 1: participants who do not qualify for any reasonably accessible ongoing clinical trials. This population represents a completely different patient population than that represented in the Platform Trial.
- Cohort 2: participants who have completed the Platform Trial Regimen E RCT and/or OLE and are not eligible for enrollment in another treatment regimen of the platform study. At the completion of their participation in the EAP, these participants may have been exposed to up to 76 weeks of IV trehalose – important long-term safety data.

Specifically, this EAP will capture safety, biomarker, and clinical efficacy data to augment the Phase 2/3 Platform Trial data of IV Trehalose.

4.0 SUBJECT SELECTION

This is a multi-center intermediate-size EAP to provide access to the investigational product, SLS-005. Planned enrollment is about 70 participants at up to 25 sites.

4.1 Inclusion Criteria

1. Sporadic or familial ALS.
2. Age 18 years or older.
3. Cohort 1: Patients do not qualify for any reasonably accessible ongoing clinical trial.
4. Cohort 2: Patients have completed Regimen E RCT and the open label extension (OLE) period of the HEALEY ALS Platform Trial, or completed Regimen E RCT of the HEALEY ALS Platform Trial if the OLE is not available at the site, and are not eligible for enrollment in another treatment regimen of the platform study.
5. Capable of providing informed consent and complying with study procedures, in the Site Investigator's (SI's) opinion.
6. Participants have established care with a physician at a specialized ALS center involved in the study and will maintain this clinical care throughout the duration of the EAP.
7. Participants must have a life expectancy of at least 6 months in SI's opinion (applicable for Cohort 1 only).

4.2 Exclusion Criteria

1. Current diagnosis or healthcare professional-recommended treatment (medication, exercise or diet) of diabetes mellitus.
2. Screening glucose >=140 mg/dl.
3. Known hypersensitivity to trehalose.
4. Current use of oral trehalose.
5. Inability for participant to return to site for weekly drug administration, until approved for home infusions.
6. Screening body weight >144 kilograms.
7. Participant with a history of any clinically significant or unstable medical condition or lab abnormality that, based on the SI's judgment, may interfere with assessment of the study objectives, safety or full participation.
8. Females who are pregnant or nursing or who plan to get pregnant during the course of the EAP.

9. Females of child-bearing potential, or males, who are unwilling or unable to use highly-effective methods of birth control.
10. Use of investigational treatments for ALS (as part of participation in a clinical trial or another EAP) within 5 half-lives (if known) or 30 days (whichever is longer) prior to the Screening Visit.
11. Permanent assisted ventilation (PAV), defined as more than 22 hours per day of noninvasive or invasive mechanical ventilation for more than seven consecutive days. The date of onset of PAV is the first day of the seven days.
12. Active cancer or history of cancer, except for the following: basal cell carcinoma or successfully treated squamous cell carcinoma of the skin, cervical carcinoma in situ, prostatic carcinoma in situ, or other malignancies curatively treated and with no evidence of disease recurrence for at least 3 years.
13. Presence of unstable psychiatric disease, cognitive impairment, dementia, or substance abuse that would impair ability of the participant to provide informed consent, in the SI's opinion.
14. Patients who choose to take experimental medications and/or supplements, and that is the only reason they are not eligible for trials, won't be eligible for the EAP.

5.0 SUBJECT ENROLLMENT

Screening and Baseline visit assessments and procedures should be completed on the same day. The combined Screening/ Baseline visit may be split into a Screening and a Baseline visit as needed. At Screening, the enrolling investigator will review the protocol procedures and consent form with the participant. The participant will receive a first dose of the IP only after all eligibility assessments are complete and participant eligibility has been confirmed by the investigator.

5.1 Participant Discontinuation

Participants who early terminate from the study will be asked to be seen for an in-person Early Termination Visit and complete a Follow-Up Safety Call. The in-person Early Termination Visit should be scheduled as soon as possible after a participant early terminates. The Follow-Up Safety Call should be completed approximately 28 days after the last dose of study drug.

If the Early Termination Visit occurs approximately 28±7 days after the last dose of study drug, the information for the Follow-Up Safety Call can be collected during the Early Termination Visit, and a separate Follow-Up Safety Call does not need to be completed. If the in-person Early Termination Visit does not occur within 28±7 days of the last dose of study drug, the Follow-Up Safety Call should occur approximately 28 days after the last dose of study drug and the Early Termination Visit will be completed after the Follow-Up Safety Call.

If SLS-005 is stopped because of an adverse event or reaction, the investigator should assess if a visit is needed. Safety labs, vital signs, and medication updates and return should be considered. Follow-up should continue until the adverse event is resolved or stabilized as per the investigator's discretion. If the participant permanently discontinues drug due to an adverse event, then the specific/detailed reason for discontinuation because of an adverse event must be documented in the source documents and the EDC system, and the onset, resolution, severity, relationship, outcome, and treatment required for the adverse event should be recorded as well.

A participant may withdraw from the EAP at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator or designee for safety, behavioral, compliance, or administrative reasons.

If a participant fails to return, or is unreachable, for a scheduled visit within the acceptable visit window, the site staff must make a reasonable attempt to contact the participant to determine the reason for missing the visit and collect any remaining drug.

The following actions must be taken if a participant fails to return to the clinic for a required visit:
The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the EAP.

Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be recorded in source documentation.

Should the participant continue to be unreachable, he/she will be considered as lost to follow-up and the site should document all attempts to contact. Their end of participation will be documented as the date of final communication in the opinion of the investigator. If a certified letter or email was sent, the date of the certified letter or email will apply.

Regardless of the circumstance, the detailed/specific reason for participant discontinuation must be recorded in the source documents and the EDC.

Documentation for discontinuation:
Detailed/specific reason for participant discontinuation

- Adverse Event
- Withdrawal of Consent by participant
- Investigator Decision
- Disease progression
- Protocol Terminated by Sponsor
- Lost to Follow-up
- Pregnancy
- Noncompliance
- Death
- Other

5.2 Data Collection and Participants' Identification in NeuroREACH™

The Center for Innovation and Bioinformatics (CIB), Neurological Clinical Research Institute (NCRI) at Massachusetts General Hospital (MGH) introduced the NeuroREACH electronic data capture (EDC) and data repository platform which will be used to collect data for this EAP. The MGH CIB acts as the Data Coordination Center (DCC), and its program management team will oversee this trial for data capture and management. Neurological Global Unique Identifiers (NeuroGUIDs) or their derivatives Neurological System-specific Transactional Anonymous PIN (NeuroSTAmPs) will be generated for each EAP research volunteer to ensure that their participation in a particular program can be tracked across sites for safety purposes. The NeuroREACH platform and participants' data reside on servers located in the Mass General Brigham Enterprise Research Infrastructure and Services (MGB ERIS) server farm that also provides restricted physical and software access to the servers, overall security, and data backup and restoration services.

A NeuroGUID is an 11-character string that is generated using encryption technology licensed by the NCRI from the NIH in 2013. The NeuroGUID is generated on a secure website that utilizes 128-bit Secure Socket Layer (SSL). Of note, this website is managed separately from NeuroREACH. On the website, the NeuroGUID is generated using an irreversible encryption algorithm – it accepts ten identifying data elements (last name at birth, first name at birth, optional middle name, gender at birth, day, month and year of birth, and city and country of birth), and produces a unique, randomly-generated alphanumeric string, or NeuroGUID. No identifying information is stored in the system; it is simply used to generate the NeuroGUID. If the same information is entered into this secure website again, the same NeuroGUID will be returned.

While patient Global Unique Identifiers (GUIDs) and the NIH method of uniquely identifying research participants are somewhat common and acceptable in academia and industry alike, in theory, utilization of GUIDs may lead to an inadvertent re-identification, especially in rare diseases research continuum, as the same volunteer may participate in multiple projects with the same GUID.

Also, when medical data from electronic health records (EHRs) are merged with research data, GUID utilization in EHR systems will make such identifiers as one of HIPAA identifiers, as GUIDs will be stored in the same databases with patients' protected health information (PHI)/personally identifiable information (PII).

Introduction and utilization of NeuroSTAmPs meant to overcome these risks by using unique identifiers (NeuroSTAmPs) per study or resource. The connection between multiple NeuroSTAmPs is established only via application programming interface (API) calls to the NeuroGUID.org server.

NeuroSTAmPs are also useful for sharing de-identified datasets that may still require future re-identification (e.g., based on analysis of clinical information with outside collaborators, more data or tissues are requested for certain research participants). In such cases, generating a new set of NeuroSTAmPs for a single-use purpose encourages collaboration and sharing without exposing NeuroGUIDs to external partners.

NeuroREACH program will use its own set of NeuroSTAmPs to further protect the identity of a research participant. NeuroSTAmP identifiers are created using the same information as in NeuroGUID generation.

6.0 STUDY PROCEDURES

Participants may receive up to 24 weeks of weekly infusions per protocol. Some assessments may be collected remotely, via telemedicine, or over the telephone with site staff.

Participants may be screened over and up to a 21-day period prior to treatment initiation. Participants who meet the inclusion criteria and none of the exclusionary criteria may be enrolled into the EAP. Participants may initiate treatment on the same day as the combined Screening/Baseline Visit, provided consent was obtained and all inclusion and exclusion criteria have been satisfied and eligibility has been confirmed by the investigator prior to treatment initiation.

6.1 Informed Consent

The enrolling investigator will complete the consent form with the participant during the Screening/Baseline Visit.

In some cases, informed consent may be obtained remotely via phone or virtual visit at SI discretion, particularly for participants who have a substantial travel burden to site due to ALS disease progression. Remote consent may only be considered for reconsent, it may not be utilized for the initial consent at the Screening/ Baseline visit unless otherwise specified (see section 6.2.1). The remote consent process will be explained to the participant and will be completed only if participant is in agreement with approach.

The remote consent process will be operationalized as such:

1. The consent form will be provided to the participant electronically or via mail carrier. The consent form will be provided to the participant a minimum of 24 hours prior to consent so there is ample time to review.
2. Consent will be obtained verbally by SI via telemedicine or phone, with sufficient time to review patient risks, potential benefits, and ask/answer questions appropriately.
3. The participant will sign and date (handwritten) their copy of the consent form. If the participant is unable to grip a pen due to hand weakness from ALS, patient will communicate consent verbally or by other preferred communication means. Another party present with the participant will sign as a witness attesting to participant's verbal consent
4. The participant will return the signed clinical consent form back to the site electronically or via mail carrier.
5. The SI will sign and date (handwritten) the consent form and provide a copy of the consent with both signatures back to the participant. Note: the consent form is not considered final and valid until both the participant and the SI have signed.

The site will retain the original clinical consent form signed by both parties and a detailed consent note will be placed in the participant's file.

6.2 Additional Protocol Procedures

The Screening/Baseline Visit and visits at Week 3 and Week 24 are in-person in-clinic visits. The Week 12 visit is remote via telemedicine or telephone with site staff. Vital sign assessments and clinical labs will be collected to assess safety according to the Schedule of Activities and recorded in the source documentation and/ or medical chart. If the visit is done remotely, clinical laboratory samples may be drawn at the study site or obtained at a local site convenient for the participant. Drug dispensation may take place via shipment to the participant from the site for remote visits, as necessary.

6.2.1 Considerations for HEALEY ALS Platform Trial Regimen E OLE Participants

Complete remote participation may be considered for select participants who join from HEALEY ALS Platform Trial Regimen E OLE on a case-by-case basis with permission from the Healey Coordination Center and Sponsor.

In these select cases, remote participation will be operationalized as such:

1. Informed consent (initial and reconsent) will be obtained remotely using the process outlined in section 6.1.
2. Participants will maintain established clinical care with a physician at a specialized ALS center or primary care provider. Participants will maintain ongoing clinical care with visits per standard of care (e.g. approximately every 3 months) throughout the duration of their study participation. The EAP SI will maintain communication with such a local provider and obtain relevant medical records throughout study participation relating to safety monitoring. For example, vital signs including body weight and clinically significant medical changes.
3. All assessments that can be completed remotely/ via telemedicine should be performed. The following assessments may be omitted if necessary: physical exam, neurological exam, vital signs, slow vital capacity, ALSAQ-40, biomarker collection (serum).
4. Clinical laboratory samples must be collected at a local site convenient for the participant.
5. As is allowed for Cohort 2, participants who join from HEALEY ALS Platform Trial Regimen E OLE, home infusions may continue for all 25 infusions. Concurrent assessments such as vital signs, reporting of any infusion related adverse events including Key Study Events and reporting of new concomitant medications should also be done weekly in conjunction with the investigational product infusion.

6.3 Disallowed Medications and Therapies

To date, there are no known pharmacokinetic drug interactions with SLS-005. Participants must not take the following medications while on IP: Oral trehalose is not permitted during the study.

6.4 Visits and Procedures

6.4.1 Screening/Baseline

The Screening/Baseline Visit (Day -21 to 0) is an in-person on-site visit that combines Screening and Baseline procedures. The combined Screening/ Baseline visit may be split into a Screening and a Baseline visit as needed. The following Screening/Baseline Visit procedures (also outlined in the SOA) will be performed prior to the first administration of IP:

1. Informed consent
2. Review Inclusion/ Exclusion criteria
3. Review demographics, ALS and medical history
4. Physical examination, neurological examination
5. Measure vital signs including weight
6. Perform slow vital capacity
7. Administer ALSFRS-R questionnaire
8. Collect ALSAQ-40
9. Collect blood samples for clinical safety labs including HbA1c and serum pregnancy testing for women of childbearing potential (WOCBP)
10. Collect blood samples for biomarker serum collection

11. Review concomitant medications
12. Review adverse events
13. Document infusion-related adverse events
14. Administer the C-SSRS Baseline questionnaire
15. Administer first infusion of study drug after all Screening/Baseline procedures have been completed
16. During each weekly infusion, vital signs associated with the infusion (systolic and diastolic pressure, respiratory rate, and heart rate are to be measured pre-infusion, 30 minutes (± 5 mins) after the start of infusion (SOI), at the end of infusion (± 10 mins), and 90 minutes (± 10 mins) after the start of infusion. If a participant requires a 90-minute infusion duration due to receiving more than 2 bags of study drug an additional vital signs measurement is to be completed approximately 30 minutes (±10 mins) after the end of the 90-minute infusion. If the infusion is interrupted, vital signs associated with the infusion may be collected at timepoints accounting for the interruption: 30 minutes (± 5 mins), 60 minutes (± 10 mins), and 90 minutes (± 10 mins) after the SOI plus the interruption duration.

6.4.2 *Week 1 and Week 2*

The Week 1 (Day 7 +/- 3 days) and Week 2 (+/- 3 days) infusion-only visits must occur in-person for Cohort 1 and Cohort 2 participants who join from HEALEY ALS Platform Trial Regimen E RCT, and may occur remotely or in-person for Cohort 2 participants who join from HEALEY ALS Platform Trial Regimen E OLE per site preference. The following visit procedures (also outlined in the SOA) will be performed:

1. Document infusion-related adverse events
2. Administer infusion of study drug
3. Measure vital signs associated with the infusion

6.4.3 Week 3 and Week 24 (or Early Termination)

Week 3 Visit (Day 21 +/- 3 days) and Week 24 (or early termination, Day 168 +/- 14 days) are in-person in-clinic visits that take place following the Screening/Baseline Visit. The following visit procedures (also outlined in the SOA) will be performed:

1. Measure vital signs including weight
2. Perform slow vital capacity (Week 24/ ET only)
3. Administer ALSFRS-R questionnaire
4. Collect ALSAQ-40 (Week 24/ ET only)
5. Collect blood samples for clinical safety labs including HbA1c and serum pregnancy testing for WOCBP (at investigator's discretion)
6. Collect blood samples for biomarker serum collection (Week 24/ ET only)
7. Review concomitant medications
8. Review adverse events
9. Administer the C-SSRS Since Last Visit questionnaire
10. Adjustment of dosing volume based on most recent weight measurement as necessary
11. Administer infusion of study drug
12. During each weekly infusion, vital signs associated with the infusion
13. Determine vital status (Week 24/ ET only)

6.4.4 Week 12

Week 12 (Day 84 +/- 7 days) is a remote telemedicine or telephone visit that takes place following the Screening/Baseline Visit. The following visit procedures (also outlined in the SOA) will be performed:

1. Administer ALSFRS-R questionnaire
2. Review concomitant medications
3. Review adverse events.

6.4.5 Follow-up Safety Call

The follow-up safety call will take place 28 +/- 7 days after the participant's last dose of IP. The following visit procedures (also outlined in the SOA) will be performed:

1. Review adverse events
2. Determine vital status

6.4.6 Protocol Deviations

A protocol deviation is any noncompliance with the sIRB approved protocol. The noncompliance may be either on the part of the participant, the SI, or the study site staff.

Procedures or visits not performed or started but not completed due to illness, injury or disability, including procedures that were attempted but failed (e.g., blood samples unable to be drawn after multiple attempts, or weight unable to be obtained due to participant immobility) will not be reported as protocol deviations.

6.5 Medical History and ALS History

The investigator will review the participant's medical history including ALS history and diagnosis, which may be obtained by the investigator or designee.

The following will be evaluated and documented at the Screening/Baseline Visit and/or other visits as specified in the SOA.

Time of ALS onset (defined as time of onset of first muscle weakness symptom date).
Date of ALS diagnosis.

6.6 Assessments

6.6.1 Physical Examination

Physical examinations (PEs) should include, at a minimum, assessments of the cardiovascular, respiratory, and gastrointestinal systems. Investigators or designees should pay special attention to clinical signs related to previous serious illnesses. Additional physical examinations should be performed as medically indicated during the protocol at the Investigator's discretion.

6.6.2 Vital Signs and Weight

Vital signs should be measured after participant has been resting for at least 5 minutes and will include systolic and diastolic BP (millimeters of mercury [mm Hg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]).

Body weight should be measured in pounds or kilograms. Vital signs and weight should be recorded in the medical chart.

6.6.3 Clinical Safety Laboratory Assessments

The investigator or designee should review the laboratory report(s) and monitor CBC with differential, complete chemistry panel, Hb A1C, and urinalysis and notify the medical monitor of any clinically relevant changes resulting in a treatment emergent serious adverse event (TESAE). Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator or designee to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the EAP should be repeated, at the investigator's discretion, until the values return to normal or baseline or are no longer considered clinically significant. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator or designee, the etiology should be considered, and the medical monitor consulted. As needed, clinical safety labs may be drawn at the study site or obtained at a local site convenient for the participant.

Serum pregnancy testing must be performed on all WOCBP at Screening/Baseline. Pregnancy tests may also be performed at any time during the protocol at the investigator's discretion.
A negative serum pregnancy test is required for WOCBP before SLS-005 initial administration.

6.6.4 Prior and Concomitant Medication Review
It is important for the investigator or a designee to review each medication the participant is taking before starting the protocol and at each visit to monitor for potential interactions.
Concomitant medications (including any medication, vitamin, herbal preparation, or supplement) and procedures are those received on or after the first protocol treatment date (Day 0), including those started before Day 0 and continued after Day 0. At each visit, participant should be questioned about any new medication, vaccines, or non-drug therapies or changes to concomitant medications and nondrug therapies since the last visit. Concomitant medications and non-drug therapies, including the reason for use, start and end dates of administration, and dosage information should be recorded in the participant's medical chart.

Any concomitant medication deemed necessary for the participant's care during the protocol, or for the treatment of any AE, along with any other medications, other than those listed as disallowed medications may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding all medications are recorded in full in the participant's medical chart.

6.6.5 Biomarker Collection (Serum)
Pharmacodynamic assessments will be performed by collecting blood samples to measure biomarkers such as neurofilament levels, and for future research. Two additional blood samples (6 mL each sample) will be collected at the in-clinic Baseline/Screening Visit and Week 24 Visit. Each 6 mL sample will yield approximately 4 cryovials. Clinical sites will collect and freeze serum biosamples. At the end of the study, frozen cryovials will be provided to NCRI BioRepository.

6.6.6 Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
The ALSFRS-Revised (Appendix B) is a validated instrument for evaluating the levels of the functional status of patients with ALS in 4 areas, including bulbar, gross motor activity, fine motor activity, and respiratory functions. The scale includes 12 functional items, and each item is rated on a 0 to 4 scale, with a maximum total score of 48. A higher score indicates greater retention of function.

In this EAP, the ALSFRS-R will be performed throughout the protocol and recorded in the EDC system by the investigator or any designee who is NEALS certified. When possible, it is highly recommended that all assessments be performed by the same assessor.

The ALSFRS-R will be assessed as indicated in the SOA. At the time points specified in the SOA, or if a patient is not able to attend the scheduled onsite visit, the ALSFRS-R can be assessed remotely via a phone call or videoconference by the investigator or trained designee.

6.6.7 The Amyotrophic Lateral Sclerosis Assessment Questionnaire-40
The ALSAQ-40 (Appendix C) consists of forty questions that are specifically used to measure the subjective well-being of participants with ALS and motor neuron disease. The ALSAQ-40 will be completed only during in-clinic visits.

6.6.8 Columbia-Suicide Severity Rating Scale (C-SSRS)
The C-SSRS asks questions about suicidal thinking and behavior. The C-SSRS will be assessed as indicated in the SOA. If there is a positive response to question 4 or 5 on the severity of ideation subscale or any positive response on the suicidal behavior subscale of suicide attempt or suicidal ideation by the participant during the administration of the C-SSRS during the treatment period, the appropriately qualified clinician will be notified during the study visit to determine the appropriate actions required to ensure the participant's safety. The site must ensure that the participant is seen by a licensed physician (or other qualified individual as required by local institutional policy) before leaving the study site. The SI will determine whether the participant should remain on study drug. Reference to the Clinical Triage Guidelines Using the C-SSRS can be found here https://cssrs.columbia.edu/wp-content/uploads/C-SSRStriageexampleguidelines.pdf.

It is recommended that a medically licensed physician, nurse, nurse practitioner, or physician assistant to assess the C-SSRS. All evaluators must be certified to perform the C-SSRS. Certification is required prior to performing the C-SSRS. The C-SSRS can be assessed remotely via a phone call or videoconference by the investigator or licensed and trained designee.

6.6.9 Slow Vital Capacity (SVC)
The vital capacity (VC) will be determined using the upright slow VC (SVC) method. All evaluators performing SVC must be NEALS certified. The SVC will be measured using the study-approved portable spirometer, and assessments will be performed using a face mask. A printout from the spirometer of all VC trials will be retained. Only the 3 best trials are recorded on the CRF. At least 3 measurable VC trials must be completed to score VC for all visits after screening. Predicted VC values and percent-predicted VC values will be calculated using the Quanjer Global Lung Initiative equations.

6.6.10 Recording Deaths and Vital Status Determination

Information on whether a participant has died may be obtained from the participant's family, from clinic notes, or from a publicly available data source like the Centers for Disease Control and Prevention (CDC) National Death Index or the Social Security Death Index.

Vital status, defined as a determination of date of death or PAV status or date last known alive and date last known to be PAV-free, will be determined by site study staff for each enrolled participant at the end of their EAP participation (generally the Week 24 visit, as indicated in the SOA). At approximately the time of the last patient last visit (LPLV) of the EAP, a second vital status check will be completed by site study staff for each enrolled participant. When prompted by the Coordination Center, sites will contact all enrolled participants to assess vital status.

We may also ascertain vital status at later time points. An outside vendor may be used to ascertain death or date of last known alive for all enrolled participants by using publicly available data sources. If prompted by the Coordination Center, sites will provide demographic information (e.g. participant name, date of birth, last known address) to the vendor using a secure method.

6.7 Investigational Drug

The investigational product is SLS-005 (trehalose injection, 90.5 mg/mL for intravenous infusion). This solution for IV infusion is administered once a week at a planned dose of 0.75 g/kg.
Trehalose is a stable, non-reducing disaccharide with 2 glucose molecules linked in an alpha 1,1 configuration. It contains no less than 97.0% and no more than 102.0% of C12H22O11, calculated on the anhydrous basis.

SLS-005, (an aqueous, sterile solution for IV infusion) is provided as a clear liquid in a 300 mL infusion bag. Each 300 mL bag contains 27.15 g of trehalose. See the IB for further details on SLS-005.
Refer to the IB for additional information regarding chemistry, manufacturing, and controls as well as manufacturing facilities.

6.7.1 Labeling and Packaging

SLS-005 will be provided in a 1 bag per kit configuration. Container(s) of investigational product will bear a label containing (at a minimum) the name of the investigational drug, lot and/or batch number and appropriate storage conditions. All packaging and labeling operations of IP will be performed according to Good Manufacturing Practice for Medicinal Product and the relevant regulatory requirement. Further details are provided in the Pharmacy Manual.

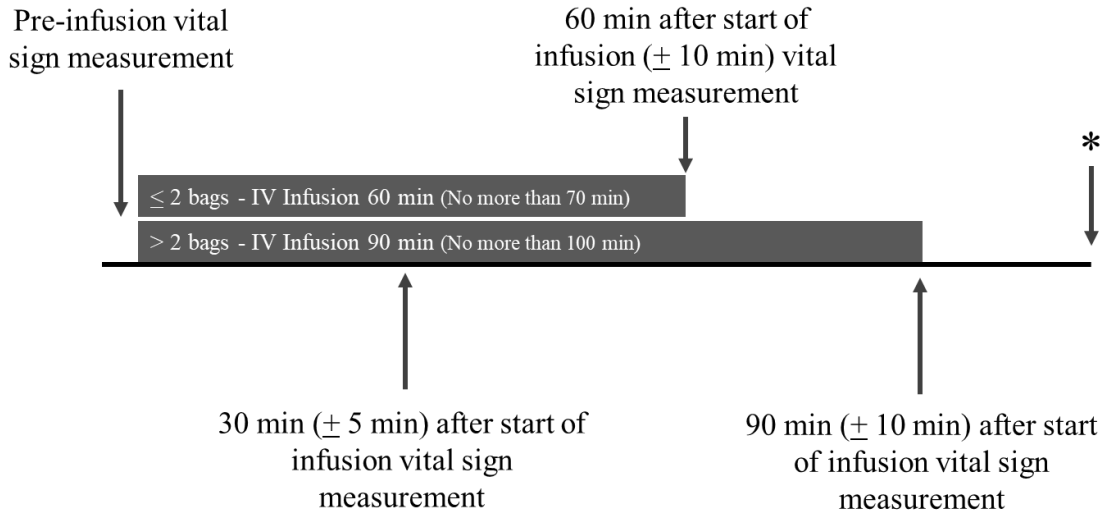
6.7.2 Storage Conditions

The investigational drug will be stored in the study site's pharmacy, at room temperature (20 to 25 ºC) with excursions permitted 15 to 30 °C. The Sponsor or its designee should be notified for any deviation from the storage conditions.

6.7.3 Study Drug Preparation

SLS-005, is provided as a clear liquid in a 300 mL infusion bag containing 27.15 grams of trehalose. No preparation is required for administration of the study drug.

The dose of SLS-005 will be calculated based on participant's body weight to determine the volume administered to each participant. Each participant's weight should be measured consistently at each in-clinic visit. Shoes and heavy winter clothes (e.g. coats, sweaters, boots) should be removed prior to weighing. If shoes cannot be removed, then weight should be assessed with the participant's shoes on at each clinic visit. Doses are adjusted based on changes in body weight (2 kg increase or decrease) noted during in-clinic visits If significant weight change is reported or suspected at any point during the study, the SI may choose to collect an additional in-clinic weight at their discretion for dose adjustment. More than 1 bag may be needed per infusion based on the participant's body weight. The intended SLS-005 total infusion time, excluding interruptions, is 60 minutes for infusion volumes up to 2 bags (i.e. up to 600mL) and should not exceed 70 minutes. For patients who require more than 2 bags (i.e. >600mL) of study drug the intended SLS-005 total infusion time should be increased to 90 minutes and not exceed 100 minutes.



**If a participant requires a 90-minute infusion duration due to receiving >2 bags of study drug an additional vital signs measurement should be done 30 minutes (± 10 min) after the end of infusion.*

Abbreviations: IV = intravenous

6.7.4 Dosing, Administration, Escalation, Duration, and Dose Changes

Drug administration and dispensing will be under the supervision of the SI or their designee to ensure participants receive the appropriate dose at the appropriate time points during the study.

Cohort 1 participants and Cohort 2 participants who join from HEALEY ALS Platform Trial Regimen E RCT will receive a weekly infusion in-clinic for the first 4 infusions of investigational product. Thereafter home infusions can be considered if the participant has had no adverse reaction to the infusion and all safety assessments are within acceptable limits. For Cohort 2 participants who join from HEALEY ALS Platform Trial Regimen E OLE, home infusions may continue for all 25 infusions including the baseline infusion.

Concurrent assessments such as vital signs, reporting of any infusion related adverse events including Key Study Events and reporting of new concomitant medications should also be done weekly in conjunction with the investigational product infusion. Decision to pursue on-site versus home infusions is per SI discretion or the institutional requirements of the site.

All infusions will be administered using an infusion pump and will be followed with an IV flush. The start calendar date and 24-hour clock time as well as the end calendar date and 24-hour clock time of each infusion will be recorded in the EDC system. If an infusion is interrupted due to infusion issues, i.e. loss of IV site, the infusion can be completed once access has been re-established unless > 30 minutes have elapsed. If 30 or more minutes have elapsed the infusion should not be restarted, and the volume infused prior to the interruption recorded in the eCRF as the total dose administered.

If needed, the use of an implanted venous access device (e.g. Mediport, PICC) or percutaneous indwelling catheter is permitted. However, small caliber indwelling catheters in peripheral vessels should only be inserted for single use. Participants are to be monitored for administration site reactions during study drug administration. Infusion site reactions or infusion reactions are to be recorded as AEs using the appropriate coding terms on the eCRF.

If for any reason a participant is unable to receive a full dose this should be documented as per participant compliance. Doses are adjusted (increased or decreased) based on a weight change of 2kg or greater from the previous in-clinic weight. A dosing chart, with volume of study drug to be administered based off body weight to achieve a dose of 0.75 g/kg, is included in Appendix A.

6.7.5 Justification for Dosage

Based on the preclinical and clinical safety and PK data SLS-005 should be dosed using a weight-based dosing up to a maximum of 0.75 g/kg. Participants should receive SLS-005 over 60 + 10 minutes for ≤2 bags or 90 + 10 minutes for >2 bags using an infusion pump.

6.7.6 Participant Compliance

Participants should be encouraged not to miss infusions, if at all possible, as it may affect the efficacy of the drug. The dosing window is 1 week ± 3 days. There should be no fewer than 4 days (96 hours) between study drug infusions. Compliance will be automatically calculated in the EDC system.

6.7.7 Drug Returns and Destruction

Refer to the Pharmacy Manual, site policy, and GCP guidelines on site investigator responsibilities, drug accountability, compliance, IP drug return and destruction, and source documentation.

6.7.8 Overdose

Certain safety events that occur in association with investigational product may require reporting. These safety events include, but are not limited to, the following:

- Overdose of the investigational product, where 'overdose' is defined as > 125% of the intended dose for a single treatment day infusion.
- Suspected abuse/misuse of the investigational product
- Inadvertent or accidental exposure to the investigational product
- Medication error involving study drug (with or without participant exposure to the investigational product, e.g., name confusion)
- The half-life of SLS-005 is approximately 1.5 hours, and there is no antidote. SLS-005 is metabolized to 2 glucose molecules, there are no other metabolites. Supportive care with monitoring of vital signs, blood glucose levels, and liver enzymes should be considered. In 1 subject who received 81 g of SLS-005, there was an increase in liver enzyme levels, but liver function remained normal and liver enzyme values returned to normal without treatment.

Safety events associated with an AE/SAE should also be reported in the EDC system. The SI should also contact the Medical Monitor within 24 hours of the SI's awareness.

6.7.9 Shipping

If SLS-005 is scheduled to be dispensed to a participant remotely, the site staff will dispense IP according to the protocol, including complete accountability for dispense, receipt, and return. Sites may refer to their institutional policies on shipping IP to a participant.
SI assessment of protocol compliance, including the collection of safety assessments to adequately monitor participation safety, should be considered prior to shipping IP to a participant.
If SLS-005 needs to be returned/collected during a visit performed remotely, the site staff will collect IP from the participant according to their institutional policies.

7.0 RISKS AND DISCOMFORTS

The safety profile from previous clinical trials of SLS-005 in adults shows no drug-related AEs other than mild, transient glycosuria which was asymptomatic and only 1 SAE, elevated liver enzymes, was considered possibly related to study drug due to temporal association of the changes and lack of alternative causation, however the event resolved without intervention.

Risks of study participation also includes the risk of an infusion reaction or infusion site reactions. There have been no infusion reactions to date in patients administered SLS-005; however, 1 patient had an infusion site reaction (erythema). In an ongoing double-blind placebo-controlled trial, less than 5% of participants reported rash, which was assessed as related to study drug. Since the study remains blinded, it is not known if the events are related to trehalose or placebo. These events were mild to moderate in severity and all, but one resolved spontaneously. The event requiring treatment resolved without sequela. Since the study remains blinded, it is unknown if this is drug related. If a patient develops a rash during or following the infusion that is assessed as related to study drug, they should not receive any further doses.

Toxicology data suggests that small indwelling catheters may result in vessel changes after multiple infusions. The inflammatory reaction noted was not associated with any generalized inflammation and there was no organ toxicity, thus it was considered a procedural complication of the indwelling catheter. If needed the use of an implanted venous access device (i.e. Mediport, PICC) or percutaneous indwelling catheter is permitted however small caliber indwelling catheters in peripheral vessels should be single use. Additional risks include those risks related to venipuncture (e.g., hematoma, bleeding, pain, infection), which are low.

The effect of SLS-005 on an embryo or fetus, or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this protocol if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding

Menopausal women who have not had a menstrual period for the past 12 months or more, do not need to have a pregnancy test. Women with any well-documented method of surgical sterilization, do not need to have a pregnancy test. Methods of surgical sterilization include hysterectomy, bilateral oophorectomy, a tubal ligation, and transvaginal occlusion. All other female participants who are of child-bearing age must have a negative pregnancy test before starting SLS-005. Women who are sexually active and able to become pregnant must agree to use the birth control methods listed below. Birth control must be used for the entire treatment protocol and for at least 2 weeks after the last dose of SLS-005.

7.1 Females:

Acceptable birth control methods for use include:

- Hormonal methods, such as birth control pills, patches, injections, vaginal rings, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)
- Abstinence (no sex)

7.2 Males:

Men who are sexually active and able to father a child, must agree to use one of the birth control methods listed below. Birth control must be used for the entire participation and for at least 2 weeks after the last dose of SLS-005.

Acceptable birth control methods for use include:

- Condoms with spermicide (a foam, cream, or gel that kills sperm)
- Abstinence (no sex)

Acceptable birth control methods for use by partner(s) include:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)

Detailed information about the known potential risks of SLS-005 is provided in the Investigator's Brochure.

8.0 BENEFITS

Participants in Expanded Access Protocols may see psychological benefit in the protocol itself, as this is one general premise behind these protocols. However, there may be no direct physical benefit to the individual for taking part in this EAP. Information learned may help others in the future.

8.1 Overall Benefit: Risk Conclusion

Given the relatively benign safety profile of SLS-005 noted thus far, and the lack of a highly effective treatment for ALS, treatment with SLS-005 for its potential to arrest or slow progression of ALS disease symptoms is justified.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of SLS-005 is provided in the Investigator's Brochure.

9.0 STATISTICAL ANALYSIS

Power calculations: There are no prior human studies directly measuring effect of IV trehalose on motor axonal integrity in ALS individuals. The estimated SD of log-transformed neurofilament light (NfL) levels in an longitudinal observational study [26] is 0.30 log-pg/mL. Preliminary data [26] on change in NfL levels over 6 months (range 4 to 8 months) among 46 ALS patients provided an estimate of the person-to-person standard deviation on the natural-log scale of 0.30 log-pg/mL. With 70 participants anticipated in the EAP, the study would have greater than 99% power to detect a 30% decline in NfL levels over 6 months. The study would have greater than 90% power to detect a true decline as small as 12% over 6 months. This power calculation is aligned with the NfL data from a separate published dataset suggesting that using a mean longitudinal ΔNfL in the untreated state of 0.011 log units/month, a sample cohort size of 26 participants (1:1) would provide 90% power at 5% significance level to detect a treatment difference of 0.065 log units/month (estimated SD of 0.048 log units/month), using a 2-sample t-test [27].

Safety Analyses (Aim 1*):* The incidence of treatment-emergent adverse events (TEAEs) occurring between screening and end of study visit/early termination visit during EAP study participation will be collected for safety assessments. In addition, for Cohort 2, TEAEs occurring during the parent HEALEY ALS Platform Trial

Regimen E screening will also be utilized for final analyses. TEAEs will be summarized by the number of events of a given classification experienced by participants in each cohort and treatment group and by the number and proportion of participants experiencing such an event in each cohort and treatment group. The number of events and proportion of participants experiencing TEAEs will be summarized without regard to MedDRA term for any TEAE, any serious TEAE, any severe TEAE, any related TEAE, and any TEAE leading to discontinuation of study drug. TEAEs will be summarized by MedDRA system organ class and preferred term for the following groups of TEAEs: all TEAEs, serious TEAEs, severe TEAEs, related TEAEs, and TEAEs leading to discontinuation of study drug. TEAEs and serious TEAEs will also be summarized by MedDRA system organ class and preferred term by cohort, treatment group, and time after randomization in the following intervals: 0 to 24 weeks (168 days), 24 to 48 weeks (336 days), and 48 to 72 weeks (504 days) or longer.

Clinical efficacy analyses (Aim 2): The median survival, decline of ALSFRS-R and SVC (in that order of priority) of IV trehalose treated EAP participants (Cohorts 1, 2) will be compared to predicted placebo progression using historical placebo controls. Such a historical placebo comparison group will be created using the pooled resource open access clinical trials (PRO-ACT) and the Natural History Consortium Study in ALS databases, which are available to the PIs will be used for completing these analyses. Propensity score stratification or model-based prediction approaches will be used for placebo control group creation from these databases. Both visual inspection and a time-to-event analysis (survival) or repeated measures analysis (ALSFRS-R and VC) will be used to compare the two groups.

For each participant in the EAP and historical control analysis data set, we will estimate their propensity score and calculate a propensity score stratification factor. Additionally, for each participant treated in the EAP, we will create a set of model-based predicted placebos. Each treated participant together with their model-based predictions will define a model-based stratification factor. Both propensity score and model-based prediction analyses will utilize a set of baseline covariates that are included in both the historical control database and the EAP.

Biomarker Analyses (Aim 3): We will perform a descriptive analysis of change in NfL levels. We will combine data from Cohort 1 and from both the RCT and OLE periods of Cohort 2.

The visit-specific profile of NfL levels will be estimated from a cohort-stratified partial-linear spline mixed model that assumes random slopes (period-specific for Cohort 2). The model will include two participant-specific random effects (an intercept and slope) in Cohort 1 and three participant-specific random effects (an intercept and two period-specific slopes) in Cohort 2, each with unstructured covariance.

10.0 MONITORING AND QUALITY ASSURANCE

The investigator will monitor for possible known side effects as well as unexpected side effects of SLS-005. In addition to scheduled visits, the participant will be encouraged to keep in close communication with the SI and site staff via regular phone calls should they have any questions or experience any changes in their health between visits. Since SLS-005 is an experimental drug with possible unknown side effects, the participant should be encouraged to report all changes to the SI.

10.1 Ethical Conduct of the Program

This intermediate-size EAP will be conducted according to applicable Code of Federal Regulations including but not limited to provision of required IND safety reports and annual reports.
The intermediate-size EAP will also be conducted in accordance with GCP defined by the ICH and the ethical principles of the Declaration of Helsinki. The intermediate-size EAP will be conducted in

compliance with the protocol. The protocol and any amendments as well as the participant informed consent will receive central IRB approval prior to initiation. Personnel involved in conducting this protocol will be qualified to perform their respective task(s) as confirmed by the site and collection of required documentation.

10.2 Medical Monitor

The Medical Monitor will act as an expert point of reference for SLS-005 for both investigative sites and protocol team members. Safety concerns can be discussed with the Medical Monitor upon occurrence or awareness to determine if a participant should continue or discontinue SLS-005. The Medical Monitor will:

- Answer inclusion and exclusion questions from investigative sites
- Answer questions specific to the protocol
- Coordinate with the protocol team to ensure information is consistent
- Address safety issues across all sites and the protocol team

10.3 Adverse Events, Suspected Adverse Drug Reactions, and Serious Adverse Events

The Adverse Event (AE) definitions and reporting procedures provided in this protocol comply with all applicable United States Food and Drug Administration (FDA) regulations and ICH guidelines. The SI will carefully monitor each participant throughout the study for possible adverse events. All AEs will be documented on CRFs designed specifically for this purpose. It is also important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

10.3.1 Definitions of AEs and Suspected Adverse Drug Reactions

An AE is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug produce or device. Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a causal relationship to the medicinal product.

Examples of AEs include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (e.g., skin rash, peripheral edema, etc.), or clinically significant abnormal test results (e.g., lab values or vital signs), with the exception of outcome measure results, which are not being recorded as adverse events in this trial (they are being collected, but analyzed separately). Stable chronic conditions (e.g., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered adverse events. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as adverse events.

Adverse events are generally detected in two ways:

1. Clinical: symptoms reported by the participant or signs detected on examination.

2. Ancillary Tests: abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures, the results of which are not being captured as AEs).

For purposes of this study, symptoms of progression/worsening of ALS, including 'normal' progression, will be recorded as adverse events.

The following measures of disease progression will not be recorded as adverse events even if they worsen (they are being recorded and analyzed separately): SVC results and ALSFRS-R results.

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the SI and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the SI to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the SI.

Participants will be monitored for adverse events from the time they sign consent for the EAP until completion of their participation as defined in the SOA.

An unexpected adverse event is any adverse event, the specificity or severity of which is not consistent with the current Investigator's Brochure. An unexpected, suspected adverse drug reaction is any unexpected adverse event for which, in the opinion of the SI or Sponsor, there is a reasonable possibility that the investigational product caused the event.

10.3.2 Definitions of Serious Adverse Events (SAEs)

A SAE is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
    a. This serious criterion applies if the study participant, in the view of the SI or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE that might hypothetically have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    a. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled "procedure" or a "treatment" is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
    a. This criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the participant's ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the participant (whether the participant is male or female).
6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical

intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse experience, and will therefore, not be considered an SAE. An example of this would include a social admission (participant admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

A serious, suspected adverse drug reaction is an SAE for which, in the opinion of the SI or Sponsor, there is a reasonable possibility that the investigational product caused the event.

The SI is responsible for classifying adverse events as serious or non-serious.

10.4 Assessment and Recording of Adverse Events

The SI will carefully monitor each participant throughout the study for possible AEs. All AEs will be documented on CRFs designed specifically for this purpose. All AEs will be collected and reported in the EDC system and compiled into reports for monthly reviewing by the MM. The MM shall promptly review all information relevant to the safety of the investigational product, including all SAEs. Special attention will be paid to those that result in permanent discontinuation of the investigational product(s) being studied, whether serious or non-serious.

10.4.1 Assessment of Adverse Events

At each visit (including remote visits), the participant will be asked if they have had any problems or symptoms since their last visit in order to determine the occurrence of adverse events. If the participant reports an adverse event, site staff will probe further to determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease
6. Action taken regarding investigational product
7. Outcome

If the infusion is done at home, confirmation of infusion and information on infusion-related adverse events, and changes in health and medications will be provided to study site by the home infusion nurse via study provided source documents. Site staff will then enter the data into the EDC system and follow up with the participant as needed to document any changes in AEs or concomitant medications in the EDC system.

10.4.2 Severity of Event

The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

10.4.3 Relatedness of Adverse Event to Investigational Product

The relationship of the AE to the investigational product should be specified by the SI based on temporal relationship and his/her clinical judgment, using the following definitions:

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

10.4.4 Recording of Adverse Events

All clinical Adverse Events and Key Study Events (e.g., Mortality, Pregnancy, PAV, and Tracheostomy) are recorded in the participant's study binder. The site should enter the AE and Key Study Event information into the EDC system as soon as possible after learning of the event or receiving an update on an existing event.

Entries on the AE Log (and into the EDC system) will include the following: description of the event, severity, seriousness, date of onset, date of resolution, relationship to investigational product, action taken, and primary outcome of event.

10.5 Adverse Events and Serious Adverse Events - Reportable Events

The following are considered reportable events and must be reported to the CC within 24 hours of the site being notified of the event: all events that meet the above criteria for SAEs.

The MM reviews AE reports, compiled by Data Management, as described in the safety monitoring plan. The MM will review data on enrollment, abnormal laboratory results and protocol deviations. These reports will collectively be known as the Medical Monitor Report. The MM communicates with the IND Holder / Sponsor, and the CC as needed for reporting of SAEs to the FDA within the required timeframe per FDA investigational new drug application (IND) regulations.

All AEs that meet the criteria for a serious, unexpected, suspected adverse drug reaction (SUSAR), for which there is a reasonable possibility that the investigational product caused the event, in the opinion of the IND Holder / Sponsor, will be submitted to FDA in an expedited fashion.

Death, respiratory failure, and hospitalization for routine procedures (i.e., g-tube placement) will not be reported individually in an expedited manner because they are anticipated to occur in the study population at some frequency independent of drug exposure.

10.6 Pregnancy

If, following the baseline visit, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of SLS-005 exposure, SLS-005 must be permanently discontinued. Protocol-required procedures for discontinuation and follow-up should be performed when possible.

Sites will instruct participants to contact the SI if they become pregnant while participating in this protocol. The SI must immediately notify the Medical Monitor of the event and complete the Pregnancy Form. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable offspring information must also be reported on a Pregnancy Report Form. Any pregnancy that occurs in a female partner of a male participant should be reported to the sponsor and Medical Monitor. Information on this pregnancy will be collected on the Pregnancy Report Form, as appropriate.

11.0 PRIVACY AND CONFIDENTIALITY

- ☐ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies (or local institutional secure communication policies)
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures (or local institutional policies and procedures) for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements (or local institutional policies) for this research
- ☒ Additional privacy and/or confidentiality protections: Study participant medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the participant's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. All local and federal guidelines and regulations regarding maintaining study participant confidentiality of data will be adhered to. Data generated by this study must be available for inspection by representatives of the US FDA, the Office for Human Research Protections (OHRP), the sponsor, all pertinent national and local health and regulatory authorities, the CC or their representative, Study Monitoring personnel, the central IRB, DSMB, Study Steering Committee personnel, study biostatistician group, and National Institutes of Health (NIH). Deidentified data generated by this study may be shared with other researchers for future medical research.

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Appendix A: Dosing Chart

The following dosing chart provides the number of bags of study drug to be administered based off body weight to achieve a dose of 0.75 g/kg. Actual volume of study drug to be administered will be calculated based off of patient weight. Refer to Pharmacy Manual Appendix 4.

Number of IV Bags	Weight Range in Kilograms
1	≤ 36.2 kg
2	36.3 to 72.4 kg
3	72.5 to 108.6 kg
4	108.7 to 144.8 kg

Dose Calculation:

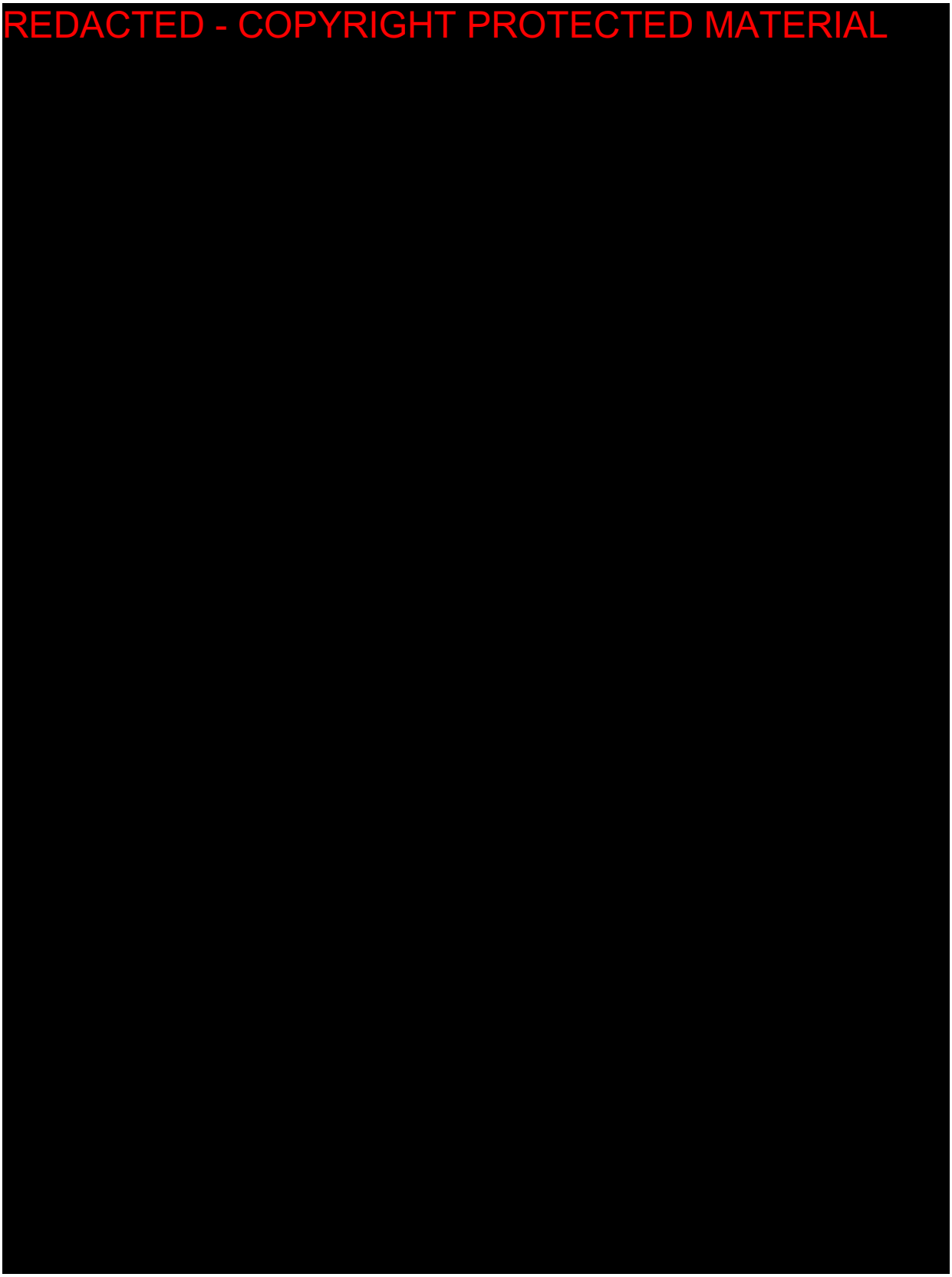
1. **Calculate Participant weight in kg**
   ___ ___ ___.___ lbs/2.2 → ___ ___ ___ . ____ kg

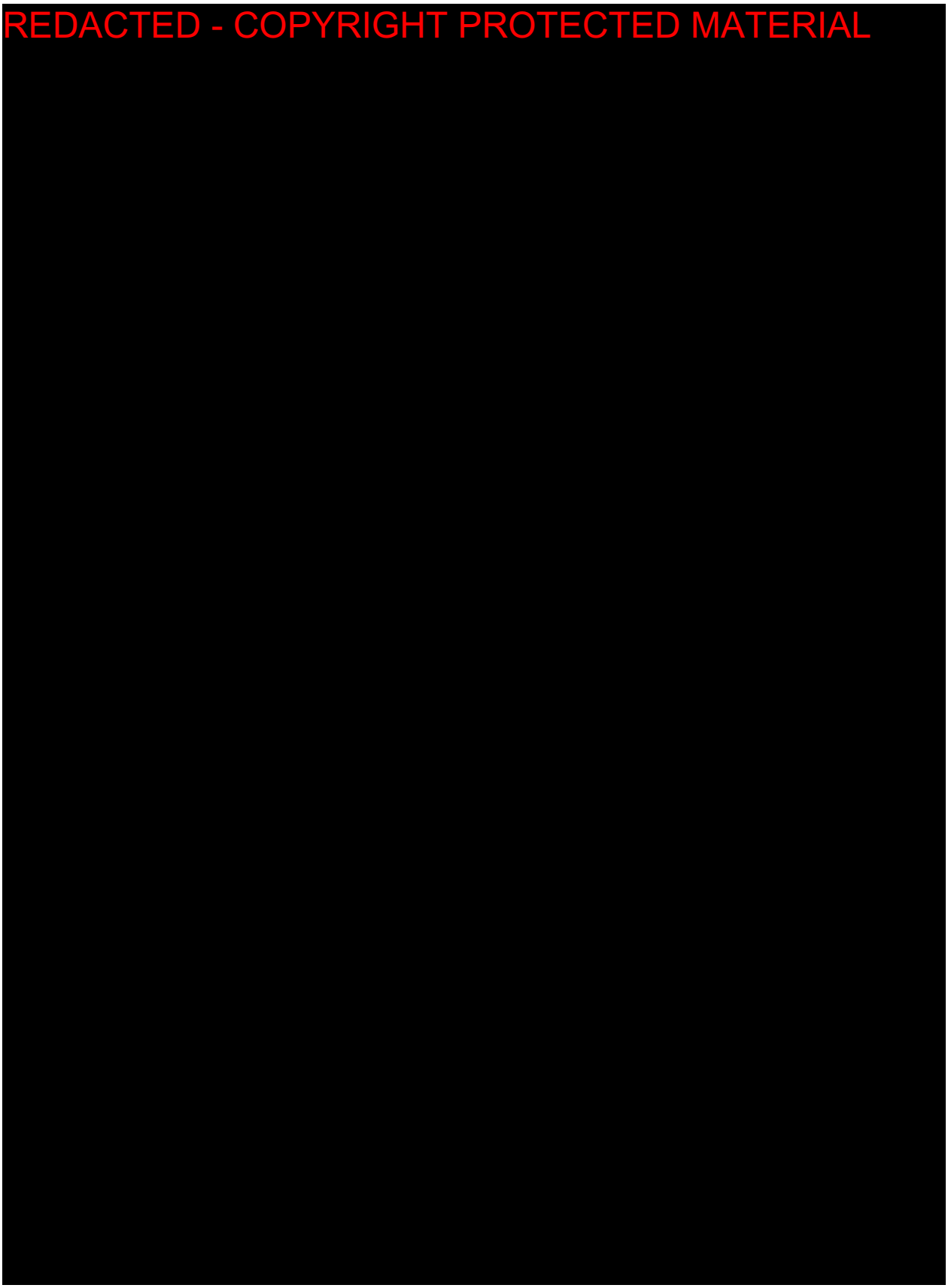
2. **Calculate dose (g) using weight from step 1**
   0.75g x ___ ___.___ kg → ___ ___ ___. ___ g

3. **Calculate Volume (mL) using calculated dose from step 2**
   ___ ___. ___ g / 0.0905 → ___ ___ ___. ___ mL

Total volume to infuse

Appendix B: ALSFRS-R

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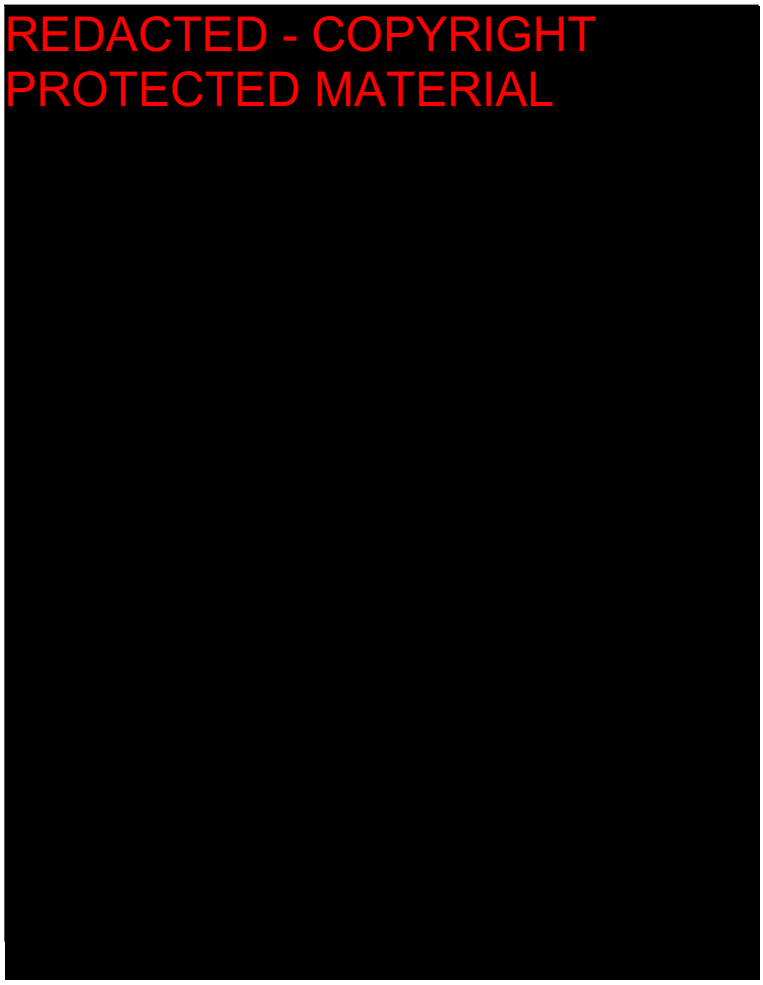
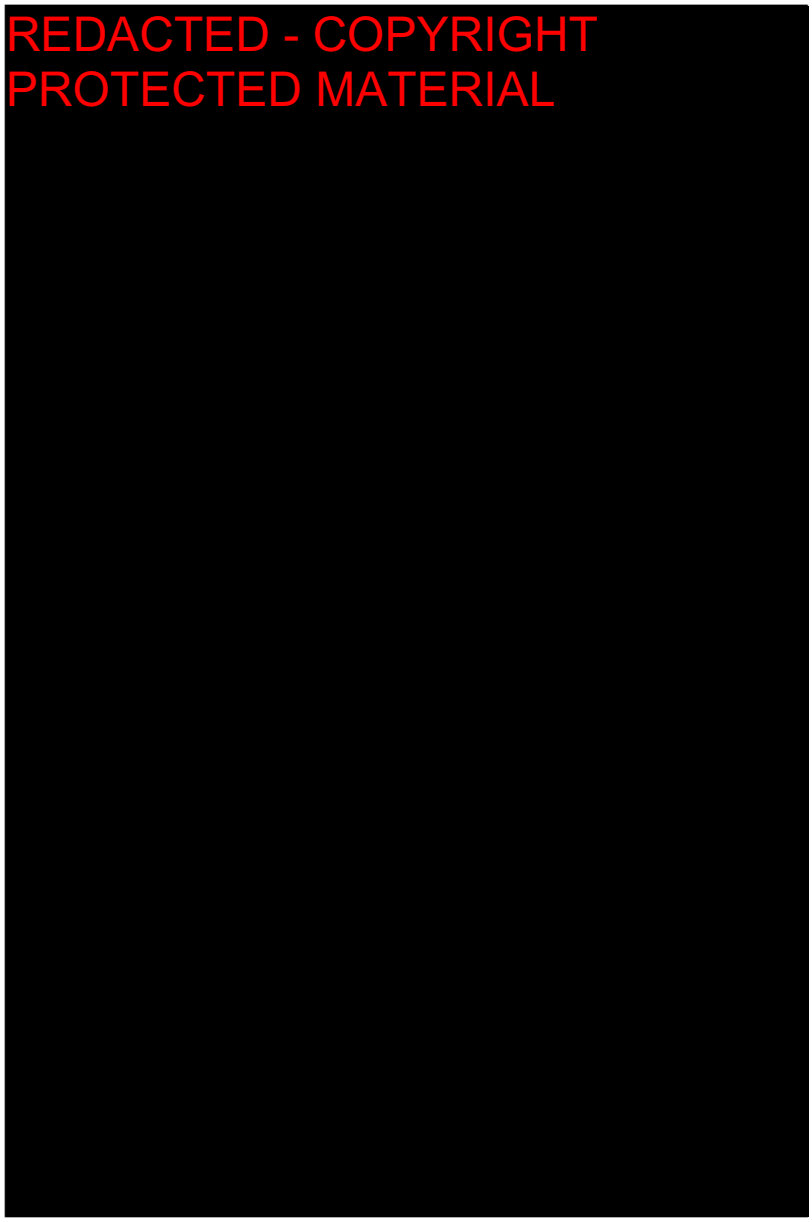
Evaluator's Initials: _____ _____ _____

Appendix C: ALSAQ-40

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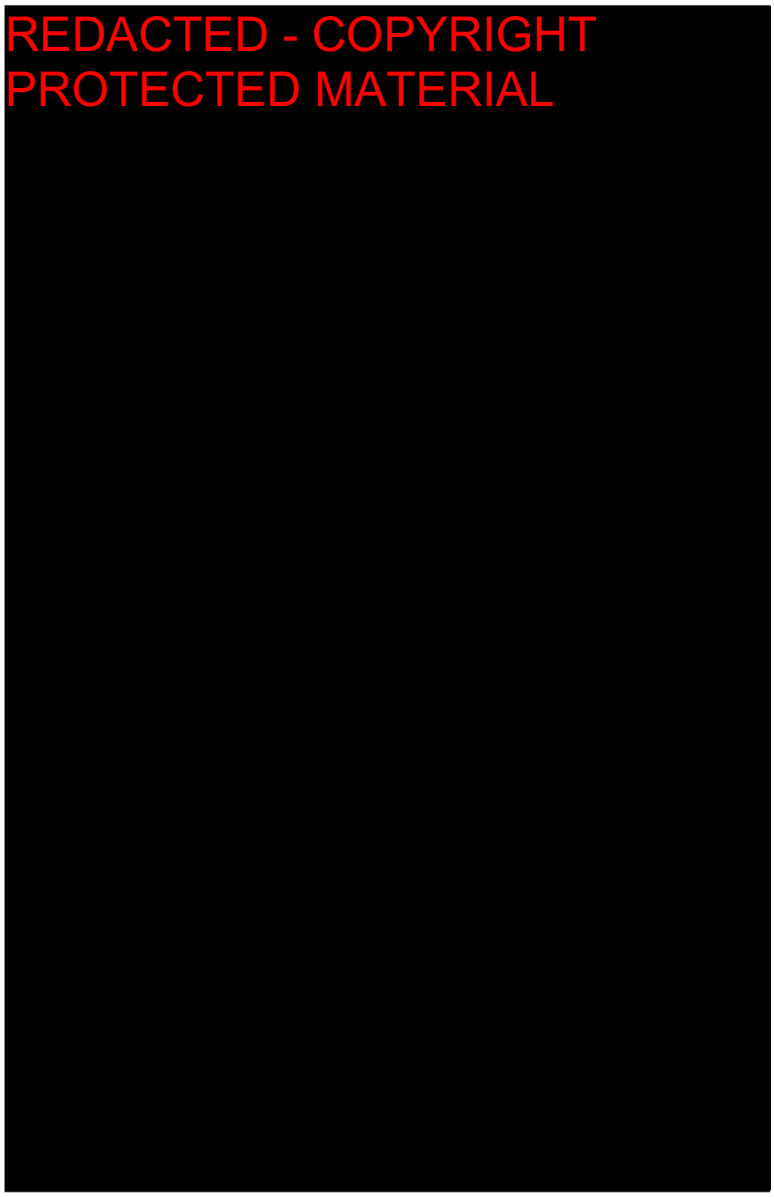
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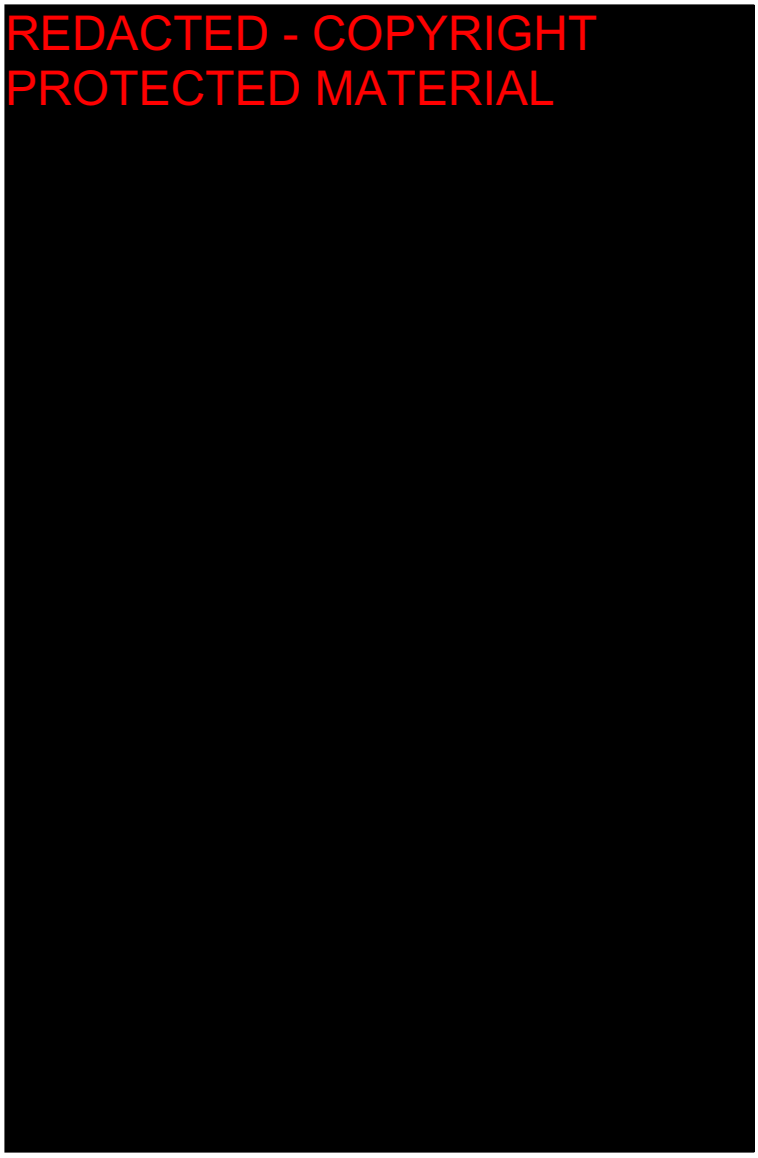
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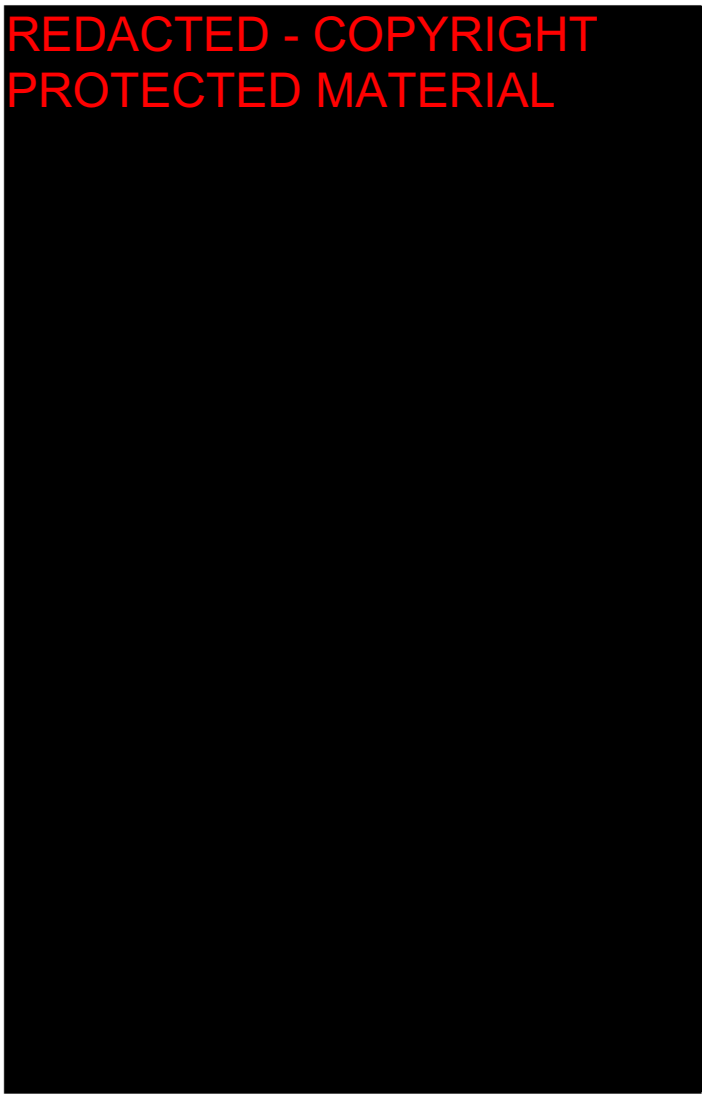
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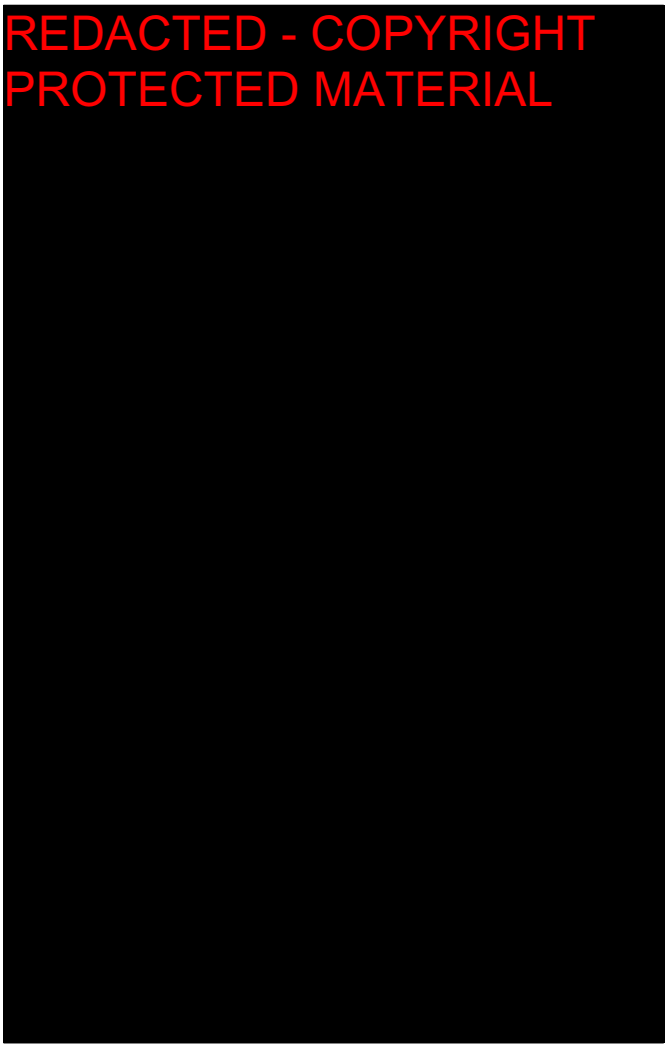
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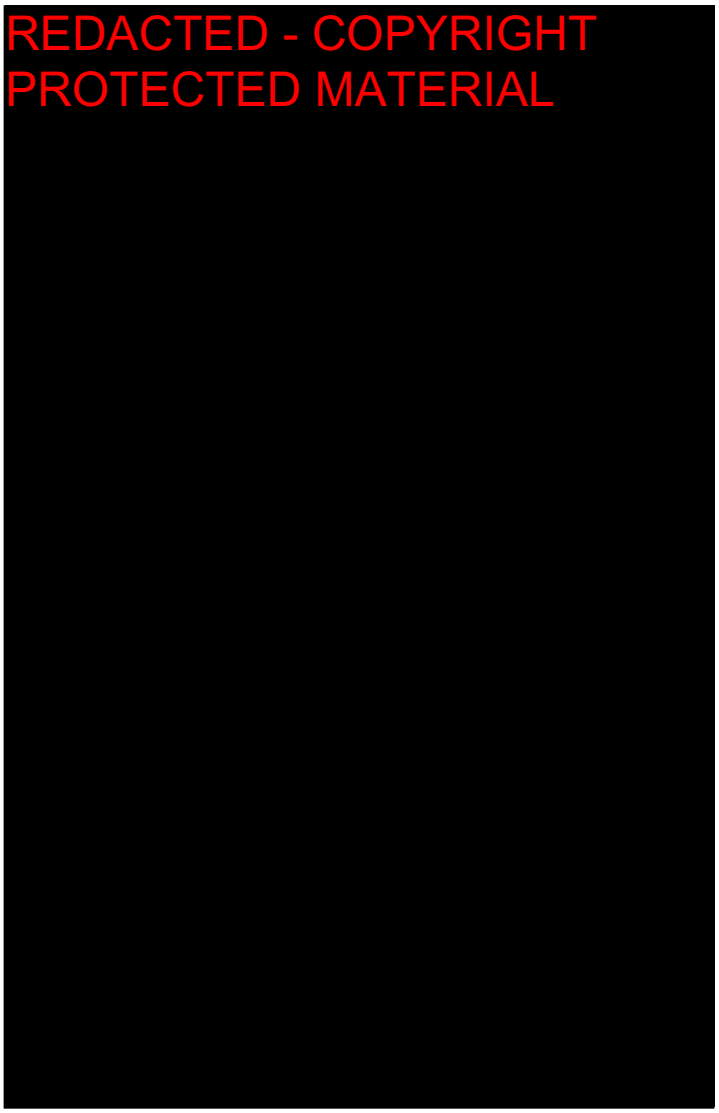
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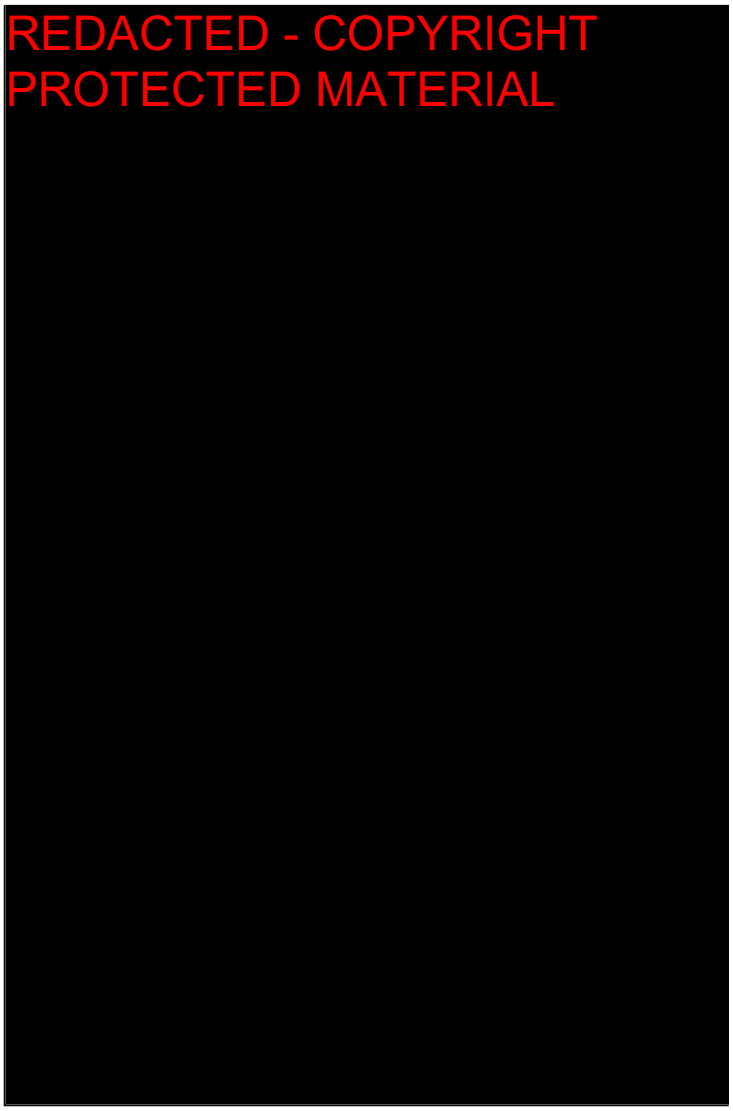
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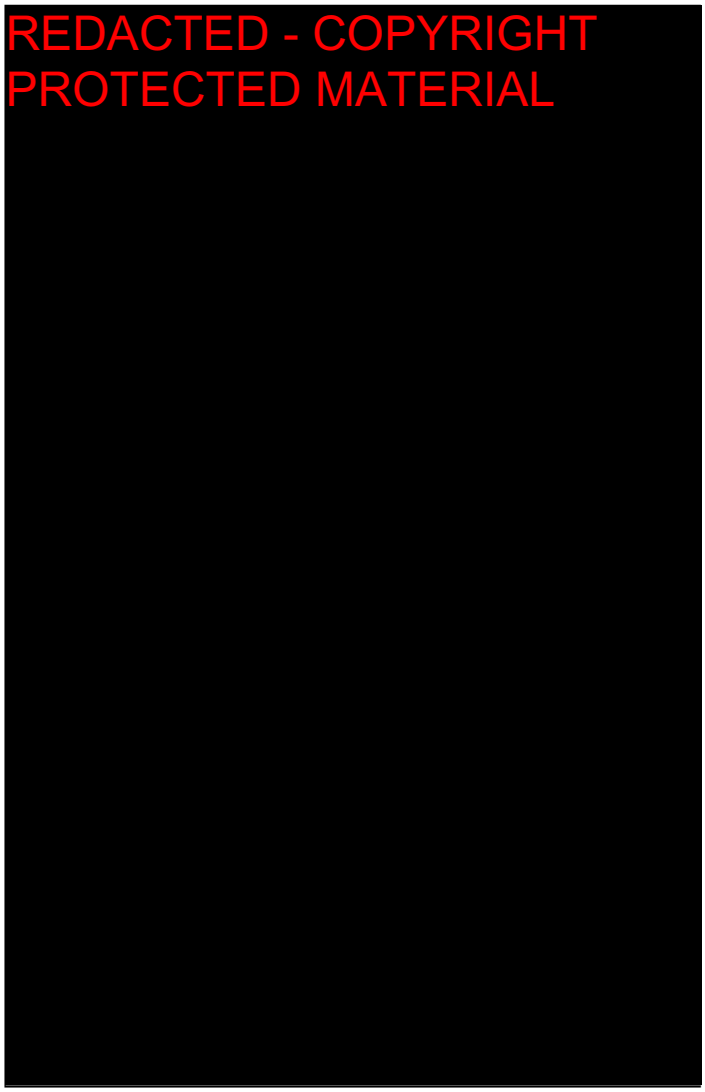
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Appendix D: Data Monitoring Committee / Data and Safety Monitoring Board

A Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DMC/DSMB convened for this study (Check all that apply):

☒ The DMC/DSMB is independent from the study team and study sponsor.

☒ A process has been implemented to ensure absence of conflicts of interest by DMC/DSMB members.

☒ The DMC/DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.

☒ Describe number and types of (i.e., qualifications of) members:
At least 3 members including statistician, endocrinologist, and neurologists

☒ Describe planned frequency of meetings:
Bi-annual

☒ DMC/DSMB reports with no findings (i.e., "continue without modifications") will be submitted to the IRB at the time of Continuing Review.

☒ DMC/DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.