Clinical Study Protocol

NCT Number: NCT03771898

Title: A Global, Multicenter, Single-arm, Matched External Control Study of Intrathecal SHP611 in Subjects with Late Infantile Metachromatic Leukodystrophy

Study Number: SHP611-201

Document Version and Date: Amendment 5.0, 12 October 2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL: SHP611-201

TITLE:	A Global, Multicenter, Single-arm, Matched External Control Study of Intrathecal SHP611 in Subjects with Late Infantile Metachromatic Leukodystrophy
SHORT TITLE:	A Single-arm Study of Intrathecal SHP611 in Subjects with Metachromatic Leukodystrophy
STUDY PHASE:	Phase 2
ACRONYM:	EMBOLDEN
DRUG:	SHP611 (HGT-1110, TAK-611, recombinant human arylsulfatase A [rhASA]); INN/USAN: *cebsulfase alfa*
IND NUMBER:	PIND 110798
EUDRACT NUMBER:	2018-003291-12
SPONSOR:	Shire Human Genetic Therapies, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter
PROTOCOL HISTORY:	Protocol Amendment 5: 12 Oct 2022 Protocol Amendment 4: 16 Sep 2020 Protocol Amendment 3.2: 02 Dec 2019 (Germany) Protocol Amendment 3.1: 18 Nov 2019 (Site 001, United States) Protocol Amendment 3: 21 Jun 2019 Protocol Amendment 2: 04 Apr 2019 Protocol Amendment 1: 10 Oct 2018 Original Protocol 1.0: 23 Aug 2018

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Appro

DocuSigned by:

Signature: [redacted]	**Date:** 13-Oct-2022 | 00:22:29 JST
[redacted], MD, PhD	

Investigator's Acknowledgement

I have read this protocol for Study SHP611-201.

Title: A Global, Multicenter, Single-arm, Matched External Control Study of Intrathecal SHP611 in Subjects with Late Infantile Metachromatic Leukodystrophy

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please handprint or type)	

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

Since finalization of Protocol Amendment 4 on 16 Sep 2020, additional changes need to be made based on feedback from health authorities that necessitate an amendment to the protocol. The purpose of this amendment is to address the concerns and provide further clarification on objectives and endpoints, statistical analysis, procedure, and safety.

Changes in grammar, spelling, punctuation, format, minor editorial changes (including changes for consistency and clarity), and refinements to the introductory text, list of abbreviations, and cross references are not reflected in this change summary.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **12 Oct 2022**	**Global**
Description of Change	**Rationale**	**Section(s) Affected by Change**
Updated the sponsor name to Shire Human Genetic Therapies, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; changed 'Shire' to 'Takeda' where applicable	As Shire was acquired by Takeda	Global
Changed the study phase from Phase 2b to Phase 2	To more accurately reflect the scope of this study	Cover Page; Section 1.1, Synopsis; Section 4.1, Overall Design; Section 4.2 Scientific Rationale for Study Design
At first use of study drug name, stated that it is now also known as TAK-611; also added the INN/USAN: *cebsulfase alfa*	Addition of new study drug name after the program was acquired by Takeda, and available INN/USAN	Cover Page; Section 1.1, Synopsis; Section 2.2, Product Background and Clinical Information
Revised terminology for study type to state 'single-arm' instead of 'open-label'; removed 'open-label'	To describe the study more precisely	Cover Page; Protocol Signature Page; Section 1.1, Synopsis; Section 4.1, Overall Design; Section 6.2.1, Allocation of Subjects to Treatment; Section 9.7.2, Extension Period

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Amendment Number **5**	**Amendment Date** **12 Oct 2022**	**Global**
Description of Change	**Rationale**	**Section(s) Affected by Change**
Revised the term 'historical control' to 'external control'; removed 'historical control'	Clarification	Cover Page; Protocol Signature Page; Section 1.1, Synopsis; Section 3.1.1, Primary Objective; Section 3.1.2 Secondary Objectives; Section 3.2, Study Endpoints; Section 4.1, Overall Design; Section 4.2 Scientific Rationale for Study Design; Section 5.2, Exclusion Criteria; Section 9.3, Sample Size and Power Considerations; Section 9.4, Statistical Analysis Sets; Section 9.5, Efficacy Analyses; Section 9.5.4, Primary Efficacy Endpoints; Section 9.6, Safety Analyses
Changed the primary efficacy endpoint to 'time to loss of locomotion, measured by progression to GMFC-MLD category 5 or higher, or death, whichever occurs first, up to Week 106, evaluated on subjects in Group A'; changed the corresponding objective to 'evaluate the effects of intrathecal (IT) administration of SHP611 on the time to loss of locomotion, as indicated by category 5 or higher in the Gross Motor Function Classification in Metachromatic Leukodystrophy (GMFC-MLD) compared with matched external control group data in children with late infantile MLD'	Regulatory authority feedback, to change to a primary endpoint that is less prone to bias	Section 1.1, Synopsis; Section 3.1.1, Primary Objective; Section 3.2, Study Endpoints; Section 4.1, Overall Design; Section 9.5.4, Primary Efficacy Endpoint
Added a secondary efficacy endpoint as response in Group A, defined as maintenance of gross motor function at Week 106, evaluated as subjects who do not experience any event within Week 106, where event is defined as a decline in GMFC-MLD to category 5 or higher, or death; added a corresponding objective to 'evaluate the effects of IT administration of SHP611 on subjects who experience decline in gross motor function as indicated by GMFC-MLD category 5 or higher, compared with matched external control group data in children with MLD'	Regulatory authority feedback, changed the previous primary endpoint to a secondary endpoint	Section 1.1, Synopsis; Section 3.1.2, Secondary Objectives; Section 3.2, Study Endpoints; Section 4.1, Overall Design

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Amendment Number **5**	**Amendment Date** **12 Oct 2022**	**Global**
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Revised the secondary objective on the decline in gross motor function using GMFC-MLD to 'evaluate the effects of IT administration of SHP611 on the decline in gross motor function, as measured by an unreversed decline in GMFC-MLD of more than 2 categories compared with matched external control group data in children with MLD, time course of declining gross motor function using the GMFC-MLD, and change from baseline of gross motor function, using the GMFC-MLD'; revised the secondary objective on time course of declining gross motor function using GMFM-88 to 'evaluate the effects of IT administration of SHP611 on the time course of decline in gross motor function using GMFM-88, as measured by • an unreversed decline from baseline in GMFM-88 total score of >20 points or unreversed decline to <40 points, whichever occurs first, • change from baseline of gross motor function, using the GMFM-88 total score, and • GMFM-88 total score decline of no more than 20 points from baseline and a total score that is ≥40'	For clarification, due to change in the primary efficacy objective and endpoint	Section 1.1, Synopsis; Section 3.1.2, Secondary Objectives, Section 3.2, Study Endpoints
Removed the timeframe 'at Week 106 and EOS' from objectives as they are in the endpoints	The timeframe for analysis of assessments can be in the endpoints	Section 1.1, Synopsis; Section 3.1.2, Secondary Objectives, Section 3.2, Study Endpoints
Moved the secondary objectives and their corresponding endpoints on evaluating the effects of IT administration of SHP611 on proton magnetic resonance spectroscopy (MRS) of the brain, specifically N-acetylaspartate/Creatine (NAA/Cr) in white matter, and on Eichler MLD MRI severity score, to exploratory objectives and endpoints	These objectives and endpoints will be analyzed as exploratory	Section 1.1, Synopsis; Section 3.1.2, Secondary Objectives, Section 3.2, Study Endpoints

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Revised the pharmacokinetic objective by separating into two objectives for CSF and serum: to evaluate the concentrations of SHP611 in CSF following single and repeat IT dosing of SHP611; and to evaluate the concentrations and PK parameters of SHP611 in serum following single and repeat IT dosing of SHP611	To separate the CSF and serum pharmacokinetic objectives	Section 1.1, Synopsis; Section 3.1.2, Secondary Objectives, Section 3.2, Study Endpoints
Revised the pharmacokinetic endpoints as follows: • CSF parameters: o Predose concentrations (C_{trough}) of SHP611 at Weeks 0, 5, 9, 13, 26, 40, 53, 79, and 106 o Postdose concentrations of SHP611 at 6 and 24 hours (Weeks 0 and 106) • Serum parameters: o PK parameters after the first dose (Week 0) and after repeated doses (Week 106) of SHP611 determined by noncompartmental analysis will include but not limited to AUC, C_{max} and CL/F o Predose concentrations (C_{trough}) of SHP611 at Weeks 0, 13, 26, 40, 53, 79, and 106	To define the pharmacokinetic endpoints more precisely	Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 3.1.2, Secondary Objectives, Section 3.2, Study Endpoints; Section 9.7.1, Pharmacokinetic Analyses
Revised language for exploratory objectives of global impression of motor function – change (GIMF-C) and global impression of motor function – severity (GIMF-S) to GIMF-C or GIMF-S, and corresponding endpoints to change over time	Clarification, to state change over time for endpoints and cover objectives more broadly	Section 1.1, Synopsis; Section 3.1.2, Secondary Objectives, Section 3.2, Study Endpoints
Removed the option that, if suitable controls cannot be matched despite the sponsor's best efforts, change from baseline results of GMFC-MLD at Week 106 may be compared with a prespecified objective threshold to evaluate primary efficacy for this study; removed the same option for GMFM-88 total score at Week 106 to evaluate secondary efficacy	Specification of potential alternative method and sensitivity analyses would be done in the SAP after propensity score matching simulations are done	Section 1.1, Synopsis; Section 3.1.1, Primary Objective; Section 9.5.4, Primary Efficacy Endpoints; Section 9.5.5, Secondary Efficacy Endpoints
Revised the secondary efficacy endpoint on maintenance of gross motor function at Week 106, defined as a GMFM-88 total score >40 to '≥40'	Clarification, for analysis	Section 1.1, Synopsis; Section 3.2, Study Endpoints

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Description of Change	**Rationale**	**Section(s) Affected by Change**
Added the phrase 'Decline in gross motor function using GMFC-MLD' to the secondary efficacy endpoints of change from baseline at Week 106 and EOS in gross motor function, using the GMFC-MLD, of subjects with unreversed decline from baseline in GMFC-MLD of more than 2 categories, and of time to unreversed decline from baseline in GMFC-MLD of more than 2 categories	Clarification, for analysis	Section 1.1, Synopsis; Section 3.2, Study Endpoints
Added the phrase 'Decline in gross motor function using GMFM-88' to the secondary efficacy endpoints of change from baseline at Week 106 and EOS in gross motor function, using the GMFM-88 total score, of subjects in Group A with GMFM-88 total score decrease, and of time to unreversed decline from baseline at Week 106 and EOS in GMFM-88 total score decrease	Clarification, for analysis	Section 1.1, Synopsis; Section 3.2, Study Endpoints
Revised the secondary efficacy endpoint on time to unreversed decline from baseline at Week 106 and EOS in GMFM-88 total score of >20 points or unreversed decline to <40 points, whichever occurs first to 'score decrease of >20 points or unreversed decline to a score <40 points, whichever occurs first'	Clarification, for analysis	Section 1.1, Synopsis; Section 3.2, Study Endpoints
Added the phrase 'total number of additional hospitalizations during the 2-year follow-up' to the exploratory endpoint on incidence of hospitalizations, number of days in hospital, reason for admission, and frequency of selected MLD-related procedures	Clarification, for analysis	Section 1.1, Synopsis; Section 3.2, Study Endpoints
For exploratory endpoints, revised the timeframe 'from baseline at Week 106 and EOS' to 'over time'	Clarification, for analysis	Section 1.1, Synopsis; Section 3.2, Study Endpoints
For extended treatment period through safety follow-up, CSF samples do not need to be collected at 6 and 24 hours after IT administration at 6-monthly visits but only at predose prior to IT administration	Clarification regarding collection time points of CSF samples in the extension period	Section 1.3, Schedule of Activities
For extended treatment period through safety follow-up, serum PK samples will be drawn up to 1 hour prior to IT administration but serial PK samples are not needed	Clarification regarding collection time points of serum PK samples in the extension period	Section 1.3, Schedule of Activities
Described that no subjects were enrolled in Groups D or E	Clarification regarding no enrollment for Groups D or E	Section 1.1, Synopsis; Section 4.1, Overall Design

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Description of Change	**Rationale**	**Section(s) Affected by Change**
Revised text that videos of gross motor function assessments will be evaluated by central video reviewers for primary scoring of gross motor function on the instrument; removed statement that central reviewers will have access to the same information as the healthcare professional who performs the local gross motor function assessment	Regulatory authority feedback; to reduce bias	Section 1.1, Synopsis; Section 4.1, Overall Design; Section 8.2.2.1, Gross Motor Function Classification in MLD
Noted that because the CRIM assay is not yet available, CRIM blood samples will be stored for future use	Clarification on handling of CRIM blood samples collected because of unavailability of the CRIM assay	Section 1.3, Schedule of Activities
For the extension period analysis population, removed the analysis on: using all data from the extension period up to EOS with baseline for the extension period (defined as Week 106); the safety analysis set for the extension period will consist of all subjects who received at least 1 dose of study medication in the extension period	This analysis exclusively for the extension period subject population is not needed	Section 1.1, Synopsis; Section 9.4, Statistical Analysis Set(s)
Removed the requirement that matched external control group must have data for post baseline gross motor function evaluation	Due to concerns on bias	Section 1.1, Synopsis; Section 4.1, Overall Design; Section 9.5, Efficacy Analyses
Added language regarding assessing the feasibility of a time to event primary endpoint under the planned sample size	To clarify sample size calculation and power considerations for the time to event endpoint	Section 1.1, Synopsis; Section 9.3, Sample Size and Power Considerations
Revised the definitions of the statistical analysis sets; added modified Full Analysis Set and Immunogenicity Analyses Set; removed Completer Analysis Set	To revise the definitions of the statistical analysis sets to reflect the revised statistical analysis approach	Section 1.1, Synopsis; Section 9.4, Statistical Analysis Sets
Noted that the same analysis populations, as in the primary treatment period, will be used for the extension period	To clarify the analysis populations for the extension period	Section 1.1, Synopsis; Section 9.4, Statistical Analysis Sets
Revised language for efficacy analysis to describe the matching process and referred to details of the matching method to be specified in the SAP	To describe the matching process and to reserve details for the SAP	Section 1.1, Synopsis; Section 9.5, Efficacy Analyses; Section 9.5.4, Primary Efficacy Endpoint
Revised language for the analysis of primary efficacy endpoint	To revise the analysis of the primary endpoint due to change in the primary endpoint	Section 1.1, Synopsis; Section 9.5, Efficacy Analyses; Section 9.5.4, Primary Efficacy Endpoint

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Description of Change	**Rationale**	**Section(s) Affected by Change**
Revised language for the analysis of secondary and exploratory efficacy endpoints, and safety analyses	Details of these endpoint analyses are to be provided in the SAP	Section 1.1, Synopsis; Section 9.5.5, Analyses of Secondary and Exploratory Efficacy Endpoints; Section 9.7.2, Extension Period
Revised language for the pharmacokinetic analyses	To revise the pharmacokinetic analyses based on updated analysis approach	Section 1.1, Synopsis; Section 9.7.1, Pharmacokinetic Analyses
Noted for the extension period that statistical inferences for the primary and selected secondary endpoints may be performed; removed language that no statistical inferences will be performed	To allow statistical inferences for the primary and selected secondary endpoints beyond Week 106	Section 1.1, Synopsis; Section 9.7.2, Extension Period
Added language on a sensitivity analysis to be conducted for Group A subjects who missed no more than two consecutive SHP611 doses due to COVID-19; referred to details of other sensitivity analyses to be specified in the SAP	As study drug dosing was affected by the COVID-19 pandemic and to reserve details for the SAP	Section 1.1, Synopsis; Section 9.5.4, Primary Efficacy Endpoint
Added description that a hematopoietic stem cell, lentiviral vector-based human ASA gene therapy, LIBMELDY™ has received a marketing authorization in the European Union for presymptomatic late infantile MLD and early juvenile MLD	Update description on the current approved therapies for MLD	Section 2.3, Study Rationale
Revised the term GMFC-MLD 'level' to 'category'	Clarification	Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 3.2, Study Endpoints; Section 4.1, Overall Design; Section 4.2, Scientific Rationale for Study Design; Section 5.1, Inclusion Criteria; Section 8.2.2.1, Gross Motor Function Classification in MLD; Section 8.2.2.5, Note Documenting Current Motor Function; Section 9.5.4, Primary Efficacy Endpoints
Clarified that study weeks 5 and 9 visits are conducted at the main site (shaded columns in the Schedule of Activities)	Clarification	Section 1.2, Schema; Section 1.3, Schedule of Activities; Section 8.1.4.2, Treatment Period – Remaining Study Visits

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For SAEs collection, stated in the Safety Analyses section that all SAEs reported by the investigator, those SAEs considered as Related and those considered as Not Related by Takeda shall be collected	Clarification regarding SAEs collection for safety analysis	Section 1.1, Synopsis; Section 9.6, Safety Analyses
Removed measurement of CSF albumin	Measurement of CSF albumin is no longer required for the study	Section 1.3, Schedule of Activities; Section 8.2.4.4, Cerebrospinal Fluid Sampling Procedure
Updated the timing of the following periodic assessments so they are not to be completed at Week 105 but are to be completed at Week 106: CSF concentration of SHP611; CSF biomarkers and antibodies; and serum PK sampling	Due to the addition of the study extension phase in Amendment 4, subjects are no longer required to end treatment after Week 105.	Section 1.3, Schedule of Activities; Section 8.2.4.6, Pharmacokinetics
For maximum duration of subject participation in the study, noted that the extension period is planned to continue until Mar 2025, or product commercialization date, or until the program is discontinued	Clarification on the length of the extension period	Section 1.1, Synopsis
Updated the schedule of activities in Table 3 to clarify that MRI and MRS will be obtained annually during the extended treatment period (not every 6 months)	Clarification to reflect change in Amendment 4	Section 1.3, Schedule of Activities
Updated the schedule of activities in Table 3 to change “urine creatinine” to “urine biomarker”	Clarification to reflect change in Amendment 4	Section 1.3, Schedule of Activities
Updated vital signs measurement window time periods	To increase window time periods for vital signs measurements in order to make them more pediatric-friendly	Section 1.3, Schedule of Activities
Updated the 24-hour CSF sample draw window time period	To increase window time period for the 24-hour CSF sample draw in order to make it more pediatric-friendly	Section 1.3, Schedule of Activities
Listed a new SOPH-A-PORT Mini S component ‘one catheter passer’ and removed language on separate packaging of components	To update the list of components in the SOPH-A-PORT Mini S package and clarify that all components are packaged together	Section 6.1.2, SOPH-A-PORT Mini S IDDD
Updated language regarding collection of vital signs to remove the requirement for collection using the same method, arm, and position throughout the study	To improve feasibility of assessments in the pediatric study population	Section 8.2.3.3, Vital Signs

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Updated CSF samples analysis of exploratory biomarkers to add glial fibrillary acidic protein and Tau and Ubiquitin C-terminal hydrolase L1, and remove myelin basic protein and Saposin B	To clarify which CSF samples exploratory biomarkers will be analyzed	Section 8.2.4.4, Cerebrospinal Fluid Sampling Procedure
For ITQOL-97, removed statement that summary scoring and norms are not yet available	As the scoring and norm documents were provided to the sponsor	Section 8.2.4.10, Health-related Quality of Life (QoL) and Other Assessments
Noted that the sponsor will remain blinded to postbaseline efficacy-related data until database lock	To emphasize the sponsor's blind to this study	Section 9.2, Planned Analysis, Adaptive Design, and Data Monitoring Committee
An integrated analysis of PK and PD will be used to evaluate the impact of antibodies	To describe the analysis method of anti-SHP611 antibodies with enzyme neutralizing activity	Section 9.6, Safety Analyses

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the "Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" within 24 hours to the Takeda Global Drug Safety Department. The fax number and e-mail address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Takeda medical monitor using the details below.

Takeda Global Drug Safety
Email: drugsafety@shire.com

Takeda Medical Monitor: [redacted], MD, PhD
E-mail: [redacted]

PPD Drug Safety:
Fax: +44-1223-374-102

For protocol- or safety-related questions or concerns the investigator must contact the Takeda medical monitor:

Takeda Medical Monitor: [redacted], MD, PhD
E-mail: [redacted]

Medical Monitor mobile number: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Takeda within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

This includes any instances wherein the quality or performance of a Takeda product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination); or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products); or a product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE, which include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg, reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

For instructions on reporting AEs related to product complaints, see Appendix 3.4.

Please use the information below as applicable to report the Product Quality Complaint or Non-Medical Complaint:

Origin of Product Quality Complaint	**E-mail Address**
Global	PQC@takeda.com

Telephone number (provided for reference if needed):

Takeda, Lexington, MA (USA)

1-800-828-2088

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: SHP611-201	**Drug:** SHP611 (also known as TAK-611; recombinant human arylsulfatase A [rhASA]); INN/USAN: *cebsulfase alfa*
Title of the study: A Global, Multicenter, Single-arm, Matched External Control Study of Intrathecal SHP611 in Subjects with Late Infantile Metachromatic Leukodystrophy	
Short title: A Single-arm Study of Intrathecal SHP611 in Subjects with Metachromatic Leukodystrophy	
Study phase: Phase 2	

Number of subjects (total and per subject group):

The study was planned to enroll a total of up to 42 subjects. Six subject groups are defined based on subject age and degree of motor dysfunction at screening.

- Group A (GMFC-MLD category 1 or 2): Approximately 16 subjects who are 18 to 48 months of age with a Gross Motor Function Classification in Metachromatic Leukodystrophy (GMFC-MLD) category of 1 or 2
- Group B (GMFC-MLD category 3): Up to 8 subjects who are 18 to 72 months of age with a GMFC-MLD category of 3
- Group C (GMFC-MLD category 4): Up to 8 subjects who are 18 to 72 months of age with a GMFC-MLD category of 4
- Group D (minimally symptomatic): Up to 3 subjects who are ≥6 to <18 months of age, with the same ASA allelic constitution as an older sibling with confirmed late infantile or juvenile onset MLD
- Group E (GMFC-MLD category 1 or 2; <18 months of age): Up to 3 subjects ≥12 to <18 months of age, with documented diagnosis of MLD per inclusion criteria 1 and 2 with a history of achieving stable walking (defined as at least 1 month of independent walking) and a GMFC-MLD category of 1 or 2
- Group F (GMFC-MLD category 5 or 6): Up to 4 subjects who are 18 to 72 months of age with a GMFC-MLD category of 5 or 6

Subjects in Groups A, B, C, and F must have an initial onset of gait disorder due to spastic ataxia or weakness and documented by a primary care physician or a specialist physician by 30 months of age. Subjects in Group E must have neurological symptoms documented by either a primary care physician or a specialist physician.

It is planned that all subjects who participated in this study through Week 106 may be included in the extension period of the study for long-term safety and efficacy follow-up.

Investigator(s): Multicenter

Site(s) and Region(s):

Investigational sites may be located in North America, Europe, Middle East, Latin America, and Japan

Study period (planned): 2019-2025	**Clinical phase:** 2

Objectives:

Primary: The primary objective of this study is to evaluate the effects of intrathecal (IT) administration of SHP611 (also known as TAK-611) on the time to loss of locomotion, as indicated by category 5 or higher in the Gross Motor Function Classification in Metachromatic Leukodystrophy (GMFC-MLD) compared with matched external control group data in children with late infantile MLD.

Secondary:

- To evaluate the effects of IT administration of SHP611 on subjects who experience decline in gross motor function as indicated by GMFC-MLD category 5 or higher, compared with matched external control group data in children with MLD
- To evaluate the effects of IT administration of SHP611 on the decline in gross motor function, as measured by an unreversed decline in GMFC-MLD of more than 2 categories compared with matched external control group data in children with MLD, time course of declining gross motor function using the GMFC-MLD, and change from baseline of gross motor function, using the GMFC-MLD
- To evaluate the effects of IT administration of SHP611 on cerebrospinal fluid (CSF) sulfatides (pharmacodynamic [PD] biomarker)
- To evaluate the effects of IT administration of SHP611 on gross motor function, using the Gross Motor Function Measure 88 (GMFM-88) total score in children with MLD
- To evaluate the effects of IT administration of SHP611 on the time course of decline in gross motor function using GMFM-88, as measured by
    - an unreversed decline from baseline in GMFM-88 total score of >20 points or unreversed decline to <40 points, whichever occurs first,
    - change from baseline of gross motor function, using the GMFM-88 total score, and
    - GMFM-88 total score decline of no more than 20 points from baseline and a total score that is ≥40
- To evaluate the effects of IT administration of SHP611 on expressive language using the Expressive Language Function Classification (ELFC-MLD)

Pharmacokinetics:

- To evaluate the concentrations of SHP611 in CSF following single and repeat IT dosing of SHP611
- To evaluate the concentrations and pharmacokinetic (PK) parameters of SHP611 in serum following single and repeat IT dosing of SHP611

Safety:

To determine the safety and tolerability of IT SHP611 based on:

- Occurrence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory testing (serum chemistry, hematology, and urinalysis) and vital signs
- Physical examination including documentation of signs and symptoms of MLD and a Developmental Questionnaire
- 12-lead electrocardiogram (ECG)
- CSF laboratory parameters (chemistries and cell counts)
- Development of anti-SHP611 antibodies in CSF and serum
- SOPH-A-PORT® Mini S device in subjects with MLD

Exploratory:

To evaluate the effects of administration of IT SHP611 on:

- CSF, serum and urine biomarkers
- Proton magnetic resonance spectroscopy (MRS) of the brain, specifically N-acetylaspartate/Creatine (NAA/Cr) in white matter
- Eichler MLD MRI severity score
- Severity score as measured by magnetic resonance imaging (MRI) of the brain

- Volumetric analysis based on MRI of the brain
- Global impression of motor function – change (GIMF-C)
- Global impression of motor function– severity (GIMF-S)
- Caregiver burden and subject's health-related quality of life impact in children with MLD by evaluating:
    - Caregiver burden as assessed by the Caregiver Impact Questionnaire (CIQ)
    - Health Related Quality of Life (HRQOL) as assessed by the Infant Toddler Quality of Life Questionnaire-97 items (ITQOL-97)
- Healthcare Utilization as measured by the Health Care Utilization Questionnaire (HCUQ)
- Caregiver work productivity and activity impairment as assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI): Specific Health Problem V2.0
- Ability to eat and drink as assessed using the Eating and Drinking Ability Classification System (EDACS) assessments

Rationale:

Deficiency of the lysosomal enzyme arylsulfatase A in MLD leads to the accumulation of sulfated glycosphingolipids, known collectively as sulfatides. These accumulate in, and are toxic to, the cells which maintain the myelin insulation sheath of axons both centrally and peripherally. It is hypothesized that IT administration of recombinant human arylsulfatase A (SHP611) would be sufficient to hydrolyze accumulated sulfatides in cells of the nervous system and could slow or prevent further accumulation, which should translate into motor system benefits. There are currently very limited approved therapies for MLD.

Administration of SHP611 via an implanted intrathecal drug delivery device (IDDD) was well tolerated in Phase 1/2 studies in pediatric subjects with MLD and the device appeared to have an acceptable safety profile. In these studies, the higher dose appeared to show a signal of stabilized motor function in 4 of 12 subjects who received the 100 mg every-other-week (EOW) dose. This Phase 2 study will investigate the potential of IT SHP611 at a higher dose of 150 mg once weekly to stabilize or slow progression of motor dysfunction in pediatric subjects with late infantile MLD. The extension period of the study will evaluate long-term safety and efficacy outcomes of treatment with IT SHP611 in subjects who have participated in the study through Week 106.

Investigational product, dose, and mode of administration:

SHP611 (formerly designated as HGT-1110), recombinant human arylsulfatase A (rhASA).

Subjects weighing ≥7 kg (15.4 lbs) will receive 150 mg IT SHP611 weekly for 105 weeks. Subjects weighing ≥5 kg (11.0 lbs) to <7 kg will receive 100 mg IT SHP611 weekly; however, when the subjects weigh more than 7 kg they will begin dosing with 150 mg IT SHP611 weekly for the remainder of the study.

SHP611 administration will be via an implanted SOPH-A-PORT Mini S IDDD. If the device becomes nonfunctional at any time during the study, it will be removed and may be replaced or revised as appropriate. If use of the IDDD is not possible, a lumbar puncture (LP) may be utilized to obtain CSF samples and/or to deliver investigational drug product. It is anticipated that LP may have to be performed with anesthesia support at the discretion of the investigator. After 12 consecutive LPs, the feasibility of further use of LPs for that subject will be determined at the discretion of the investigator and the Takeda medical monitor and documented in a note to file.

Methodology:

SHP611-201 is a single-arm, matched external control, global, multicenter, Phase 2 trial. The study was planned to enroll up to 42 subjects with late infantile MLD who have an initial onset of neurological symptoms documented prior to 30 months of age (Groups A, B, C, and F), or who are minimally symptomatic and ≥6 to <18 months of age (Group D), or who are early symptomatic and ≥12 to <18 months of age (Group E). Minimally symptomatic is defined as being without clear symptoms of late infantile MLD or only showing mild symptoms (such as weakness) that do not meet the criteria for a GMFC-MLD category of >0 (NB: no subjects were enrolled in Groups D or E). The rate and severity of disease progression is well documented in late infantile MLD. A distinguishing feature of the definition of late infantile MLD is the early age at disease symptom onset with a majority of patients with late infantile MLD showing first motor dysfunction before the age of 18 months. Six subject groups are defined for this study based on age and motor dysfunction at screening:

• Group A (GMFC-MLD category 1 or 2):	18 to 48 months of age with a GMFC-MLD category of 1 or 2
• Group B (GMFC-MLD category 3):	18 to 72 months of age with a GMFC-MLD category of 3
• Group C (GMFC-MLD category 4):	18 to 72 months of age with a GMFC-MLD category of 4
• Group D (minimally symptomatic):	≥6 to <18 months of age with the same ASA allelic constitution as an older sibling with confirmed late infantile or juvenile onset MLD
• Group E (GMFC-MLD category 1 or 2)	≥12 to <18 months of age, with documented diagnosis of MLD per inclusion criteria 1 and 2 with a history of achieving stable walking (defined as at least 1 month of independent walking) and a GMFC-MLD category of 1 or 2
• Group F (GMFC-MLD category 5 or 6):	18 to 72 months of age with a GMFC-MLD category of 5 or 6

Subjects weighing ≥7 kg (15.4 lbs) will receive 150 mg IT SHP611 weekly. It is anticipated that the majority of subjects will receive 150 mg IT weekly for a total treatment duration of 105 weeks; however, subjects weighing ≥5 kg (11.0 lbs) to <7 kg (15.4 lbs) will receive 100 mg IT SHP611 weekly until they weigh ≥7 kg, at which time they will begin dosing with 150 mg IT SHP611 weekly.

The study will evaluate safety and efficacy of the treatment regimen on gross motor function using the GMFC-MLD and GMFM-88 total score to measure disease progression (Groups A, B, C, E, and F). Subjects in Group D will be assessed with the Alberta Infant Motor Scale (AIMS) and the GMFM-88 until they are ambulating or 18 months of age, whichever comes first. Once the AIMS is no longer being used, the GMFC-MLD and GMFM-88 will be used to measure motor function in this group.

The primary efficacy endpoint is time to loss of locomotion, measured by progression to GMFC-MLD category 5 or higher, or death, whichever occurs first, up to Week 106, evaluated on subjects in Group A. A secondary efficacy endpoint is response in Group A, defined as maintenance of gross motor function at Week 106, evaluated as subjects who do not experience any event within Week 106, where event is defined as a decline in GMFC-MLD to category 5 or higher, or death.

The efficacy of SHP611 will be evaluated by comparison of SHP611-201 enrolled subjects in Group A with a matched external control group. The data from these untreated MLD subjects (ie, subjects who have received no investigational product or therapy) will come from the ongoing Global Leukodystrophy Initiative (GLIA-MLD) natural history study.

The matched external control group must have data for at least baseline gross motor function evaluation. The filtering criteria for these external control subjects will be very similar to the inclusion/exclusion criteria for enrolled subjects in Group A of this present study.

Subjects will be implanted with the SOPH-A-PORT Mini S IDDD. Procedures for implantation are detailed in the device's Instructions for Use (IFU) manual. Standard hospital procedures for surgery will be followed and the subject may be under anesthesia for this procedure. Prior to implantation, individual neurosurgeons may order additional imaging to estimate the canal size and spinal cord conus location in younger patients. After implantation, a leak test is performed by the neurosurgeon to ensure a sealed system is in place. X-rays may be performed as needed, particularly for younger subjects, throughout the study to confirm placement of the device and/or evaluate a nonworking catheter. In order to facilitate healing, subjects should remain under observation in the hospital setting until deemed clinically stable by the investigator and should limit activity for 24 hours after IDDD implantation. To allow for healing, a waiting period of 3 to 5 days after device implantation must be observed before the first administration of SHP611 may occur. If the device becomes nonfunctional at any time during the study, it may be removed, replaced, or revised as appropriate. After IDDD replacement or revision, a waiting period of 3-5 days must be observed before IT SHP611 dosing may resume. Examination of both the port and catheter track will be performed before each IT injection, which includes aspiration of CSF via the port.

During the treatment period, subjects will undergo assessments of gross motor function, brain imaging, and health-related quality of life. Initial assessment of gross motor function using the GMFC-MLD scale will be conducted by local, trained healthcare professionals and video-recorded. Videos of GMFC-MLD assessments will be evaluated by central video reviewers for primary scoring of gross motor function on the instrument.

Safety will be assessed by collection of adverse events, physical examinations, vital signs, concomitant medications, ECG, clinical laboratory testing, and monitoring of anti-SHP611 antibodies. Periodic assessments will be performed before and after SHP611 administration at specific study visits (eg, serum/CSF PK sampling and CSF, serum, and urine biomarkers sampling and testing).

The study will consist of a screening period of up to 28 days. Implantation of the SOPH-A-PORT Mini S IDDD may occur during a period of up to 10 days prior to the first administration of IT SHP611 to 28 days after the first administration of IT SHP611. IT SHP611 administrations that occur prior to implantation of the IDDD will be administered via LP.

Subjects will be assessed according to the following schedule:

- Screening (-28 to -1 days)
- Surgical implantation of IDDD (-10 to 28 days)
- Primary treatment period (Week 0 [baseline assessments prior to dosing] through Week 105)
- End of primary treatment period (Week 106)
- Extension treatment period (from Week 106 administration of SHP611)
- End of treatment (EOT) (last administration of SHP611)
- End of study (EOS) (1 week after EOT)
- Safety follow-up (2 weeks after EOS)

After the primary treatment period is completed at Week 106, subjects may participate in the extension period of the study where they may continue to receive treatment with SHP611 for an extended duration of time.

Subjects will receive weekly treatment until they or their parents/guardians decide to discontinue treatment; the sponsor discontinues the study; the subject is discontinued from the study due to medical or safety concerns; or the product becomes commercially available in the subject's country of residence, whichever comes first. During the extension period, main site assessments will be scheduled every 6 months. These assessments may be skipped for a visit at the discretion of the investigator and upon discussion of the investigator with the Medical Monitor if it is determined that the subject is unable to perform the assessments. At the EOT visit, subjects will receive their last administration of SHP611 and comprehensive assessments will be completed at the EOS visit.

If a subject discontinues from the study earlier than EOS, every effort should be made to complete assessments for the EOS and the safety follow-up visits. Subjects are to have the IDDD removed when they discontinue from the study, unless the subject is continuing to receive treatment with SHP611 through another mechanism (eg, commercially available) or the investigator determines that the IDDD should not be removed from the subject based upon a safety assessment and the IDDD (full or partial) should remain in the subject.

Inclusion and Exclusion Criteria:

Inclusion criteria: Patients must meet all of the following criteria to be considered eligible for inclusion as a subject in the study:

1. The subject must have a documented diagnosis of MLD (Groups A-F)
   a. Low ASA activity in leukocytes (compared to laboratory normal range)
   AND
   b. Elevated sulfatides in urine
2. The subject must have a gait disorder due to spastic ataxia or weakness attributable to MLD by the investigator and documented by a primary care physician or a specialist physician by 30 months of age (Groups A-C, and F), or be minimally symptomatic and ≥6 to <18 months of age (Group D); or be early symptomatic and ≥12 to <18 months of age (Group E). Subjects in Group E must have neurological symptoms documented by either a primary care physician or a specialist physician.
3. The subject's age at the time of informed consent, must be:
   - Group A: 18 to 48 months of age
   - Group B: 18 to 72 months of age
   - Group C: 18 to 72 months of age
   - Group D: ≥6 to <18 months of age
   - Group E: ≥12 to <18 months of age
   - Group F: 18 to 72 months of age
4. The subject's GMFC-MLD category at screening must be:
   - Group A: GMFC-MLD category of 1 or 2
   - Group B: GMFC-MLD category of 3
   - Group C: GMFC-MLD category of 4
   - Group D: minimally symptomatic, and has the same ASA allelic constitution as an older sibling with confirmed late infantile or juvenile onset MLD
   - Group E: GMFC-MLD category of 1 or 2 with a history of achieving stable walking (defined as at least 1 month of independent walking)
   - Group F: GMFC-MLD category of 5 or 6
5. The subject and his/her parent/representative(s) must have the ability to comply with the clinical protocol
6. Subject's parent or legally authorized representative(s) must provide written informed consent prior to performing any study-related activities. Study-related activities are any procedures that would not have been performed during normal management of the subject

Exclusion criteria:

1. Multiple sulfatase disorder as determined by abnormal activity of another lysosomal sulfatase (based upon the reference laboratory's normal range) or a known genetic disorder other than MLD
2. History of bone marrow transplant (BMT), hematopoietic stem cell transplantation (HSCT), or gene therapy; or undergoes BMT, HSCT, or gene therapy at any point during the study
3. Primary presentation of MLD was behavioral or cognitive symptoms (per investigator's clinical judgment); behavioral symptoms that are secondary to motor deficits (eg: tantrums in response to loss of motor skills) are not exclusionary.
4. The subject has any known or suspected hypersensitivity to agents used for anesthesia or has history of difficult airway or potential for airway compromise

5. Any other medical condition or serious comorbid illness that in the opinion of the investigator would preclude participation in the study
6. Subjects with laboratory, ECG or vital sign abnormalities reflecting intercurrent illness that may compromise their safety during the trial should not be enrolled. Abnormal laboratory, vital sign and ECG results at screening should be reviewed with the Takeda medical monitor.
7. The subject is enrolled in another clinical study that involves use of any investigational product (drug or device) within 30 days or 5 half-lives (whichever is longer) prior to study enrollment or at any time during the study
8. The subject has had prior exposure to SHP611.
9. Subjects weighing <5 kg
10. The subject has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use
    a. The patient has had, or may have, an allergic reaction to the materials of construction
    b. The patient has shown an intolerance to an implanted device
    c. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port
    d. The patient's drug therapy requires substances known to be incompatible with the materials of construction
    e. The patient has a known or suspected local or general infection
    f. The patient is at risk of abnormal bleeding due to a medical condition or therapy
    g. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
    h. The patient has a functioning CSF shunt device

Filtering criteria for the selection of the matched external control group will be provided in the Statistical Analysis Plan (SAP).

Maximum duration of subject participation in the study:

The primary treatment period is planned for 106 weeks with an extension period starting at Week 106 administration of SHP611. The planned overall duration of each subject's involvement in the study is approximately 26 months from screening to the last scheduled visit for the primary treatment period with the extension period planned to continue until Mar 2025, or product commercialization date, or until the program is discontinued.

Subjects will continue treatment until they or their parents/guardians decide to discontinue treatment; the sponsor discontinues the study; the subject is discontinued from the study due to medical or safety concerns; or the product becomes commercially available in the subject's country of residence, whichever comes first.

Statistical analysis:

Analysis populations

- The Screened Set will consist of all subjects who have signed informed consent
- The Safety Analysis Set will consist of all subjects from Study SHP611-201 (Groups A-F) who receive at least 1 dose of SHP611, or subjects who have undergone the IDDD implantation procedure
- The Full Analysis Set (FAS) will consist of all subjects from the SHP611-201 Safety Analysis Set who receive at least 1 dose of SHP611 and have at least a screening GMFC-MLD assessment
- The modified Full Analysis Set (mFAS) will consist of all subjects from Group A in the FAS and the matched external control subjects for Group A from GLIA-MLD natural history study obtained after matching as described in the SAP
- The PK Analyses Set will consist of all subjects from the SHP611-201 Safety Analysis Set who receive at least 1 dose of SHP611 and have at least 1 postdose measurable [ie, not below quantifiable limits (BQL)] concentration of SHP611 in serum or CSF

- The Immunogenicity Analyses Set will consist of all subjects from the SHP611-201 Safety Analysis Set who receive at least 1 dose of SHP611 and have at least 1 anti-SHP611 antibody assessment with reportable result in serum or CSF

Extension period:

The same analysis populations, as in the primary treatment period, will be used for the extension period.

Device-related analyses will be conducted in the subset of subjects in the Safety Analysis Set who had the device implant procedure performed.

Primary efficacy endpoint

The primary efficacy endpoint is time to loss of locomotion, measured by progression to GMFC-MLD category 5 or higher, or death, whichever occurs first, up to Week 106, evaluated on subjects in Group A.

Secondary efficacy endpoint(s)

The secondary efficacy endpoints of this study are:

- Response in Group A, defined as maintenance of gross motor function at Week 106, evaluated as subjects who do not experience any event within Week 106, where event is defined as a decline in GMFC-MLD to category 5 or higher, or death
- Decline in gross motor function using GMFC-MLD:
  - Change from baseline at Week 106 and EOS in gross motor function, using the GMFC-MLD
  - Subjects with unreversed decline from baseline in GMFC-MLD of more than 2 categories, defined as any decline of more than 2-categories that has not reverted to a 2-category decline (or better) at Week 106, evaluated on subjects in Group A
  - Time to unreversed decline from baseline in GMFC-MLD of more than 2 categories, defined as any decline of more than 2-categories that has not reverted to a 2-category decline (or better) as of the last recorded observation
- Change from baseline at Week 106 and EOS in CSF sulfatides levels
- Response in Group A, defined as maintenance of gross motor function at Week 106, defined as a GMFM-88 total score ≥40
- Decline in gross motor function using GMFM-88:
  - Time to unreversed decline from baseline at Week 106 and EOS in GMFM-88 total score decrease of >20 points or unreversed decline to a score <40 points, whichever occurs first
  - Change from baseline at Week 106 and EOS in gross motor function, using the GMFM-88 total score
  - Subjects in Group A with GMFM-88 total score decrease of ≤20 points from baseline and a total score that is ≥40 at Week 106 and EOS
- Change from baseline at Week 106 and EOS in expressive language using the ELFC-MLD

Pharmacokinetic endpoints

- CSF parameters:
  - Predose concentrations (C_{trough}) of SHP611 at Weeks 0, 5, 9, 13, 26, 40, 53, 79, and 106
  - Postdose concentrations of SHP611 at 6 and 24 hours (Weeks 0 and 106)
- Serum parameters:
  - PK parameters after the first dose (Week 0) and after repeated doses (Week 106) of SHP611 determined by noncompartmental analysis will include but not limited to area under the concentration (AUC), maximum concentration (C_{max}), and clearance after IT administration (CL/F)
  - Predose concentrations (C_{trough}) of SHP611 at Weeks 0, 13, 26, 40, 53, 79, and 106

Safety endpoints

- Treatment-emergent adverse events (TEAEs)
- Changes from baseline at Week 106 and EOS in clinical laboratory testing (serum chemistry, hematology, and urinalysis)
- Change from baseline at Week 106 and EOS in physical examination including documentation of signs and symptoms of MLD (tone, reflexes, and vision)
- Change from baseline at Week 106 and EOS in 12-lead electrocardiogram (ECG)
- Change from baseline at Week 106 and EOS in CSF laboratory parameters (chemistries, cell counts)
- Anti-SHP611 antibodies in CSF and serum at Week 106 and EOS
- SOPH-A-PORT Mini S assessments will be evaluated using assessments of device implantation, device function, device longevity, and adverse events (AEs) associated with the implant surgery or device

Exploratory endpoints

- Change in CSF, serum, and urine biomarkers over time
- Change in MRS metabolite levels, specifically: N-acetylaspartate/Creatine over time
- Change in Eichler MLD MRI severity score over time
- Change in the total MLD severity score based on brain MRI over time
- Change in volumetric analysis of the brain based on MRI over time
- Change in global impression of motor function–change (GIMF-C) over time
- Change in global impression of motor function–severity (GIMF-S) over time
- Change in caregiver burden and subject's health-related quality of life:
  - Descriptive statistics of the Caregiver Impact Questionnaire (CIQ) item responses over time to inform scoring
  - Change in each of the parent and infant/toddler concepts as assessed by the Infant Toddler Quality of Life Questionnaire – 97 items (ITQOL-97) over time
- Change in incidence of hospitalizations, number of days in hospital, reason for admission, and frequency of selected MLD-related procedures (use of feeding tube, use of intubation, and type of respiratory support) over time; total number of additional hospitalizations during the 2-year follow-up
- Change in caregiver work productivity and activity impairment as assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI): Specific Health Problem V2.0 over time
- Change in ability to eat and drink as assessed using the Eating and Drinking Ability Classification System (EDACS) assessments over time

Sample size calculation and power considerations

Per original Protocol, sample size was calculated based on the response in Group A, (ie, the maintenance of gross motor function at Week 106, evaluated as no greater than 2 categories decline from baseline in GMFC-MLD), and at least 12 paired completers is required to detect a treatment difference for a desired power of 90%, using McNemar's test at a 2-sided significance level of 0.05, with the assumption that the response rates in Group A of current study and the matched external control group are 65% and 10% respectively. Furthermore, to adjust for potential unmatched and early discontinuation of subjects, a total of 16 subjects were originally planned to be enrolled into Group A of the current study. As the GLIA-MLD external control group for Group A cohort was expected to be large, efficient matching was plausible and incorporated in the assumptions.

Type I error and power were assessed for the time to event primary endpoint for sample sizes similar to that planned in the original protocol, through simulations using an interval censoring approach. Comparable assumptions were made on the response rates for the time to event primary endpoint in simulations. The response rates (ie, proportion of subjects not reaching GMFC-MLD category 5 or higher, or death) at Week 106 for Group A in the current study and the matched external control group are 65% and 10%, respectively.

The encounter structure from a subset of external control group for Group A subjects in the natural history study was considered. A simulated event time was randomly matched to a GLIA-MLD encounter schedule and was considered censored if it could not be observed within Week 106 under the matched schedule. The event time was assumed to follow a Weibull distribution, with a range of compatible shape parameters that allow approximation of the target response rates of 65% and 10% in the two groups, and a 25% censoring proportion for the GLIA-MLD control group. The type I error was preserved well. The power is assessed to be approximately between 71% to 82%. Matching efficiency is not assumed in the simulations.

Efficacy analysis

The efficacy of SHP611 in SHP611-201 Group A will be compared to matched external control group data from untreated MLD subjects in the Global Leukodystrophy Initiative natural history study (GLIA-MLD).

For Group A subjects in this study, the time to event (TTE) starting point is set at the Baseline visit where patients receive the first dose of SHP611. The external control group for Group A subjects will be selected from the GLIA-MLD database using appropriate filtering criteria. For each external control subject, a collection of "qualifying encounters" when the subject is in the appropriate age range for Group A and GMFC-MLD category of 1 or 2, will be identified and an appropriate TTE starting point will be defined. Details of this definition will be provided in the SAP.

For this matched external control study, an appropriate matching process will be applied to balance the baseline observed characteristics between the treatment and matched external control groups. Matching diagnostics will be conducted. Further details will be provided in the SAP.

For the analysis of the primary efficacy endpoint, the time to event data for Group A and matched external control group up to Week 106 will be compared using the stratified log-rank test, where the matching identification created from the matching process will be used as strata. Interval censoring methods will be used, with event assumed to have first happened between the last visit/encounter prior to the event observation, and the visit/encounter when the event is first observed. The null hypothesis of the stratified log-rank test will be evaluated at the 1-sided 0.025 level of significance. Kaplan-Meier (KM) survival curves suitable for interval censoring data will be presented.

As study drug dosing was affected by the COVID-19 pandemic, a sensitivity analysis will be conducted for Group A subjects who missed no more than two consecutive SHP611 doses due to COVID-19.

The details of the matching method and other sensitivity analyses, as well as the secondary and exploratory efficacy endpoints, will be specified in the SAP.

Safety analysis

Treatment-emergent adverse events (TEAEs) are defined as AEs that occurred at or after the first dose of investigational product or device implant surgery (whichever occurs first) and through the last follow-up date plus 14 days (inclusive). Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events and percentage of TEAEs will be calculated overall, by system organ class (SOC), by preferred term, and by subject groups (A-F). TEAEs will be further summarized by severity, relationship to investigational product, disease and outcomes, the IDDD, the IDDD surgical procedure, anesthesia, and IT administration process. Adverse events related to investigational product, AEs leading to withdrawal, serious adverse events (SAEs; all SAEs reported by the investigator, those SAEs considered as Related and those considered as Not Related by Takeda shall be collected), and deaths will be similarly summarized and listed.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by subject groups (A-F) and visit. Potentially clinically important findings will also be summarized and listed. Descriptive summaries will also be provided for 12-lead ECG, CSF laboratory parameters (chemistries, cell counts), anti-SHP611 antibodies in CSF and serum.

SOPH-A-PORT Mini S assessments

SOPH-A-PORT Mini S assessments will be evaluated using assessments of device implantation, device function, device longevity, and AEs associated with the implant surgery or device. These data will be collected on the subject's electronic case report form (eCRF) from the time of implantation and continue throughout the study as long as the SOPH-A-PORT Mini S remains implanted.

Pharmacokinetic analyses

All PK analyses will be performed using the PK Analysis Set.

Blood and CSF samples will be collected for determination of SHP611 levels after IT administration. SHP611 concentrations in serum and CSF will be determined using the validated Enzyme-Linked Immunosorbent Assays (ELISA) method which was used for the previous SHP611 clinical studies (HGT-MLD-070/HGT-MLD-071). SHP611 activity in CSF and serum will also be determined by validated Activity assays. The SHP611 Activity results will be used as surrogate marker for anti-SHP611 neutralizing antibodies and its impact on PK profile.

Details of the PK analysis including handling of PK data, parameters estimated, and presentation of PK data will be provided in the Clinical Pharmacology Analysis Plan (CPAP).

There will be no inferential statistical analysis of the PK data. Summary statistics (number of observations [N], mean, SD, coefficient of variation [CV%], median, maximum, minimum, geometric mean and geometric CV%) will be determined for all serum PK parameters and presented by bioanalytical method and visit for each group and for overall population. Serum and CSF concentrations at each nominal sampling time will also be summarized by bioanalytical method and visit for each group and for overall population using descriptive statistics. More details will be provided in the CPAP.

At the investigator's discretion a blood sample for PK analysis may be collected at the time of occurrence of an SAE or AE of special interest.

The serum and CSF concentration data from this study may be pooled with the data from Studies HGT-MLD-070 and HGT-MLD-071 in a population PK analysis. A population PK/PD and exposure-response analyses may be conducted using data from this study and reported separately.

Extension period

Summary statistics for continuous variables will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using the number and percentage of subjects in each category, including a missing category if applicable.

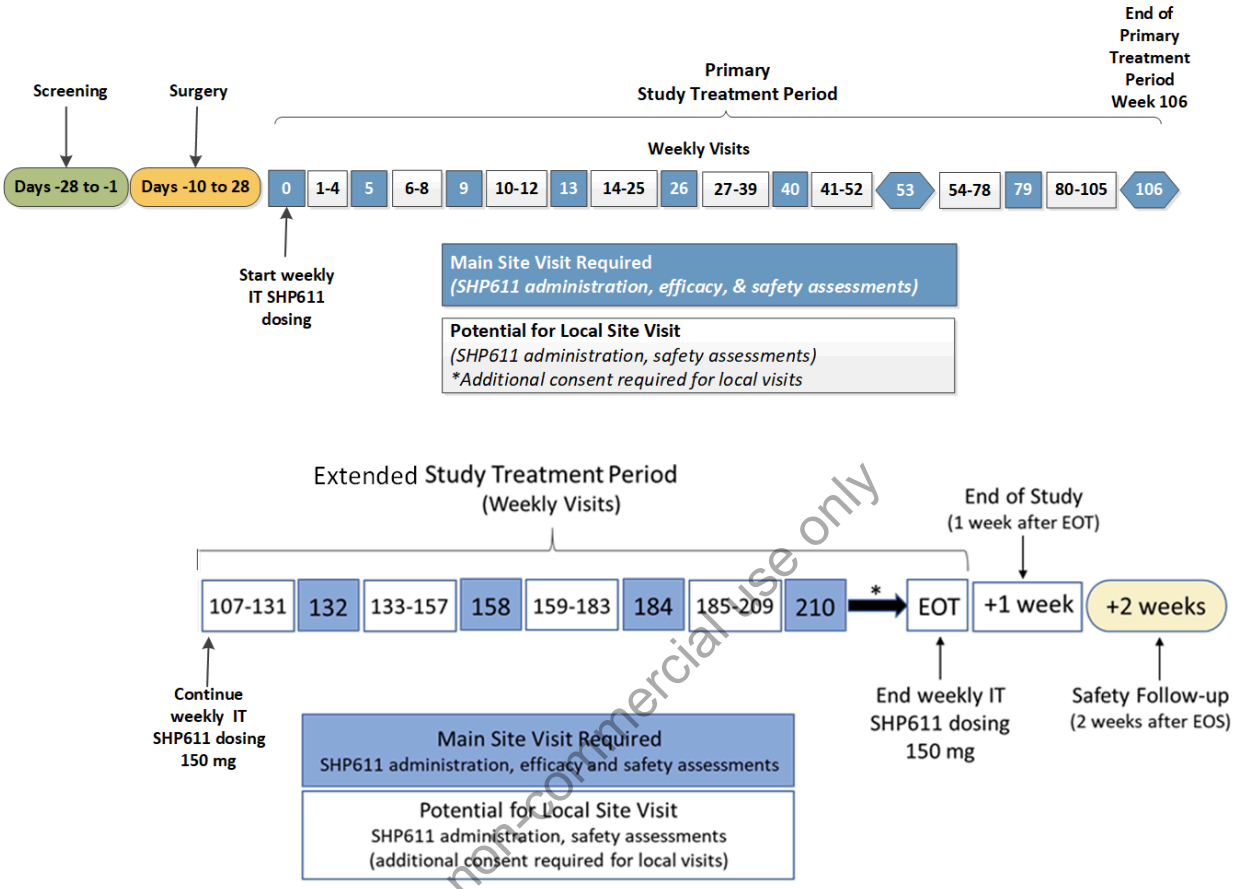
Statistical inferences for the primary and selected secondary endpoints may be performed during the extension period.

The safety analyses will be performed using all data through Week 106 and the extension period up to EOS. Baseline will be defined as the same as that for the study (this baseline is clinically relevant for assessing the long-term safety and efficacy outcomes of extended treatment with IT SHP611).

The same analysis populations, as in the primary treatment period, will be used for the extension period.

1.2 Schema

Figure 1 Study Schematic Diagram: Primary and Extension Treatment Periods



EOS=end of study; EOT=end of treatment; IT=intrathecal.

*Subjects may continue treatment in the study beyond Week 210. They will continue to follow the same schedule of assessments, ie, weekly dosing and main site visits every 6 months. Subjects will continue treatment until they or their parents/guardians decide to discontinue treatment; the sponsor discontinues the study; the subject is discontinued from the study due to medical or safety concerns; or the product becomes commercially available in the subject's country of residence, whichever comes first.

1.3 Schedule of Activities

Table 1 Schedule of Activities: Part 1 (Screening through Week 53)

	-28 to -1 days	-10 to 28 days	Primary Treatment Period												
			Shaded columns=Visits must be conducted at the Main Site												
Study Week	**SCR[a]**	**SUR[a]**	**0[a]**	**1-4[b]**	**5[b]**	**6-8[b]**	**9[b]**	**10-12[b]**	**13[a]**	**14-25[b]**	**26[a]**	**27-39[b]**	**40[a]**	**41-52[b]**	**53[a]**
Informed consent[b, c]	•														
Inclusion & exclusion criteria	•														
MLD diagnosis	•														
Sample collection for ASA genotyping	•														
Sample collection for exploratory genotyping[d]					•										
Arylsulfatase A activity	•														
CRIM[r]	•														
Medical history & demographics	•														
Enrollment *(pending sponsor and investigator approval)*	•														
IDDD surgery & x-ray[e, f]		•													
Anesthesia[e]		•	•								•				•
Administration of SHP611[e, f, g]			•[h]	•	•	•	•	•	•	•	•	•	•	•	•
Vital signs[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Height and weight			•						•		•		•		•
Head circumference			•						•		•		•		•
Symptom-directed physical exam[j]				•	•	•	•	•	•	•	•	•	•	•	•
Full physical exam[j]	•		•												•
Auditory exam[j]			•												•
Vision exam[j]			•												•
Video recording[k]	•		•		•		•		•		•		•		•
GMFC-MLD[g, j]	•		•[l]		•		•		•		•		•		•
GMFM-88[g, j]	•		•[l]						•		•		•		•
GIMF-C[g]									•		•		•		•
GIMF-S[g]			•						•		•		•		•
AIMS (Group D only)[g]			•						•		•		•		•
Note in source describing motor function[s]			•						•		•		•		•
ELFC-MLD[j]			•						•		•		•		•
Brain MRS[e]	•[t]														•
Brain MRI[e]	•[t]														•
12-lead ECG	•														•
CIQ			•						•		•		•		•
ITQOL (*HRQOL*)			•						•		•		•		•
HCUQ									•		•		•		•

Table 1 Schedule of Activities: Part 1 (Screening through Week 53)

	-28 to -1 days	-10 to 28 days	Primary Treatment Period												
			Shaded columns=Visits must be conducted at the Main Site												
Study Week	**SCR[a]**	**SUR[a]**	**0[a]**	**1-4[b]**	**5[b]**	**6-8[b]**	**9[b]**	**10-12[b]**	**13[a]**	**14-25[b]**	**26[a]**	**27-39[b]**	**40[a]**	**41-52[b]**	**53[a]**
WPAI			•						•		•				•
EDACS			•												•
Signs & symptoms of MLD			•						•		•		•		•
MLD Developmental Assessment			•						•		•		•		•
Serum chemistry with albumin & hematology	•		•		•		•		•		•		•		•
CSF routine analysis, including cell count, total protein, & glucose[o]			•	•	•	•	•	•	•	•	•	•	•	•	•
CSF concentration of SHP611 (*prior to dosing*)[e, p]			•		•		•		•		•		•		•
CSF biomarkers			•		•		•		•		•		•		•
CSF antibodies			•		•		•		•		•		•		•
Serum PK sampling[q]			•						•		•		•		•
Serum antibodies			•		•		•		•		•		•		•
Serum biomarkers			•		•		•		•		•		•		•
Urine biomarkers			•				•		•		•		•		•
Urine sulfatides	•		•		•		•		•		•		•		•
Urinalysis	•		•						•		•		•		•
Concomitant medications, therapies, & procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
IDDD removal[e, m, n]															

AIMS=Alberta Infant Motor Scale; CIQ=Caregiver Impact Questionnaire; CRA=clinical research associate; CRIM=cross-reacting immunologic material; CSF=cerebrospinal fluid; ECG=electrocardiogram; EDACS=Eating and Drinking Ability Classification System; ELFC-MLD=Expressive Language Function Classification in MLD; EOS=end of study; EOT=end of treatment; GIMF-C=global impression of motor function change; GIMF-S=global impression of motor function severity; GMFC-MLD=Gross Motor Function Classification for MLD; HCUQ=Healthcare Utilization Questionnaire; HRQOL=Health Related Quality of Life; ITQOL=Infant Toddler Quality of Life; MLD=metachromatic leukodystrophy; GMFM-88=Gross Motor Function Measure-88; IDDD=intrathecal drug delivery device; MRI=magnetic resonance imaging; MRS=magnetic resonance spectroscopy; PK=pharmacokinetics; SCR=screening; SUR=surgery; WPAI=Work Productivity and Activity Impairment

[a] Visit must be conducted at the main site (shaded columns) and the window will be ±1 week. Visit 0 (baseline) assessments other than labs, PK, or vital signs may be conducted on Day -1 or on Day 0.

[b] Subject's parent(s), or legally authorized representative(s) must provide a separate written informed consent to participate in study procedures at local sites prior (non-shaded columns) to the conduct of these procedures.

[c] Written informed consent, and assent if applicable, must be provided by the subjects' parent(s), or legally authorized representative(s) prior to conducting any study procedures.

[d] Assessment is optional.

Table 1 Schedule of Activities: Part 1 (Screening through Week 53)

	-28 to -1 days	-10 to 28 days	Primary Treatment Period												
			Shaded columns=Visits must be conducted at the Main Site												
Study Week	**SCR[a]**	**SUR[a]**	**0[a]**	**1-4[b]**	**5[b]**	**6-8[b]**	**9[b]**	**10-12[b]**	**13[a]**	**14-25[b]**	**26[a]**	**27-39[b]**	**40[a]**	**41-52[b]**	**53[a]**

[e] Anesthesia may be required (as determined by the investigator) for the following procedures: IDDD implantation, IDDD removal, SHP611 administration, CSF sample collection, brain MRS, and brain MRI. If only one assessment can be completed, the MRS assessment should be done as a priority over MRI. MRI and MRS may be repeated if there is too much motion in the first attempt.

[f] X-rays may be performed as needed, especially for younger subjects, throughout the study to check for placement of the device and/or evaluate a nonworking catheter. In order to facilitate healing, subjects should remain under observation in the hospital setting until deemed clinically stable by the investigator and limit activity for 24 hours after IDDD implantation.

[g] For each study visit the window will be ±3 days for the IT administration of SHP611. All assessments will be performed prior to IT administration of SHP611 unless otherwise indicated; motor assessments (eg, GMFC-MLD, GMFM-88, GIMF-C, GIMF-S, and AIMS) have a window of 0 to -3 days relative to dosing. At each main site visit, the investigator or sub-investigator is to write a note within the source documentation describing the subject's current motor function.

[h] To allow for healing, a waiting period of 3 to 5 days after IDDD implantation must be observed before the first administration of SHP611 may occur. This waiting period must also be observed after any subsequent re-implantation or revision of the IDDD.

[i] Vital signs will include measurements of blood pressure, heart rate, respiratory rate, and body temperature. Vital signs will be measured within 30 minutes prior to IT administration of SHP611 and 30 (±15), minutes, 60 (±30) minutes, and 120 (±30) minutes post IT SHP611 administration. Normal ranges for vital signs are presented in Appendix 7.

[j] The physical examinations, GMFC-MLD, GMFM-88, ELFC-MLD, auditory exam, and vision exam must be performed prior to the administration of anesthesia, or after the subject has fully recovered from the anesthesia.

[k] Assessments of gross motor function will be video-recorded.

[l] GMFC-MLD and GMFM-88 assessment is to be completed at baseline (Week 0) only if the timing of the visit is >28 days from the time of the GMFC-MLD assessment at screening.

[m] If the subject discontinues from the study earlier than EOS, every effort should be made to complete assessments for the EOS and the safety follow-up visits. If based on safety considerations, the investigator determines that the IDDD should not be removed and the IDDD (full or partial) should remain in the subject, then a safety follow-up visit via telephone should occur 2 weeks (±7 days) after the EOS visit. When the IDDD is explanted, an incision check should occur within 2 weeks (±7 days) after surgery.

[n] Data from the follow-up safety visit(s) may be collected as part of an extension period if subjects elect to continue their treatment.

[o] To be done by the local lab.

[p] CSF samples will be collected up to 1 hour prior to IT administration and then at Weeks 0 and 106 at 6 and 24 hours (+30 minutes) after IT administration; however, if the subject's IDDD is not functioning or the subject is receiving doses via LP, the 6 and 24 hour samples do not need to be collected.

[q] At Weeks 0 and 106, serum samples will be drawn for PK assessments up to 1 hour prior to IT administration and then drawn at 0.5 (±5 minutes), 1 (±5 minutes), 2 (±5 minutes), 4 (±5 minutes), 8 (±15 minutes), 12 (±15 minutes), 24 (±15 minutes), and 48 hours (±15 minutes) following completion of IT administration. At other visits, samples will be collected predose to assess attainment of steady state. The actual time of each PK draw must be recorded.

[r] 10 cc blood will be collected for CRIM in subjects weighing ≥11.5 kg; 3 cc blood will be collected for CRIM in subjects weighing <11.5 kg at screening visit. Because the CRIM assay is not yet available, CRIM samples will be stored for future use.

Table 1 Schedule of Activities: Part 1 (Screening through Week 53)

	-28 to -1 days	-10 to 28 days	Primary Treatment Period												
			Shaded columns=Visits must be conducted at the Main Site												
Study Week	**SCR[a]**	**SUR[a]**	**0[a]**	**1-4[b]**	**5[b]**	**6-8[b]**	**9[b]**	**10-12[b]**	**13[a]**	**14-25[b]**	**26[a]**	**27-39[b]**	**40[a]**	**41-52[b]**	**53[a]**

[s] At baseline and each main site visit, the investigator or sub-investigator will document the subjects current motor function, including observations supporting the current GMFC-MLD category assignment, in a text note entered into the source documents.

[t] The MRI/MRS may be conducted anytime between Screening and Week 0.

Table 2 Schedule of Activities: Part 2 (Week 54 through Week 106)

	Primary Treatment Period								
	Shaded columns=Visits must be conducted at the Main Site								
Study Week	**54-64[b]**	**65[b]**	**66-78[b]**	**79[a]**	**80-93[b]**	**94[b]**	**95-104[b]**	**105**	**106[a]**
Informed consent[b, c]									
Inclusion & exclusion criteria									
MLD diagnosis									
Sample collection for ASA genotyping									
Sample collection for exploratory genotyping[d]									
Arylsulfatase A activity									
CRIM[r]									
Medical history & demographics									
Enrollment									
IDDD surgery & x-ray[e, f]									
Anesthesia[e]									•
Administration of SHP611[e, f, g, h]	•	•	•	•	•	•	•	•	•
Vital signs[i]	•	•	•	•	•	•	•	•	•
Height and weight		•		•		•			•
Head circumference		•		•		•			•
Symptom-directed physical exam[j]	•	•	•	•	•	•	•	•	
Full physical exam[j]									•
Auditory exam[j]									•
Vision exam[j]									•
Video recording[k]				•					•
GMFC-MLD[g, j, l]				•					•
GMFM-88[g, j, l]				•					•
GIMF-C[g]				•					•
GIMF-S[g]				•					•
AIMS (Group D only)[g]				•					•
Note in source describing motor function[s]				•					•
ELFC-MLD[j]				•					•
Brain MRS[e, g]									•
Brain MRI[e, g]									•
12-lead ECG									•
CIQ				•					•
ITQOL (*HRQOL*)				•					•
HCUQ				•					•
WPAI									•
EDACS									•
Signs & symptoms of MLD				•					•
MLD Developmental Assessment				•					•

Table 2 Schedule of Activities: Part 2 (Week 54 through Week 106)

	Primary Treatment Period								
	Shaded columns=Visits must be conducted at the Main Site								
Study Week	**54-64[b]**	**65[b]**	**66-78[b]**	**79[a]**	**80-93[b]**	**94[b]**	**95-104[b]**	**105**	**106[a]**
Serum chemistry with albumin & hematology				•					•
CSF routine analysis, including cell count, total protein, & glucose[o]	•	•	•	•	•	•	•	•	•
CSF concentration of SHP611 (*prior to dosing*)[e, p]				•					•
CSF biomarkers				•					•
CSF antibodies				•					•
Serum PK sampling[q]				•					•
Serum (antibodies)				•					•
Serum (biomarkers)				•					•
Urine biomarkers				•					•
Urine sulfatides				•					•
Urinalysis				•					•
Concomitant medications, therapies, & procedures	•	•	•	•	•	•	•	•	•
Adverse events	•	•	•	•	•	•	•	•	•
IDDD removal[e, m, n]									•

AIMS=Alberta Infant Motor Scale; CIQ=Caregiver Impact Questionnaire; CRA=clinical research associate; CRIM=cross-reacting immunologic material; CSF=cerebrospinal fluid; ECG=electrocardiogram; EDACS=Eating and Drinking Ability Classification System; ELFC-MLD=Expressive Language Function Classification in MLD; EOS=end of study; EOT=end of treatment; GIMF-C=global impression of motor function change; GIMF-S=global impression of motor function severity; GMFC-MLD=Gross Motor Function Classification for MLD; HCUQ=Healthcare Utilization Questionnaire; HRQOL=Health Related Quality of Life; ITQOL=Infant Toddler Quality of Life; MLD=metachromatic leukodystrophy; GMFM-88=Gross Motor Function Measure-88; IDDD=intrathecal drug delivery device; MRI=magnetic resonance imaging; MRS=magnetic resonance spectroscopy; PK=pharmacokinetics; SCR=screening; SUR=surgery; WPAI=Work Productivity and Activity Impairment

[a] Visits must be conducted at the main site (shaded columns) and the window will be ±1 week.

[b] Subject's parent(s), or legally authorized representative(s) must provide a separate written informed consent to participate in study procedures at local sites prior (non-shaded columns) to the conduct of these procedures.

[c] Written informed consent, and assent if applicable, must be provided by the subjects' parent(s), or legally authorized representative(s) prior to conducting any study procedures.

[d] Assessment is optional.

[e] Anesthesia may be required (as determined by the investigator) for the following procedures: IDDD implantation, IDDD removal, SHP611 administration, CSF sample collection, brain MRS, and brain MRI. If only one assessment can be completed, the MRS assessment should be done as a priority over MRI. MRI and MRS may be repeated if there is too much motion in the first attempt.

[f] X-rays may be performed as needed, especially for younger subjects, throughout the study to check for placement of the device and/or evaluate a nonworking catheter. In order to facilitate healing, subjects should remain under observation in the hospital setting until deemed clinically stable by the investigator and limit activity for 24 hours after IDDD implantation.

Table 2 Schedule of Activities: Part 2 (Week 54 through Week 106)

	Primary Treatment Period								
	Shaded columns=Visits must be conducted at the Main Site								
Study Week	**54-64[b]**	**65[b]**	**66-78[b]**	**79[a]**	**80-93[b]**	**94[b]**	**95-104[b]**	**105**	**106[a]**

[g] For each study visit the window will be ±3 days for the IT administration of SHP611. All assessments will be performed prior to IT administration of SHP611 unless otherwise indicated; motor (eg, GMFC-MLD, GMFM-88, GIMF-C, GIMF-S, and AIMS), MRI, and MRS assessments have a window of 0 to -3 days relative to dosing. At each main site visit, the investigator or sub-investigator is to write a note within the source documentation describing the subject's current motor function.

[h] To allow for healing, a waiting period of 3 to 5 days after IDDD implantation must be observed before the first administration of SHP611 may occur. This waiting period must also be observed after any subsequent re-implantation or revision of the IDDD.

[i] Vital signs will include measurements of blood pressure, heart rate, respiratory rate, and body temperature. Vital signs will be measured within 30 minutes prior to IT administration of SHP611 and 30 (±15), minutes, 60 (±30) minutes, and 120 (±30) minutes post IT SHP611 administration. Normal ranges for vital signs are presented in Appendix 7.

[j] The physical examinations, GMFC-MLD, GMFM-88, ELFC-MLD, auditory exam, and vision exam must be performed prior to the administration of anesthesia, or after the subject has fully recovered from the anesthesia.

[k] Assessments of gross motor function will be video-recorded.

[l] GMFC-MLD and GMFM-88 assessment is to be completed at baseline (Week 0) only if the timing of the visit is >28 days from the time of the GMFC-MLD assessment at screening.

[m] If the subject discontinues from the study earlier than EOS, every effort should be made to complete assessments for the EOS and the safety follow-up visits. If based on safety considerations, the investigator determines that the IDDD should not be removed and the IDDD (full or partial) should remain in the subject, then a safety follow-up visit via telephone should occur 2 weeks (±7 days) after the EOS visit. When the IDDD is explanted, an incision check should occur within 2 weeks (±7 days) after surgery.

[n] Data from the follow-up safety visit(s) may be collected as part of an extension period if subjects elect to continue their treatment.

[o] To be done by the local lab.

[p] CSF samples will be collected up to 1 hour prior to IT administration and then at Weeks 0 and 106 at 6 and 24 hours (+30 minutes) after IT administration; however, if the subject's IDDD is not functioning or the subject is receiving doses via LP, the 6 and 24 hour samples do not need to be collected.

[q] At Weeks 0 and 106, serum samples will be drawn for PK assessments up to 1 hour prior to IT administration and then drawn at 0.5 (±5 minutes), 1 (±5 minutes), 2 (±5 minutes), 4 (±5 minutes), 8 (±15 minutes), 12 (±15 minutes), 24 (±15 minutes), and 48 hours (±15 minutes) following completion of IT administration. At other visits, samples will be collected predose to assess attainment of steady state. Actual time of each PK draw must be recorded.

[r] 10 cc blood will be collected for CRIM in subjects weighing ≥11.5 kg; 3 cc blood will be collected for CRIM in subjects weighing <11.5 kg at screening visit. Because the CRIM assay is not yet available, CRIM samples will be stored for future use.

[s] At baseline and each main site visit, the investigator or sub-investigator will document the subjects current motor function, including observations supporting the current GMFC-MLD category assignment, in a text note entered into the source documents.

Table 3 Schedule of Activities: Extended Treatment Period through Safety Follow-up

	Extended Treatment Period					
	Weekly Visits	6-monthly Visits[a]	Annual Visits	EOT[a]	EOS[a]	Safety Follow-up[a]
Study Week	**Starting at Week 107-131, 133-157, 159-183, 185-209 till EOT**	**Starting at Week 132, 158, 184, 210 till EOT[b]**	**Starting at Week 158, 210 till EOT**	**Last Administration of SHP611**	**1 Week (±1 week) After EOT[a]**	**2 Weeks After EOS[a]**
Anesthesia[c]		•		•	•	
Administration of SHP611[c, d, e, f]	•	•		•		
Vital signs[g]	•	•		•	•	•
Height and weight		•			•	
Head circumference		•			•	
Symptom-directed physical exam[h]	•	•		•		•
Full physical exam[h]					•	
Auditory exam[h]					•	
Vision exam[h]					•	
Video recording[i]		•			•	
GMFC-MLD[e, h, j]		•			•	
GMFM-88[e, h, j]		•			•	
GIMF-C[e, j]		•			•	
GIMF-S[e, j]		•			•	
ELFC-MLD[h, j]		•			•	
Brain MRS[c, e]			•		•	
Brain MRI[c, e]			•		•	
12-lead ECG					•	
CIQ[j]		•			•	
ITQOL (*HRQOL*)[j]		•			•	
HCUQ		•			•	
WPAI[j]					•	
EDACS[j]					•	
Signs & symptoms of MLD		•			•	
MLD developmental assessment		•			•	
Serum chemistry with albumin & hematology		•			•	
CSF routine analysis, including cell count, total protein, & glucose[k]	•	•		•	•	
CSF concentration of SHP611 (*prior to dosing*)[c, l]		•		•	•	
CSF biomarkers		•		•	•	
CSF antibodies		•		•	•	

Table 3 Schedule of Activities: Extended Treatment Period through Safety Follow-up

	Extended Treatment Period					
	Weekly Visits	6-monthly Visits[a]	Annual Visits	EOT[a]	EOS[a]	Safety Follow-up[a]
Study Week	Starting at Week 107-131, 133-157, 159-183, 185-209 till EOT	Starting at Week 132, 158, 184, 210 till EOT[b]	Starting at Week 158, 210 till EOT	Last Administration of SHP611	1 Week (±1 week) After EOT[a]	2 Weeks After EOS[a]
Serum PK sampling[m]		•		•		
Serum (antibodies)		•			•	
Serum (biomarkers)		•			•	
Urine biomarker		•			•	
Urine sulfatides		•			•	
Urinalysis		•			•	
Concomitant medications, therapies, & procedures	•	•		•	•	•
Adverse events	•	•		•	•	•
IDDD removal[n]					•	

CIQ=Caregiver Impact Questionnaire; CRA=clinical research associate; CSF=cerebrospinal fluid; ECG=electrocardiogram; EDACS=Eating and Drinking Ability Classification System; ELFC-MLD=Expressive Language Function Classification in MLD; EOS=end of study; EOT=end of treatment; GIMF-C=global impression of motor function change; GIMF-S=global impression of motor function severity; GMFC-MLD=Gross Motor Function Classification for MLD; HCUQ=Healthcare Utilization Questionnaire; HRQOL=Health Related Quality of Life; ITQOL=Infant Toddler Quality of Life; MLD=metachromatic leukodystrophy; GMFM-88=Gross Motor Function Measure-88; IDDD=intrathecal drug delivery device; MRI=magnetic resonance imaging; MRS=magnetic resonance spectroscopy; PK=pharmacokinetics; WPAI=Work Productivity and Activity Impairment

[a] Shaded Columns=Visits must be conducted at the Main Site and the window will be ±1 week.

[b] Subjects may continue treatment in the study beyond Week 210. They will continue to follow the same schedule of assessments, ie, weekly dosing and main site visits scheduled every 6 months. Subjects will continue treatment until they or their parents/guardians decide to discontinue treatment; the sponsor discontinues the study; the subject is discontinued from the study due to medical or safety concerns; or the product becomes commercially available in the subject's country of residence, whichever comes first.

[c] Anesthesia may be required (as determined by the investigator) for the following procedures: IDDD implantation, IDDD removal, SHP611 administration, CSF sample collection, brain MRS, and brain MRI. If only one assessment can be completed, the MRS assessment should be done as a priority over MRI. MRI and MRS may be repeated if there is too much motion in the first attempt.

[d] X-rays may be performed as needed, especially for younger subjects, throughout the study to check for placement of the device and/or evaluate a nonworking catheter. In order to facilitate healing, subjects should remain under observation in the hospital setting until deemed clinically stable by the investigator and limit activity for 24 hours after IDDD implantation.

[e] For each study visit the window will be ±3 days for the IT administration of SHP611. All assessments will be performed prior to IT administration of SHP611 unless otherwise indicated; motor (eg, GMFC-MLD, GMFM-88, GIMF-C, and GIMF-S), MRI, and MRS assessments have a window of 0 to -3 days relative to dosing. At each main site visit, the investigator or sub-investigator is to write a note within the source documentation describing the subject's current motor function.

Table 3 Schedule of Activities: Extended Treatment Period through Safety Follow-up

	Extended Treatment Period					
	Weekly Visits	6-monthly Visits[a]	Annual Visits	EOT[a]	EOS[a]	Safety Follow-up[a]
Study Week	Starting at Week 107-131, 133-157, 159-183, 185-209 till EOT	Starting at Week 132, 158, 184, 210 till EOT[b]	Starting at Week 158, 210 till EOT	Last Administration of SHP611	1 Week (±1 week) After EOT[a]	2 Weeks After EOS[a]

[f] To allow for healing, a waiting period of 3 to 5 days after IDDD implantation must be observed before the next administration of SHP611 may occur. This waiting period must also be observed after any subsequent re-implantation or revision of the IDDD.

[g] Vital signs will include measurements of blood pressure, heart rate, respiratory rate, and body temperature. Vital signs will be measured within 30 minutes prior to IT administration of SHP611 and 30 (±15), minutes, 60 (±30) minutes, and 120 (±30) minutes post IT SHP611 administration. Normal ranges for vital signs are presented in Appendix 7.

[h] The physical examinations, GMFC-MLD, GMFM-88, ELFC-MLD, auditory exam, and vision exam must be performed prior to the administration of anesthesia, or after the subject has fully recovered from the anesthesia.

[i] Assessments of gross motor function will be video-recorded.

[j] The efficacy outcome assessments (GMFC-MLD, GMFM-88, ELFC-MLD, GIMF-C and GIMF-S, CIQ, ITQOL, WPAI, and EDACS) will be performed every 6 months or as deemed appropriate by the investigator. These assessments may be skipped for a visit at the discretion of the investigator and upon discussion of the investigator with the Medical Monitor if it is determined that the subject is unable to perform the assessments.

[k] To be done by the local lab.

[l] CSF samples will be collected at predose prior to IT administration at 6-monthly visits. Samples will be collected at EOS, despite no SHP611 administration, in order to align with collection of all biomarkers.

[m] Collected at the 6-monthly visits and at EOT. Serum samples will be drawn for PK assessments up to 1 hour prior to IT administration. Actual time of each PK draw must be recorded.

[n] If the subject discontinues from the study earlier than EOS, every effort should be made to complete assessments for the EOS and the safety follow-up visits. If based on safety considerations, the investigator determines that the IDDD should not be removed and the IDDD (full or partial) should remain in the subject, then a safety follow-up visit via telephone should occur 2 weeks (±7 days) after the EOS visit. When the IDDD is explanted, an incision check should occur within 2 weeks (±7 days) after surgery.

2. INTRODUCTION

2.1 Indication and Current Treatment Options

Metachromatic leukodystrophy (MLD) is an inherited, autosomal recessive disorder of lipid metabolism characterized by deficient activity of the lysosomal enzyme, arylsulfatase A (ASA), which results in progressive accumulation of galactosylceramide-3-O-sulfate (cerebroside sulfate or sulfatide) and a cytotoxic metabolite of sulfatide (lysosulfatide or galactosylsphingosine-3-O-sulfate) (Hans et al. 2009; Sugiyama et al. 1990; Toda et al. 1990). Clinical manifestations are severe peripheral nerve damage, areflexic spasticity, and cognitive dysfunction (Kehrer et al. 2014; Wang et al. 2011). Approximately 200 ASA allele types have been reported in patients with MLD. The most frequently reported alleles (465 +1G>A, 1283 C>T, and 542 T>G) account for 37% of the mutations (Barth et al. 1993a; Barth et al. 1993b; Cesani et al. 2016; Gieselmann et al. 1991; Lugowska et al. 2005; Luzi et al. 2013; Virgens et al. 2015; Zlotogora et al. 1995). The rapidity with which the disease progresses clinically correlates with the level of residual enzymatic activity in vitro within the lysosomes (Kroos et al. 2008; Schaefer et al. 2005; Scott et al. 1995); however, the phenotypic variability due to factors other than ASA gene mutations do not allow genotype to consistently predict the disease course (Gieselmann and Krageloh-Mann 2014).

MLD presents with various neurological signs and symptoms with more severe types of the disease presenting earlier in life (Alam et al. 2015; Costello et al. 2009; Fluharty 2014; Gulati et al. 2016). Usually 3 main clinical subtypes are differentiated based on age of onset: late infantile MLD (40%-60% of cases), juvenile MLD (20%-35%), and adult MLD (15%-25%) (Wang et al. 2011). While this grouping into types is useful clinically and for genetic counseling, MLD is a continuum of clinical severity and the typing is somewhat arbitrary with an overlap of these clinical subtypes in some cases.

The late infantile MLD type is the most frequent presentation of the disorder and is usually diagnosed in the second year of life (Kolodny and Fluharty 1995). Development in children with late infantile MLD appears normal until onset of the initial symptoms. The natural history of disease progression is well documented in late infantile MLD with median onset of first motor symptoms at 17 months (Kehrer et al. 2011b) and in most patients before the age of 30 months (van Rappard et al. 2015). The typical initial presentation is a gait disturbance that progresses rapidly to complete loss of motor capabilities (median time 15 months) (Kehrer et al. 2011b). The disease progresses rapidly with seizures, motor deficits, and significant peripheral nerve damage resulting in an inability to walk, stand, or sit; frequent crying and irritability due to painful contractures; swallowing difficulties resulting in an inability to eat with resultant weight loss requiring a feeding tube; respiratory difficulties; an inability to speak; and sometimes blindness. The child's ability to respond to caretakers and engage in social interactions becomes increasingly limited with eventual nonresponsiveness due to progressive neurodegeneration (Gieselmann and Krageloh-Mann 2014). There is evidence of cognitive impairment and failure to achieve developmental milestones, which are also likely manifestations of a demyelinating process in the central and peripheral nervous systems (PNS) (í Dali et al. 2010; Kehrer et al. 2014). This demyelination likely results in axonal damage that is severe and possibly irreversible (Eichler et al. 2009; í Dali et al. 2015).

The visceral involvement in MLD may occasionally manifest as gallbladder disease; the lack of ASA in the kidney results in high excretion of urinary sulfatide. The disease is typically fatal, progressing to a decerebrate state with death occurring approximately 5 years after disease onset, generally due to complications from an infection (Eichler et al. 2016; Kehrer et al. 2014; Wang et al. 2011).

2.2 Product Background and Clinical Information

SHP611 (also known as TAK-611; formerly known as HGT-1110, with the INN/USAN *cebsulfase alfa*), is a recombinant human arylsulfatase A (rhASA) that is under development as an enzyme replacement therapy for the treatment of MLD. SHP611 (rhASA) is a multimeric glycoprotein produced using a genetically engineered human cell line (HT-1080) to secrete the human lysosomal enzyme, ASA. The glycans of SHP611 contain mannose-6-phosphate (M6P), which allows for target cell uptake and internalization into the lysosomal site of action via membrane-bound M6P receptors.

A particular challenge for lysosomal storage diseases, such as MLD, which affect the brain, is targeting enzyme replacement therapy to the central nervous system (CNS), as the blood brain barrier prevents passive diffusion of proteins from systemic circulation into the CNS (Vellodi 2005). This program attempts to overcome this physical challenge by administering directly into the CNS. In nonclinical studies, SHP611 administered via the IT route was taken up by the meninges, glial cells (oligodendrocytes), and neurons and deposited in the lysosomal compartment of target cells in cynomolgus monkeys, thus demonstrating that IT administration successfully delivers SHP611 to the site of action in the lysosomes of the oligodendrocytes. Furthermore, in a mouse model of MLD, IT administration of SHP611 reduced accumulation of sulfatides and LAMP-1, a lysosomal marker that is elevated in lysosomal storage diseases (Parkinson-Lawrence et al. 2005) in the brain and spinal cord of the affected animals indicating that SHP611 reached the tissues of interest in this model.

In subjects with MLD, SHP611 is administered directly to the CNS using a surgically implanted intrathecal drug delivery device (IDDD). The advantage of using an IDDD is that it obviates the need for multiple lumbar punctures (LPs) which would otherwise be required for drug delivery. The safety of SHP611 was evaluated in the first-in-human, multicenter, Phase 1/2 dose escalation study of SHP611 in children with MLD (HGT MLD-070, completed) and its extension study (HGT-MLD-071, ongoing). Intrathecal administration of SHP611 in children with MLD was well tolerated in these studies. Through 104 weeks, there appeared to be a signal of stabilization of motor function and magnetic resonance imaging (MRI) MLD severity.

Refer to the latest version of the SHP611 investigator's brochure (IB) for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy, and safety of SHP611.

2.3 Study Rationale

Currently there are very limited approved therapies for MLD, a progressive, ultimately fatal, genetic neurological disease. Children with MLD typically receive supportive care with palliative care later during the course of their disease.

Children may live for 5-10 years before they die and require complete care with feeding, diapering, clothing, and bathing as well as controls of pain and avoidance of complications of paralysis such as joint contractures and decubitus ulcers. The selection of supportive and palliative care is focused on management of the clinical symptoms (Kolodny and Fluharty 1995; van Rappard et al. 2015). Hematopoietic stem cell transplantation (HSCT) using bone marrow transplantation (BMT) or umbilical cord blood and gene therapy using lentiviral hemopoietic stem-cell therapy (Sessa et al. 2016) has been attempted for MLD with mixed results. A hematopoietic stem cell, lentiviral vector-based human ASA gene therapy, LIBMELDY™ (Orchard Therapeutics) has received a marketing authorization in the European Union (EU). LIBMELDY is indicated for use in children with late infantile or early juvenile forms of MLD who have not yet developed symptoms, and in early juvenile MLD who have initial symptoms but can still walk independently and have not yet developed mental deterioration.

The unmet medical need extends to families, caregivers, and providers, with great cost and multidisciplinary provider management required. Novel disease-modifying approaches that hold the potential for altering the clinical course of disease progression are needed. Intrathecal administrations of SHP611 in subjects with MLD could potentially stabilize or slow progression of neurological dysfunction by restoring a level of CNS and PNS ASA enzymatic activity that would be sufficient to hydrolyze accumulated sulfatide and slow or prevent further substrate accumulation. This study has been designed to evaluate the safety and efficacy of IT administration of SHP611 in MLD.

2.4 Benefit/Risk Assessment

MLD is a rapidly progressive neurological disorder that results in motor dysfunction and premature death, and for which there is no effective treatment. The initial clinical safety results in Phase 1/2 studies indicate a favorable benefit/risk profile for SHP611. The SOPH-A-PORT Mini S IDDD has been generally well tolerated in the HGT-MLD-070/071 clinical trials.

Always refer to the latest version of the IB for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics, efficacy, and safety of SHP611

2.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; E6 R2, 2017), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

The responsibilities of the study sponsor and investigator(s) are described fully in Appendix 1.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of this study is to evaluate the effects of intrathecal (IT) administration of SHP611 on the time to loss of locomotion, as indicated by category 5 or higher in the Gross Motor Function Classification in Metachromatic Leukodystrophy (GMFC-MLD) compared with matched external control group data in children with late infantile MLD.

3.1.2 Secondary Objectives

Secondary Objectives:

- To evaluate the effects of IT administration of SHP611 on subjects who experience decline in gross motor function as indicated by GMFC-MLD category 5 or higher, compared with matched external control group data in children with MLD
- To evaluate the effects of IT administration of SHP611 on the decline in gross motor function, as measured by an unreversed decline in GMFC-MLD of more than 2 categories compared with matched external control group data in children with MLD, time course of declining gross motor function using the GMFC-MLD, and change from baseline of gross motor function, using the GMFC-MLD
- To evaluate the effects of IT administration of SHP611 on cerebrospinal fluid (CSF) sulfatides (pharmacodynamic [PD] biomarker)
- To evaluate the effects of IT administration of SHP611 on gross motor function, using the Gross Motor Function Measure 88 (GMFM-88) total score in children with MLD
- To evaluate the effects of IT administration of SHP611 on the time course of declining gross motor function using GMFM-88, as measured by
    - an unreversed decline from baseline in GMFM-88 total score of >20 points or unreversed decline to <40 points, whichever occurs first,
    - change from baseline of gross motor function, using the GMFM-88 total score, and
    - GMFM-88 total score decline of no more than 20 points from baseline and a total score that is ≥40
- To evaluate the effects of IT administration of SHP611 on expressive language using the Expressive Language Function Classification in Metachromatic Leukodystrophy (ELFC-MLD)

Pharmacokinetics:

- To evaluate the concentrations of SHP611 in CSF following single and repeat IT dosing of SHP611
- To evaluate the concentrations and PK parameters of SHP611 in serum following single and repeat IT dosing of SHP611

Safety:

To determine the safety and tolerability of IT SHP611 based on:

- Occurrence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory testing (serum chemistry, hematology, and urinalysis) and vital signs
- Physical examination including documentation of signs and symptoms of MLD and a Developmental Questionnaire
- 12-lead electrocardiogram (ECG)
- CSF laboratory parameters (chemistries and cell counts)
- Development of anti-SHP611 antibodies in CSF and serum
- SOPH-A-PORT® Mini S device in subjects with MLD

Exploratory:

To evaluate the effects of administration of IT SHP611 on:

- CSF, serum and urine biomarkers
- Proton magnetic resonance spectroscopy (MRS) of the brain, specifically N-acetylaspartate/Creatine (NAA/Cr) in white matter
- Eichler MLD MRI severity score
- Severity score as measured by magnetic resonance imaging (MRI) of the brain
- Volumetric analysis based on MRI of the brain
- Global impression of motor function – change (GIMF-C)
- Global impression of motor function– severity (GIMF-S)
- Caregiver burden and subject's health-related quality of life impact in children with MLD by evaluating:
    - Caregiver burden as assessed by the Caregiver Impact Questionnaire (CIQ)
    - Health Related Quality of Life (HRQOL) as assessed by the Infant Toddler Quality of Life Questionnaire – 97 items (ITQOL-97)

- Healthcare Utilization as measured by the Health Care Utilization Questionnaire (HCUQ)
- Caregiver work productivity and activity impairment as assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI): Specific Health Problem V2.0
- Ability to eat and drink as assessed using the Eating and Drinking Ability Classification System (EDACS) assessments

3.2 Study Endpoints

The study objectives and endpoints are summarized in Table 4. Refer to Section 9 for a detailed description of endpoints and the planned statistical analysis.

Table 4 Objectives and Endpoints

Objective	Endpoint(s)
Primary	
• The primary objective of this study is to evaluate the effects of intrathecal (IT) administration of SHP611 on the time to loss of locomotion, as indicated by category 5 or higher in the Gross Motor Function Classification in Metachromatic Leukodystrophy (GMFC-MLD) compared with matched external control group data in children with late infantile MLD	• The primary efficacy endpoint is time to loss of locomotion, measured by progression to GMFC-MLD category 5 or higher, or death, whichever occurs first, up to Week 106, evaluated on subjects in Group A
Secondary	
• To evaluate the effects of IT administration of SHP611 on subjects who experience decline in gross motor function as indicated by GMFC-MLD category 5 or higher, compared with matched external control group data in children with MLD	• Response in Group A, defined as maintenance of gross motor function at Week 106, evaluated as subjects who do not experience any event within Week 106, where event is defined as a decline in GMFC-MLD to category 5 or higher, or death
• To evaluate the effects of IT administration of SHP611 on the decline in gross motor function, as measured by an unreversed decline in GMFC-MLD of more than 2 categories compared with matched external control group data in children with MLD, time course of declining gross motor function using the GMFC-MLD, and change from baseline of gross motor function, using the GMFC-MLD	• Decline in gross motor function using GMFC-MLD: Change from baseline at Week 106 and EOS in gross motor function, using the GMFC-MLD
• To evaluate the effects of IT administration of SHP611 on the decline in gross motor function, as measured by an unreversed decline in GMFC-MLD of more than 2 categories compared with matched external control group data in children with MLD, time course of declining gross motor function using the GMFC-MLD, and change from baseline of gross motor function, using the GMFC-MLD	• Decline in gross motor function using GMFC-MLD: Subjects with unreversed decline from baseline in GMFC-MLD of more than 2 categories, defined as any decline of more than 2-categories that has not reverted to a 2-category decline (or better) at Week 106, evaluated on subjects in Group A

Table 4 Objectives and Endpoints

Objective	Endpoint(s)
• To evaluate the effects of IT administration of SHP611 on the decline in gross motor function, as measured by an unreversed decline in GMFC-MLD of more than 2 categories compared with matched external control group data in children with MLD, time course of declining gross motor function using the GMFC-MLD, and change from baseline of gross motor function, using the GMFC-MLD	• Decline in gross motor function using GMFC-MLD: Time to unreversed decline from baseline in GMFC-MLD of more than 2 categories, defined as any decline of more than 2 categories that has not reverted to a 2-category decline (or better) as of the last recorded observation
• To evaluate the effects of IT administration of SHP611 on CSF sulfatides (PD biomarker)	• Change from baseline at Week 106 and EOS in CSF sulfatides levels
• To evaluate the effects of IT administration of SHP611 on gross motor function, using the Gross Motor Function Measure 88 (GMFM-88) total score in children with MLD	• Response in Group A, defined as maintenance of gross motor function at Week 106, defined as a GMFM-88 total score ≥40
• To evaluate the effects of IT administration of SHP611 on the time course of declining gross motor function using GMFM-88, as measured by o an unreversed decline from baseline in GMFM-88 total score of >20 points or unreversed decline to <40 points, whichever occurs first, o change from baseline of gross motor function, using the GMFM-88 total score, and o GMFM-88 total score decline of no more than 20 points from baseline and a total score that is ≥40	• Decline in gross motor function using GMFM-88: Time to unreversed decline from baseline at Week 106 and EOS in GMFM-88 total score decrease of >20 points or unreversed decline to a score <40 points, whichever occurs first
	• Decline in gross motor function using GMFM-88: Change from baseline at Week 106 and EOS in gross motor function, using the GMFM-88 total score
	• Decline in gross motor function using GMFM-88: Subjects in Group A with GMFM-88 total score decrease of ≤20 points from baseline and a total score that is ≥40 at Week 106 and EOS
• To evaluate the effects of IT administration of SHP611 on expressive language using the Expressive Language Function Classification (ELFC-MLD)	• Change from baseline at Week 106 and EOS in expressive language using the ELFC-MLD
Pharmacokinetic	
• To evaluate the concentrations of SHP611 in CSF following single and repeat IT dosing of SHP611	• CSF parameters: o Predose concentrations (C_{trough}) of SHP611 at Weeks 0, 5, 9, 13, 26, 40, 53, 79, and 106 o Postdose concentrations of SHP611 at 6 and 24 hours (Weeks 0 and 106)

Table 4 Objectives and Endpoints

Objective	Endpoint(s)
• To evaluate the concentrations and PK parameters of SHP611 in serum following single and repeat IT dosing of SHP611	• Serum parameters: o PK parameters after the first dose (Week 0) and after repeated doses (Week 106) of SHP611 determined by noncompartmental analysis will include but not limited to area under the concentration (AUC), maximum concentration (C_{max}), and clearance after IT administration (CL/F) o Predose concentrations (C_{trough}) of SHP611 at Weeks 0, 13, 26, 40, 53, 79, and 106
Safety	
• Occurrence of treatment-emergent adverse events (TEAEs)	• Treatment-emergent adverse events (TEAEs)
• Clinical laboratory testing (serum chemistry, hematology, and urinalysis) and vital signs	• Changes from baseline at Week 106 and EOS in clinical laboratory testing (serum chemistry, hematology, and urinalysis)
• Physical examination including documentation of signs and symptoms of MLD and Developmental Questionnaire	• Change from baseline at Week 106 and EOS in physical examination including documentation of signs and symptoms of MLD (tone, reflexes, and vision)
• 12-lead electrocardiogram (ECG)	• Change from baseline at Week 106 and EOS in 12-lead electrocardiogram (ECG)
• CSF laboratory parameters (chemistries and cell counts)	• Change from baseline at Week 106 and EOS in CSF laboratory parameters (chemistries, cell counts)
• Development of anti-SHP611 antibodies in CSF and serum	• Anti-SHP611 antibody responses in CSF and serum at Week 106 and EOS
• SOPH-A-PORT® Mini S device in subjects with MLD	• SOPH-A-PORT Mini S assessments will be evaluated using assessments of device implantation, device function, device longevity, and adverse events (AEs) associated with the implant surgery or device
Exploratory	
To evaluate the effects of administration of IT SHP611 on:	**Change in:**
• CSF, serum and urine biomarkers	• CSF, serum, and urine biomarkers over time
• Proton magnetic resonance spectroscopy (MRS) of the brain, specifically N-acetylaspartate/Creatine (NAA/Cr) in white matter	• MRS metabolite levels specifically: N-acetylaspartate/Creatine over time
• Eichler MLD MRI severity score	• Eichler MLD MRI severity score over time
• Severity score as measured by magnetic resonance imaging (MRI) of the brain	• Total MLD severity score based on brain MRI over time
• Volumetric analysis based on MRI of the brain	• Volumetric analysis of the brain based on MRI over time

Table 4 Objectives and Endpoints

Objective	Endpoint(s)
• Global impression of motor function – change (GIMF-C)	• GIMF-C over time
• Global impression of motor function – severity (GIMF-S)	• GIMF-S over time
• Caregiver burden and subject's health-related quality of life impact in children with MLD by evaluating: o Caregiver burden as assessed by the Caregiver Impact Questionnaire (CIQ) o Health Related Quality of Life (HRQOL) as assessed by the Infant Toddler Quality of Life Questionnaire – 97 items (ITQOL-97)	• Caregiver burden and subject's health-related quality of life: Descriptive statistics of the Caregiver Impact Questionnaire (CIQ) item responses over time to inform scoring
	• Caregiver burden and subject's health-related quality of life: change in each of the parent and infant/toddler concepts as assessed by the Infant Toddler Quality of Life Questionnaire – 97 items (ITQOL-97) over time
• Healthcare Utilization as measured by the Health Care Utilization Questionnaire (HCUQ)	• Incidence of hospitalizations, number of days in hospital, reason for admission, and frequency of selected MLD-related procedures (use of feeding tube, use of intubation, and type of respiratory support) over time; total number of additional hospitalizations during the 2-year follow-up
• Caregiver work productivity and activity impairment as assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI): Specific Health Problem V2.0	• Caregiver work productivity and activity impairment as assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI): Specific Health Problem V2.0 over time
• Ability to eat and drink as assessed using the Eating and Drinking Ability Classification System (EDACS) assessments	• Change in ability to eat and drink as assessed using the Eating and Drinking Ability Classification System (EDACS) assessments over time

4. STUDY DESIGN

4.1 Overall Design

SHP611-201 is a single-arm, matched external control, global, multicenter, Phase 2 trial. The study was planned to enroll up to 42 subjects with late infantile MLD who have an initial onset of neurological symptoms documented prior to 30 months of age (Groups A, B, C, and F), or who are minimally symptomatic and ≥6 to <18 months of age (Group D), or who are early symptomatic and ≥12 to <18 months of age (Group E). Minimally symptomatic is defined as being without clear symptoms of MLD or only showing mild symptoms (such as weakness) that do not meet the criteria for a GMFC-MLD category of >0 (NB: no subjects were enrolled in Groups D or E). The rate and severity of disease progression is well documented in late infantile MLD (Kehrer et al. 2011b; Kehrer et al. 2011a). A distinguishing feature of the definition of late infantile MLD is the early age at disease symptom onset with a majority of patients with late infantile MLD showing first motor dysfunction before the age of 18 months. Six subject groups are defined for this study based on age and motor dysfunction at screening:

- Group A (GMFC-MLD category 1 or 2): Approximately 16 subjects who are 18 to 48 months of age with a GMFC-MLD category of 1 or 2
- Group B (GMFC-MLD category 3): Up to 8 subjects who are 18 to 72 months of age with a GMFC-MLD category of 3
- Group C (GMFC-MLD category 4): Up to 8 subjects who are 18 to 72 months of age with a GMFC-MLD category of 4
- Group D (minimally symptomatic): Up to 3 subjects who are ≥6 to <18 months of age, with the same ASA allelic constitution as an older sibling with confirmed late infantile or juvenile onset MLD
- Group E (GMFC-MLD category 1 or 2, <18 months of age): Up to 3 subjects who are ≥12 to <18 months of age, with documented diagnosis of MLD per inclusion criteria 1 and 2 who have achieved stable walking (defined as at least 1 month of independent walking) and who have a GMFC-MLD category of 1 or 2
- Group F (GMFC-MLD category 5 or 6): Up to 4 subjects who are 18 to 72 months of age with a GMFC-MLD category of 5 or 6

Subjects weighing ≥7 kg (15.4 lbs) will receive 150 mg IT SHP611 weekly. It is anticipated that the majority of subjects will receive 150 mg IT weekly for a total treatment duration of 105 weeks; however, subjects weighing ≥5 kg (11.0 lbs) to <7 kg (15.4 lbs) will receive 100 mg IT SHP611 weekly until they weigh ≥7 kg, at which time they will begin dosing with 150 mg IT SHP611 weekly.

The study will evaluate safety and efficacy of the treatment regimen on gross motor function using the GMFC-MLD and GMFM-88 total score to measure disease progression (Groups A, B, C, E, and F). Subjects in Group D will be assessed with the Alberta Infant Motor Scale (AIMS) (Piper and Darrah 1994) and the GMFM-88 until they are able to walk or reach 18 months of age, whichever comes first. After this, motor function of subjects in Group D will be assessed using the GMFC-MLD and the GMFM-88.

The primary efficacy endpoint is time to loss of locomotion, measured by progression to GMFC-MLD category 5 or higher, or death, whichever occurs first, up to Week 106, evaluated on subjects in Group A. A secondary efficacy endpoint is response in Group A, defined as maintenance of gross motor function at Week 106, evaluated as subjects who do not experience any event within Week 106, where event is defined as a decline in GMFC-MLD to category 5 or higher, or death.

The efficacy of SHP611 will be evaluated by comparison of SHP611-201 enrolled subjects in Group A with matched external control group. The data from these untreated MLD subjects (ie, subjects who have received no investigational product or therapy) will come from the ongoing Global Leukodystrophy Initiative (GLIA-MLD) natural history study. The matched external control group must have data for at least baseline gross motor function evaluation. The filtering criteria for these controls will be very similar to the inclusion/exclusion criteria for enrolled subjects in Group A of this present study.

Subjects will be implanted with the SOPH-A-PORT Mini S IDDD. Procedures for implantation are detailed in the device's Instructions for Use (IFU) manual. Standard hospital procedures for surgery will be followed and the subject may be under anesthesia for this procedure. Prior to implantation, individual neurosurgeons may order additional imaging to estimate the canal size and spinal cord conus location in younger subjects. After implantation, a leak test is performed by the neurosurgeon to ensure a sealed system is in place. X-rays may be performed as needed, particularly for younger subjects, throughout the study to confirm placement of the device and/or evaluate a nonworking catheter. In order to facilitate healing, subjects should remain under observation in the hospital setting until deemed clinically stable by the investigator and should limit activity for 24 hours after IDDD implantation. To allow for healing, a waiting period of 3 to 5 days after device implantation must be observed before the first administration of SHP611 may occur. If the device becomes nonfunctional at any time during the study, it may be removed, replaced or revised as appropriate. A 3-5 day waiting period should also be observed after IDDD revision or re-implantation prior to resumption of dosing. Examination of both the port and catheter track will be performed before each IT injection, which includes aspiration of CSF via the port.

If use of the IDDD is not possible, a lumbar puncture (LP) may be utilized to obtain CSF samples and/or to deliver investigational drug product. It is anticipated that LP may have to be performed with anesthesia support at the discretion of the investigator. After 12 consecutive LPs, the feasibility of further use of LPs for that subject will be determined at the discretion of the investigator and the Takeda medical monitor and documented in a note to file.

During the treatment period, subjects will undergo assessments of gross motor function, brain imaging, and quality of life. Initial assessment of gross motor function using the GMFC-MLD scale will be conducted by local, trained healthcare professionals and video-recorded. Videos of GMFC-MLD assessments will be evaluated by central video reviewers for primary scoring of gross motor function on the instrument.

Safety will be assessed by collection of adverse events (AEs), physical examinations, vital signs, concomitant medications, ECG, clinical laboratory testing, and monitoring of anti-SHP611 antibodies. Periodic assessments will be performed before and after SHP611 administration at specific study visits (eg, serum/CSF PK sampling and CSF, serum, and urine biomarkers sampling and testing).

The study will consist of a screening period of up to 28 days. Surgical implantation of the SOPH-A-PORT Mini S IDDD may occur during a period of 10 days prior to the first administration of IT SHP611 to 28 days following the first administration of IT SHP611. IT SHP611 administered prior to IDDD implantation will be administered by LP.

Subjects will be assessed according to the following schedule:

- Screening (-28 to -1 days)
- Surgical implantation of IDDD (-10 to 28 days)
- Primary treatment period (Week 0 [baseline assessments prior to dosing {-1 to 0 days}] through Week 105)
- End of primary treatment period (Week 106)
- Extension treatment period (from Week 106 administration of SHP611)
- End of treatment (EOT) (last administration of SHP611)
- End of study (EOS) (1 week after EOT)
- Safety follow-up (2 weeks after EOS)

After the primary treatment period is completed at Week 106, subjects may continue in the extension period of the study where they may continue to receive treatment with SHP611 for an extended duration of time.

Subjects will receive weekly treatment until they or their parents/guardians decide to discontinue treatment; the sponsor discontinues the study; the subject is discontinued from the study due to medical or safety concerns; or the product becomes commercially available in the subject's country of residence, whichever comes first. During the extension period, main site assessments will be scheduled every 6 months. These assessments may be skipped for a visit at the discretion of the investigator and upon discussion of the investigator with the Medical Monitor if it is determined that the subject is unable to perform the assessments. At the EOT visit, subjects will receive their last administration of SHP611 and comprehensive assessments will be completed at the EOS visit.

If a subject discontinues from the study earlier than EOS, every effort should be made to complete assessments for the EOS and the safety follow-up visits. Subjects are to have the IDDD removed when they discontinue from the study, unless the subject is continuing to receive treatment with SHP611 through another mechanism (eg, commercially available) or the investigator determines that the IDDD should not be removed from the subject based upon a safety assessment and the IDDD (full or partial) should remain in the subject.

Sites will employ all efforts to see subjects for the clinical assessments; however, in unavoidable circumstances, such as the COVID-19 public health emergency, sites should use their judgment in conducting the study visits to maintain continuity of subject dosing and to collect as much data as possible while ensuring the protocol is being followed. Due to COVID-19 control measures, there may be unavoidable protocol deviations which will be documented in the study records using already established procedures. These data may be handled differently in the final data analysis, with this documented in the Statistical Analysis Plan.

4.2 Scientific Rationale for Study Design

Deficiency of the lysosomal enzyme ASA in MLD leads to the accumulation of sulfated glycosphingolipids, known collectively as sulfatides. These accumulate in, and are toxic to, the cells which maintain the myelin insulation sheath of axons both centrally and peripherally. It is hypothesized that IT administration of rhASA (SHP611) would be sufficient to hydrolyze accumulated sulfatides in cells of the nervous system and could slow or prevent further accumulation, which should translate into motor system benefits. There are currently very limited approved therapies for MLD.

Administration of SHP611 via an implanted IDDD was well tolerated in Phase 1/2 studies in pediatric subjects with MLD and the device appeared to have an acceptable safety profile. In these studies, the higher dose appeared to show a signal of stabilized motor function in 4 of 12 subjects who received the 100 mg every-other-week (EOW) dose. This Phase 2 study will investigate the potential of IT SHP611 at a higher dose of 150 mg once weekly to stabilize or slow progression of motor dysfunction in pediatric subjects with late infantile MLD.

In the extension treatment period of the study, subjects who have participated in the primary treatment of the study may receive treatment with SHP611 for an extended duration of time to evaluate long-term safety and efficacy outcomes of treatment with IT SHP611.

While a randomized concurrent double-blind placebo control is the preferred clinical trial design, there are no active-comparators for this life-threatening, rapidly progressive disease. Concurrent controls such as delayed start, no-treatment, and placebo controls have been evaluated and deemed infeasible due to challenges with enrollment and lack of support from parents of patients and investigators. Nonconcurrent, matched external control group will be used for this study as this is the only feasible and ethical option; other options would not be supported by families and investigators.

Both the GMFC-MLD (Kehrer et al. 2011b; Kehrer et al. 2011a) and the GMFM-88 (Iannaccone and Hynan 2003; Linder-Lucht et al. 2007; Russell et al. 2013; Russell et al. 1989) instruments will be used to measure gross motor function of study subjects.

The GMFC-MLD instrument will be used for the primary endpoint as it was developed specifically for MLD patients, based on experiences with the GMFCS instrument used for cerebral palsy (Palisano et al. 1997). It has been reported to be an established and reliable tool for the standardized assessment of gross motor function in MLD that can be used to classify the stages of disease progression and for evaluation of therapeutic options for MLD. The GMFC-MLD covers clinically relevant gross motor stages occurring in patients with MLD and consists of 7 categories based primarily on locomotion, and in more advanced disease also includes sitting and other motions. The GMFC-MLD is applicable from the age of 18 months onwards, or in younger subjects if stable walking has been achieved (able to walk independently for at least a month) and can be assessed retrospectively based on medical records. The intra-rater reliability of the tool has been reported to be high, with kappa coefficient k=0.90 for overall rater agreement (95% CI 0.87-0.93).

The GMFM-88 instrument will be used as a secondary endpoint and is included as a supportive method of measuring clinical response to that used for the primary endpoint. The GMFM-88 has demonstrated valid and reliable measurement properties in several different patient populations, including cerebral palsy (from 5 months through 16 years old), by evaluation of a broad range of tasks that could be accomplished independently by a child of 5 years of age without any motor disability. The GMFM-88 assesses gross motor function across 5 dimensions: lying and rolling; sitting; kneeling and crawling; standing; and walking, running, and jumping. The GMFM-88 instrument is administered by a trained physical therapist in about 45 to 60 minutes. It can be administered in a standardized, reliable, and reproducible manner to subjects.

Inclusion of subjects ≥6 to <18 months of age who are minimally symptomatic will be allowed in Group D as long as inclusion/exclusion criteria are satisfied. Subjects in Group D will have the same ASA allelic constitution as an older sibling with confirmed infantile or juvenile onset MLD. Subjects in Group E will be ≥12 to <18 months of age, with documented diagnosis of MLD per inclusion criteria 1 and 2 who have achieved stable walking (defined as at least 1 month of independent walking) at some point prior to screening, and who are early symptomatic with a GMFC-MLD category of 1 or 2 at screening. Group E allows for enrollment of young subjects with MLD who are not necessarily siblings of enrolled subjects in the other groups. In addition to safety and biomarker data, this group will allow for assessment of IT SHP611 effect in a younger group who may be earlier in their disease progression.

As discussed above, this study design is limited by the lack of available concurrent controls.

4.3 Justification for Dose

Subjects weighing ≥7 kg (15.4 lbs) will receive 150 mg IT SHP611 weekly. It is anticipated that the majority of subjects will receive 150 mg IT weekly for a total treatment duration of 105 weeks; however, subjects weighing ≥5 kg (11.0 lbs) to <7 kg (15 lbs) will receive 100 mg IT SHP611 weekly until they weigh ≥7 kg, at which time they will begin dosing with 150 mg IT SHP611 weekly for the remainder of the study for 105 weeks. For the extension period, dosing will be once weekly administration of IT SHP611 at 150 mg.

The dose of 150 mg to be investigated in this study (SHP611-201) is supported by the current Phase 1/2 clinical safety data as well as nonclinical studies.

The 150 mg dose of SHP611 was selected based on safety, clinical activity, and PK data from the Phase 1/2 dose escalation study (HGT-MLD-070). Pharmacokinetic modeling and clinical activity of SHP611 in the Phase 1/2 program suggest that IT administration of SHP611 (150 mg once weekly) may produce a more rapid and sustained therapeutic benefit in a greater number of subjects with MLD. No clinical therapeutic effect was observed for lower doses evaluated previously in Takeda studies HGT-MLD-070/071.

As would be expected with both a larger dose amount and a greater frequency, a population PK/PD model simulation of the 150 mg weekly dose predicts higher peak C_{max} and total concentrations of SHP611 in serum, CSF, and CNS compartments than the 100 mg dose EOW administered in studies HGT-MLD-070/071. The 150 mg regimen is expected to produce 50% higher SHP611 concentrations in the CSF and the CNS than the 100 mg regimen.

4.4 Duration of Subject Participation and Study Completion Definition

Once it has been confirmed that all eligibility criteria have been met, a subject will be considered enrolled in the study. Enrollment of subjects may occur prior to IDDD implantation of the first dose of SHP611. The subject's duration of participation in the primary treatment period is expected to be approximately 106 weeks. Upon completion of the primary treatment period, subjects may participate in the extension period of the study.

If a subject discontinues from the study earlier than EOS, every effort should be made to complete assessments for the EOS and the safety follow-up visits. Refer to the Schedule of Activities: Extended Treatment Period through Safety Follow-up for details.

The Study Completion Date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s). This includes the follow-up visit or contact, whichever is later (refer to Section 8.1.6 for the defined follow-up period for this protocol).

4.5 Sites and Regions

This is a multicenter study. Investigational sites are planned in North America, Europe, Middle East, Latin America, and Japan.

5. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

5.1 Inclusion Criteria

Inclusion criteria: Patients must meet all of the following criteria to be considered eligible for inclusion as a subject in the study:

1. The subject must have a documented diagnosis of MLD (Groups A-F)
   - Low ASA activity in leukocytes (compared to laboratory normal range)

     AND

   - Elevated sulfatides in urine
2. The subject must have a gait disorder due to spastic ataxia or weakness attributable to MLD by the investigator and documented by a primary care physician or a specialist physician by 30 months of age (Groups A-C, and F), or be minimally symptomatic and ≥6 to <18 months of age (Group D); or be early symptomatic and ≥12 to <18 months of age (Group E). Subjects in Group E must have neurological symptoms documented by either a primary care physician or a specialist physician.
3. The subject's age at the time of informed consent, must be:
   - Group A: 18 to 48 months of age
   - Group B: 18 to 72 months of age
   - Group C: 18 to 72 months of age
   - Group D: ≥6 to <18 months of age
   - Group E: ≥12 to <18 months of age
   - Group F: 18 to 72 months of age
4. The subject's GMFC-MLD category at screening must be:
   - Group A: GMFC-MLD category of 1 or 2
   - Group B: GMFC-MLD category of 3
   - Group C: GMFC-MLD category of 4
   - Group D: minimally symptomatic, ≥6 to <18 months of age, with the same ASA allelic constitution as an older sibling with confirmed late infantile or juvenile onset MLD
   - Group E: early symptomatic, ≥12 to <18 months of age with a GMFC-MLD category of 1 or 2, and with a history of achieving stable walking (defined as at least 1 month of independent walking)
   - Group F: GMFC-MLD category of 5 or 6

5. The subject and his/her parent/representative(s) must have the ability to comply with the clinical protocol.
6. Subject's parent or legally authorized representative(s) must provide written informed consent prior to performing any study-related activities. Study-related activities are any procedures that would not have been performed during normal management of the subject.

5.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met.

Exclusion Criteria:

1. Multiple sulfatase disorder as determined by abnormal activity of another lysosomal sulfatase (based upon the reference laboratory's normal range) or a known genetic disorder other than MLD
2. History of bone marrow transplant (BMT), hematopoietic stem cell transplantation (HSCT), or gene therapy; or undergoes BMT, HSCT, or gene therapy at any point during the study
3. Primary presentation of MLD was behavioral or cognitive symptoms (per investigator's clinical judgment); behavioral symptoms that are secondary to motor deficits (eg, tantrums in response to loss of motor skills) are not exclusionary
4. The subject has any known or suspected hypersensitivity to agents used for anesthesia or has history of difficult airway or potential for airway compromise
5. Any other medical condition or serious comorbid illness that in the opinion of the investigator would preclude participation in the study
6. Subjects with laboratory, ECG, or vital sign abnormalities reflecting intercurrent illness that may compromise their safety during the trial should not be enrolled. Abnormal laboratory, vital sign and ECG results at screening should be reviewed with the Takeda medical monitor.
7. The subject is enrolled in another clinical study that involves use of any investigational product (drug or device) within 30 days or 5 half-lives (whichever is longer) prior to study enrollment or at any time during the study
8. The subject has had prior exposure to SHP611
9. The subject must weigh >11 lbs (5 kg)
10. The subject has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use (IFU)
    a. The patient has had, or may have, an allergic reaction to the materials of construction
    b. The patient has shown an intolerance to an implanted device
    c. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port
    d. The patient's drug therapy requires substances known to be incompatible with the materials of construction

e. The patient has a known or suspected local or general infection
f. The patient is at risk of abnormal bleeding due to a medical condition or therapy
g. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
h. The patient has a functioning CSF shunt device

Inclusion and exclusion criteria for the matched external control group will be provided in the Statistical Analysis Plan (SAP).

5.3 Restrictions

The use of the IDDD will be restricted to SHP611-201 study-related activities and should not be accessed for any other purpose, including administration of concomitant medications. The safety of SHP611 IT in patients receiving other drugs intrathecally has not been assessed. Therefore, administration of intrathecal drugs other than SHP611 during study participation is contraindicated. In this setting, SHP611 will be discontinued for the subject. Subject activity restrictions may be imposed at the discretion of the investigator.

Please refer to the SOPH-A-PORT Mini S IFU for details regarding patient activity restrictions for patients to be implanted with this device. Activities that may include sudden, excessive, or repetitive bending, twisting, bouncing, or stretching can damage or dislodge IDDD components and should be avoided.

5.4 Reproductive Potential

This study will not enroll subjects of child-bearing potential.

5.4.1 Female Contraception

Not applicable.

5.4.2 Male Contraception

Not applicable.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The investigational product is SHP611, which will be provided in vial form. Additional information is provided in the current SHP611 IB.

SHP611 drug product is a sterile solution of recombinant human arylsulfatase A (rhASA), 30 mg/mL, in 154 mM sodium chloride (NaCl), at pH 6.0 with (vol/vol) 0.005% polysorbate 20. SHP611 drug product is packaged in ISOI 2R, Type I borosilicate glass vials with a butyl rubber stopper with a fluoro-resin coating. Vials are sealed with and aluminum overseal. Each vial contains 1.6 mL of drug product to deliver a minimum extractable volume of 1.3 mL per vial with minimal waste, and for handling convenience in the clinical setting.

Investigational drug product will be clearly labeled according to country specifications. This will include, but is not limited to, manufacturer's name, protocol number, lot number, storage conditions, and expiration date.

See the Pharmacy Manual for additional details.

6.1.2 SOPH-A-PORT Mini S IDDD

After IDDD implantation, the drug product will be administered via the SOPH-A-PORT Mini S Implantable Access Port. The SOPH-A-PORT Mini S device is intended for long-term, intermittent access to the IT space for the delivery of investigational drug.

The Sophysa SOPH-A-PORT Mini-S is an intrathecal drug delivery device that has been used in all of Takeda's intrathecal enzyme replacement programs (Sanfilippo Syndrome type A, Hunter Syndrome, and MLD). It is an implantable port access system designed to provide repeated access to the intrathecal space for drug delivery. This device is manufactured by Sophysa SA (Sophysa), Orsay, France. The development of the SOPH-A-PORT Mini S was based on a kit component modification of an existing CE-marked device in the EU. SOPH-A-PORT Mini S is approved in the EU exclusively for long-term intrathecal administration of Takeda's enzyme replacement therapies per the medical device directives.

The SOPH-A-PORT line of products has been CE-marked in the EU since 1998 and was authorized for marketing in Japan in 2000. The SOPH-A-PORT Mini S has been characterized and tested through a series of development studies, eg, functional and performance testing and long-term biocompatibility. Functional, performance, and long-term biocompatibility test results have shown that the SOPH-A-PORT Mini S is suitable for its intended use. In the EU, the SOPH-A-PORT Mini S was added to the CE mark certificate for the SOPH-A-PORT Product Family, effective on 16 May 2013, and updated on 13 Oct 2013. The indication was expanded to include long-term intrathecal administration of Takeda's enzyme replacement therapies on 13 Mar 2019. The SOPH-A-PORT Mini S is an investigational device in all other non-EU countries. In the United States, the SOPH-A-PORT Mini S device is considered a device constituent part of the SHP611 combination product, per 21 CFR part 4.

Sophysa maintains the original Investigational Device Master File (I-MAF) MAF2173 to support the SOPH-A-PORT Mini S investigational presentation for use in clinical development of SHP611. Sophysa has submitted an Investigational Device Master File which includes information for an Investigational Device Exemption (IDE) application for a "significant risk" clinical investigation of a Class III device subject to Premarket Approval (PMA). Sophysa has issued letters of authorization to Takeda and to FDA accordingly. Sophysa submits amendments to the Investigational Master File for Devices as required for any changes to the SOPH-A-PORT Mini S investigational presentation. The current IDE equivalent MAF2173 has been maintained to provide on-going support of Takeda's clinical trial efforts for Hunter Intrathecal (HIT) and Metachromatic Leukodystrophy (MLD) programs.

Takeda conducts internal quarterly safety reviews to discuss the safety profile of the device. As of 31 Aug 2018, there were 139 devices implanted in 106 subjects across all intrathecal programs at Takeda. Overall, 53 (50%) subjects needed no additional surgery, 38 (36%) subjects had failure of initial device, 22 (21%) subjects had adjustment of initial device without device failure, and 17 (14%) subjects ultimately had complete device removal without replacement. These medical safety review meetings have determined a positive benefit risk ratio and therefore all ongoing clinical trials will continue utilizing the device for enzyme replacement studies.

The SOPH-A-PORT Mini S is comprised of the following components:

- One SOPH-A-PORT Mini S Access Port
- One intrathecal port closed-tip catheter
- One guidewire
- Two suture wings
- One 14-gauge Tuohy needle
- One 22-gauge non-coring Huber needle
- One Luer lock Connector
- One catheter passer

The SOPH-A-PORT Mini S Access Port is available in one size, individually packaged, with other SOPH-A-PORT Mini S components in double peel-off, sterile, pyrogen-free packaging, sterilized with ethylene oxide. Instructions for Use are also included in the packaging.

Labels are provided on the outer carton on the SOPH-A-PORT Mini S box.

Further details are provided in the IFU.

The use of the IDDD will be restricted to SHP611-201 study-related activities and should not be accessed for any other purpose, including administration of concomitant medications. The safety of SHP611 IT in patients receiving other drugs intrathecally has not been assessed. Therefore, administration of intrathecal drugs other than SHP611 during study participation is contraindicated. In this setting, SHP611 will be discontinued for the subject.

6.1.3 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

6.2.1 Allocation of Subjects to Treatment

This is a single-arm study.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

Once a unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a unique identifier is allocated incorrectly, the clinical research associate (CRA)/study monitor must be notified as soon as the error is discovered.

Investigational product packaging identification numbers, separate from unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject.

6.2.2 Dosing

Subjects weighing ≥7 kg (15.4 lbs) will receive 150 mg IT SHP611 weekly. It is anticipated that the majority of subjects will receive 150 mg IT weekly for a total treatment duration of 105 weeks; however, subjects weighing ≥5 kg (11.0 lbs) to <7 kg (15.4 lbs) will receive 100 mg IT SHP611 weekly until they weigh ≥7 kg, at which time they will begin dosing with 150 mg IT SHP611 weekly for the remainder of the study.

Dosing may only occur at an approved investigational site.

6.2.3 Unblinding the Treatment Assignment

Not applicable.

6.2.4 Dose Modification

The once weekly IT dose of SHP611 150 mg to be investigated in this study is supported by the current Phase 1/2 clinical safety data as well as nonclinical studies.

As with all clinical studies evaluating a new dose or dosing regimen, the sponsor will closely monitor the emerging safety profile to determine if the expected higher exposure from using a once weekly 150 mg dosing regimen alters the investigational product's safety profile and benefit/risk ratio. Based on the observed safety profile of SHP611 with doses up to 100 mg administered EOW to subjects for more than 5 years of treatment, and Takeda's experience with other enzyme replacement therapies, a significant change in the overall safety profile of SHP611 is not expected with the proposed dose and dosing regimen.

The maximum administered dose will not exceed 150 mg once weekly.

6.3 Labeling, Packaging, Storage, and Handling of Investigational Product

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

Investigational drug product will be clearly labeled according to country specifications. This will include, but is not limited to, drug name, protocol number, lot number, storage conditions, and expiration date. All packaging and labeling will be done in accordance with applicable regulatory requirements.

See Pharmacy Manual for additional details.

Space is allocated on the label so that the site representative can record a unique subject identifier.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label.
- Obscure the clinical study label.
- Identify the study subject by name.

Additional labels may not be added without the sponsor's prior full agreement.

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

CARTON 37x37x47 Millimeter white Crash-Lock

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions, including refrigeration at 2 to 8ºC (36 to 46ºF). Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3.4 Special Handling

Do not freeze. Avoid exposure to intense direct sunlight. Investigational drug product may not be used beyond the expiration date on the labeling.

6.4 Drug and Device Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered investigational product will be documented in the subject's source and/or other investigational product record.

No investigational product stock or returned inventory from a Takeda-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

With the written agreement of the sponsor, at the end of the study all unused stock, and empty/used investigational product packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of investigational product must be in accordance with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

The disposition of all SOPH-A-PORT Mini S IDDDs delivered to the investigator must be recorded on a patient-by-patient basis by completing the accountability log. The date and time of administration of the investigational drug product and use of the SOPH-A-PORT Mini S device must be documented on the subject's appropriate electronic case report form (eCRF). The investigator, Clinical Research Coordinator, or designee (eg, pharmacist) must ensure that all documentation regarding receipt, storage, dispensing, loss/damaged SOPH-A-PORT Mini S IDDDs and return of used/unused IDDDs) is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the SOPH-A-PORT Mini S devices are available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

The SOPH-A-PORT Mini S and its components are sterile, single-use devices. Please refer to the IDDD Manual for device return instructions.

Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

6.5 Treatment Compliance

Treatment with the investigational product will be administered via an IDDD (or LP) under the supervision of the investigator and in the controlled environment of a clinical center; therefore, full subject compliance with treatment is anticipated in this study.

The initial implantation and revision and/or explantation of the SOPH-A-PORT Mini S will be performed by pediatric or general neurosurgeons, anesthesiologists, or interventional radiologists who have experience in port and catheter implant procedures and intrathecal access procedures, and have completed training with the SOPH-A-PORT Mini S. Please refer to the IFU for further details.

Investigational product administration will be performed in a clinical setting by appropriately trained and skilled healthcare providers (nurses or physicians) with knowledge of the subject's drug regimen and experienced in accessing vascular or CNS ports or CNS infusion pumps.

Subjects and subjects' families will not be directly using the device to administer drugs and will have limited direct interaction with the device as there is minimal care required both during the immediate postoperative period as the implant site heals, and at times of drug administration.

6.6 Prior and Concomitant Treatment

6.6.1 Prior Treatment

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, as appropriate) received within 30 days prior to the screening visit (Day -28 to -1) (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period) must be recorded in the subject's source document.

6.6.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of initial implantation of the IDDD or the first dose of investigational product, whichever occurs first, and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded in the subject's source document. Subjects must receive all other standard treatments for their condition and its complications, including treatment for decubitus ulcers, seizures, and spasticity.

6.6.3 Permitted Treatment

Medications not indicated as prohibited are permitted, including treatments for non-exclusionary medical conditions. In the event of an emergency, any needed medications may be prescribed without prior approval by the sponsor, but the medical monitor must be notified of the use of any prohibited medications immediately thereafter.

6.6.4 Prohibited Treatment

As noted in the Exclusion Criteria (Section 5.2), the use of any investigational therapy (drug/device, HSCT, gene therapy, bone marrow transplant) other than that received in study SHP611-201 is prohibited within 30 days prior to enrollment or at any time during the study.

Treatments not listed above are considered allowable.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

If investigational product is discontinued, regardless of the reason, the evaluations listed for EOS, including a safety follow-up 2 weeks after EOS, will be performed as completely as possible. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for discontinuation, date of discontinuation of the investigational product, and the total amount of investigational product administered must be recorded in the source documents.

If subjects do not receive intercurrent disease modifying treatment (eg, gene therapy, BMT, HSCT), they may be asked to return to complete EOS assessments during the week that would have been EOS week for the subject if he/she had continued in the study.

Subjects who discontinue will not be replaced.

7.2 Reasons for Discontinuation

The reason for discontinuation must be determined by the investigator and recorded in the subject's source document, including unavoidable circumstances, such as the COVID-19 public health emergency. If a subject is discontinued for more than 1 reason, each reason should be documented in the source and the most clinically relevant reason should be indicated.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Lost to follow-up
- Lack of efficacy
- Withdrawal by subject
- Other

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF. If a subject chooses to withdraw from study participation due to personal concerns related to the COVID-19 public health emergency (other than a COVID-19-related adverse event), this should be specified as the reason for subject withdrawal in the eCRF.

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Takeda
- Loss of the ability of the parent/legal guardian to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Inability to comply with protocol
- Discretion of the investigator

7.3 Withdrawal from the Study

A subject may withdraw from the study at any time and for any reason without prejudice to his/her future medical care by the physician or at the institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

Reasons for withdrawal include but are not limited to:

- Completed
- Death (provide cause)
- Adverse event (specify)
- Lost to follow-up (specify)
- Noncompliance with study drug
- Noncompliance with study procedures (specify)
- Other (specify)

7.4 Temporary Hold of Dosing

Dosing may be held until safety information can be reviewed in the event that:

- Two or more subjects experience the same severe adverse event that is considered related to SHP611
- Review of the safety and tolerability data, or clinical judgment of the investigator, suggest the emergence of a new potentially serious safety signal related to SHP611.

Dosing may not be resumed until a thorough review of safety and tolerability data has been completed and the Takeda medical monitor, Takeda pharmacovigilance representative, and the investigators agree that it is safe to proceed.

Any subject for whom dosing is stopped permanently or who is otherwise removed from the study should enter the post-treatment follow-up phase of the study.

7.5 Subjects "Lost to Follow-up" Prior to the Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject who is lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that the subject return to the site for final safety evaluations.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Study Periods

The detailed study procedures/assessments to be performed throughout the study are outlined in the Schedule of Activities (see Table 1, Table 2, and Table 3); which must be referred to in conjunction with the instructions provided in this section and in the relevant study manuals. Study assessments are detailed in Section 8.2.

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the subject, subject's parent(s), guardian, or legally authorized representative (as per local requirements) will provide written informed consent; the subject will provide verbal or written assent as appropriate. Refer to Appendix 1.5 for additional details.

All data collected are to be recorded on the appropriate eCRF.

All efforts should be made to ensure subject comfort during study procedures. Procedures should be performed in an age appropriate setting (pediatric unit or clinic) with caregivers present where permitted by the local institution. Topical, local or general anesthetic agents, administered by appropriately trained personnel, should be deployed to minimize pain.

Additional details for study procedures, including sample collection, are described in the Study Manual of Operations or Laboratory Manual and other manuals as appropriate for this study.

In acknowledgement of hospital, local, state, or national government restrictions or other site related factors caused by unavoidable circumstances, such as the COVID-19 public health emergency, which may prevent investigators from conducting the study according to the Schedule of Activities at the clinical study site, investigators may seek approval from the medical monitor to continue patients in the study despite departure from the Schedule of Activities. Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for patients to continue. In evaluating such requests, the medical monitor will give the highest priority to the safety and welfare of the subjects. For patients that are impacted any procedures not conducted per the original study plan will be documented in the study records.

When approval is given for a patient to miss an in-person study visit, a study site physician will speak directly with the parent(s)/LAR(s) of the patient by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status. During this contact, the study site physician or other qualified site staff should conduct the following assessments: AE/SAE collection and concomitant medication documentation. Assessments that cannot be completed during the protocol specified window will be considered missing data and such departures will be recorded in the study records. Alternatively, sites may seek approval to extend the visit window in order to conduct an on-site visit.

8.1.1 Screening Period

Screening (-28 to -1 days)

The Screening Period is from -28 to -1 days and assessments may take place across several days during this period to allow an appropriate time frame in which to complete all procedures and confirm study eligibility. Screening procedures beginning with informed consent will be performed as outlined in Table 1 and will be completed prior to enrollment. The Screening Period will allow for the determination of eligibility of each subject's inclusion into the study. Subjects who meet all study entrance criteria will be enrolled in the study pending sponsor and investigator approval.

A screen failure is a subject who has given informed consent and failed to meet all of the inclusion criteria and/or has met at least 1 of the exclusion criteria. Patient eligibility according to the study inclusion and exclusion criteria will be assessed during the Screening period. Sites will be allowed one opportunity to rescreen any patient who fails initial screening or withdraws consent prior to device implantation. If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study.

All AEs occurring after completion of informed consent must be recorded in the source documents and eCRF. Any abnormal laboratory results at screening should be discussed with the medical monitor. Normal ranges for vital signs and key ECGs parameters are presented in Appendix 7.

8.1.2 Surgical Implantation of IDDD, Day -10 to 28

Procedures for implantation are detailed in the device's IFU manual. Standard hospital procedures for surgery will be followed and the subject may be under anesthesia for this procedure. Prior to implantation, individual neurosurgeons may order additional imaging to estimate the canal size and spinal cord conus location in younger patients. After implantation, a leak test is performed by the neurosurgeon to ensure a sealed system is in place. X-rays may be performed as needed, particularly for younger subjects, throughout the study to confirm placement of the device and/or evaluate a nonworking catheter. In order to facilitate healing, subjects should remain under observation in the hospital setting until deemed clinically stable by the investigator and should limit activity for 24 hours after IDDD implantation. To allow for healing, a waiting period of 3 to 5 days after device implantation must be observed before the first administration of SHP611 may occur. This waiting period must also be observed after any subsequent re-implantation or revision of the IDDD. Examination of both the port and catheter track will be performed before each IT injection, which includes aspiration of CSF via the port.

Surgical implantation of the IDDD is allowed from 10 days before to 28 days after the first dose of SHP611. If use of the IDDD is not possible a lumbar puncture (LP) may be utilized to obtain CSF samples and/or to deliver investigational drug product. As LP can be painful, it is anticipated that LP may have to be performed with anesthesia support at the discretion of the investigator. No more than two attempts of LP should be made for a single administration of study drug. Subjects undergoing LP should be monitored closely following the procedure for signs of infection or spinal fluid leakages.

After 12 consecutive LPs, the feasibility of further use of LPs for that subject will be determined at the discretion of the investigator and the Takeda medical monitor and documented in a note to file.

8.1.3 Baseline Assessments (prior to first administration of SHP611; Day -1 to 0)

Baseline assessments must be completed prior to the first administration of SHP611 at Week 0. Refer to Section 1.3 for details on which assessments are to be completed.

8.1.4 Treatment Period

8.1.4.1 Treatment Period - Study Week 0

SHP611 will be administered weekly, and the first administration of SHP611 will be considered Week 0. Examination of both the port and catheter track will be performed before each IT injection, which includes aspiration of CSF via the port.

Please refer to the Manual of Operations for details regarding investigational drug product administration.

Week 0 and other treatment period assessments (Table 1, Table 2, and Table 3) and collection of samples must be performed prior to the administration of anesthesia and SHP611.

8.1.4.2 Treatment Period – Remaining Study Visits

Table 1, Table 2, and Table 3 detail the Treatment Period assessments to be performed at each visit. Most assessments and collection of sampling should be performed prior to the administration of anesthesia and SHP611 with the exception of X-rays or assessments designated as post-administration.

Study Week Visits 0, 5, 9, 13, 26, 40, 53, 79, and 106 during the primary treatment period of the study must be conducted at the main site (shaded columns in the Schedule of Activities). For the extension period of the study, 6-month visits, EOT, EOS, and Safety Follow-up must be conducted at the Main Site (shaded columns in the Schedule of Activities).

Study Week Visits 1-4, 6-8, 10-12, 14-25, 27-39, 41-52, 54-78, and 80-105 may be conducted at local sites (unshaded columns in the Schedule of Activities) if subjects' parent(s) or legally authorized representative(s) provide a separate written informed consent/assent to participate in study procedures to be conducted at local sites prior to the conduct of these procedures. For the extension period, Weekly Visits may be conducted at local sites (unshaded columns in the Schedule of Activities) if subjects' parent(s), or legally authorized representative(s) provide a separate written informed consent/assent to participate in study procedures to be conducted at local sites prior to the conduct of these procedures. At the discretion of the investigator and upon discussion of the investigator with the Medical Monitor, if it is determined that the subject is unable to perform an efficacy outcome assessment, such as GMFC-MLD, GMFM-88, ELFC-MLD, GIMF-C and GIMF-S, CIQ, ITQOL, WPAI, and EDACS, these assessments may be skipped for a visit.

8.1.5 Final Visit End of Study (EOS)

Table 3 details the comprehensive assessments that will be conducted at the EOS Visit.

Subjects may continue in the extension period of the study, where they may continue to receive treatment with SHP611 for an extended duration of time.

If a subject discontinues from the study earlier than EOS, every effort should be made to complete assessments for the EOS and the safety follow-up visits.

8.1.6 Safety Follow-up

The safety follow-up for this protocol is 14 days after EOS.

At the end of this study there will be a safety follow-up visit to conduct a symptom-directed physical exam and query for serious adverse events (SAEs), adverse events (AEs), and concomitant treatments. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Appendix 3.2). This visit is to occur for all subjects, regardless if administration of study drug is discontinued for any reason or the IDDD remains in the subject. No additional safety follow-up of such subjects will be required.

8.1.7 Additional Care of Subjects after the Study

No aftercare is planned for this study.

8.2 Study Assessments

8.2.1 Demographic and Other Baseline Characteristics

Subject demographic information including gender, age, and race will be collected prior to the subject receiving the first dose of investigational product.

Demographic information will be recorded for each subject and will include the following information: gender, age, race, and ethnic origin. MLD-related history will be recorded and will include age at onset of first MLD symptoms, age at MLD diagnosis, genotype, and family history of MLD. A copy of the subject's medical record showing documentation of a gait disorder attributable to MLD by 30 months of age must be included in the source documentation. Medical records for family members of the subject may be requested.

8.2.1.1 Medical and Medication History

Medical and medication history will be collected and recorded in the subject's source documents. The medical history must include history of non-pharmacologic treatments and history of any medication hypersensitivities, as well as document any gait disorder attributable to MLD by 30 months of age.

Medical and surgical history will include the following systems: head, neck, eyes, mouth, ears, nose, throat, chest, lungs, cardiovascular, abdomen, gastrointestinal, genito-urinary, skin, musculoskeletal, neurological, and psychiatric system.

8.2.1.2 MLD Diagnosis

Sample collection and assays for leukocyte ASA enzyme activity, urine sulfatide, and genotype determination will be performed to confirm the diagnosis of MLD. Abnormal ASA enzyme activity and urine sulfatide concentration consistent with a diagnosis of MLD is required for study eligibility, but genotype results are not. If ASA enzyme activity and urine sulfatide results from a reliable lab are available at screening, these lab results may be used for the eligibility criteria; however, samples for leukocyte ASA enzyme activity and urine sulfatides must still be collected at screening.

8.2.1.3 Cross Reacting Immunologic Material (CRIM)

A blood sample will be obtained from each subject at Screening and the leukocytes from it will be tested for the presence of ASA CRIM. In subjects weighing ≥11.5 kg, 10 cc will be collected for CRIM evaluation; 3 cc will be collected for CRIM evaluation in subjects weighing <11.5 kg.

The peripheral blood mononuclear cells (PBMC) will be isolated and the tests will be performed at a Takeda designated test facility.

8.2.2 Efficacy

For all assessments to be conducted in this study, refer to the relevant manual for detailed instructions.

8.2.2.1 Gross Motor Function Classification in MLD

The GMFC-MLD instrument was developed specifically for MLD patients, based on experiences with the GMFCS instrument used for cerebral palsy (Palisano et al. 1997). The GMFC-MLD is applicable from the age of 18 months onwards and can be assessed retrospectively based on medical records. It is an established and reliable tool for the standardized assessment of gross motor function in MLD which can be used to classify the stages of disease progression. The GMFC-MLD covers clinically relevant gross motor stages occurring in patients with MLD and consists of 7 categories based primarily on locomotion (see Table 5), and in more advanced disease also includes sitting and other motions.

Table 5 Gross Motor Function Classification in MLD

Category	Gross Motor Function
Category 0	Walking without support with quality of performance normal for age
Category 1	Walking without support but with reduced quality of performance, ie instability when standing or walking
Category 2	Walking with support. Walking without support not possible (fewer than five steps)
Category 3	Sitting without support **and** locomotion such as crawling or rolling. Walking with or without support not possible
Category 4	(a) Sitting without support but no locomotion **or** (b) Sitting without support not possible, but locomotion such as crawling or rolling
Category 5	No locomotion nor sitting without support, but head control is possible
Category 6	Loss of any locomotion as well as loss of any head and trunk control

Source: (Kehrer et al. 2011a). Note: The term 'category' is used as 'level' in the source.

Initial assessment of gross motor function using the GMFC-MLD scale will be conducted by local, trained healthcare professionals and video-recorded. Videos of GMFC-MLD assessments will be evaluated by central video reviewers for primary scoring of gross motor function on the instrument.

8.2.2.2 Gross Motor Function Measure-88

The GMFM-88 is a clinician-evaluated assessment of motor function across five dimensions: 1) lying and rolling 2) sitting 3) kneeling and crawling 4) standing and 5) walking, running, and jumping. GMFM-88 will be performed by a trained physiotherapist. Scoring is based on the percentage of accomplished tasks within each of the dimensions, and a total score is calculated by averaging each of the dimension scores. Each of the 88 items is rated by a trained evaluator on a 4-point scale: 0=does not initiate; 1=initiates; 2=partially completes; and 3=completes. The GMFM-88 was originally developed to assess gross motor function in patients with cerebral palsy (from 5 months through 16 years old) by evaluation of a broad range of tasks that could be accomplished independently by a child of 5 years of age without any motor disability (Russell et al. 2013). GMFM-88 total scores range from 0% (no mobility) to a score of 100%, which can be obtained by an average child, 5 years of age or older with unimpaired motor abilities. Although the GMFM-88 is widely used for patients with cerebral palsy, the assessment has also been used across numerous other populations, including patients with traumatic brain injury (Linder-Lucht et al. 2007), Down syndrome (Russell et al. 1998), and spinal muscular atrophy (Iannaccone and Hynan 2003), among others (Russell et al. 2013).

Assessments of gross motor function using the GMFM-88 will be video-recorded.

8.2.2.3 Global Impression of Motor Function Change and Severity

The GIMF-C and GIMF-S will be used to evaluate the minimal clinically important change in GMFM-88 response to IT administration of SHP611. Each questionnaire contains 6 items addressing the clinician's global impression of change or severity in the 5 GMFM-88 dimensions and overall. The GIMF-C assessment will be compared to baseline.

8.2.2.4 Alberta Infant Motor Scale (Group D only)

The AIMS will be used to assess motor function in subjects <18 months of age. This observational assessment scale was constructed to measure gross motor maturation in infants from birth through independent walking. Fifty-eight items are generated and organized into 4 positions: prone (21 items), supine (9 items), sitting (12 items), and standing (16 items). Each item is scored as 'observed' or 'not observed' and all items combined describe 3 aspects of motor performance: weight-bearing, posture, and antigravity movements (Piper et al. 1992).

8.2.2.5 Note Documenting Current Motor Function

At baseline and each main site visit, the investigator or sub-investigator will document the subject's current motor function, including a description of observations that support the GMFC-MLD category assigned at that visit, in a text note entered into the source documents.

8.2.2.6 Expressive Language Function Classification in MLD (ELFC-MLD)

The ELFC-MLD (Table 6) is a 5-category rating system that was developed by researchers to describe the regression of language abilities of patients with late infantile and juvenile MLD (Kehrer et al. 2014).

Table 6 Expressive Language Function Classification-MLD

Category	Description
E0	Communicates in complete sentences at a quality and performance normal for age
E1	Communicates in complete sentences at a reduced quality of performance for age
E2	Cannot communicate in complete sentences, but able to use 2-word phrases
E3	Cannot communicate 2-word phrases, but able to use single, meaningful words/ideas
E4	Complete loss of expressive language

Source: (Kehrer et al. 2014)

8.2.2.7 The Eating and Drinking Ability Classification System (EDACS)

The EDACS (Table 7) is a 5-category rating system that was developed by researchers to describe feeding and swallowing abilities in patients with cerebral palsy. It has been shown to be valid and highly reliable (Benfer et al. 2017; Goh et al. 2018; Sellers et al. 2014; Tschirren et al. 2018).

Table 7 The Eating and Drinking Ability Classification System

Level	Description	Level of Assistance
I	Eats and drinks safely and efficiently	Independent
II	Eats and drinks safely but with some limitations to efficiency	Requires assistance
III	Eats and drinks with some limitations to safety; there may be limitations to efficiency	Totally dependent
IV	Eats and drinks with significant limitations to safety	Totally dependent
V	Unable to eat and drink safely – tube feeding may be considered to provide nutrition	Totally dependent

Source: (Sellers et al. 2014)

8.2.2.8 Anesthesia

Anesthesia may be required for certain procedures (at the discretion of the investigator). Any anesthesia used will be recorded as Concomitant Medications (see Section 6.6).

Administration of anesthesia may be given prior to obtaining CSF by lumbar puncture, if the use of the IDDD is precluded.

Anesthesia may also be administered prior to performing the following:

- Brain MRI and MRS
- Lumbar puncture
- Implantation of the IDDD
- Injection of SHP611

The physical examination, GMFC-MLD, GMFM-88, AIMS, ELFC-MLD, auditory, and visual assessments **must** be performed **prior** to the administration of anesthesia, or after the patient has fully recovered from anesthesia.

8.2.2.9 Magnetic Resonance Imaging and Brain Magnetic Resonance Spectroscopy

Each subject will have an MRI and MRS of the brain (may be performed under anesthesia), using methods specified in the Imaging Protocol contained in the Imaging Manual. Review of the images will focus on MLD-related abnormalities with measurement of metabolite levels (N-acetylaspartate, choline, and creatine) in regions of interest, eg, the frontal and parieto-occipital white matter, corpus callosum, centrum semiovale, and occipital cortex. Other metabolites and regions of interest may be explored.

8.2.3 Safety

8.2.3.1 Physical Examination

A physical examination will be performed by the investigator. A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, neurological systems, and an evaluation of the port and catheter track. A symptom-directed physical examination will include at a minimum, neurological systems and other assessments at the discretion of the investigator. An auditory and vision exam will also be conducted. Abnormalities will be recorded in the subject's source documents.

Height or length (cm) measured supine on a standard measuring board and weight (kg) will be recorded and used to calculate growth velocity. The clinical site staff will be instructed to use calibrated scales for weight measurement. It is recommended that the same scale be used at the clinical site for all subjects at each specified time point during the study. Body weight and height measurements will be used to calculate the body mass index (BMI). Head circumference will be measured in a uniform manner for all subjects.

If results of the physical examination show clinically significant worsening from the previous visit, the change will be documented as an AE/serious AE (SAE) in the eCRF and will be followed as an AE consistent with the procedure outlined in Appendix 3. Clinical significance is defined as any variation in physical findings that has medical relevance resulting in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

Abnormalities identified at the Screening Visit will be documented in the subject's source documents and on the medical history eCRF. Changes after the Screening Visit will be captured as AEs on the AE eCRF page, as deemed appropriate by the investigator.

8.2.3.2 Adverse Events

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. Refer to Appendix 3.1 for AE definitions, assessment, collection time frame, and reporting procedures. Refer to Appendix 3.2 for Collection of Adverse Events.

8.2.3.3 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be obtained at each visit and recorded on the eCRF. Blood pressure should be determined by cuff. Note that height, weight, and head circumference will be recorded as part of vital signs, but will be done less frequently than vital signs per the Schedule of Activities (Table 1, Table 2, and Table 3).

The investigator will assess whether a change from baseline in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE. Normal ranges for vital signs are presented in Appendix 7.

8.2.3.4 Clinical Laboratory Tests

All clinical laboratory tests will be performed according to the laboratory's standard procedures. Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. The investigator will assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Blood, urine, and CSF samples will be collected as described in the Laboratory Manual in the section for clinical laboratory testing. A complete list of the clinical laboratory tests to be performed is provided in Appendix 2.

8.2.3.5 Immunoassay for Anti-SHP611 Antibodies

Samples will be collected for the determination of anti-SHP611 antibodies in serum and CSF. Anti-SHP611 antibody testing will follow a tiered approach per regulatory guidance and industry best practices.

8.2.3.6 Electrocardiogram

The eligibility of the subject will be based on the assessment of the electrocardiogram (ECG) by the investigator. If abnormal results are observed, the investigator, in consultation with the appointed medical monitor, will reconfirm the subject's eligibility to continue. Normal ranges for key ECG parameters are presented in Appendix 7.

8.2.4 Intrathecal Drug Delivery Device Considerations

8.2.4.1 Intrathecal Drug Delivery Device Implantation, Replacement, or Revision

The IDDD will be surgically implanted at the clinical site. Procedures for implantation are detailed in the device's IFU Manual. Standard hospital procedures for surgery will be followed; the patient may be under general anesthesia for this procedure. It is planned that device explantation will occur at the main site unless urgent device removal is medically required to be performed locally or patient travel to the main site is medically inadvisable.

An additional medical device, the catheter passer, is necessary for the implantation procedure for patients receiving the SOPH-A-PORT Mini S. The catheter passer is a sterile, single-use device that will be used in the subcutaneous placement of the catheter. The Phoenix Neuro Disposable Catheter Passer, manufactured by Sophysa, is CE-marked in the European Union and cleared under K853370 in the United States (US) and may be provided; however, use of other catheter passers compatible with the SOPH-A-PORT Mini S is allowed.

At a minimum, the date of the implantation and spinal placement will be documented on the eCRF. If the device becomes nonfunctional at any time during the study, it will be removed and may be replaced or revised as appropriate.

8.2.4.2 X-ray Verification of Intrathecal Drug Delivery Device Placement

A post-operative X-ray check of the IDDD will be performed following surgery to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. X-rays may be performed to check placement of the device, as needed, throughout the study. An X-ray will be performed at the end of the study (to verify that the IDDD is in the correct position).

At a minimum, the date of the X-ray verifying correct IDDD placement and the date that the X-ray is read will be documented on the eCRF. If the device requires revision or replacement during the study, additional X-rays will be taken to document proper positioning of the device.

Fluoroscopy should be used during device implantation procedures.

8.2.4.3 SOPH-A-PORT Mini S Assessments in CSF and Serum

As part of the assessment of the SOPH-A-PORT Mini S, it may be necessary to determine the levels of leachables from the device into the CSF and blood. The subject's parent(s) or legally authorized representative(s) has/have the option to allow testing of residual CSF and serum samples to determine the levels of leachable materials related to the IDDD.

8.2.4.4 Cerebrospinal Fluid Sampling Procedure

Cerebrospinal fluid will be obtained from patients via an IDDD in aliquots appropriate for the specified analyses prior to each IT injection. If on a scheduled day of dosing, the use of the IDDD is precluded, the CSF samples may be obtained by LP, under anesthesia (if deemed necessary by the investigator). Instructions for CSF withdrawal are included in the Manual of Operations. If it is not possible to withdraw CSF through the IDDD, study drug should not be administered through the IDDD. Assessment of the IDDD should occur as described in the IDDD manual.

CSF samples collected will be analyzed for cell count, protein, glucose, SHP611 levels, anti-SHP611 antibodies, and biomarkers (sulfatide, lysosulfatide, and exploratory biomarkers (eg, neurofilament light chain, glial fibrillary acidic protein, Tau and Ubiquitin C-terminal hydrolase L1) according to the Schedule of Activities (Table 1, Table 2, and Table 3).

Additional biomarker testing and additional testing related to the SOPH-A-PORT Mini S may be performed with any residual volume of sample, which will determine the CSF levels of other analytes.

8.2.4.5 Intrathecal Drug Delivery Device Removal

If at the time of a scheduled dosing, due to a device-related issue it is not possible to aspirate CSF prior to dose administration, administer a full medication dosage using the standard administration steps detailed in the device's IFU, or flush the system following dose administration, the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a partial or full device revision or removal, the IDDD will be declared a device failure, starting from the date of the initial malfunction. The IDDD will then be surgically removed or revised and a new device and/or device components will be re-implanted at the earliest possible opportunity, preferably at the same time.

A waiting period of 3 to 5 days after device re-implantation or revision must be observed before the administration of SHP611 may resume.

Details of the device removal will be recorded in the subject's eCRF. Refer to the relevant IFU for further details.

Subjects are to have the IDDD removed when they discontinue from or complete the study, unless the subject is continuing to receive treatment through another mechanism (eg, commercial availability of the product) or the investigator determines that the IDDD should not be removed from the subject based upon a safety assessment and the IDDD (full or partial) should remain in the subject.

If at any time during the study, administration of the study drug is discontinued for any reason and the investigator determines that the IDDD should not be removed from the subject, then the subject will have a safety follow-up visit via telephone upon completion of their last treatment period visit. When the IDDD is explanted, an incision check should occur within 2 weeks (±7 days) after surgery.

8.2.4.6 Pharmacokinetics

Blood and CSF samples for determination of SHP611 concentration will be collected at the following nominal times.

Blood samples for PK will be obtained per the Schedule of Activities (Table 1, Table 2, and Table 3).

The concentration of SHP611 in CSF will be assessed as indicated in the Schedule of Activities (Table 1, Table 2, and Table 3). The CSF samples will be drawn prior to IT injection and post injection through the IDDD. Should the IDDD become clogged, undergo mechanical complications, or otherwise not be accessible, the CSF sample may also be obtained by LP.

The effect of anti-SHP611 antibodies on SHP611 concentration-time profiles and PK parameters will be evaluated, if applicable.

- At Weeks 0 and 106, serum samples will be drawn for PK assessments within 1 hour prior to IT administration and then drawn at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT administration. At other visits, samples will be collected predose to assess attainment of steady state.
- At Weeks 0 and 106, CSF samples will be collected within 1 hour prior to IT administration and then at 6 and 24 hours (+30 minutes) after administration; however, if the subject's IDDD is not functioning or the subject is receiving doses via LP, the 6 and 24 hour samples do not need to be collected. At other visits, samples will be collected predose.

8.2.4.7 Sulfatide/Lysosulfatide Biomarker Assessments

Samples of blood, urine, and CSF will be collected from subjects according to the Schedule of Activities (Table 1, Table 2, and Table 3) and will be analyzed for determination of concentrations of sulfatides and lysosulfatide in CSF, and sulfatides in serum and urine.

8.2.4.8 Additional Biomarker Assessments

Additional biomarker analyses may be performed at the Takeda research laboratory or at Takeda-designated laboratories. A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Samples of blood, urine, and CSF will be collected from subjects participating in this trial according to the Schedule of Activities (Table 1, Table 2, and Table 3) and stored for biomarker studies that may elucidate the pathogenesis of MLD and help to better characterize the response to the experimental treatment.

Testing of residual blood, urine, and CSF samples for additional biomarker research is optional. The subject and/or subject's parent(s) or legal representative(s) has the option to allow this testing for additional research assessments.

The identification of biomarkers that reflect the disease process and/or treatment response represent a potentially important exploratory aspect to this study that may contribute to subject and/or dose selection for future trials. Given our incomplete understanding of the pathogenesis of MLD, the range of biomarkers that might be informative is extensive. The CSF, serum, and urine samples will be examined for accumulation of sulfatides (and lysosulfatide in CSF), which are known to reflect the primary biochemical lesion in MLD.

Additional testing of residual sample volumes may include biomarkers that reflect the known pathological processes in MLD – demyelination, neuroaxonal degeneration, and neuroinflammation – as well as markers of lysosomal dysregulation (lysosomal proteins, enzymes, and their substrates).

Urine and serum will be examined in parallel with CSF samples to:

- Assess CSF/blood quotients for biomarkers of interest to provide insight into their CNS versus peripheral provenance
- Identify potential peripheral urinary and/or serum biomarkers that might reflect CNS disease and/or treatment response

8.2.4.9 Genetics

All subjects in this study will undergo genotyping of the ASA gene.

In addition, Takeda intends to apply genomic research across the SHP611-201 development program. The intent of this exploratory research is to aid in biomarker development, design and interpretation of clinical studies, exploration of guided treatment strategies, and to increase disease understanding.

To support these aims, subjects will have the option to provide additional blood samples. Donation of samples is optional, has no impact on participation in the main study, and may require a separate informed consent. To ensure subject confidentiality, samples will be stored and analyzed in a de-identified format. Samples will be stored in biorepositories for up to 15 years.

The scope of any present and/or future research will be restricted to candidate gene/proteins/markers related to the disease and/or responses to SHP611-201 and background products and concomitant medications.

The intent of this research is not to return results to subjects, unless required to do so by law. Subjects can request return of individual results, but it will not be possible to interpret these. No record of participation in any pharmacogenomic research, or any results derived from it should be recorded in a subject's personal medical records.

Any results of this exploratory research will be reported separately from the main clinical study report. Results may be used internally to help support the design of additional clinical studies, form part of scientific publication, or be made known to the regulatory authorities as part of a new drug application. The sponsor has no obligation to perform this additional exploratory research.

For additional information and details, see Appendix 4.

8.2.4.10 Health-related Quality of Life (QoL) and Other Assessments

Further information concerning health-related QoL assessments included in the study is provided in Appendix 5.

Caregiver Impact Questionnaire (CIQ)

Caregiver burden will be assessed by the Caregiver Impact Questionnaire (CIQ). The CIQ includes 30 items in total and covers the key areas of impact for caregivers of patients with late infantile and juvenile MLD, including: 1) impact on relationships, family, social life, and leisure activities; 2) impact on personal time and daily activities; 3) psychological impacts; 4) impact on physical health; and 5) impact on finances and productivity. This measure is still being developed and scoring has not been finalized; therefore, the data will be collected and summarized descriptively, with the results providing an opportunity to contribute to the recommended scoring for studies.

Infant Toddler Quality of Life Questionnaire – 97 items (ITQOL-97)

Health Related Quality of Life (HRQOL) will be assessed using the Infant Toddler Quality of Life Questionnaire – 97 items (ITQOL-97). The ITQOL-97 was developed for use in infants and toddlers at least 2 months of age up to 5 years. It measures infant/toddler focused concepts and parent-focused concepts. Infant/toddler concepts include overall health (1 item), amount of limitation in physical activities (10 items), satisfaction with development (10 items), amount, frequency of bodily discomfort and the extent to which pain/discomfort interferes with normal activities (3 items), frequency of certain moods and temperaments (18 items), perceptions of current, past and future behavior (12 items), overall behavior (1 item) and frequency of behavior problems (15 items), perception of current, past and future health (11 items), perceptions of changes in health over the past year (1 item). Parent-focused concepts include amount of worry experienced by parent (7 items), amount of time limitations experienced by parent (7 items) and rating time of family's ability to get along with one another (1 item). For each concept, item responses are scored, summed, and transformed to a scale from 0 (worst health) to 100 (best health).

Healthcare Utilization Questionnaire (HCUQ)

Measures of health-services utilization will include the number of hospitalizations, days in hospital, and reasons for admission as well as use of selected MLD-related procedures including use of a feeding tube, intubation, and type of respiratory support.

Utilization should be ascertained since the last study visit. Study visit is defined as that occurring at the main study site.

Work Productivity and Activity Impairment Questionnaire (WPAI) – Specific Health Problem V2.0

The Work Productivity and Activity Impairment (WPAI) Questionnaire is a well-validated instrument to measure impairments in work and activities. It measures absenteeism, reduced performance at work, and reduced duration of work. It has been validated to quantify work impairments for numerous diseases such as asthma, psoriasis, irritable bowel syndrome, ankylosing spondylitis, and Crohn's disease. In addition, it has been used to compare work impairments between treatment groups in clinical trials or between subjects with different disease severity levels (Zhang et al. 2010).

Developmental and MLD Symptom Assessments

Developmental status and signs and symptoms of MLD will be assessed as indicated in the Schedule of Activities (Table 1, Table 2, and Table 3).

All assessments will be administered by qualified study personnel.

Volume of Blood to Be Drawn from Each Subject

It is expected that the cumulative maximum total volume of blood drawn per subject over the duration of this study will be approximately 162.5 mL.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the maximum total volume drawn over the course of the study per subject should not exceed approximately 162.5 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include descriptions of sensitivity analyses for main efficacy outcomes, and a description of how missing, unused and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using Version 9.0 (or newer) SAS® (SAS Institute, Cary, NC 27513) on a suitably qualified environment.

9.2 Planned Analysis, Adaptive Design, and Data Monitoring Committee

The primary analysis will be performed after all subjects complete the primary treatment period of the study; the database will be locked with the results presented in a clinical study report (NB: **the sponsor will remain blinded to postbaseline efficacy-related data until database lock**). Following completion of the extension period, the database will be locked again and the results of the entire study (primary treatment and extension periods) will be described in the final clinical study report.

An external independent Data Monitoring Committee (DMC) will be involved in the conduct of this study. The purpose of the DMC is to review the data pertaining to safety, tolerability, and benefit/harm of the study therapy for the duration of the study. The DMC will oversee both administration of IT SHP611 and device safety. The DMC will be notified of IDDD failures and related complications on a periodic basis. Further details regarding the DMC can be found in the DMC Charter, which will be available prior to the administration of investigational product.

9.3 Sample Size and Power Considerations

Per original Protocol, sample size was calculated based on the response in Group A, (ie, the maintenance of gross motor function at Week 106, evaluated as no greater than 2 categories decline from baseline in GMFC-MLD), and at least 12 paired completers is required to detect a treatment difference for a desired power of 90%, using McNemar's test at a 2-sided significance level of 0.05, with the assumption that the response rates in Group A of current study and the matched external control group are 65% and 10% respectively. Furthermore, to adjust for potential unmatched and early discontinuation of subjects, a total of 16 subjects were originally planned to be enrolled (19 enrolled) into Group A of the current study. As the GLIA-MLD external control group for Group A cohort was expected to be large, efficient matching was plausible and incorporated in the assumptions.

Type I error and power were assessed for the time to event primary endpoint for sample sizes similar to that planned in the original protocol, through simulations using an interval censoring approach. Comparable assumptions were made on the response rates for the time to event primary endpoint in simulations. The response rates (ie, proportion of subjects not reaching GMFC-MLD category 5 or higher, or death) at Week 106 for Group A in the current study and the matched external control group are 65% and 10%, respectively. The encounter structure from a subset of external control group for Group A subjects in the natural history study was considered. A simulated event time was randomly matched to a GLIA-MLD encounter schedule and was considered censored if it could not be observed within Week 106 under the matched schedule. The event time was assumed to follow a Weibull distribution, with a range of compatible shape parameters that allow approximation of the target response rates of 65% and 10% in the two groups, and a 25% censoring proportion for the GLIA-MLD control group. The type I error was preserved well. The power is assessed to be approximately between 71% to 82%. Matching efficiency is not assumed in the simulations.

9.4 Statistical Analysis Set(s)

Analysis Populations

- The Screened Set will consist of all subjects who have signed informed consent
- The Safety Analysis Set will consist of all subjects from Study SHP611-201 (Groups A-F) who receive at least 1 dose of SHP611, or subjects who have undergone the IDDD implantation procedure
- The Full Analysis Set (FAS) will consist of all subjects from the SHP611-201 Safety Analysis Set who receive at least 1 dose of SHP611 and have at least a screening GMFC-MLD assessment
- The modified Full Analysis Set (mFAS) will consist of all subjects from Group A in the FAS and the matched external control subjects for Group A from GLIA-MLD natural history study obtained after matching as described in the SAP
- The Pharmacokinetic (PK) Analyses Set will consist of all subjects from the SHP611-201 Safety Analysis Set who receive at least 1 dose of SHP611 and have at least 1 postdose measurable [ie, not below quantifiable limits (BQL)] concentration of SHP611 in serum or CSF
- The Immunogenicity Analyses Set will consist of all subjects from the SHP611-201 Safety Analysis Set who receive at least 1 dose of SHP611 and have at least 1 anti-SHP611 antibody assessment with reportable result in serum or CSF

Extension period

The same analysis populations, as in the primary treatment period, will be used for the extension period.

Device-related analyses will be conducted in the subset of subjects in the Safety Analysis Set who have the device implant procedure performed.

9.5 Efficacy Analyses

9.5.1 Matched External Control

The efficacy of SHP611 in SHP611-201 Group A will be compared to matched external control group data from untreated MLD subjects in the Global Leukodystrophy Initiative natural history study (GLIA-MLD).

For Group A subjects in this study, the time to event (TTE) starting point is set at the Baseline visit where patients receive the first dose of SHP611. The external control group for Group A subjects will be selected from the GLIA-MLD database using appropriate filtering criteria. For each external control subject, a collection of "qualifying encounters" when the subject is in the appropriate age range for Group A and GMFC-MLD category of 1 or 2, will be identified and an appropriate TTE starting point will be defined. Details of this definition will be provided in the SAP.

For this matched external control study, an appropriate matching process will be applied to balance the baseline observed characteristics between the treatment and matched external control groups. Matching diagnostics will be conducted. Further details will be provided in the SAP.

An unblinded statistical group outside of the Sponsor's SHP611-201 statistical analysis team will be formed to work on the available external control group data, in order to identify potential prognostic baseline variables and reduce potential matching biases, and the final matching variables recommended by this exercise will be specified in the SAP.

9.5.2 Multiplicity Adjustments

In order to protect the study-wide type I error at the 1-sided 0.025 level for testing the primary and secondary hypotheses, the Fixed-Sequence Test procedure will be applied. The hypotheses will be tested for the primary endpoint at the 1-sided 0.025 significance level first, and then all other efficacy endpoints will be tested in a prespecified order. A subsequent test for the secondary endpoints can only be reported as significant if all prior 1-sided tests are also found significant at the 0.025 level of significance. Details will be provided in the SAP.

9.5.3 Missing Data Imputations

For the primary and relevant secondary efficacy assessments, if a subject prematurely discontinues from the study, a "failure" response status will be assigned to the subject.

9.5.4 Primary Efficacy Endpoint

9.5.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is time to loss of locomotion, measured by progression to GMFC-MLD category 5 or higher, or death, whichever occurs first, up to Week 106, evaluated on subjects in Group A, and analyzed using the mFAS.

For the analysis of the primary efficacy endpoint, the time to event data for Group A and matched external control group up to Week 106 will be compared using the stratified log-rank test, where the matching identification created from the matching process will be used as strata. Interval censoring methods will be used, with event assumed to have first happened between the last visit/encounter prior to the event observation, and the visit/encounter when the event is first observed. The null hypothesis of the stratified log-rank test will be evaluated at the 1-sided 0.025 level of significance. Kaplan-Meier (KM) survival curves suitable for interval censoring data will be presented.

9.5.4.2 Sensitivity Analysis

As study drug dosing was affected by the COVID-19 pandemic, a sensitivity analysis will be conducted for Group A subjects who missed no more than two consecutive SHP611 doses due to COVID-19.

The details of the matching method and other sensitivity analyses will be specified in the SAP.

9.5.5 Analyses of Secondary and Exploratory Efficacy Endpoints

All inferential efficacy analyses will be based on the mFAS. All statistical tests will be 1-sided hypothesis tests performed at the 0.025 level of significance. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. Sensitivity analyses of the primary and secondary endpoints will also be based on the mFAS.

Descriptive analysis of efficacy endpoints for all groups (A-F) will be conducted over the FAS. For categorical variables, descriptive statistics will include n, frequency, and proportions/percentages.

Only exploratory statistical and graphical evaluations involving Groups B, C, D, E, and F may be conducted.

In general, Baseline for the treatment group is defined as the last assessment prior to the first administration of the investigational product, unless other clarification is made. For SHP611-201 subjects, the GMFC-MLD assessment at the Screening visit will be treated as the last clinically valid assessment prior to the administration of the investigational product. However, the TTE starting point in Group A subjects of SHP611-201 is set at the Baseline visit where subjects receive the first dose of SHP611.

For continuous variables, descriptive statistics will include the number of subjects with nonmissing values, mean, median, standard deviation (SD), minimum, and maximum values, unless specified otherwise. These will be tabulated by subject group and overall.

Means and medians will be presented to 1 more decimal place than the recorded data. The SDs will be presented to 2 more decimal places than the recorded data.

Where applicable, analysis of covariance, utilizing the corresponding baseline levels as covariate, will be utilized to assess the treatment effect for the parametric endpoints. Two-sided 95% Confidence Intervals will be constructed for the difference between the two comparator arms.

For the binary variables, descriptive statistics will include the counts and proportions of each value, including a missing category if applicable, unless specified otherwise. These will be tabulated by subject group and overall.

Where applicable, confidence intervals of two-sided 95% coverage will be constructed for the proportions for each comparator arm using the Clopper-Pearson method, and for the difference between the two comparator arms using the Wilson score method.

Categorical variables will be summarized in a contingency table by the number and percentage of subjects in each category, including a missing category if applicable. For categorical variables, descriptive statistics will include counts and proportions of each category, unless specified otherwise. These will be tabulated by subject group and overall.

All time-to-event variables will be presented with Kaplan-Meier survival curves, along with its 95% confidence bands. Where applicable, interval or right censoring method will be used for the time to event variables (details specific to endpoints will be provided in the SAP).

A full description of analyses for the secondary and exploratory efficacy endpoints will be included in the SAP.

9.6 Safety Analyses

Safety analysis

Treatment-emergent adverse events (TEAEs) are defined as AEs that occurred at or after the first dose of investigational product or device implant surgery (whichever occurs first) and through the last follow-up date plus 14 days (inclusive). Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events and percentage of TEAEs will be calculated overall, by system organ class (SOC), by preferred term, and by subject groups (A-F). TEAEs will be further summarized by severity, relationship to investigational product, disease and outcomes, the IDDD, the IDDD surgical procedure, anesthesia, and IT administration process. Adverse events related to investigational product, AEs leading to withdrawal, serious adverse events (SAEs; all SAEs reported by the investigator, those SAEs considered as Related and those considered as Not Related by Takeda shall be collected), and deaths will be similarly summarized and listed.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by subject groups (A-F) and visit. Potentially clinically important findings will also be summarized and listed. Descriptive summaries will also be provided for 12-lead ECG, CSF laboratory parameters (chemistries, cell counts), anti-SHP611 antibodies in CSF and serum. An integrated analysis of PK and PD will be used to evaluate the impact of antibodies.

SOPH-A-PORT Mini S assessments

SOPH-A-PORT Mini S assessments will be evaluated using assessments of device implantation, device function, device longevity, and AEs associated with the implant surgery or device. These data will be collected on the subject's electronic case report form (eCRF) from the time of implantation and continue throughout the study as long as the SOPH-A-PORT Mini S remains implanted.

9.7 Other Analyses

9.7.1 Pharmacokinetic Analyses

Pharmacokinetic analyses

All PK analyses will be performed using the PK Analysis Set.

Blood and CSF samples will be collected for determination of SHP611 levels after IT administration. SHP611 concentrations in serum and CSF will be determined using the validated Enzyme-Linked Immunosorbent Assays (ELISA) method which was used for the previous SHP611 clinical studies (HGT-MLD-070/HGT-MLD-071). SHP611 activity in CSF and serum will also be determined by validated Activity assays. The SHP611 Activity results will be used as surrogate marker for anti-SHP611 neutralizing antibodies and its impact on PK profile.

CSF parameters:

- Predose concentrations (C_{trough}) of SHP611 at Weeks 0, 5, 9, 13, 26, 40, 53, 79, and 106
- Postdose concentrations of SHP611 at 6 and 24 hours (Weeks 0 and 106)

Serum parameters:

- PK parameters after the first dose (Week 0) and after repeated doses (Week 106) of SHP611 determined by noncompartmental analysis will include but not limited to AUC, C_{max} and CL/F
- Predose concentrations (C_{trough}) of SHP611 at Weeks 0, 13, 26, 40, 53, 79, and 106

Details of the PK analysis including handling of PK data, parameters estimated, and presentation of PK data will be provided in the Clinical Pharmacology Analysis Plan (CPAP).

There will be no inferential statistical analysis of the PK data. Summary statistics (number of observations [N], mean, SD, coefficient of variation [CV%], median, maximum, minimum, geometric mean and geometric CV%) will be determined for all serum PK parameters and presented by bioanalytical method and visit for each group and for overall population. Serum and CSF concentrations at each nominal sampling time will also be summarized by bioanalytical method and visit for each group and for overall population using descriptive statistics. More details will be provided in the CPAP.

At the investigator's discretion a blood sample for PK analysis may be collected at the time of occurrence of an SAE or AE of special interest.

The serum and CSF concentration data from this study may be pooled with the data from Studies HGT-MLD-070 and HGT-MLD-071 in a population PK analysis. A population PK/PD and exposure-response analyses may be conducted using data from this study and reported separately.

9.7.2 Extension Period

Summary statistics for continuous variables will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using the number and percentage of subjects in each category, including a missing category if applicable.

Statistical inferences for the primary and selected secondary endpoints may be performed during the extension period.

The safety analyses will be performed using all data through Week 106 and the extension period up to EOS. Baseline will be defined as the same as that for the study (this baseline is clinically relevant for assessing the long-term safety and efficacy outcomes of extended treatment with IT SHP611).

The same analysis populations, as in the primary treatment period, will be used for the extension period.

10. APPENDICES - SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix 1 Regulatory, Ethical, and Study Oversight Considerations

Appendix 1.1 Regulatory and Ethical Considerations

This study is conducted in accordance with current applicable regulations including ICH E6, EU Directive 2001/20/EC, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

Appendix 1.2 Sponsor's Responsibilities

Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO\investigator as necessary.

Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

The timing for study registration and results summary posting must be in accordance with applicable local and national requirements.

Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

Appendix 1.3 Investigator's Responsibilities

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The investigator and any sub-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

Documentation and Retention of Records

Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the eCRF.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

Incorrect entries must be crossed with a single line as to not obscure the original entry. Corrections must be made adjacent to the item to be altered, initialed, and dated by an authorized investigator or designee as stated in the site delegation log. Overwriting of this information or use of liquid correcting fluid is not allowed.

The eCRFs should be approved by the investigator per study specifications and the sponsor's data delivery requirements.

Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's source documents.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor.

The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

Compliance to all Local, State, and National Controlled-substance Biohazard and Infectious Disease Regulations and Legislation

When using controlled substances, biohazardous material, or substances for infectious diseases, the investigator must at all times comply with all local, state, and national laws pertaining to registration and reporting with the appropriate regulatory body and control and handling of such substances.

Appendix 1.4 Data Management Considerations

Data Collection

Study SHP611-201 will be monitored according to GCP.

The investigators' authorized site personnel must enter the information required by the study eCRF Completion Guidelines or similar for all data requiring transcription of the source. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting.

A Monitoring Plan Addendum has been developed to provide guidance and study specific instructions to Project Management team and CRAs for the monitoring of the investigational sites in the study. This plan provides specific instructions in order to ensure oversight and consistency in study monitoring and site management activities in the context of unavoidable circumstances, such as the COVID-19 public health emergency.

Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan or similar. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

Appendix 1.5 Ethical Considerations

Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent, where applicable from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time. During the COVID-19 public health emergency, informed consent from a potential or current trial participant may be obtained via electronic informed consent (eIC) capabilities, or an electronic face-to-face consent interview when these individuals are unable to travel to the site.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the consent form (and assent form where applicable) that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement. Investigational product supplies will not be released until the CRO has received written IRB/EC approval.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue. If required by local law, substantial amendments to the protocol must also be approved by the appropriate regulatory agency prior to implementation.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. This can be the responsibility of the sponsor or investigator for sites within the EU; or for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs as required by IRB/EC procedures.

Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP611; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities. Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

Study Results/Publication Policy

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form. The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other investigators prior to publication or oral presentations of the study results on an individual basis. The site agrees not to publish or present the site's study results until such time as either the aggregate multi-site study results are published in a cooperative publication or for a period of one (1) year after termination or completion of the study at all participating sites, whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the sponsor by the site for review. Upon the sponsor's request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the sponsor time to file any patent application(s). All publications of the study results shall appropriately reference the multi-site study publication, if any, or the fact that the study results are a subset of data resulting from a larger multi-site study.

Takeda is committed to transparent dissemination of all scientific, technical and medical manuscripts generated from Takeda-supported research. Therefore, after 01 Jan 2018, Takeda will require the submission of all Takeda-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an investigator does not confer any rights to authorship of publications.

Appendix 2 Clinical Laboratory Tests

The following clinical laboratory and biomarkers tests will be performed. All blood samples will be collected via venipuncture. Subjects will be in a seated or supine position during blood collection.

List of Clinical Laboratory and Biomarker Tests

Hematology
- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Platelet count
- Red blood cell count
- White blood cell count with differential

Urinalysis
- Bilirubin
- Glucose
- Ketones
- Nitrite
- pH
- Protein
- Specific gravity

Cerebrospinal fluid
- Routine analysis
- Anti-SHP611 antibodies
- SHP611 levels

Serum SHP611 level and anti-SHP611 antibodies

Serum chemistry
- Albumin
- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Amylase
- Blood urea nitrogen (BUN)
- Calcium
- Creatinine
- Creatine kinase
- Gamma-glutamyl transferase (GGT)
- Inorganic phosphate
- Iron
- Lactate dehydrogenase (LDH)
- Magnesium
- Potassium
- Sodium
- Total bilirubin (BILI)

Biomarkers (urine, serum, and CSF)
- Sulfatides
- Lysosulfatides (CSF only)
- Other biomarkers (optional)

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Appendix 3.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this investigational product or medicinal product. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not causality is suspected (ICH Guidance E2A 1995).

Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the investigational product or medicinal product.

Serious Adverse Event

A serious adverse event (SAE) is any untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to investigational product or not and at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of hospitalization.
  Note: Hospitalizations that are the result of elective or previously scheduled investigations procedures or surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs.
- For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Results in a congenital abnormality/birth defect

- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include:
    - Bronchospasm associated with anaphylaxis requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.
    - Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

Unexpected Adverse Event

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB information as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB information as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form the pharmacological properties of a product.

Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (ie, including active-comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study protocol or product labeling; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected disease progression and are part of the efficacy or effectiveness data collected in the study. Significant worsening of symptoms should be recorded as an AE.

Preexisting conditions prior to randomization or initiation of study medication are described in the medical history, and those that manifest with the same severity, frequency, or duration after drug exposure, are not be recorded as AEs. However, when there is an increase in the severity, duration or frequency of a preexisting condition, the event must be described on the AE eCRF.

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value, vital sign, or ECG parameter is clinically significant and represents an AE.

Collection of ECG parameters is suggested to be performed in triplicates and conducted by a central laboratory for all study subjects.

Appendix 3.2 Collection of Adverse Events

All AEs/SAEs are collected from the time the informed consent document is signed until the defined follow-up period stated in Section 8.1.6. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered.

All AEs/SAEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained.

Appendix 3.3 Assessment of Adverse Events

Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity is captured as a new event. Worsening medical conditions, signs or symptoms present prior to initiation of investigational product, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the investigational product, and the dyspepsia becomes severe and more frequent after first dose a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source.

The medical assessment of severity is determined by using the following definitions:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related".

Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

Table A1 The following additional guidance may be helpful: Adverse Event Relationship Categorization

Related	The temporal relationship between the event and the administration of the investigational product is compelling enough and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

Outcome Categorization

The outcome of AEs must be documented in the source during the course of the study. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

If applicable, action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE eCRF.

Appendix 3.4 Safety Reporting

Reference Safety Information

The RSI for this study is the investigator's brochure which the sponsor has provided under separate cover to all investigators.

Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Takeda Global Drug Safety Department and the CRO/Takeda medical monitor immediately and within no more than 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Appendix 3.9) unless they result in an SAE.

The investigator must complete, sign, and date the Shire "Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol", verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested), and fax or e-mail the form to the Takeda Global Drug Safety Department. A copy of the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO/Takeda medical monitor using the details specified in the emergency contact information section of the protocol.

Medical Device Safety Reporting

All serious injuries and UADEs must be reported to the sponsor as an SAE in the same process as described above. Serious injury (SI) is defined as:

- Led to death
- Led to a serious deterioration in health of a patient, user, or others that
- Results in a life-threatening illness or injury
- Results in a permanent impairment/ damage of a body function or body structure
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in medical or surgical intervention to prevent permanent impairment/damage to body function/ structure.
- Led to fetal distress, fetal death or a congenital abnormality/birth defect

Appendix 3.5 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.1.6 and must be reported to the Takeda Global Drug Safety Department and the CRO/Takeda medical monitor immediately and within no more than 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Takeda Global Drug Safety Department immediately and within no more than 24 hours of the first awareness of the event.

Appendix 3.6 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms reported by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

Appendix 3.7 Fatal Outcome

Any SAE that results in the subject's death (eg, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

Appendix 3.8 Pregnancy

This study will not enroll subjects of child-bearing potential.

Appendix 3.9 Abuse, Misuse, Overdose and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Appendix 3.1.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category:

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- Misuse – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)

- Overdose – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally authorized representative/caregiver.

Appendix 3.10 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm, these do not constitute de facto deviation from the protocol. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the sponsor. In the event(s) of an apparent direct hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, and within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

Appendix 3.11 Device-associated Definitions

Device Revision (Partial and Full)

Partial device revision: surgical revision/replacement of one or more component(s) of the device; other component(s) of the original device remain implanted and are not affected (eg, port revision).

Full device revision: The device is removed (explanted) in its entirety, and a completely new device is implanted.

Device Malfunction

The device does not perform as intended, based on the description in the device's IFU, but does not require either a partial or full device revision.

Device Failure

The device irreversibly fails to perform as intended and requires either a partial or full device revision or removal.

Device Adjustment

Surgery of the device which does not result in partial or complete device revision or removal (eg, surgical exploration only or placement of additional sutures, tissue glue, and/or fascial repair).

Appendix 3.12 Expected Adverse Device Effects

A list of the adverse effects expected with the SOPH-A-PORT Mini S is reproduced below from the device's IFU.

Procedure-Related Complications

- Components handled improperly before, during, or after implantation
- Access port implanted incorrectly
- Catheter positioned improperly
- Injection through septum performed incorrectly
- Injection of incorrect medication through access port
- Injection outside the access port into pocket or subcutaneous tissue or extravasation
- Pocket seroma, hematoma, erosion, or infection

Intrathecal Access Complications

- Surgical complications such as hemorrhage or hematoma
- Infection of the implant site or catheter track
- Radiculitis or arachnoiditis
- Intrathecal space infection resulting in meningitis or encephalitis
- Bleeding
- Spinal cord damage or trauma to the spinal cord or nerve roots
- Post-lumbar puncture, cerebrospinal fluid (CSF) leak, leading to headache, or subcutaneous CSF collection
- Epidural instead of intrathecal placement of catheter
- Inflammatory mass resulting in neurological impairment, including paralysis
- Pain on injection
- Complications of anesthesia
- Pseudomeningocele

System-Related Complications

- Improperly positioned access port
- Erosion of the skin because of the underlying access port or the catheter
- Wound dehiscence
- Access port migration, fracture, breakage or occlusion
- Catheter damage, dislodgement, migration, disconnection, kinking or occlusion, fibrosis, or hygroma, resulting in tissue damage or a loss of or change in therapy, or other potentially serious adverse health consequences
- Catheter breakage and migration of residual catheter fragments, potentially resulting in serious adverse health consequences and the need for surgical removal
- Local immunological or fibrous reaction to the presence of a foreign body (the device)
- End of device service life or component failure, requiring surgical replacement
- Component failure, resulting in loss of therapy
- Access port inversion (“flipping”), rotation, or extrusion
- Access port or catheter rejection
- Fibrin sheath formation around catheter tip

Appendix 3.13 Regulatory Agency, Institutional Review Board, Ethics Committee and Site Reporting

The sponsor and CRO are responsible for notifying the relevant regulatory authorities, central IRBs, and central ECs of related, unexpected SAEs.

In addition, the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP611-201 program.

The investigator is responsible for notifying the local IRB/EC of SAEs or significant safety findings that occur at his or her site as required by IRB/EC procedures (see Appendix 1.5).

Appendix 4 Genetics

All subjects will undergo genotyping of the ASA gene.

In addition, Takeda intends to apply genetic research across the SHP611-201 development program to explore how genomic variations may affect the clinical parameters associated with and response to SHP611-201 (and any background products, comparators, and concomitant medications), and potentially the basis of the indications under study in the protocol, in this case late infantile MLD. Collection of appropriate samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies, genetically guided treatment strategies, and a better understanding of disease etiology, which may lead to new therapeutic approaches.

Candidate genes which may be studied include those potentially related to the mechanism of action of SHP611-201 as well as those potentially responsible for absorption, disposition, metabolism, and excretion of SHP611-201. Future research may suggest other genes, gene categories, proteins, etc., as candidates for influencing not only response to SHP611-201, but also susceptibility to disease for which SHP611-201 may be evaluated. Thus, this additional genomic research may involve the future study of additional unnamed genes or gene categories, but only as they relate to disease susceptibility and drug action. Samples may only be collected from subjects who provide separate informed consent, as detailed in the laboratory manual.

Samples will be labeled with the study protocol number, the subject's study identification number, and information related to the sample. No personal identifiers will be recorded on the sample labels.

Subjects terminating early from the study due to AE, tolerability, or drug-related issues should, where possible, be approached for their remaining protocol-defined samples at the earliest possible time. Unscheduled samples should be labeled with free text capturing study protocol number, subject's study identification number, and information related to the sample (RNA or protein, sampling date, and time). Samples will be shipped to and stored at biorepositories as detailed in the laboratory manual. DNA, RNA, and protein will be extracted from the samples only when, and if, any separate exploratory research will be undertaken.

As an added level of security, the sample will be recoded with a new, unique number at the biorepository laboratory. This unique number is the only code used in any subsequent analysis and will be used to link a sample to a subject and to ensure that the subject's identity remains confidential.

A link file linking the first and second codes will be kept in a secure place at the sponsor, with restricted access. This will be in a secure environment outside of the clinical study database and separate to any analysis results. This file will be used to identify the relevant samples for analysis, facilitate correlation of any results with clinical data, allow regulatory audit, and trace samples for destruction in the case of withdrawal of consent. No record of participation in this pharmacogenomics portion of the protocol, or any results derived from it, should be recorded in the subjects' personal medical records.

A record of participation in the pharmacogenomics portion of the protocol will, however, be captured in the study-specific source documentation records or eCRF.

The sponsor, sponsor's representatives, biorepositories, and any specialty laboratories will be blinded to the subject's identity. The sample and/or extracted material will otherwise be stored for up to 15 years from the end of the study after which time it will be destroyed. Upon written request, subjects will be permitted to withdraw their sample from the analysis and have their sample and/or extracted material destroyed. The link will also be destroyed at the same time as any remaining sample(s) are destroyed. Any results already generated from the samples will not be removed from any analyses that have already been performed.

Participation in this portion of the study is optional and does not impact the subject's eligibility for participation in the main clinical study. Subjects may continue to participate in the primary study if they refuse to provide a blood sample or if they withdraw their samples.

Results of the genetic analyses may contribute to the global understanding of late infantile MLD and its treatment and may be used internally to help support the design of additional clinical studies, form part of scientific publication, or be made known to the regulatory authorities as part of a new drug application. Any results generated will be for exploratory research purposes only and will not be made available unless required by law (ie, to regulatory authorities). Additionally, as any potential analysis does not form part of predefined analysis within the clinical study protocol, any results will be reported separately from the main clinical study report. Subjects may request the results of any analysis on their samples, although the significance of genetic variation in individuals is often not known. Genetic counseling will be made available to subjects when the results of genetic analyses performed in this study are shared with them.

Appendix 5 Scales and Assessments

The following scales/assessments will be utilized in this study. Refer to the current version of the relevant user manual for detailed instructions.

Full Title of Scale/Assessment
Gross Motor Function Classification in MLD (GMFC-MLD)
Gross Motor Function Measure 88 (GMFM-88)
Global impression of motor function-change (GIMF-C)
Global impression of motor function-severity (GIMF-S)
Alberta Infant Motor Scale (AIMS)
Elective Language Function Classification in MLD (ELFC-MLD)
Caregiver Impact Questionnaire (CIQ)
Infant Toddler Quality of Life Questionnaire (ITQOL) (HRQOL)
Healthcare Utilization Questionnaire (HCUQ)
Work Productivity and Activity Impairment (WPAI) Questionnaire – Specific Health Problem, V2.0
Eating and Drinking Ability Classification System (EDACS)

Appendix 6 Bioanalysis

All assessments referenced in the protocol, including sample collection instructions for the investigator, are in the study operations manual and the laboratory manual.

Appendix 7 Normal Ranges for Pulse, Systolic & Diastolic Blood Pressure, and ECG Parameters by Age

Normal ranges for pulse, systolic and diastolic blood pressure, and ECG parameters are presented by age below (Dickinson 2005; Fleming et al. 2011; National Institutes of Health 2005; Rijnbeek et al. 2001).

Normal Heart Rate by Age (beats/min)		
Age	**Awake Rate**	**Sleeping Rate**
Infant (1mo-1 y)	100-190	90-160
Toddler (1-2 y)	98-140	80-120
Preschool (3-5 y)	80-120	65-100
School-age (6-11 y)	75-118	58-90
Adolescent (12-15 y)	60-100	50-90

Normal Blood Pressure by Age (mmHg)		
Age	**Systolic Pressure**	**Diastolic Pressure**
Infant (1-12 mo)	72-104	37-56
Toddler (1-2 y)	86-106	42-63
Preschooler (3-5 y)	89-112	46-72
School-age (6-9 y)	97-115	57-76
Preadolescent (10-11 y)	102-120	61-80
Adolescent (12-15 y)	110-131	64-83

Normal ECG range for PR & QTc* Intervals (ms) by Age for Boys		
Age	**PR interval (ms)**	**QTc interval (ms)**
1-3 mo	85-120	396-458
3-6 mo	87-134	391-453
6-12 mo	82-141	379-449
1-3 yr	86-151	383-455
3-5 yr	98-152	377-448
5-8 yr	99-160	371-443
8-12 yr	105-174	373-440
12-16 yr	107-178	362-449

*Corrected QT interval, according to Bazett's formula: $QTc=QT \times \sqrt{((\text{heart rate})/60)}$

Normal ECG range for PR & QTc* Interval (ms) by Age for Girls		
Age	**PR interval (ms)**	**QTc interval (ms)**
1-3 mo	78-133	381-454
3-6 mo	84-127	386-448
6-12 mo	88-133	381-446
1-3 yr	78-147	381-447
3-5 yr	99-153	338-442
5-8 yr	92-153	375-449
8-12 yr	103-163	365-447
12-16 yr	106-176	370-457

*Corrected QT interval, according to Bazett's formula: QTc=QT x √((heart rate)/60)

Upper Limit of Normal for R, S & Q Wave Amplitude in Select Precordial Leads by Age for Boys			
Age	**R Wave Amp, V6 (mV)**	**S Wave Amp, V1 (mV)**	**Q Wave Amp, V6 (mV)**
1-3 mo	2.23	1.57	0.31
3-6 mo	2.73	2.02	0.35
6-12 mo	2.79	1.88	0.60
1-3 yr	2.96	2.27	0.56
3-5 yr	3.14	2.11	0.42
5-8 yr	2.98	2.29	0.39
8-12 yr	3.24	2.46	0.43
12-16 yr	3.05	2.44	0.43

Upper Limit of Normal for R, S & Q Wave Amplitude in Select Precordial Leads by Age for Girls			
Age	**R Wave Amp, V6 (mV)**	**S Wave Amp, V1 (mV)**	**Q Wave Amp, V6 (mV)**
1-3 mo	2.67	1.59	0.37
3-6 mo	2.80	1.64	0.40
6-12 mo	2.74	1.86	0.39
1-3 yr	2.67	2.13	0.49
3-5 yr	2.91	2.11	0.42
5-8 yr	3.25	2.49	0.41
8-12 yr	3.04	2.58	0.34
12-16 yr	2.52	2.05	0.23

Appendix 8 Premature Closure of the Study

If the sponsor, investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable subject risk, the study may be terminated after appropriate consultation between the sponsor and the investigator(s). In addition, a decision on the part of the sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure of the investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the sponsor or other pertinent regulatory authorities
- Insufficient adherence by the investigator to protocol requirements

Appendix 9 Abbreviations

Abbreviation	Definition
Ab	antibody
AE	adverse event
AIMS	Alberta Infant Motor Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase (synonymous with SGPT)
AST	aspartate aminotransferase (synonymous with SGOT)
AUC	area under the curve
$AUC_{0-\infty}$	area under the curve from time 0 to infinity
AUC_{0-t}	area under the curve from time 0 to the time of last concentration measured
BBB	blood brain barrier
β-hCG	beta-human chorionic gonadotropin
BILI	total bilirubin
BMI	body mass index
BMT	bone marrow transplantation
CAS	completer analysis set
CFR	Code of Federal Regulations
CI	confidence interval
CL	Clearance
CL/F	clearance after IT administration
C_{max}	maximum concentration
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CPAP	Clinical Pharmacology Analysis Plan
CRA	clinical research associate
CRIM	cross-reacting immunologic material
CRO	contract research organization
CSF	cerebrospinal fluid
CV	coefficient of variation
DMC	data monitoring committee

Abbreviation	Definition
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
eIC	electronic informed consent
ELISA	Enzyme-linked Immunosorbent Assay
EOT	end of treatment
EOS	end of study
EU	European Union
EUDRA	European Union Drug Regulatory Authorities
EUDRACT	European Union clinical trials database
FDA	Food and Drug Administration
EDACS	Eating and Drinking Ability Classification System
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transpeptidase
GIMF-C	Global impression of motor function-change
GIMF-S	Global impression of motor function-severity
GMFC-MLD	Gross Motor Function Classification in Metachromatic Leukodystrophy
GMFM-88	Gross Motor Function Measure-88
GMP	Good Manufacturing Practice
Hct	Hematocrit
HCUQ	Healthcare Utilization Questionnaire
Hgb	Hemoglobin
HSCT	hematopoietic stem cell transplantation
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDDD	intrathecal drug delivery device
IFU	Instructions for Use
INN/USAN	International Nonproprietary Name/United States adopted name
IRB	institutional review board

Abbreviation	Definition
IT	intrathecal(ly)
ITQOL-97	Infant Toddler Quality of Life Questionnaire – 97 items
Local Site	approved investigational site at which a subject may complete study procedures for dosing visits
LP	lumbar puncture
Main Site	approved investigational site at which a subject is enrolled into the study and must complete certain study procedures for dosing visits
MedDRA	Medical Dictionary for Regulatory Activities
MLD	metachromatic leukodystrophy
MNC	mononuclear leukocytes
MPS I	mucopolysaccharidosis I
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAA/Cr	N-acetylaspartate/creatine
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNS	peripheral nervous system
QoL	quality of life
rhASA	recombinant human arylsulfatase A
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
Shire	Shire Human Genetic Therapies, Inc.
SI	serious injury
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TBD	to be determined

Abbreviation	Definition
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TTE	time to event
UADE	unanticipated adverse device effect
UK	United Kingdom
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire

Appendix 10 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	23 Aug 2018	Global
Amendment 1	10 Oct 2018	Global
Amendment 2	04 Apr 2019	Global
Amendment 3	21 Jun 2019	Global
Amendment 3.1	18 Nov 2019	Site Specific - 001, United States
Amendment 3.2	02 Dec 2019	Country - Germany
Amendment 4	16 Sep 2020	Global
Amendment 5	12 Oct 2022	Global

Previous Protocol Amendments Summaries of Changes

Amendment 1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **10 Oct 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
The acronym for the study has been chosen and added to the Title Page.		Title Page
New text has been added to describe and clarify the procedure for study IDDD implantation; the potential use of lumbar puncture and limits; the potential to administer SHP611 after surgery and IDDD revisions; and the steps to be taken to ensure safety for subjects, with particular attention to younger subjects.		Synopsis Section 4.1 Section 8.1.2
A new appendix has been added to detail the Expected Adverse Device Effects and is referenced in the text.		Section 4.1 Appendix 3.11
Footnote "f" was revised to indicate procedures to take for subject safety after IDDD implantation.		Table 1 Table 2
A new footnote, "o", was added to allow for the conditional option to administer SHP611 after IDDD implantation per neurosurgeon request.		Table 1
Exclusion Criteria 1 has been reworded for clarification.		Synopsis Section 5.2
Addition text detailing the Sophysa SOPH-A-PORT Mini S IDDD development and use:		Section 6.1.2
Text for drug accountability was moved from Section 6.5 to 6.4 to align better with section content.		Section 6.4
The title of Section 6.5 was changed from Subject Compliance to Treatment Compliance to better reflect added text.		Section 6.5
Text was clarified to indicate that the first administration of SHP611 will be considered Week 0 and text was added to detail the option and limits of lumbar puncture use.		Section 8.1.3.1
New text was added to detail the potential risks of partial IDDD removal.		Section 8.1.4
A statement was added to indicate that an auditory and vision exam will be conducted in order to align with the Schedule of Activities.		Section 8.2.3.1
Text has been deleted to streamline content and update accuracy for the Caregiver Impact Questionnaire.		Section 8.2.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 10 Oct 2018	Global
Description of Change and Rationale		Section(s) Affected by Change
Text has been deleted to streamline content and update accuracy for the Healthcare Resource Utilization and Impact Questionnaires.		Section 9.7.1

Amendment 2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	Amendment Date 4 Apr 2019	Global
Description of Change	Rationale	Section(s) Affected by Change
Updated emergency contact from [redacted]	Personnel change	Emergency Contact Information
Clarified contact e-mail for product complaints.	Shire decommissioned separate e-mail for outside of the US	Product Quality Complaints
Removed the assessments, objectives, and endpoints for FEES and Battelle and added the new assessments of WPAI, VABS-III, and EDACS.	Regulatory authority feedback , clinical decision	Synopsis, Schedule of Activities, Section 3.1, Section 3.3, Section 8.2.2.6, Section 9.5.2
Added a qualifying statement to the primary objective: If suitable controls cannot be matched despite the sponsor's best efforts, change from baseline results of GMFC-MLD at Week 106 will be compared with a prespecified objective threshold to evaluate primary efficacy for this study.	Regulatory authority feedback requesting backup to analysis approach	Synopsis, Section 3.1, Section 9.5.2
Removed the key secondary objective/endpoint per health authority request. This objective/endpoint is now a secondary objective/endpoint: To evaluate the effects of IT administration of SHP611 on gross motor function, using the Gross Motor Function Measure 88 (GMFM-88) total score in children with MLD.	Regulatory authority request (FDA)	Synopsis, Section 3.2.1, Section 3.3, Section 9.5.2
Added a new secondary objective/endpoint. To evaluate the effects of IT administration of SHP611 on Eichler MLD MRI severity score.	Clinical decision	Synopsis, Section 3.2.1, Section 3.3, Section 9.5.2
GIMF-C and GIMF-S were added to the exploratory objectives and endpoints.	Consistency with content in other protocol sections and support of other gross motor function assessments	Synopsis, Section 3.2.1, Section 3.3, Section 9.5.2
Increased the total number of subjects to enroll from 35 to 38 to allow for a fifth enrollment group.	Clinical decision	Synopsis, Section 4.1
Updated Group D from presymptomatic to minimally symptomatic.	Clinical decision	Synopsis, Section 4.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	Amendment Date 4 Apr 2019	Global

Description of Change	Rationale	Section(s) Affected by Change
Added a fifth enrollment Group – Group E (early symptomatic, <18 months of age): Approximately 3 subjects ≥12 to <18 months of age, with documented diagnosis of MLD per inclusion criteria 1 and 2 with a history of achieving stable walking (defined as at least 1 month of independent walking) and a GMFC-MLD level of 1 or 2. Subjects in Group E must have neurological symptoms documented by a pediatric neurologist or medical geneticist.	Clinical decision; Group E was added to allow for enrollment of young subjects with MLD who are not necessarily siblings of enrolled subjects in the other groups. In addition to safety and biomarker data, this group will allow for assessment of IT SHP611 effect in a younger group who may be earlier in their disease progression.	Synopsis, Section 4.1, Section 4.2, Section 5.1
Repetitive text was deleted regarding subjects who discontinue treatment and do not have the IDDD removed due to safety considerations.	To eliminate excessive text in non-relevant locations regarding an exception to the study protocol	Synopsis, Section 4.1, Section 4.4 Section 8.1.6
Extended the screening period from 14 to 28 days.	Clinical decision	Synopsis, Schedule of Activities Table 1, Section 4.1, Section 6.6
Added clarifying text to ensure proper healing after IDDD implantation and prior to the first dose of SHP611.	Subject safety, Regulatory authority request - FDA	Synopsis, Section 4.1, Schedule of Activities Table 1 and Table 2 footnotes "f " and "h", Section 8.1.2
Added additional detail regarding the process for video-recording of motor function.	Clarification, only a subset of videos would be reviewed by 2 central assessors	Synopsis, Section 4.1, Schedule of Activities Table 1 and Table 2 footnote "k", Section 8.2.2.1
Removed text indicating use of data from prior Shire studies	Regulatory authority request (EMA)	Synopsis, Section 4.1, Section 9.5
The inclusion criteria for matched historical controls was updated to require gait disorder attributed to MLD be documented by 30 months of age in order to better align with the inclusion criteria for Groups A-C.	Clinical decision, to better align with the inclusion criteria for Groups A-C	Synopsis, Section 5.1
Exclusion criteria were updated to add BMT and require primary symptoms of MLD to be motor rather than cognitive.	Clinical decision, for consistency to match other sections	Synopsis, Section 5.1.1, Section 5.2, Section 5.2.1
A list of contraindications from the SOPH-A-PORT Mini S IFU were added to the exclusion criteria	Regulatory authority request (BfArM)	Synopsis, Section 5.2.1
Text was added to restrict IDDD use to SHP611 administration only.	Subject safety	Synopsis, Section 5.3, Section 6.1.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	Amendment Date 4 Apr 2019	Global
Description of Change	**Rationale**	**Section(s) Affected by Change**
Numbers for device profile safety were updated.	New data available	Section 6.1.2
Updates made to indicate that the SOPH-A-PORT Mini S is approved in the EU for long-term intrathecal administration of Shire's enzyme replacement therapies per the medical device directives.	New approval of device received in EU	Section 6.1.2
Text was added to confirm that dosing may only occur at an approved investigational site and definitions for local and main sites were updated for clarity.	Regulatory authority request (ANSM)	Section 6.2.2, Abbreviations
Temperature range was added to provide more clarity to the storage of the investigational product.	Clarification request from vendor	Section 6.3.3
Potential reasons for withdrawal from the study were clarified.	Clarification	Section 7.3
To help distinguish baseline from screening and surgical implantation of the IDDD and its study timeframe, it was separated into its own section.	Clarification request from vendor	Section 8.1.3
Text was modified and streamlined to clarify safety follow-up process if subjects do not continue in the extension study and do not have the IDDD fully explanted due to safety considerations.	Subject safety	Schedule of Activities Table 1 footnote "m", Schedule of Activities Table 2 footnote "m", Section 8.1.5, Section 8.2.4.5
Clarification was added to indicate that CRIM will be collected at screening only if the subject weighs ≥11.5kg	Subject safety	Schedule of Activities Table 1, Schedule of Activities Table 2, Section 8.2.1.3
PK sampling was moved from Week 106/EOS to Week 105/EOT when the last dose of SHP611 will be administered.	Correction, PK sampling occurs after SHP611 administration	Schedule of Activities Table 2, Section 8.2.5.1, Section 9.5.2
A statement was added to indicate that, for all assessments to be conducted in this study, the current user manuals should be referenced for details.	Clinical operations decision	Section 8.2.2
New classification tables and references were added for the newly added assessments of WPAI, VABS-III, and EDACS.	Clinical decision, new assessment information	Section 8.2.2.5, Section 8.2.2.6, Section 8.2.5.5, References

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	Amendment Date 4 Apr 2019	Global
Description of Change	**Rationale**	**Section(s) Affected by Change**
Neurofilament Light Chain (NFL) and Myelin Basic Protein (MBP) were added as potential biomarkers to assess.	Clinical decision	Section 8.2.4.4
The expected cumulative maximum total volume of blood drawn per subject over the duration of this study was updated to be approximately 131.5 mL.	Subject safety	Section 8.2.5.5
Text was added indicating that an unblinded statistical group outside of the Sponsor's SHP611-201 statistical analysis team will be formed to work on the available historical control data, in order to identify predictive baseline variables and reduce potential matching biases, and the final matching variables identified by this exercise will be specified in the SAP.	Regulatory authority feedback regarding analysis conduct	Section 9.5
Additional detail was added to clarify how historical controls may be matched and to clarify the corresponding analyses.	Regulatory authority feedback regarding analysis conduct	Section 9.5
Minor editorial changes were made for increased clarity.	Regulatory authority feedback regarding analysis conduct	Section 9.5
The following endpoint was removed: "Mean change from baseline at end of study in GMFC-MLD will be compared between matched historical control and subject groups, using a paired t-test and corresponding CI will be constructed."	Regulatory authority feedback regarding analysis conduct	Section 9.5.2
Added 2 new statistical methodologies indicating that classifications of GMFC-MLD will be analyzed as an ordered categorical variable and that a similar analysis as used for the primary efficacy endpoint will be conducted for the GMFM-88 response in Group A at Week 106.	Regulatory authority feedback regarding analysis conduct	Section 9.5.2
The window for main site visits was revised from ±6 weeks to ±2 weeks	Clinical decision	Synopsis, Schedule of Activities Table 1 and Table 2
Rows were added to the Schedule of Activities for sample collection for ASA genotyping at screening and optional sample collection for exploratory genotyping at Week 5.	Clarification	Schedule of Activities Table 1 and Table 2
In order to clarify and align footnotes between Schedule of Activities Tables 1 and 2, the table footnotes were re-ordered	Clarification	Schedule of Activities Table 1 and Table 2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	Amendment Date 4 Apr 2019	Global
Description of Change	**Rationale**	**Section(s) Affected by Change**
A third Schedule of Activities: Part 3 (Safety Follow-up for Subjects Discontinuing from Study Treatment) was added to clarify the safety follow-up period activities for subjects who do not have the IDDD fully explanted.	Clarification	Schedule of Activities Table 3

Amendment 3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3	Amendment Date 21 Jun 2019	Global
Description of Change	**Rationale**	**Section(s) Affected by Change**
Updated emergency contact information	Administrative change	Emergency Contact Information
Added lower age limit of ≥6 months of age for Group D	Regulatory authority feedback	Synopsis; Section 4.1, Overall Design; Section 4.2, Scientific Rationale for Study Design; Section 5.1, Inclusion Criteria
Added of a 6th subject group, Group F, 18 to 72 months of age with a GMFC-MLD level of 5 or 6. Due to this addition, modified group names to include GMFC-MLD levels for improved clarity. Group F will include approximately 4 subjects, increasing the total number of subjects included in the study to 42.	Clinical decision: inclusion of this group will allow for preliminary assessment of safety and efficacy in patients with more advanced disease	Synopsis; Section 4.1, Overall Design; Section 4.2, Scientific Rationale for Study Design; Section 5.1, Inclusion Criteria
Clarified the description of groups to specify GMFC-MLD levels rather than disease state, ie, Group A (GMFC-MLD level 1 or 2) rather than Group A (early symptomatic).	Clarification	Synopsis; Section 4.1, Overall Design; Section 4.2, Scientific Rationale for Study Design; Section 5.1, Inclusion Criteria
Added exclusion criteria excluding patients with a known genetic disorder other than MLD	To ensure a homogeneous sample of subjects with mutations only in the ASA gene are included	Synopsis; Section 5.2, Exclusion Criteria
Added exclusion criterion to restrict inclusion of subjects with laboratory, ECG, or vital sign abnormalities reflecting intercurrent illness that may compromise their safety. Required review by medical monitor of abnormal results at screening	Regulatory authority feedback	Synopsis; Section 5.2, Exclusion Criteria; Section 8.1.1.1, Screening (-28 to -1 days)

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3	Amendment Date 21 Jun 2019	Global
Description of Change	**Rationale**	**Section(s) Affected by Change**
Clarified exclusion criterion to specify that subjects may not be enrolled in another clinical study involving use of any investigational product within 30 days or 5 half-lives (whichever is longer)	Regulatory authority feedback	Synopsis; Section 5.2, Exclusion Criteria
Added language indicating that CSF routine analysis is to be done by the local lab. If the local lab is unable to perform CSF albumin assay, a CSF sample for albumin assay should be sent to the central lab with the CSF antibody sample.	Clinical decision	Table 1, Schedule of Activities: Part 1 (Screening through Week 53); Table 2, Schedule of Activities: Part 2 (Week 54 through Safety Follow-up)
Window for visits at main site reduced from ±2 weeks to ±1 week	To ensure consistency of dosing over time	Table 1, Schedule of Activities: Part 1 (Screening through Week 53); Table 2, Schedule of Activities: Part 2 (Week 54 through Safety Follow-up)
Added normal ranges for vital signs (pulse, blood pressure) and key ECG parameters by age to new appendix (Appendix 7, Normal Ranges for Pulse, Systolic & Diastolic Blood Pressure, and ECG Parameters by Age)	Regulatory authority feedback	Table 1, Schedule of Activities: Part 1 (Screening through Week 53); Table 2, Schedule of Activities: Part 2 (Week 54 through Safety Follow-up); Section 8.2.3.3, Vital Signs; Appendix 7
Clarified the windows for PK serum sample assessments and indicated that the actual time of each PK draw must be recorded.	Clarification	Table 1, Schedule of Activities: Part 1 (Screening through Week 53); Table 2, Schedule of Activities: Part 2 (Week 54 through Safety Follow-up)
Removed requirement for informed consent at the first 6 month visit after the EOT period for safety follow-up for subjects discontinuing from study treatment who do not have the IDDD fully explanted	Clinical decision as such consent is not planned	Table 3: Schedule of Activities: Part 3 (Safety Follow-up for Subjects Discontinuing from Study Treatment Who Do Not Have the Intrathecal Drug Delivery Device Fully Explanted)
Specified prior and concomitant treatment rather than therapy, and indicated that concomitant treatment refers to treatment taken between the dates of initial implantation of the IDDD or the first dose of investigational product, whichever occurs first, and the end of the follow-up period, inclusive	Clarification	Section 6.6, Prior and Concomitant Treatment

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3	Amendment Date 21 Jun 2019	Global
Description of Change	**Rationale**	**Section(s) Affected by Change**
Added language regarding reasons for which subjects must discontinue investigational product	Regulatory authority feedback	Section 7.2, Reasons for Discontinuation
Added new section to describe stopping rules leading to temporary dosing discontinuation	Regulatory authority feedback	New Section 7.4, Temporary Discontinuation
Clarified that abnormal ASA enzyme activity and urine sulfatide concentration consistent with diagnosis of MLD is required for study eligibility. Replaced term "biochemical confirmation". Clarified that ASA enzyme activity and urine sulfatide results from a reliable lab can be used at screening for eligibility criteria although such samples must still be collected at that time.	Regulatory authority feedback and clinical decision	Section 8.2.1.2, MLD Diagnosis
Clarified that study drug should not be administered through the IDDD if it is not possible to withdraw CSF through the device. The device should then be assessed as described in the IDDD manual.	To ensure that dosing occurs only when location of the intrathecal catheter within the intrathecal space is confirmed	Section 8.2.4.4, Cerebrospinal Fluid Sampling Procedure
Clarified that the VABS-III assessment is not required if the site cannot administer in English or Spanish	The VABS-III is not available in languages other than English and Spanish at this time.	Section 8.2.5.5, Health-related Quality of Life (QoL)
Added device-associated definitions	Alignment with Phase 1/2 Studies HGT-MLD-070/071	New Appendix 3.11, Device-Associated Definitions
Clarified that the significant of genetic variations in individuals is often not known although subjects may request genetic analysis results from their samples and genetic counseling will be available when these results are shared	Clarification	Appendix 4, Genetics
New literature references added to support Appendix 7 normal range tables for vital signs and key ECG parameters	Supportive of Appendix 7	Appendix 7, Normal Ranges for Pulse, Systolic & Diastolic Blood Pressure, and ECG Parameters by Age

Amendment 3.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3.1	**Amendment Date 18 Nov 2019**	**Site Specific**
Description of Change	**Rationale**	**Section(s) Affected by Change**
Modified Group D to include infants with the same allelic constitution as an older sibling with confirmed infantile or juvenile onset MLD	To permit assessment of safety and potential efficacy of IT SHP611 in subjects with juvenile onset MLD	Section 1.1, Synopsis; Section 4.1, Overall Design; Section 4.2, Scientific Rationale for Study Design; Section 5.1, Inclusion Criteria
Modified minimum weight requirements for dosing: for the 150 mg weekly dose, subjects must weigh ≥7 kg (15.4 lbs); subjects weighing ≥5 kg (11.0 lbs) but <7 kg may receive 100 mg weekly dosing; and subjects weighing <5 kg should be excluded.	Compliance with weight-based limits on endotoxin exposure from SHP611 and saline flush.	Section 1.1, Synopsis; Section 4.1, Overall Design; Section 4.3, Justification for Dose; Section 5.2, Exclusion Criteria; Section 6.2.2, Dosing
Changed weight requirement for CRIM: all subjects will have CRIM evaluated; for subjects weighing <11.5 kg, the CRIM sample will be limited to 3cc volume.	Regulatory authority feedback and adherence to weight-based phlebotomy volume limits	Table 1and Table 2, Schedules of Activities; Section 8.2.1.3, Cross Reacting Immunologic Material (CRIM)

Amendment 3.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3.2	**Amendment Date 02 Dec 2019**	**Global**
Description of Change	**Rationale**	**Section(s) Affected by Change**
Added a description of all measures to reduce pain and discomfort during study procedures	Regulatory authority feedback	Section 8.1, Study Periods
Added a more detailed description of monitoring, burden, and risk threshold if use of IDDD is not possible and lumbar puncture is used to obtain CSF samples and/or administer study drug	Regulatory authority feedback	Section 8.1.2, Surgical Implantation of IDDD, Day -10 to 28
Added requirement for documentation of gait disorder by 30 months of age in a copy of the medical record included in the source documents	This change will help to ensure that inclusion criteria for the study are met by all subjects.	Section 8.2.1, Demographic and Other Baseline Characteristics
Added requirement for inclusion in medical history of use of non-pharmacologic treatments and any medication hypersensitivities	Regulatory authority requirement	Section 8.2.1.1, Medical and Medication History

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3.2	Amendment Date 02 Dec 2019	Global
Description of Change	**Rationale**	**Section(s) Affected by Change**
Added details regarding the DMC members	Regulatory authority feedback	Section 9.2, Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee
Clarification that SAEs must be reported immediately and within no more than 24 hours of first awareness of the event	Regulatory authority feedback	Appendix 3.5, Serious Adverse Event Collection Time Frame

Amendment 4

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 4	Amendment Date 16 SEP 2020	Global
Description of Change	**Rationale**	**Section(s) Affected by Change**
Added the extension period of the study, where subjects may continue to receive treatment with SHP611 for an extended duration of time	To evaluate long-term safety and efficacy outcomes of treatment with IT SHP611 in subjects who have participated in Study SHP611-201 through Week 106	Section 1.1, Synopsis; Section 1.2, Schema; Section 1.3, Schedule of Activities; Section 3.2, Study Endpoints; Section 4.1, Overall Design; Section 4.2, Scientific Rationale for Study Design; Section 4.3, Justification for Dose; Section 4.4, Duration of Subject Participation and Study Completion Definition; Section 8.1, Study Periods; Section 8.1.4.1, Treatment Period – Study Week 0; Section 8.1.4.2, Treatment Period – Remaining Study Visits; Section 8.1.5, Final Visit End of Study (EOS); Section 8.2.4.4, Cerebrospinal Fluid Sampling Procedure; Section 8.2.4.6, Pharmacokinetics; Section 8.2.4.7, Sulfatide/Lysosulfatide Biomarker Assessments; Section 8.2.4.8, Additional Biomarker Assessments; Section 8.2.4.10,

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **16 SEP 2020**	**Global**
Description of Change	**Rationale**	**Section(s) Affected by Change**
		Health-related Quality of Life (QoL); Section 9.4, Statistical Analysis Set; Section 9.5.2, Secondary Efficacy Endpoints; Section 9.7.3, Extension Period
Removed the collection of Vineland Adaptive Behavior Scales Third Edition as an exploratory endpoint	Decision made due to the combination of a delay of initiating the set up and the limited availability of the Group A testing to analyze baseline to EOS; would have only been able to analyze approximately 10% of the Group A study subjects in the best-case scenario	Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 3.1.2, Secondary Objectives; Section 3.2, Study Endpoints; Section 8.2.4.10, Health-related Quality of Life (QoL); Section 9.5.2, Secondary Efficacy Endpoints; Appendix 5, Scales and Assessments;
Changed the wording of the total number of subjects per group for Groups B through F from "approximately" to "up to"	Greater clarity	Section 1.1, Synopsis; Section 4.1, Overall Design
Added that subjects in Group D will be assessed with the AIMS and GMFM-88 until they are able to walk or reach 18 months of age, after which motor function will be assessed using the GMFC-MLD and GMFM-88	Clarification that age-appropriate motor function assessments will be used for all subjects	Section 1.1, Synopsis; Section 4.1, Overall Design
Modified Group D to include infants with same allelic constitution as an older sibling with confirmed infantile or juvenile onset MLD	To permit assessment of safety and potential efficacy of IT SHP611 in subjects with infantile or juvenile onset MLD	Section 1.1, Synopsis; Section 4.1, Overall Design; Section 4.2, Scientific Rationale for Study Design; Section 5.1, Inclusion Criteria
Clarified that a gait disorder due to spastic ataxia or weakness and attributable to MLD must be documented by a primary care physician or specialist physician rather than exclusively by a pediatric neurologist or medical geneticist	Documentation of a gait disorder by a primary care or a specialist medical physician is valid. Primary care physicians are often the first to observe initial symptoms of MLD	Section 1.1, Synopsis; Section 5.1, Inclusion Criteria; Section 8.2.1, Demographics and Other Baseline Characteristics
Removed the exploratory objective for nerve conduction assessment by electroneurography	This exploratory endpoint is being removed to reduce study burden to subjects.	Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 3.1.2, Secondary Objectives; Section 3.2, Study Endpoints; Section 8.2.2.7, Electroneurography Studies (removed section); Section 8.2.2.8, Anesthesia; Section 9.5.2, Secondary Efficacy Endpoints

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **16 SEP 2020**	**Global**
Description of Change	**Rationale**	**Section(s) Affected by Change**
Modified minimum weight requirements for dosing: for the 150 mg weekly dose, subjects must weigh ≥7 kg (15.4 lbs); subjects weighing ≥5 kg (11.0 lbs) but <7 kg may receive 100 mg weekly dosing; and subjects weighing <5 kg should be excluded	Compliance with weight-based limits on endotoxin exposure from SHP611 and saline flush. All subjects enrolled prior to this amendment weighed >7 kg at screening.	Section 1.1, Synopsis; Section 4.1, Overall Design; Section 4.3, Justification for Dose; Section 5.2, Exclusion Criteria; Section 6.2.2, Dosing
Defined minimally symptomatic for Group D as being without clear late infantile MLD symptoms or only having mild symptoms not meeting criteria for GMFC-MLD level of >0	Regulatory authority request for "minimally symptomatic" to be defined	Section 1.1, Synopsis; Section 4.1, Overall Design
Added a 3-5 day waiting period for study drug administration after re-implantation or revision of the IDDD	Re-implantation or revision should be followed by the same healing period prior to dosing as that following initial implantation.	Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 4.1, Overall Design; Section 8.1.2, Surgical Implantation of IDDD, Day -10 to 28; Section 8.2.4.5, Intrathecal Drug Delivery Device Removal
Added a window for baseline assessments of -1 to 0 days	Allow some distribution of baseline measures to avoid exhausting the subjects.	Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 4.1, Overall Design; Section 8.1.3, Baseline Assessments (prior to first administration of SHP611; Day -1 to 0)
Removed the inclusion/exclusion criteria for the matched historical controls as such details will be provided in the Statistical Analysis Plan	Historical controls will not participate in study SHP611-201. Criteria for selection of the natural history controls will be described in the SAP.	Section 1.1, Synopsis; Section 5.1, Inclusion Criteria for Matched Historical Controls (removed section); Section 5.2, Exclusion Criteria for Matched Historical Controls (removed section); Section 5.2, Exclusion Criteria
Added prior exposure to SHP611 as an exclusion criterion	Restrict to a SHP611 naïve sample to ensure interpretability of results.	Section 1.1, Synopsis; Section 5.2, Exclusion Criteria
Corrected exploratory endpoints regarding global impression of motor function to clarify that GIMF-C is change over time and GIMF-S is change from baseline to Week 106	Clarification	Section 1.1, Synopsis; Section 3.1.2, Secondary Objectives; Section 3.2, Study Endpoints; Section 9.5.2, Secondary Efficacy Endpoints

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 4	**Amendment Date 16 SEP 2020**	**Global**
Description of Change	**Rationale**	**Section(s) Affected by Change**
Revised the definition of the Full Analysis Set (FAS) to include 'or any subject who only provides a baseline GMFC-MLD assessment but can be determined as failure prior to Week 106 (such as death)'	Clarify definition of the Full Analysis Set (FAS) for statistical analysis	Section 1.1, Synopsis; Section 9.4, Statistical Analysis Set(s)
For matched historical control study matching method, removed the statement 'To perform this matching, the absolute value difference will be used as distance, and a fraction of common standard deviation (SD) of difference of the propensity score will be used as a threshold.'	Correction, as this method may not be used literally	Section 1.1, Synopsis; Section 9.5, Efficacy Analyses
For matched controls, removed the statement that controls will have 'comparable efficacy assessment at similar time points' to enrolled subjects in SHP611-201 Group A	Correction, as this may be unrealistic and therefore, may not be used	Section 1.1, Synopsis; Section 4.1, Overall Design; Section 9.5, Efficacy Analyses
Removed MRI/MRS measures from Weeks 26 and 79; MRI/MRS will now be obtained at baseline and then annually	This change is being made to reduce the burden of study participation on subjects	Section 1.3, Schedule of Activities
Increased the time period that MRI/MRS may be done to any time from Screening to Week 0.	Increased flexibility for sites to collect this data	Section 1.3, Schedule of Activities
For performing CSF albumin assay, revised that if the local lab is unable to perform CSF albumin assay, inform the CRA to identify other options (instead of sending sample to the central lab)	Clarification to identify other options, as central lab may not be able to perform CSF albumin assay	Section 1.3, Schedule of Activities
Added clarification to allow for flexibility for timing of pre-dose PK draw	Improve operational feasibility	Section 1.3, Schedule of Activities
Added that serum and CSF samples for PK assessments will be drawn at Week 105, not Weeks 95-104, and that trough CSF will be drawn at Week 106	Clarification	Section 1.3, Schedule of Activities
Changed weight requirement for CRIM: all subjects will have CRIM evaluated; for subjects weighing <11.5 kg, CRIM sample will be limited to 3 cc volume.	Regulatory authority feedback and adherence to weight-based phlebotomy volume limits	Section 1.3, Schedule of Activities; Section 8.2.1.3, Cross Reacting Immunologic Material (CRIM)
Added a requirement for the investigator/sub-investigator to write a note within the source documents describing the subject's current motor function at each main site visit	These research notes may be used to generate data for blinded central scoring of GMFC-MLD	Section 1.3, Schedules of Activities; Section 8.2.2.5, Note Documenting Current Motor Function
Clarification of procedure to explant IDDD, ie incision check within 2 weeks (±7 days) after surgery	Improved safety follow-up	Section 1.3, Schedules of Activities; Section 8.2.4.5, Intrathecal Drug Delivery Device Removal

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **16 SEP 2020**	**Global**
Description of Change	**Rationale**	**Section(s) Affected by Change**
Added that CSF has a +15 minutes post-dose collection window	Improve operational feasibility	Section 1.3, Schedules of Activities; Section 8.2.4.6, Pharmacokinetics; Section 9.5.2, Secondary Efficacy Endpoints
Added for CSF samples that if the subject's IDDD is not functioning, or the subject is receiving doses via LP, the 6 and 24 hour samples do not need to be collected.	Clarification	Section 1.3, Schedules of Activities; Section 8.2.4.6
Removed separate safety follow-up for subjects discontinuing from study treatment who do not have the IDDD fully explanted; these subjects will be followed at the Safety Follow-up visit occurring 2 weeks after the EOS visit	Remove unnecessary safety follow-up to reduce patient burden	Section 1.3, Schedules of Activities (removed Table 3 for Part 3); Section 8.1.5, Final Visit End of Study (EOS); Section 8.1.6, Safety Follow-up; Section 8.2.4.5, Intrathecal Drug Delivery Device Removal
Added language to allow for some flexibility for unavoidable circumstances, such as the COVID-19 public health emergency, for exceptions to be granted for missed or delayed subjects visits with approval of the Medical Monitor, with documentation in the study records. Such data may be handled differently in the final data analysis, as to be documented in the Statistical Analysis Plan	Increase flexibility during unavoidable circumstance of the COVID-19 public health emergency	Section 4.1, Overall Design; Section 8.1, Study Periods
Subjects who discontinue treatment before the End of Study Visit may complete the EOS visit if they have not received intercurrent disease modifying treatment, such as HSCT or gene therapy	Allow collection of EOS data from all subjects with SHP611 exposure who do not meet the study exclusion criteria regarding BMT, HSCT, and gene therapy.	Section 7.1, Discontinuation of Study Treatment
Added COVID-19-related criteria for discontinuation or withdrawal of a subject	To ensure that subject discontinuations due to COVID-19 related factors are documented in the eCRF	Section 7.2, Reasons for Discontinuation
Clarification that Section 7.4 provides information about temporary hold of dosing not discontinuation	Clarification	Section 7.4, Temporary Hold of Dosing (previously Temporary Discontinuation)
Added a description of all measures to reduce pain and discomfort during study procedures	Regulatory authority feedback	Section 8.1, Study Periods
Added a more detailed description of monitoring, burden, and risk threshold if use of IDDD is not possible and lumbar puncture is used to obtain CSF samples and/or administer study drug	Regulatory authority feedback	Section 8.1.2, Surgical Implantation of IDDD, Day -10 to 28

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Added requirement for documentation of gait disorder by 30 months of age in a copy of the medical record included in the source documents	This change will help to ensure that inclusion criteria for the study are met by all subjects	Section 8.2.1, Demographic and Other Baseline Characteristics
Added clarification that medical records for family members of the subject may be requested	This change will allow collection of data from affected siblings, who may then serve as a control	Section 8.2.1, Demographic and Other Baseline Characteristics
Added requirement for inclusion in medical history of use of non-pharmacologic treatments and any medication hypersensitivities, as well as document any gait disorder attributable to MLD by 30 months of age	Regulatory authority feedback	Section 8.2.1.1, Medical and Medication History
Corrected language to remove references to a central ECG reader	No central ECG reader will be used in this study (due to minimizing use)	Section 8.2.3.6, Electrocardiogram
Revised the cumulative maximum total volume of blood drawn per subject over the duration of this study to be approximately 162.5 mL	Blood volume amount revised due to inclusion of the extension period in the study	Section 8.2.4.10, Additional Biomarker Assessments
Added that a main analysis will be performed after all subjects complete the primary treatment period; the database will be locked with the results presented in a clinical study report, and following completion of the study, the database will be locked again and the results of the entire study (primary treatment and extension treatment periods) will be described in the final clinical study report	Incorporate the main analysis to occur at completion of the primary treatment period (through Week 106) due to addition of the extension period in the study	Section 9.2, Planned Analysis, Adaptive Design, and Data Monitoring Committee
Revised that an unblinded statistical group outside of the Sponsor's SHP611-201 statistical analysis team will be formed to work on the available historical control data, in order to identify 'potential prognostic' (rather than 'predictive') baseline variables and reduce potential matching biases, and the final matching variables 'recommended' (rather than 'identified') by this exercise will be specified in the SAP	Clarification due to revised plan of work on the available historical control data	Section 9.5, Efficacy Analyses

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Added that a Monitoring Plan Addendum has been developed to provide guidance and study specific instructions to Project Management team and CRAs for the monitoring of the investigational sites in the study, and that this plan provides specific instructions in order to ensure oversight and consistency in study monitoring and site management activities in the context of unavoidable circumstances, such as the COVID-19 public health emergency	To describe the existence and purpose of an addendum to the Monitoring Plan	Appendix 1.4, Data Management Considerations
Added that during the COVID-19 public health emergency, informed consent from a potential or current trial participant may be obtained via electronic informed consent (eIC) capabilities, or an electronic face-to-face consent interview when these individuals are unable to travel to the site	To permit the use of electronic informed consent (eIC) during the COVID-19 public health emergency	Appendix 1.5, Ethical Considerations
Clarification that SAEs must be reported immediately and within no more than 24 hours of first awareness of the event	Regulatory authority feedback	Appendix 3.4, Safety Reporting; Appendix 3.5, Serious Adverse Event Collection Time Frame

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