Clinical Study Protocol

NCT Number: NCT05058391

Title: A Prospective, Multicenter, Single-arm, Open-label, Interventional Phase IV Study to Evaluate the Safety and Efficacy of Idursulfase (r-DNA origin) (Elaprase™) in Indian Pediatric and Adult Population With Hunter Syndrome (Mucopolysaccharidosis II)

Study Number: TAK-665-4001

Document Version and Date: Version 3.0, 27 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

A Prospective, Multicenter, Single-arm, Open-label, Interventional Phase IV Study to Evaluate the Safety and Efficacy of Idursulfase (r-DNA origin) (Elaprase™) in Indian Pediatric and Adult Population with Hunter Syndrome (Mucopolysaccharidosis II)

Sponsor:	Takeda Biopharmaceuticals India Pvt. Ltd. Building No. 8, 6th Floor, Tower C DLF Cyber City Gurgaon 122002 Haryana, India		
Study Number:	TAK-665-4001		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	Idursulfase (r-DNA origin) (Elaprase™)		
Date:	27 October 2022	**Version:**	3.0

the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduct of the study.

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	India Contact
Serious adverse event and pregnancy reporting	JSS Medical Research India Private Limited Tower 2, 1st Floor, South Wing, L&T Business Park, Plot no 12/4, Sector 27 D, Delhi Mathura Road, Near Sarai Khawja Metro Station, Faridabad -121003, Haryana, India
Medical Monitor (medical advice on protocol and study drug)	Dr [redacted] JSS Medical Research India Private Limited Tower 2, 1st Floor, South Wing, L&T Business Park, Plot no 12/4, Sector 27 D, Delhi Mathura Road, Near Sarai Khawja Metro Station, Faridabad -121003, Haryana, India [redacted]
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Dr [redacted] JSS Medical Research India Private Limited Tower 2, 1st Floor, South Wing, L&T Business Park, Plot no 12/4, Sector 27 D, Delhi Mathura Road, Near Sarai Khawja Metro Station, Faridabad -121003, Haryana, India
Takeda Responsible Medical Officer	Dr [redacted] [redacted] [redacted] Floor 6th, Building No.8, Tower C, Cyber City, Gurgaon-122002, India
Project management	Dr [redacted] JSS Medical Research India Private Limited Tower 2, 1st Floor, South Wing, L&T Business Park, Plot no 12/4, Sector 27 D, Delhi Mathura Road, Near Sarai Khawja Metro Station, Faridabad -121003, Haryana, India [redacted]

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual subjects in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories can be found on the signature page.

Dr [redacted]

[redacted]-India, Takeda Date

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator. (Appendix B)

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in **Error! Reference source not found.** of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

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1.3 Protocol version Summary of Changes

Applicable Sections	Original text from the study protocol Protocol version 2.0, dated 22 February 2021 (Struck-out text is text deleted)	Amended text Protocol version 3.0, dated 27 October 2022 (Bold underlined text is the new text added)	Justification
Sponsor Name	~~Shire Biotech India Pvt. Ltd.~~ ~~Plot No. 70, A-26,~~ ~~Second Floor, Rama Road, Industrial Area,~~ ~~New Delhi – 110015, India~~	**Takeda Biopharmaceuticals India Pvt. Ltd.** **Floor 6th, Building No.8, Tower C,** **Cyber City, Gurgaon-122002, India**	Change in entity name
Section 1.1 - Contacts	~~TDC sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.~~		Change in entity name & study is India specific
Section 3.4 – Corporate Identification	~~TDC Asia – Takeda Development Centre Asia Pte Ltd.~~	**Takeda India – Takeda Biopharmaceuticals India Pvt. Ltd.**	Change in entity name

Applicable Sections	Original text from the study protocol Protocol version 1.0, dated 08 September 2020 (Struck-out text is text deleted)	Amended text Protocol version 2.0, dated 24 February 2021 (Bold underlined text is the new text added)	Justification
Study Title and Section 2	A Prospective, Multicenter, Single-arm, Open-label, Interventional Phase IV Study to Evaluate the Safety and Efficacy of Elaprase in Indian Pediatric and Adult Population with Hunter Syndrome (Mucopolysaccharidosis II)	A Prospective, Multicenter, Single-arm, Open-label, Interventional Phase IV Study to Evaluate the Safety and Efficacy of **Idursulfase (r-DNA origin)** (Elaprase™) in Indian Pediatric and Adult Population with Hunter Syndrome (Mucopolysaccharidosis II)	Title updated to include the product INN name.
Section 2 Study Summary and Section 7.1	Male or female* Elaprase naïve subjects of any age with confirmed diagnosis of Hunter syndrome based on the following documented biochemical and genetic criteria:	Male or female* Elaprase naïve subjects **(and who are not part of any other program at the time of study enrollment and during the study period)** of any age with confirmed diagnosis of Hunter syndrome based on the following documented biochemical and genetic criteria:	Recommendations from SEC (meeting held on 19th January 2021)
Section 2 Study Summary and Section 7.2	The subject has a chronic kidney disease and is on dialysis	The subject has a chronic kidney disease **with estimated Glomerular Filtration rate less than 15 mL/min/1.73** m^2 and/**or** is on dialysis	Recommendations from SEC (meeting held on 19th January 2021)

Section 7.4	7. Lack of efficacy. The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject	7. Lack of efficacy. The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject. **Lack of efficacy shall be defined as below:** **Patients fulfilling all of the below criteria should be evaluated by the treating investigators to withdraw the patient from further continuing Elaprase** **1. No change in normalized urine GAG (uGAG) from baseline at week 27** **2. No change or increase in liver and spleen volumes from baseline at week 27** **3. No improvement or decline in cardiac function as assessed by left ventricular mass index and ejection fraction from baseline at week 27** **4. No improvement or decline in 6 Minute Walk Test (6MWT) and percentage Forced Vital Capacity (%FVC) from baseline at week 27** **(Change in anthropometric measurements can also be considered for patients with age less than 18 years)** **5. No improvement or decline in health-related quality of life (HRQoL) from baseline at week 27**	Recommendations from SEC (meeting held on 19th January 2021)

Applicable Sections	Original Text Protocol version 2.0, dated 24 February 2021	Amended Text Protocol version 2.0, dated 23 April 2021	Justification
NA	Plot No. 70, A-26, Second Floor, Rama Road, Industrial Area, New Delhi-110015, India	Building No. 8, 6th Floor, Tower C DLF Cyber City Gurgaon 122002 Haryana, India	To update the new registered address
Section 1.1 Contacts : Serious adverse event and pregnancy reporting	SIRO Clinpharm Private Limited Kalpataru Prime, Unit 3 and 4, 1st floor, Plot no D-3, Road No. 16, Wagle Industrial Estate, Thane West (400604), Maharashtra, India	JSS Medical Research India Private Limited Tower 2, 1st Floor, South Wing, L&T Business Park, Plot no 12/4, Sector 27 D, Delhi Mathura Road, Near Sarai Khawja Metro Station, Faridabad – 121003, Haryana, India	Change in CRO partner
Section 1.1 Contacts: Medical Monitor (medical advice on protocol and study drug)	Dr [redacted] / Dr [redacted] SIRO Clinpharm Private Limited Kalpataru Prime, Unit 3 and 4, 1st floor, Plot no D-3, Road No. 16, Wagle Industrial Estate 022-61088000 [redacted]	Dr [redacted] JSS Medical Research India Private Limited Tower 2, 1st Floor, South Wing, L&T Business Park, Plot no 12/4, Sector 27 D, Delhi Mathura Road, Near Sarai Khawja Metro Station, Faridabad – 121003, Haryana, India [redacted]	Change in CRO partner
Section 1.1 Contacts: Responsible Medical Officer (carries	Dr [redacted] / Dr [redacted] SIRO Clinpharm Private Limited	Dr [redacted] JSS Medical Research India Private Limited Tower 2, 1st Floor, South Wing, L&T Business Park,	Change in CRO partner

overall responsibility for the conduct of the study)	Kalpataru Prime, Unit 3 and 4, 1st floor, Plot no D-3, Road No. 16, Wagle Industrial Estate	Plot no 12/4, Sector 27 D, Delhi Mathura Road, Near Sarai Khawja Metro Station, Faridabad – 121003, Haryana, India	
Section 1.1 Contacts: Project Management	[redacted] SIRO Clinpharm Private limited, Kalpataru Prime, Unit 3 and 4, 1st floor, Plot no D-3, Road No. 16, Wagle Industrial Estate, Thane West (400604), Maharashtra, India [redacted]	Dr [redacted] JSS Medical Research India Private Limited Tower 2, 1st Floor, South Wing, L&T Business Park, Plot no 12/4, Sector 27 D, Delhi Mathura Road, Near Sarai Khawja Metro Station, Faridabad – 121003, Haryana, India [redacted]	Change in CRO partner

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Biopharmaceuticals India Pvt. Ltd.	**Compound:** Idursulfase (r-DNA origin) (Elaprase™)	
Title of Protocol: A Prospective, Multicenter, Single-arm, Open-label, Interventional Phase IV Study to Evaluate the Safety and Efficacy of Idursulfase (r-DNA origin) (Elaprase™) in Indian Pediatric and Adult Population With Hunter Syndrome (Mucopolysaccharidosis II)	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: TAK-665-4001	**Phase:** 4	

Study Design:

This is a prospective, open-label, multicenter, interventional single-arm Phase IV study to be conducted at multiple sites in India to evaluate the safety and efficacy of Elaprase in Indian pediatric and adult population with Hunter syndrome (Mucopolysaccharidosis II [MPS II]).

A total of 5 subjects with Hunter syndrome (MPS II) will be enrolled in this study. The total duration of the study for each subject will be up to 55 weeks, consisting of 14 days screening period (Days -14 to -1), a 52-weeks treatment period (Week 1 to Week 52), followed by 1 week follow-up period after the last dose of Elaprase (Week 53). At Week 53, the subject will be assessed for safety and efficacy which will also be considered the end of study (EOS). The total duration of the study will be approximately 3 years, based on the anticipated recruitment rate, however the study duration may get extended beyond 3 years until the last enrolled subject completes the EOS visit.

After obtaining written informed consent from the subjects or their parents/guardians/legally authorized representatives (LARs), the subjects will be screened. An assent form will be provided and should be signed by subjects of ≥7 to <18 years of age. Subjects who meet all the inclusion criteria and none of the exclusion criteria will be administered Elaprase at the site. Subjects will visit the site for dosing on Week 1, Day 1 followed by every week till Week 52, Day 358. The visit on Week 52, Day 358 will be considered as end of treatment (EOT). The study drug will be administered as 0.5 mg/kg given intravenously every week. The intravenous infusion will be administered over a 3 hour period, which may be gradually reduced to 1 hour if no infusion-associated reactions are observed.

Efficacy assessments will be done at Week 27, Day 183 and Week 53, Day 365. Urine glycosaminoglycan (uGAG) and clinical laboratory assessments will also be done at at Week 14, Day 92 and Week 40, Day 27. If the subject discontinues study treatment, the subject will have to complete assessments done at Week 53, Day 365 (Visit 54/EOS). Subjects will be evaluated for safety from initiation of Elaprase treatment until 53 weeks (EOS), or for at least 1 week following discontinuation of Elaprase, whichever occurs earlier.

A subject diary will be provided to the subjects/subject's parents/guardians/LAR to be filled at home. The diary will be used to capture information of any concomitant medications taken, and other adverse events (AEs) that may occur in between visits.

Apart from that, an unscheduled visit can be performed at investigator's discretion or if the trial subject experiences safety concerns.

Primary Objectives:

- To evaluate the safety of Elaprase in pediatric and adult subjects with Hunter syndrome during 53 weeks of study duration.

Secondary Objectives:

<table>
<tr><td colspan="2">

- To evaluate the efficacy of Elaprase in pediatric and adult subjects with Hunter syndrome during 53 weeks of study duration.

</td></tr>
<tr><td colspan="2">Subject Population:
Male or female subjects of any age with confirmed diagnosis of Hunter syndrome.</td></tr>
<tr><td>Number of Subjects:

5 subjects will be enrolled in this study</td><td>Number of Sites:

Approximately 4-5 Sites in India</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Dose Level:

Elaprase is administered at a dose of 0.5 mg/kg body weight every week by intravenous infusion over a 3 hour period, which may be gradually reduced to 1 hour if no infusion-associated reactions are observed.</td><td>Route of Administration:

Intravenous</td></tr>
<tr><td>Duration of Treatment:

52 weeks</td><td>Period of Evaluation:

The study duration for each subject will be approximately 55 weeks, which will include 14 days of screening, 52 weeks of treatment, and 1 week follow-up after the last dose of Elaprase (Week 53). At Week 53, the subject will be assessed for safety and efficacy which will also be considered as the EOS. The total duration of the study will be approximately 3 years, based on the anticipated recruitment rate, however the study duration may get extended beyond 3 years until the last enrolled subject completes the EOS visit.</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion:

- Male or female* Elaprase naïve subjects (and who are not part of any other program at the time of study enrollment and during the study period) of any age with confirmed diagnosis of Hunter syndrome based on the following documented biochemical and genetic criteria:
  - Documented deficiency in iduronate 2-sulfatase (IDS [12S]) enzyme activity of less than or equal to 10% of the lower limit of the normal range as measured in plasma, fibroblasts, or leukocytes (based on normal range of measuring laboratory).
  - A normal enzyme activity level of one other sulfatase as measured in plasma, fibroblasts, or leukocytes (based on normal range of measuring laboratory).
  - The patient has a documented mutation in the IDS gene.

**It is known that Hunter syndrome almost exclusively affects males and it is highly unlikely that females will be affected by Hunter syndrome.*</td></tr>
<tr><td colspan="2">Main Criteria for Exclusion:

- Subject has received hematopoietic stem cell transplantation or a bone marrow transplant at any time.
- Subject is suffering from any comorbid conditions (including hepatic impairment, acute or chronic) or having any other clinical observation or history during the screening examination, which would interfere with the objectives of the study as per investigators judgement.
- The subject has a chronic kidney disease with estimated Glomerular Filtration rate less than 15 mL/min/1.73 m2 and/or is on dialysis.</td></tr>
</table>

- Subject has participated in any other clinical study or received any investigational compound or non-investigational idursulfase beta within the past 30 days before informed consent.

Main Criteria for Evaluation and Analyses:

Primary endpoint

The primary endpoint includes:

- Incidence of AEs, serious AEs (SAEs), treatment emergent AEs, treatment emergent SAEs, adverse drug reactions (ADRs), discontinuation due to AEs, infusion-related reactions, and death.

Secondary endpoints

The secondary endpoints include:

- Change from baseline in percentage Forced Vital Capacity (%FVC) as a measure of respiratory function at Weeks 27 and 53.
- Change from baseline in 6 Minute Walk Test (6MWT) as a measure of physical functional capacity at Weeks 27 and 53.
- Change from baseline in Cardiac Left Ventricular Mass Index (LVMI) and Ejection Fraction at Weeks 27 and 53.
- Change from baseline in liver volume at Weeks 27 and 53.
- Change from baseline in spleen volume at Weeks 27 and 53.
- Change from baseline in uGAG levels at Weeks 14, 27, 40, and 53.
- Change from baseline in Global Joint Range of Motion (JROM) score at Weeks 27 and 53
- Changes from baseline in anthropometric parameters including height in subjects <18 years at baseline and weight in all subjects at Weeks 27 and 53.
- Changes from baseline in the health-related quality of life based on Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS) (shortened version) and Childhood Health Assessment Questionnaire (CHAQ) in subjects between age of ≥1 year to ≤18 years at Weeks 27 and 53.

Statistical Considerations:

The statistical analysis will be carried out using available data from all subjects to be enrolled. The statistical analysis for this study will be descriptive in nature. Data on continuous and categorical scale will be expressed with appropriate descriptive statistics. It will include number of observations, mean, standard deviation, median, 10^{th} and 90^{th} percentiles, minimum, maximum for continuous parameters, and proportions, frequency counts for categorical parameters, and 90% confidence intervals of point estimates as appropriate. Complete details of the statistical methodology will be described in a separate statistical analysis plan, to be finalized before database lock.

Sample Size Justification:

According to the observed recruitment trend from other published trial results on clinicalTrials.gov and considering the rarity of the disease (based on rare disease epidemiology with the estimated incidence of 0.6-1.3 in 100,000 live male births) and the low availability of subjects, 5 Elaprase naive subjects whose disease condition is clinically confirmed will be enrolled. No formal sample size calculation is performed.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

Abbreviation	Definition
6MWT	6 Minute Walk Test
ADR	adverse drug reaction
AE	adverse event
ALP	alanine phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BPI	Brief Pain Inventory
CHAQ	Childhood Health Assessment Questionnaire
CRA	clinical research associate
CRO	Contract Research Organization
DCGI	Drug Controller General of India
DOH	Declaration of Helsinki
ECG	Electrocardiogram
Ecrf	electronic case report form
EOT	end-of-treatment
EOS	end-of-study
ERT	enzyme replacement therapy
FAS	full analysis set
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
hCG	human chorionic gonadotropin
HRQoL	health related quality of life
HSCT	hematopoietic stem cell transplant
HS-FOCUS	Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDS	iduronate-2-sulfatase
IEC	Independent Ethics Committee
IRB	Institutional Review Board
GAG	Glycosaminoglycans
JROM	Joint Range of Motion
LAR	legal authorized representative
LVMI	Left ventricular mass index
M6P	mannose-6-phosphate
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
PTE	pretreatment event
RBC	red blood cell

SAE	serious adverse event
SOC	System Organ Class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USG	Ultrasonography
uGAG	urine glycosaminoglycan
WBC	white blood cell

3.4 Corporate Identification

Takeda India Takeda Biopharmaceuticals India Pvt. Ltd.

4.0 INTRODUCTION

4.1 Background

Hunter syndrome (Mucopolysaccharidosis II)

Hunter syndrome (Mucopolysaccharidosis II [MPS II]), is a rare X-linked lysosomal storage disorder caused by a deficiency of iduronate-2-sulfatase (IDS), involved in the catabolism of glycosaminoglycans (GAG) (1). Mutations in the IDS gene located at Xq28 are responsible for Hunter syndrome (2-5). Affected patients show a progressive accumulation of GAG in the lysosomes of many organs and tissues, which contribute to the clinical manifestations of Hunter syndrome. In Hunter syndrome, multiple organ systems are affected, with signs and symptoms usually emerging in the first few years of life. Disease presentation and rate of progression vary greatly, and the few manifestations of Hunter syndrome typically include recurrent respiratory infections, coarse facial features, joint stiffness, otitis media, umbilical/inguinal hernias, cardiomyopathies and hepatosplenomegaly (6,7); the characteristic short stature is usually apparent by ~8 years of age (8,9). Patients may also develop neurological symptoms, such as carpal tunnel syndrome, communicating hydrocephalus, spinal cord compression and hearing loss. For clinical purposes, patients are generally considered to fall into one of two categories according to the presence or absence of progressive central nervous system (CNS) involvement (typified by cognitive impairment, with behavioral difficulties and regression in developmental milestones), which occurs in as many as two-thirds of patients (10-14). The phenotypical spectrum of Hunter syndrome is variable: In patients with the neuronopathic (severe) form, the onset of clinical symptoms is usually between 2 and 4 years of age, with progressive neurologic symptoms that lead to cognitive impairment (1). This group of patients die in the first or second decade, usually due to obstructive airway disease and/or cardiac failure associated with progressive neurologic deterioration (1). On the other hand, patients with the non-neuronopathic (attenuated) form show milder somatic symptoms and minimal neurological involvement. These patients have normal intelligence and survive until their fifth or sixth decade (15,16). The disease is inherited in an X-linked manner and primarily affects males, although a small number of female patients have been described (17,18).

The treatment of Hunter syndrome was palliative prior to the introduction of enzyme replacement therapy (ERT). Hematopoietic stem cell transplant (HSCT)/bone marrow transplant (BMT) for the treatment of patients with Hunter syndrome is not supported by consistent evidence of somatic or neurological symptom improvements (19)(20). In contrast, successful clinical trials (21,22) have led to the approval of ERT with human recombinant idursulfase (Elaprase, Takeda Human Genetic Therapies, Lexington, MA) by the United States Food and Drug Administration (FDA) in 2006 and European Medical Evaluation Agency (EMEA) and Japan in 2007.

4.1.1 Elaprase

Elaprase is a formulation of idursulfase, a purified form of human IDS, a lysosomal enzyme produced by recombinant deoxyribonucleic acid (DNA) technology in a human cell line. Idursulfase is an enzyme that hydrolyzes the 2-sulfate esters of terminal iduronate sulfate residues from the glycosaminoglycans dermatan sulfate and heparan sulfate in the lysosomes of various cell types (1).

Due to the missing or defective IDS (12S) enzyme in patients with Hunter syndrome, GAG progressively accumulate in the lysosomes of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction (1).

Elaprase is intended to provide exogenous enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow binding of the enzyme to the M6P receptors on the cell surface, leading to cellular internalization of the enzyme, targeting to intracellular lysosomes and subsequent catabolism of accumulated GAG.

4.2 Rationale for the Proposed Study

The current study will be conducted to generate the safety and efficacy data of Elaprase in Indian population to meet the regulatory requirements of Drug Controller General of India (DCGI). Considering this to be a rare disease, and based on the rare epidemiology of Hunter syndrome with the estimated incidence of 0.6–1.3 in 100,000 live male births (23-25), the approximate number of subjects enrolled in this study will be 5 (23-25).

4.3 Benefit/Risk Profile

Data on the safety and efficacy profile of Elaprase is not available in India. This Phase 4 study is designed to gather important information on the safety and efficacy of Elaprase in subjects with Hunter syndrome. The dosing and administration regimen and study population in this study are consistent with the approved Elaprase label. Overall, Elaprase has been well tolerated in clinical studies. The procedures performed during the study are part of usual clinical practice. Taking into account the risks associated with procedures and the disease worsening in this population, the benefit-risk profile is anticipated to remain positive for Elaprase in this study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To evaluate the safety of Elaprase in pediatric and adult subjects with Hunter syndrome during 53 weeks of study duration.

5.1.2 Secondary Objective

- To evaluate the efficacy of Elaprase in pediatric and adult subjects with Hunter syndrome during 53 weeks of study duration.

5.2 Endpoints

5.2.1 Primary Endpoint

- Incidence of adverse events (AEs), serious AEs (SAEs), treatment emergent AEs, treatment emergent SAEs, adverse drug reactions (ADRs), discontinuations due to AEs, infusion-related reactions, and death.

5.2.2 Secondary Endpoints

- Change from baseline in percentage Forced Vital Capacity (%FVC) as a measure of respiratory function at Weeks 27 and 53
- Change from baseline in 6 Minute Walk Test (6MWT) as a measure of physical functional capacity at Weeks 27 and 53
- Change from baseline in Cardiac Left Ventricular Mass Index (LVMI) and Ejection Fraction at Weeks 27 and 53.
- Change from baseline in liver volume at Weeks 27 and 53.
- Change from baseline in spleen volume at Weeks 27 and 53.
- Change from baseline in normalized urine GAG (uGAG) levels at Weeks 14, 27, 40, and 53.
- Change from baseline in Global Joint Range of Motion (JROM) score at Weeks 27 and 53
- Changes from baseline in anthropometric parameters including height in subjects <18 years at baseline and weight in all subjects at Weeks 27 and 53.
- Change from baseline in the health-related quality of life (HRQoL) based on Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS) (shortened version) in all subjects and Childhood Health Assessment Questionnaire (CHAQ) in subjects between age of ≥1 year to ≤18 years at Weeks 27 and 53.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is prospective, open-label, multicenter, interventional single-arm Phase IV study to be conducted at multiple sites in India to evaluate the safety and efficacy of Elaprase in Indian pediatric and adult population with Hunter syndrome (MPS II).

A total of 5 subjects with Hunter syndrome will be enrolled in this study. The total duration of the study for each subject will be up to 55 weeks, consisting of 14 days screening period (Days

-14 to -1), a 52-weeks treatment period (Week 1 to Week 52), followed by 1 week follow-up period after the last dose of Elaprase (Week 53). At Week 53, the subject will be assessed for safety and efficacy which will also be considered the end of study (EOS). The total duration of the study will be approximately 3 years, based on the anticipated recruitment rate, however the study duration may get extended beyond 3 years until the last enrolled subject completes the EOS visit.

After obtaining written informed consent from the subjects or their parents/guardians/legally authorized representatives (LARs), the subjects will be screened. An assent form will be provided and should be signed by subjects of ≥7 to <18 years of age. Subjects who meet all the inclusion criteria and none of the exclusion criteria will be administered Elaprase at the site. Subjects will visit the site for dosing from Week 1, Day 1 followed by every week till Week 52, Day 358. The visit on Week 52, Day 358 will be considered as end of treatment (EOT) visit. The study drug will be administered as 0.5 mg/kg given intravenously every week. The intravenous infusion will be administered over a 3 hour period, which may be gradually reduced to 1 hour if no infusion-associated reactions are observed.

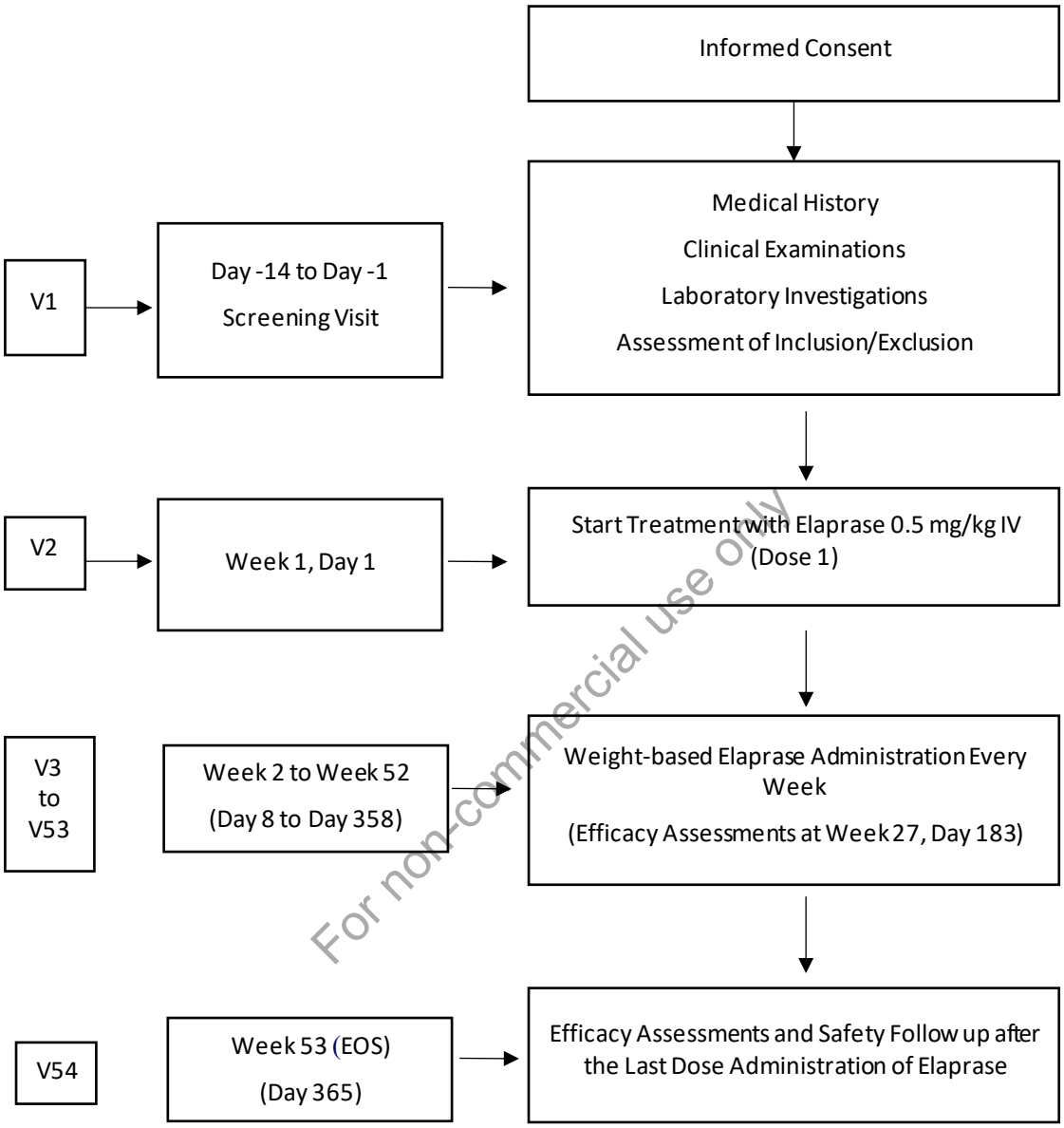
Efficacy assessments will be done at Week 27, Day 183 and Week 53, Day 365. Urine glycosaminoglycan (uGAG) and clinical laboratory assessments will also be done at Week 14, Day 92 and Week 40, Day 27. If the subject discontinues study treatment, the subject will have to complete assessments done at Week 53, Day 365 (EOS). Subjects will be evaluated for safety from initiation of Elaprase treatment until 53 weeks (EOS), or for at least 1 week following discontinuation of Elaprase, whichever occurs earlier.

A subject diary will be provided to the subjects/subject's parents/guardians to be filled at home. The diary will be used to capture information of any concomitant medications taken, and other AEs that occur in between visits.

Apart from that, an unscheduled visit can be performed at investigator's discretion or if the trial subject experience safety concerns.

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

The study is being undertaken to collect data on the safety and efficacy of Elaprase in Indian subjects with Hunter syndrome for regulatory submission. DCGI has granted marketing authorization for Elaprase in India based on efficacy studies of Elaprase in Hunter syndrome conducted across the globe; and so, safety data of Elaprase in Indian subjects needs to be submitted to DCGI. Considering rare disease, a single-arm, open-label design is the most appropriate design to generate such data, as the focus of the study is primarily to collect information on safety and to additionally explore the clinical efficacy of the study drug.

Elaprase 0.5 mg/kg IV infusion is approved for the indications planned to be studied. The safety and treatment efficacy endpoints are similar to those used in other outcome studies in Hunter syndrome. The study period of 55 weeks includes 14 days of screening period, 52 weeks treatment period and 1 week follow-up after the last dose of Elaprase (Week 53). This study duration will help us in reporting safety endpoints of interest including AEs, SAEs, and ADRs.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the Elaprase, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to first dose administration.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. Male or female[#] Elaprase naive subjects (and who are not part of any other program at the time of study enrollment and during the study period) of any age with confirmed diagnosis of Hunter syndrome based on the following documented biochemical and genetic criteria:

- Documented deficiency in IDS (12S) enzyme activity of less than or equal to 10% of the lower limit of the normal range as measured in plasma, fibroblasts, or leukocytes (based on normal range of measuring laboratory).
- A normal enzyme activity level of one other sulfatase as measured in plasma, fibroblasts, or leukocytes (based on normal range of measuring laboratory).
- The patient has a documented mutation in the IDS gene.

2. In the opinion of the investigator, the subject or the subject's parents/guardians are capable of understanding and complying with protocol requirements.
3. The subject or, when applicable, the subject's parents/guardians/LAR signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures. If the subject participating in this study is ≥7 and <18 years of age signs and dates an assent form.
4. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential#* agrees to use barrier method of contraception (eg, condom with or without spermicide)* from signing of informed consent throughout the duration of the study. The female partner of a male subject should also be advised to use a highly effective/effective method of contraception.*
5. A female subject of childbearing potential#* who is sexually active with a nonsterilized* male partner agrees to use a highly effective method of contraception* from signing of informed consent throughout the duration of the study.

*Definitions and highly effective methods of contraception are defined in Section 9.1.11 and reporting responsibilities are defined in Section 9.1.12.

#It is known that Hunter syndrome almost exclusively affects males and it is highly unlikely that females will be affected by Hunter syndrome.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Subject has received HSCT or a bone marrow transplant at any time.
2. Subject is unable to comply with the protocol, eg, uncooperative with protocol schedule, refusal to agree to all of the study procedures, inability to return for safety evaluations, or is otherwise unlikely to complete the study, as determined by the investigator.
3. Subject is suffering from any comorbid conditions (including hepatic impairment, acute or chronic) or having any other clinical observation or history during the screening examination, which would interfere with the objectives of the study as per investigators judgement.
4. The subject has a chronic kidney disease with estimated Glomerular Filtration rate less than 15 mL/min/1.73 m^2 and/or is on dialysis.

5. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
6. The subject has a history of hypersensitivity or allergies to related compounds including any associated excipients.
7. If female, the subject is pregnant or lactating or intending to become pregnant before participating in this study, during the study; or intending to donate ova during such time period.
8. If male, the subject intends to donate sperm during the course of this study.
9. The subject has participated in another clinical study or received any investigational compound or non-investigational idursulfase beta within the past 30 days before informed consent.

7.3 Excluded Medications

No formal medicinal product interaction studies have been conducted with Elaprase (Refer Appendix F).

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.14.

1. Pretreatment event (PTE) or AE: The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Significant protocol deviation: The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up: The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal: The subject (or subject's parents/guardian/ LAR) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).
5. Study termination: The sponsor, IRB/IEC or regulatory agency terminates the study.
6. Pregnancy: The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.12.

7. Lack of efficacy. The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.

   Lack of efficacy shall be defined as below:

   Patients fulfilling **all of the below criteria** should be evaluated by the treating investigators to withdraw the patient from further continuing Elaprase

   1. No change in normalized urine GAG (uGAG) from baseline at week 27
   2. No change or increase in liver and spleen volumes from baseline at week 27
   3. No improvement or decline in cardiac function as assessed by left ventricular mass index and ejection fraction from baseline at week 27
   4. No improvement or decline in 6 Minute Walk Test (6MWT) and percentage Forced Vital Capacity (%FVC) from baseline at week 27

      (Change in anthropometric measurements can also be considered for patients with age less than 18 years)
   5. No improvement or decline in health-related quality of life (HRQoL) from baseline at week 27

8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. If subject discontinues the treatment early, an early termination visit should be scheduled at 7 days after the last dose. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. The assessments and procedures for the early termination visit will be the same as for the Visit 54/EOS Visit. If the subject withdraws from the study, then efforts should be made to perform all the assessments scheduled on early termination as early as possible. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Study Drug

The Elaprase supplied for this study is a clear to slightly opalescent, colourless solution of 1 mL concentrate for solution for infusion containing 2 mg of Elaprase. The content of Elaprase is provided in 5 mL vial containing 3.0 mL concentrate corresponding to 6 mg Elaprase.

The ingredients of 1 mL concentrate are described below.

Ingredient	Quantity per mL	Grade
Elaprase	2.0 mg	In-house monograph
Sodium phosphate, monobasic, monohydrate	2.25 mg	USP
Polysorbate 20	0.0002 mL	NF, EP
Sodium chloride	8.0 mg	USP, EP, JP
Sodium hydroxide	Qs	USP, EP, JP
Water for Injection	Qs	USP, EP, JP

Abbreviations: EP=European Pharmacopoeia; JP=Japanese Pharmacopoeia; NF=National Formulary; Qs=quantity sufficient; USP=United States Pharmacopoeia

Each vial of Elaprase is intended for single use only and contains 6 mg of idursulfase in 3 mL of solution. Elaprase is for intravenous infusion and must be diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion prior to use. Elaprase is administered using a low-protein-binding infusion set equipped with a low-protein-binding 0.2 µm in-line filter.

Since the drug is given as weight-based regimen, weight of participant will be recorded prior to dose calculation which is to be administered. After recording the weight of participant, the dose and number of Elaprase vials needed will be calculated. The total volume of Elaprase concentrate required will be diluted in 100 mL of 9 mg/mL (0.9%) sodium chloride solution for infusion. Care must be taken to ensure the sterility of the prepared solutions since Elaprase does not contain any preservative or bacteriostatic agent; aseptic technique must be observed. Once diluted, the solution should be mixed gently but not shaken. The solution should be inspected visually for particulate matter and discolouration prior to administration. Since no preservative is present, it is recommended that infusion should be started as soon as possible after dilution.

Elaprase 0.5 mg/kg is given every week as intravenous infusion over a 3 hours period, which may be gradually reduced to 1 hour if no infusion-associated reactions are observed. Participants may require longer infusion times if hypersensitivity reactions occur; however, infusion times should not exceed 8 hours. The initial infusion rate should be 8 mL per hour for the first 15 minutes. If the infusion is well tolerated, the rate of infusion may be increased by

8 mL per hour increments every 15 minutes. The infusion rate should not exceed 100 mL per hour.

The solution for infusion is for single use only therefore any unused product or waste material should be disposed of in accordance with local requirements. Elaprase should not be infused with other medicinal products in the infusion tubing.

8.1.1.2 Packaging and Labelling

Packaging and labelling will be controlled by Clinical Trial Supply Management Team of sponsor/Contract Research Organization (CRO).

All packaging and labelling as well as the production of study drug will be in compliance with Good Manufacturing Practices (GMP) specifications, as per applicable Indian laws and regulations.

A sponsor Qualified Person/Representative will release all the clinical supplies prior to shipment to investigational sites. A Certificate of Compliance will be issued stating the expiry date of the clinical supplies.

The contents of the label will be in accordance with DCGI requirements.

The labels will show the following information:

- Name of the drug or code number
- Batch number/lot number
- Date of manufacture
- Expiry date/use before date
- Storage conditions
- Name of the institute/organization/centre where clinical trial is being conducted
- Name and address of the manufacturer
- "For clinical trial use only"

8.1.2 Storage

The vials should be stored in a refrigerator at 2 to 8 °C. Vials should be kept with outer carton in order to protect from light.

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

The dose and dosing regimen for all subjects is provided below.

Treatment Group	Dose	Treatment Description
All subjects	Elaprase 0.5 mg/kg IV	Week 1, Day 1 and every week thereafter till Week 52, Day 358.

No dose modifications will be allowed during the study.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE page of eCRFs according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Assignment and Dispensing Procedures

Since this is an open-label single-arm study, randomization procedures will not be applicable for this study. Subjects will receive treatment sequentially as they enter the study and according to the study schedule. The subject identification number will be entered in to the eCRF.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee. The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment. If there are any discrepancies

between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot/medication ID used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, date and amount dispensed including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time when informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include age, sex, height, weight, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of study drug) will be performed on Week 1, Day 1. Physical examination includes general appearance; assessments of head, neck, and thyroid; eyes, ears, nose, and throat; chest and lungs; heart; lymph nodes; abdomen; anorectal; genitourinary; skin; musculoskeletal; endocrine; neurological; and other.

All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

9.1.4 Weight, Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place.

9.1.5 Vital Sign Procedure

Vital signs will include body temperature, respiratory rate, blood pressure, and pulse (beats per minute). Blood pressure will be measured when subjects are in the supine position.

If the vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hours before or after the scheduled blood draw. On dosing days, vitals are taken predose.

The investigator will assess whether a change from baseline in vital signs may be deemed within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at screening/baseline examination, according the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.8 Primary Efficacy Measurement

9.1.8.1 Percentage Forced Vital Capacity (% FVC)

Pulmonary function will be assessed by spirometry to measure FVC (26, 27).

Change from baseline will be measured at Weeks 27 and 53 to evaluate the efficacy of Elaprase..

Feasibility of Pulmonary function assessment in subjects <5 years can be assessed by the Investigator prior to performing the procedure if the subject is not found to be fit for the procedure, testing procedure can be deffered/avoided.

9.1.8.2 6 Minute Walk Test (6MWT)

6 Minute Walk Test will be conducted as per standard practice for patients with delayed development (28). The 6MWT will be conducted by a single specialist.

Change from baseline will be measured at Weeks 27 and 53 to evaluate the efficacy of Elaprase.

Feasibility of 6 Minute Walk Test in subjects <5 years can be assessed by the Investigator prior to performing the procedure , if the subject is not found to be fit for the procedure, testing procedure can be deffered/avoided

9.1.8.3 Cardiac Left Ventricular Mass Index (LVMI) and Ejection Fraction

Cardiac LVMI and Ejection Fraction will be determined by 2D echocardiography. Cardiac LVMI is the left ventricular mass (LVM, in g) indexed to body surface area (BSA), in square meter (m^2). Cardiac LVMI (in gram per square meter [g/m^2])=LVM divided by BSA.

Change from baseline will be measured at Weeks 27 and 53 to evaluate the efficacy of Elaprase.

9.1.8.4 Liver Volume

Liver volume will be determined by USG. Hepatomegaly is defined as a liver volume (L) >3.5% of body weight (kg) in subjects aged 5-12 years, 2.2% of body weight in subjects aged 13-17 years, and >2.6% in subjects more than 18 years old (30).

Change from baseline will be measured at Weeks 27 and 53 to evaluate the efficacy of Elaprase.

9.1.8.5 Spleen Volume

Spleen volume will be determined by USG. Splenomegaly is defined as having a splenic volume greater than the 95th percentile of the normal distribution in children (31).

Change from baseline will be measured at Weeks 27 and 53 to evaluate the efficacy of Elaprase.

9.1.8.6 Glycosaminoglycan

Normalized uGAG will be analyzed using urine testing (32). The uGAG levels will be normalized to urine creatinine and will be reported as microgram GAG per milligram creatinine (µg GAG/mg creatinine).

Change from baseline will be measured at Weeks 14, 27, 40, and 53 to evaluate the efficacy of Elaprase. Urine GAG may also be analysed at Weeks 14 and/or 40 at investigator's discretion.

9.1.8.7 Global Joint Range of Motion (JROM)

Passive joint mobility is defined as the range of motion of the shoulder, elbow, wrist, hip, knee, and ankle joints, as assessed by one expert physician using universal goniometry method.

Global JROM (% of normal range of motion) is the average of 11 ratios multiplied by 100. Ratios are left/right means of passive range of motion in shoulder (flexion/extension, abduction, internal/external rotation), elbow (flexion/extension), wrist (flexion/extension), index finger (flexion/extension [combined metacarpophalangeal joint, proximal interphalangeal joint, distal interphalangeal joint motion]), hip (flexion/extension, abduction, internal/external rotation),

knee (flexion/extension), and ankle (dorsiflexion) divided by the normal range (American Academy of Orthopedic Surgeons and American Medical Association) (33).

Change from baseline will be measured at Weeks 27 and 53 to evaluate the efficacy of Elaprase.

9.1.8.8 Anthropometric Parameters

Change from baseline in anthropometric parameters including height and weight will be assessed at Weeks 27 and 53 to evaluate the efficacy of Elaprase.

Change in height will be assessed in subjects <18 years and weight will be assessed in all subjects.

9.1.9 Health-related Quality of Life (HRQoL) Measures

The HRQoL measures of this study includes one disease-specific and one generic questionnaire.

9.1.9.1 Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS)

The HS-FOCUS was developed as a disease-specific measure of the impact of Hunter syndrome on HRQoL. The HS-FOCUS is designed to gather information on the patient's daily life and wellbeing, satisfaction with treatment, and hospitalizations, as well as on how Hunter syndrome impacts the patient's general quality of life. The HS-FOCUS includes 2 validated components: a parent version and a patient self -reported version for those over age 12 years. To increase the validity and efficiency of completion of HS-FOCUS, some items were removed from the original questionnaire (Version 1.0) to produce a shorter version (Version 2.0).

The HS-FOCUS (shortened version) questionnaire has 5 function domains (walking/standing, grip/reach, school/work, activities, and breathing). (34). The scale of the 5 function domains ranges from 0 to 3, with 0 signifying an ability to complete the activity-related functions 'without any difficulty' and 3 score denoting highest disability. Complete item responses are averaged to calculate the six individual function domain scores and the overall function score, with higher scores representing a higher degree of incapacity. If more than half of the items for a function domain are missing or marked 'not applicable', that domain score is deemed to be 'missing' and not included in the analysis (35).

For each of the 5 functional domains, the respective domain scores will be calculated as follows:

$$\text{Domain score} = \frac{\sum \ item\ scores\ within\ domain}{No.of\ items\ completed\ within\ domain}$$

The HRQoL assessment based on HS-FOCUS will be performed in all subjects at screening, Weeks 27 and 53 and the changes from baseline will be measured and reported (Appendix E).

9.1.9.2 Childhood Health Assessment Questionnaire (CHAQ)

The CHAQ was initially developed for assessing juvenile idiopathic arthritis, from the perspective of the parent or patient, and has been previously applied to other chronic disabling conditions such as Hunter syndrome (36). It is a 30-item instrument that measures functional capacity and independence in activities of daily life across eight domains: dressing and grooming, arising, eating, walking, reach, grip, hygiene, and activities. For each domain, there is a 4-level difficulty scale that is scored from 0 to 3, with 0 corresponding to 'without any difficulty' and 3 to 'unable to do'. An additional question asks for any aids or devices children usually use for any of the above activities, which is used to adjust the scores of the domains into the CHAQ disability index score (CHAQ DIS). This is used as the outcome measure of functional disabilities in severely disabled patients, with a scale from 0 to 3, where 3 represents the worst functions. CHAQ also presents two visual analogue scales for pain evaluation and overall well-being evaluation, where 0 represents 'no pain' and 'doing very well' and 100 represents 'very severe pain' and feeling 'very poor' (35).

The HRQoL assessment based on CHAQ will be performed in subjects between age of ≥1 year to ≤18 years at screening, Weeks 27 and 53 and the changes from baseline will be measured and reported (Appendix F).

9.1.10 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The approximate total volume of blood for the study is 28 mL. Details of these procedures and required safety monitoring will be given in the laboratory manual.

Table 9-a lists the tests that will be obtained for each laboratory specimen.

Table 9-a: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells (RBCs)	ALT	Specific gravity
White blood cells (WBCs) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils)	Albumin	pH
Hemoglobin	Globulin	Glucose
Hematocrit	Alkaline phosphatase	Protein blood
Mean corpuscular volume (MCV)	AST	Ketones
Mean corpuscular haemoglobin concentration (MCHC)	Total bilirubin	Bilirubin
Platelets	Total protein	Urobilinogen
	Creatinine	Nitrite
	Blood urea nitrogen	RBCs
	γ-Glutamyl transferase (GGT)	WBCs
	Potassium	Epithelial cells
	Sodium	Crystals
	Chloride	Casts
	Bicarbonate	Bacteria.
	Glucose	
	Urea	

	High-density lipoprotein
	Low-density lipoprotein
	Triglycerides
	Total cholesterol
Other:	
Urine	
Urine pregnancy test (Female subjects of childbearing potential)	

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

The clinical laboratory tests will be performed at screening, Weeks 14, 27, 40, and 53, and the changes from baseline will be measured and reported.

9.1.11 Contraception and Pregnancy Avoidance Procedure

9.1.11.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below.

9.1.11.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a two highly effective methods/one highly effective and one effective method of contraception (from the list below).

In addition they must be advised not to donate ova during this period.

9.1.11.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

*A woman is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

**Sterilized males should be at least 1 year postbilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:
    - Non-hormonal methods:
        - Intrauterine device (IUD)
        - Bilateral tubal occlusion
        - Vasectomised partner (provided that partner is the sole sexual partner of the trial subject and that the vasectomised partner has received medical assessment of the surgical success
    - Hormonal methods:
        - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
            - Oral
            - Intravaginal (eg, ring)
            - Transdermal
        - Progestogen-only hormonal contraception associated with inhibition of ovulation1 initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;
            - oral
            - Injectable
            - Implantable
2. Unacceptable methods of contraception are:
    - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
    - Spermicides only.
    - Withdrawal.
    - No method at all.
    - Use of female and male condoms together.

- Cap/diaphragm/sponge without spermicide and without condom.
- Sexual abstinence is not an acceptable method of contraception.

3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
4. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) contraceptive requirements of the study
   b) reasons for use of barrier methods (ie, condom) in males with pregnant partners
   c) assessment of subject compliance through questions such as
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
      iv. Is there a chance you could be pregnant?
5. In addition to a negative urine hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative urine hCG pregnancy test prior to first dose of study medication on Week 1, Day 1 and every week before dosing till Week 52.

9.1.11.4 General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- Assessment of subject compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
  - Is there a chance you could be pregnant?

9.1.12 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study, should also be recorded following authorization from the subject's partner.

Note 1: Pregnancies during pretreatment phase need not be reported to regulatory authorities. Therefore, please enter the correct visit number above for when first sponsor-supplied drug is administered.

Note 2: The period for reporting pregnancies following last dose of study drug is same as the period for AE reporting.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received.

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.13 ECG Procedure

The triplicate 12-lead ECG (each taken about 1 minute apart within a 5-minute window per timepoint) safety evaluation will be performed at screening/baseline, Weeks 27 and 53, and the changes from baseline will be measured and reported. The ECG can also be performed at Weeks 14 and/or 40, or any visit at investigator's discretion. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. When blood sampling, vital signs, and ECG are scheduled on same day, the blood sampling should be done last and sequence should be ECG, vital signs, and blood sampling.

9.1.14 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is withdrawn at the screening visit, the investigator should complete the eCRF.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria
- Lost to follow-up

- Voluntary withdrawal
- Study termination
- Other study-specific (specify reasons)

Subject identification numbers assigned to subjects who fail screening should not be reused.

9.1.15 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for enrolment into the treatment phase.

If the subject is found to be not eligible for treatment phase, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

All supplies used to administer study drug to the subject will be recorded on the eCRFs.

If a subject is persistently noncompliant with the study drug, it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time points.

9.3.1 Screening/Visit 1/Days -14 to -1

Subjects will be screened within 14 days prior to baseline. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.14 for procedures for documenting screening failures.

Procedures to be completed at Screening (Visit 1) include:

- Informed consent
- Demographics, medical history, and medication history
- Physical examination
- Vital signs
- Weight, height
- Concomitant medications
- Concurrent medical conditions

- Screening clinical laboratory tests
- 12-Lead ECG
- Urine pregnancy test for females* of childbearing potential
- Efficacy measures:
  - Percentage FVC based on spirometry**
  - 6MWT based on the standard method used for patients with developmental delay
  - JROM using universal goniometry method
  - Cardiac LVMI and Ejection Fraction using 2D echocardiography**
  - Liver and spleen volume using Ultrasonography (USG)**
  - Urine GAG by urine test
  - HRQoL based on HS-FOCUS and CHAQ

Note: *It is known that Hunter syndrome almost exclusively affects males and it is highly unlikely that females will be affected by Hunter syndrome.

Note: **2D echocardiography, USG (liver and spleen volume), and spirometry tests should have been performed within 30 days of subject's enrolment or at the time of screening.

The laboratory and efficacy evaluations done at screening will be considered as baseline for study evaluations. After meeting the eligibility criteria, the investigator or his/her designee will instruct subjects to come for the next visit at the study site.

9.3.2 Study Enrollment/Treatment Phase

The study drug administration during the treatment phase will be done weekly starting from Visit 2 (Week 1, Day 1) till Visit 53 (Week 52, Day 358). The subjects must attend visits as close as possible to the planned day, and ideally within ±3 days.

9.3.2.1 Baseline Visit/Week 1, Day 1/Visit 2

Study enrollment will take place on Week 1, Day 1. If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria, the subject should be enrolled in the study. The following procedures will be performed and documented at study entrance:

- Physical examination
- Height and weight
- Vital signs
- 12-Lead ECG at investigator's discretion or if not performed at screening visit
- Urine pregnancy test for females of childbearing potential
- Documentation of AEs and concomitant medications

The procedure for documenting Screening failures is provided in Section 9.1.14.

9.3.2.2 Visit 3 (Week 2, Day 8) through Visit 53 (Week 52, Day 358)

The following assessments will be performed at these visits:

- Physical examination
- Vital signs
- Urine pregnancy test for females of childbearing potential
- Study diary will be checked
- Documentation of AEs and concomitant medications

9.3.2.3 Efficacy Assessment Visit 28 (Week 27, Day 183)

The mandatory scheduled assessments during the treatment phase will be done at Visit 28 (Week 27, Day 183). The subject will receive the routine dose of study drug on these days. In addition to the assessments done at drug administration visits, the following assessments will be performed at this visit:

- Height and weight
- 12-Lead ECG
- Efficacy measures:
  - Percentage FVC based on spirometry
  - 6MWT based on the standard method used for patients with developmental delay
  - JROM using universal goniometry method
  - Cardiac LVMI and Ejection Fraction using 2D echocardiography
  - Liver and spleen volume using USG
  - Urine GAG by urine test (will be done at Week 14, Day 92 and Week 40, Day 274 also)
  - HRQoL assessments based on HS-FOCUS and CHAQ
- Samples will be collected to assess the clinical laboratory parameters including haematology, urinalysis, and clinical chemistry (will be done at Week 14, Day 92 and Week 40, Day 274 also). Additional tests may be performed at investigator's discretion.

Please refer to Appendix A for list of assessments to be performed from Visit 3 (Week 2, Day 8) to Visit 53 (Week 52, Day 358).

9.3.3 Final Visit/Early Termination/End of Study/Visit 54/Week 53/Day 365

The last scheduled efficacy assessment and safety follow-up visit is Visit 54 (Week 53, Day 365). The following assessments will be performed at this visit:

- Physical examination
- Height and weight
- Vital signs
- Urine pregnancy test for females of childbearing potential
- Efficacy measures:
  - Percentage FVC based on spirometry
  - 6MWT based on the standard method used for patients with developmental delay
  - JROM using universal goniometry method
  - Cardiac LVMI and Ejection Fraction using 2D echocardiography
  - Liver and spleen volume using USG
  - Urine GAG by urine test
  - HRQoL assessments based on HS-FOCUS and CHAQ
- Samples will be collected to assess the clinical laboratory parameters including haematology, urinalysis, and clinical chemistry. Additional test may be performed at investigator's discretion.
- Study diary will be checked and retrieved
- Documentation of AEs and concomitant medications

The study doctor will enquire about any AEs, and any concomitant medications that may have started after the last dose of Elaprase. 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.

9.3.4 Unscheduled Visit

An unscheduled visit can be performed at investigator's discretion or if the trial subject experiences safety concerns. The assessments at unscheduled visits will be performed at investigator's discretion as clinically indicated.

Please refer Appendix A for detailed list of assessments to be performed throughout the study period.

9.3.5 Post Study Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for preexisting conditions or underlying disease should not be considered PTEs or AEs).
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in infusion or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should not be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Preexisting conditions:

- Preexisting conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should not be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should not be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a preexisting episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg, "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs /Serious PTEs:

- If the subject experiences changes in intensity of an AE/serious PTE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the preexisting condition, the worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should not be recorded as an AE. The investigator must make the distinction between exacerbation of preexisting illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are not considered PTEs or AEs, but instead will be documented on an overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" 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 that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.

- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 ADRs

All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility ie, the relationship cannot be ruled out.

The ADRs associated with Elaprase noted during pre- and postmarketing evaluation for Hunter syndrome, are summarized in Tabel 10 a.

Tabel 10 a : Adverse drug reactions associated with use of Elaprase

System organ class	Adverse reaction (preferred term)			
	Very common	**Common**	**Uncommon**	**Not known**
Immune system disorders				Anaphylactoid/anaphylactic reaction
Nervous system disorders	Headache	Dizziness, tremor		
Cardiac disorders		Cyanosis, arrhythmia, tachycardia		
Vascular disorders	Flushing	Hypertension, Hypotension		
Respiratory, thoracic and mediastinal disorders	Wheezing, dyspnoea	Hypoxia, bronchospasm, cough	Tachypnoea	
Gastrointestinal disorders	Abdominal pain, nausea, diarrhoea, vomiting	Swollen tongue, dyspepsia		
Skin and subcutaneous tissue disorders	Urticaria, rash, pruritus, erythema			
Musculoskeletal and connective disorders		Arthralgia		
General disorders and administration site conditions	Pyrexia, chest pain	Infusion-site swelling, face oedema, oedema peripheral		
Injury, poisoning	Infusion-related			

and procedural complications	reaction			

10.1.6 Intensity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.
Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.
Severe: The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study drug will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as not related. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the study drug qualify as ADRs.

10.1.9 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or investigator.

The start date of PTEs/AEs will be determined using the following criteria:

PTEs/AEs	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms/diseases were noted by the subject and/or the investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings or the onset time can be estimated.
Worsening or complication of concurrent medical conditions or any signs/symptoms/diseases before treatment	The date that a worsening or complication of the condition was noted first by the subject and/or the investigator should be recorded.
The examination after start of the study drug showed abnormal values/findings.	The date of examination when an abnormal value or findings that was judged to be clinically significant was noted should be recorded.
The examination at the start of the study drug showed abnormal values/findings and the subsequent examinations showed worsening of the symptoms.	The date of examination when apparent elevation, reduction, increase or decrease was confirmed in judgment according to the trends in those values or findings should be recorded.

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.11 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Dose interrupted – the dose was interrupted due to the particular AE.

10.1.13 Outcome

- Recovered/Resolved – subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Week1, Day 1) or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time the subject signs the ICF and will continue until Week 53, Day 365.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedures, including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

PRO and subject diary will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Subject identification number.
- Investigator's name.
- Name of the study drug
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of serious PTEs will follow the procedure described for SAEs.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor or its designate will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor or its designate will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization drug dictionary.

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

The investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

Electronic CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), and detailed records of drug disposition to enable evaluations or audits from regulatory

authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

The SAP will also include a description of how missing, unused and spurious data will be addressed. All statistical analyses will be performed using SAS® (SAS Institute Inc., NC, USA).

13.1.1 Analysis Sets

Full analysis set (FAS): FAS will comprise all enrolled subjects who received at least one dose of study drug and with at least one post-baseline evaluation of any of the efficacy endpoints. This analysis set will be used for the efficacy analyses.

Safety analysis set (SAF): SAF will comprise all subjects who received at least one dose of study drug at any time during trial.

The definition of each analysis set will be described in the Handling Rules for Analysis Data.

The sponsor or its designate will verify the validity of the definitions of the analysis sets as well as the rules for handling data, with consulting a medical expert as needed. If necessary, the Handling Rules for Analysis Data will be supplemented with new handling rules that were not discussed at the planning stage. The Handling Rules for Analysis Data must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

The number and percentage of all the subjects entering, completing the study, discontinued from study along with primary reasons for discontinuation will be provided. The listing of subjects who discontinued from the study along with reason of discontinuation will be presented.

Descriptive statistics for various continuous demographic variables: age (in years), height (in cm), and weight (in kg) will be provided. The frequency count (n) and percentages (%) for categorical variables: sex, ethnic origin, and race will be provided. Other baseline data will be summarized and listed appropriately.

Medical history will be coded using the latest available version of MedDRA. The frequency count (n) and percentage (%) of subjects will be summarized according to the coded terms of system organ class (SOC) and preferred term (PT).

13.1.3 Efficacy Analysis

The efficacy analysis will be performed on all the subjects in the FAS.

Efficacy Endpoint Analysis

All secondary efficacy endpoints will be analysed using the FAS population who received at least one dose of study drug.

Descriptive summary of the secondary efficacy endpoints, ie, baseline,post-baseline, and change from baseline will be provided along with 90% CI.

Health-related quality of life measured using HS-FOCUS and CHAQ will be summarised descriptively.

13.1.4 Safety Analysis

Adverse events will be summarized by SOC and PT. Adverse events will be coded using the most recent version of MedDRA. A subject will only be counted once per system organ class and once per PT.

Treatment-emergent AEs will be summarized for all subjects in SAF by SOC and PT. Each TEAE will be counted only once for a given subject. If the same TEAE occurs on multiple occasions, the highest severity and relationship will be considered for analysis. Summary of serious TEAEs will be presented separately. All other TEAEs will be summarized in similar manner.

The counts and percentage of subjects will be presented for the following summaries:

a) All AEs
b) All TEAEs

c) All serious TEAEs
d) All TEAEs by severity
e) All TEAEs by relationship to study treatment
f) All TEAEs related to study treatment
g) All TEAEs related to study treatment by severity
h) All serious TEAEs by relatedness and severity
i) All TEAEs leading to death
j) All TEAEs leading to discontinuation from study
k) Infusion-related reactions
l) ADRs (refer to Tabel 10 a)
m) Unexpected ADRs

No statistical inference will be performed on AEs. Listings will be presented for all AEs and TEAEs listed above.

13.1.4.1 Physical Examination

Counts (and percentages) plus shift-changes from baseline data in the physical exam will be summarized.

Individual data listings of change from baseline data in the physical exam will be presented.

13.1.4.2 Vital Signs

The observed and change from baseline data of vital signs: blood pressure and pulse rate will be summarized descriptively.

Individual data listings of each vital sign parameter will be presented.

13.1.4.3 Laboratory assessments

The observed data of clinical laboratory assessments will be summarized and presented descriptively as appropriate. Clinical significant changes will be summarized categorically (normal, clinically significant and clinically not significant).

Individual data listings of each laboratory parameter will be presented.

13.1.4.4 12-Lead ECG

The observed data of 12-lead ECG will be summarized and presented descriptively as appropriate. Clinically significant changes will be summarized categorically (normal, clinically significant, and clinically not significant).

13.1.4.5 Individual data listings of 12-lead ECG will be presented. Urine Pregnancy Test

Individual data listings of urine pregnancy test will be presented for each subject (if any).

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

A total of 5 subjects will be enrolled in this study. According to the observed recruitment trend from other published trial results on clinicalTrials.gov and considering the rarity of the disease (based on rare disease epidemiology in India and poor diagnostic rate of ~0.1%) and the low availability of subjects, 5 Elaprase naive subjects whose disease condition is clinically diagnosed and confirmed will be enrolled.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the investigator's binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study

assessment. A Deviation Form should be completed by the site clinical research associate and signed/approved by the project manager/clinical team lead for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the drug is stored and prepared, and any other facility used during the study. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB/IEC Approval

IRBs and IECs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the package insert, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification, no protocol activities including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the subject and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's parents/guardian/LAR may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's parents/guardian/LAR, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's parents/guardian/LAR, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be

signed and dated by the subject, or the subject's parents/guardian/LAR, at the time of consent and prior to the subject entering into the study. The subject or the subject's parents/guardian/LAR should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. An assent form must be signed by participants of ≥7 to <18 years of age The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's parents/guardian/LAR in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document as per ICMJE guidelines. All publications and presentations must be prepared in accordance with this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

Visits	V1	V2	V3 to V14	V15	V16 to V27	28	V29 to V40	V41	V42 to V53 (EOT)	V54	Unscheduled visit
	Screening	Baseline	Treatment and Assessments							EOS/ET Assessments[c]	
Weeks (W) /Days(D)	Day -14 to Day -1	W1D1 (Day 1)[a]	W2 D1 to W13D1 (Day 8 to Day 85)[b]	W14 D1 (Day 92)[b]	W15 D1 to W26 D1 (Day 99 to Day 176)[b]	W27 D1 (Day 183)[b]	W28 D1 to W39 D1 (Day 190 to Day 267)[b]	W40 D1 (Day 274)[b]	W41 D1 to W52 D1 (Day 281 to Day 358)[b]	W53 D1 (Day 365)[b]	
Informed Consent	X										
Demographics (Age and Sex)	X										
Anthropometry (Height, Weight)[d]	X	X	X	X	X	X	X	X	X	X	
Diagnosis and Baseline Disease Characteristics[e]	X										
Medical History	X										
Prior Medications	X										
Prior Disease-Specific Therapies/ Medications	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[f]	X	X	X	X	X	X	X	X	X	X	X

Visits	V1	V2	V3 to V14	V15	V16 to V27	28	V29 to V40	V41	V42 to V53 (EOT)	V54	Unscheduled visit
	Screening	Baseline	Treatment and Assessments							EOS/ET Assessments[c]	
Weeks (W) /Days(D)	Day -14 to Day -1	W1D1 (Day 1)[a]	W2 D1 to W13D1 (Day 8 to Day 85)[b]	W14 D1 (Day 92)[b]	W15 D1 to W26 D1 (Day 99 to Day 176)[b]	W27 D1 (Day 183)[b]	W28 D1 to W39 D1 (Day 190 to Day 267)[b]	W40 D1 (Day 274)[b]	W41 D1 to W52 D1 (Day 281 to Day 358)[b]	W53 D1 (Day 365)[b]	
Vital Signs [g]	X	X	X	X	X	X	X	X	X	X	X
Inclusion and Exclusion Criteria	X	X									
12-Lead ECG [h,i]	X					X				X	
Subject Diary Dispensed		X									
Subject Diary Retrieved and Reviewed			X	X	X	X	X	X	X	X	
Study Drug Administration		0.5 mg/kg IV infusion every week									
FVC, percent predicted/ FVC absolute[j,i] (Spirometry)	X[k]					X				X	
6MWT[l,i]	X					X				X	
Cardiac LVMI & Ejection Fraction[m,i] (2D echocardiography)	X[k]					X				X	
Liver and spleen volume[n,i] (USG)	X[k]					X				X	

Visits	V1	V2	V3 to V14	V15	V16 to V27	28	V29 to V40	V41	V42 to V53 (EOT)	V54	Unscheduled visit
	Screening	Baseline	Treatment and Assessments							EOS/ET Assessments[c]	
Weeks (W) /Days(D)	Day -14 to Day -1	W1D1 (Day 1)[a]	W2 D1 to W13D1 (Day 8 to Day 85)[b]	W14 D1 (Day 92)[b]	W15 D1 to W26 D1 (Day 99 to Day 176)[b]	W27 D1 (Day 183)[b]	W28 D1 to W39 D1 (Day 190 to Day 267)[b]	W40 D1 (Day 274)[b]	W41 D1 to W52 D1 (Day 281 to Day 358)[b]	W53 D1 (Day 365)[b]	
Global Joint Range of Motion (JROM) Score[i]	X	X				X				X	
HRQoL (HS-FOCUS and CHAQ)[o,i]	X					X				X	
Sample Collection											
Urinalysis[p,i]	X			X		X		X		X	
Clinical chemistry[q,i]	X			X		X		X		X	
Hematology[r,i]	X			X		X		X		X	
Urine GAG, µg GAG/mg creatinine[s,i]	X			X		X		X		X*	
Urine Pregnancy Test for Female of Childbearing Potential[t]	X	X	X	X	X	X	X	X	X	X	
AEs collection	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: 6WMT=6 Minute Walk Test, AE=Adverse event, ALP=Alkaline phosphatase, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, BUN=Blood urea nitrogen, CHAQ=Childhood Health Assessment Questionnaire, D=Day, ECG=Electrocardiogram, ET=Early termination, FVC=Forced vital capacity,

GAG=Glycosaminoglycan, GGT=Gamma-glutamyltransferase, HRQoL=health related quality of life, HS-FOCUS=Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale; IV=intravenous; JROM=Joint Range of Motion, LVMI=Left Ventricular Mass Index, USG=Ultrasonography, V=Visit, W=Week.

a. The day of first study drug administration for treatment period is Day 1. The day before first study drug administration for treatment period is Day -1.
b. The subjects must attend visits as close as possible to the planned day, and ideally within ±3 days.
c. The end of study visit is defined as the date of the last visit (Week 53) of the subject or until discontinuation of study drug.
d. Height will be measured at baseline for all subjects; for subjects <18 years at baseline, height will also be measured at the assessment visits (Week 27, Day 183 and Week 53, Day 365). Height can also be optionally measured at Visit 15 (Week 14, Day 92) and Visit 41 (Week 40, Day 274) at investigator's discretion, and if measured the data will be recorded in eCRF. Weight will be measured for all the subjects at all the visits.
e. Including date of diagnosis, past and present illnesses/complications due to Hunter syndrome.
f. Physical examination includes general appearance; assessments of head, neck, and thyroid; eyes, ears, nose, and throat; chest and lungs; heart; lymph nodes; abdomen; anorectal; genitourinary; skin; musculoskeletal; endocrine; neurological; and other (at investigator's discretion).
g. Include blood pressure, pulse, respiratory rate, and temperature. Vital signs are taken immediately before and after every infusion (within 10 minutes).
h. Can be performed at Visit 2 if not done at screening and repeated at other visits at investigator's discretion.
i. All these assessments can also be performed at unscheduled visit at investigator's discretion. If these assessments are done at investigator's discretion at any unscheduled visit, the data will be recorded in eCRF.
j. As the trial includes pediatric population also, feasibility of FVC procedure in subjects < 5 years of age can be performed by the investigator prior to performing the procedure.
k. 2D echocardiography, USG (Liver and spleen volume), and spirometry tests should have been performed within 30 days of subject's enrolment or at the time of screening.
l. As the trial includes pediatric population also, feasibility of 6MWT procedure in subjects < 5 years of age can be performed by the investigator prior to performing the procedure.
m. Cardiac LVMI and Ejection Fraction will be determined by 2D echocardiography.
n. Liver and spleen volumes will be determined by Ultrasonography.
o. HRQoL assessment based on HS-FOCUS will be done in all subjects and CHAQ will be done in subjects between age of ≥6 months to ≤18 years.
p. Includes specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, red blood cells, white blood cells, epithelial cells, crystals, casts, and bacteria.
q. Includes glucose, urea, potassium, sodium, chloride, total bilirubin, total protein, albumin, globulin, ALP, ALT, AST, BUN, and GGT and fasting lipids profile (high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides, and total cholesterol).
r. Includes haemoglobin, haematocrit, red blood cell count, and white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), and platelet count.
s. Mean normalized urine GAG will be analyzed using urine testing. The urine GAG levels will be normalized to urine creatinine and will be reported as microgram GAG per milligram creatinine (µg GAG/mg creatinine).

t. It is known that Hunter syndrome almost exclusively affects males and it is highly unlikely that females will be affected by Hunter syndrome.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 Good Clinical Practice (ICH GCP) and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are not performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's parents/guardian/LAR.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an serious adverse event (SAE), notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's parents/guardian/LAR is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's parents/guardian/LAR may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

21. A statement that the subject or the subject's parents/guardian/LAR will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.
25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

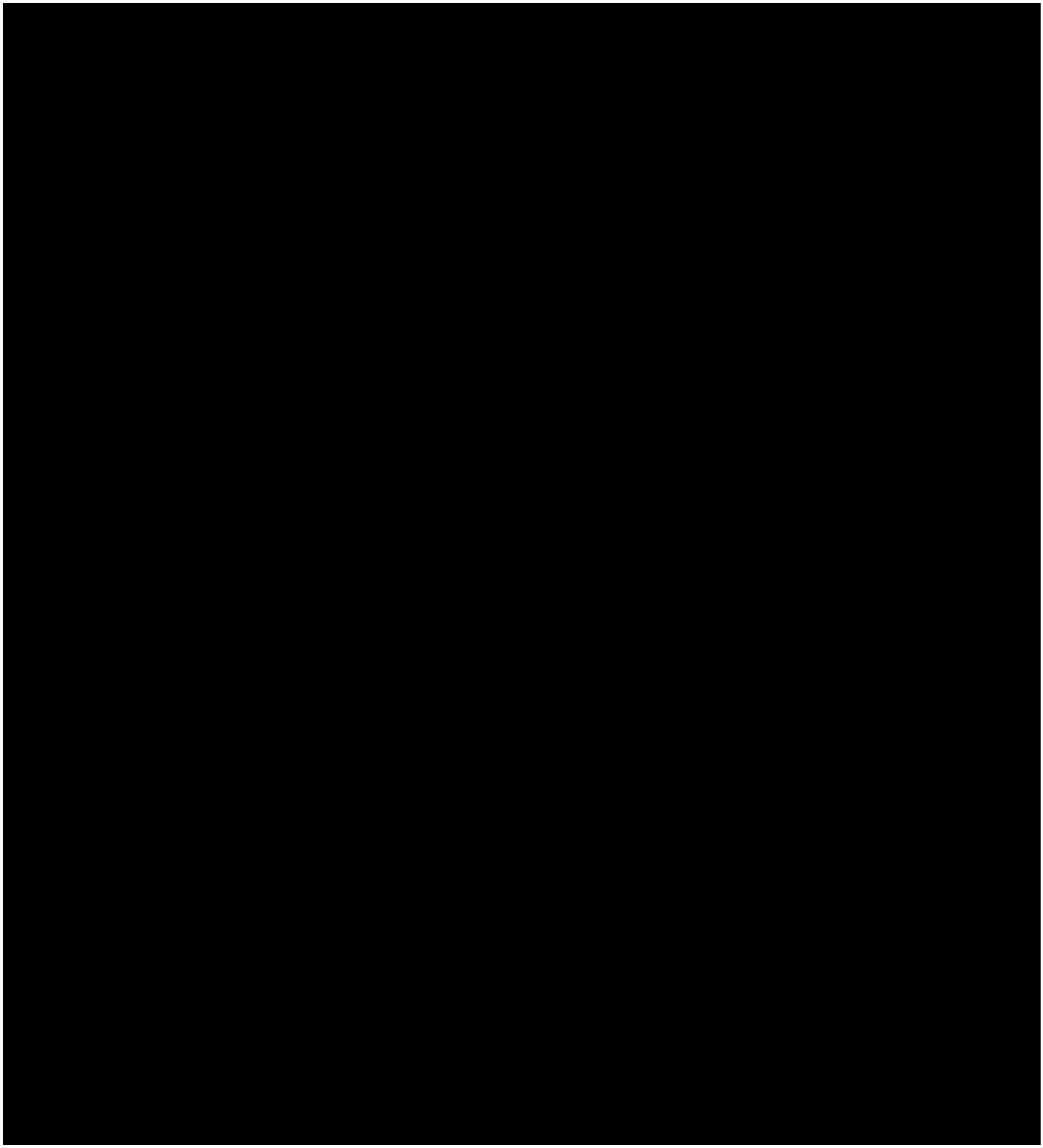
Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

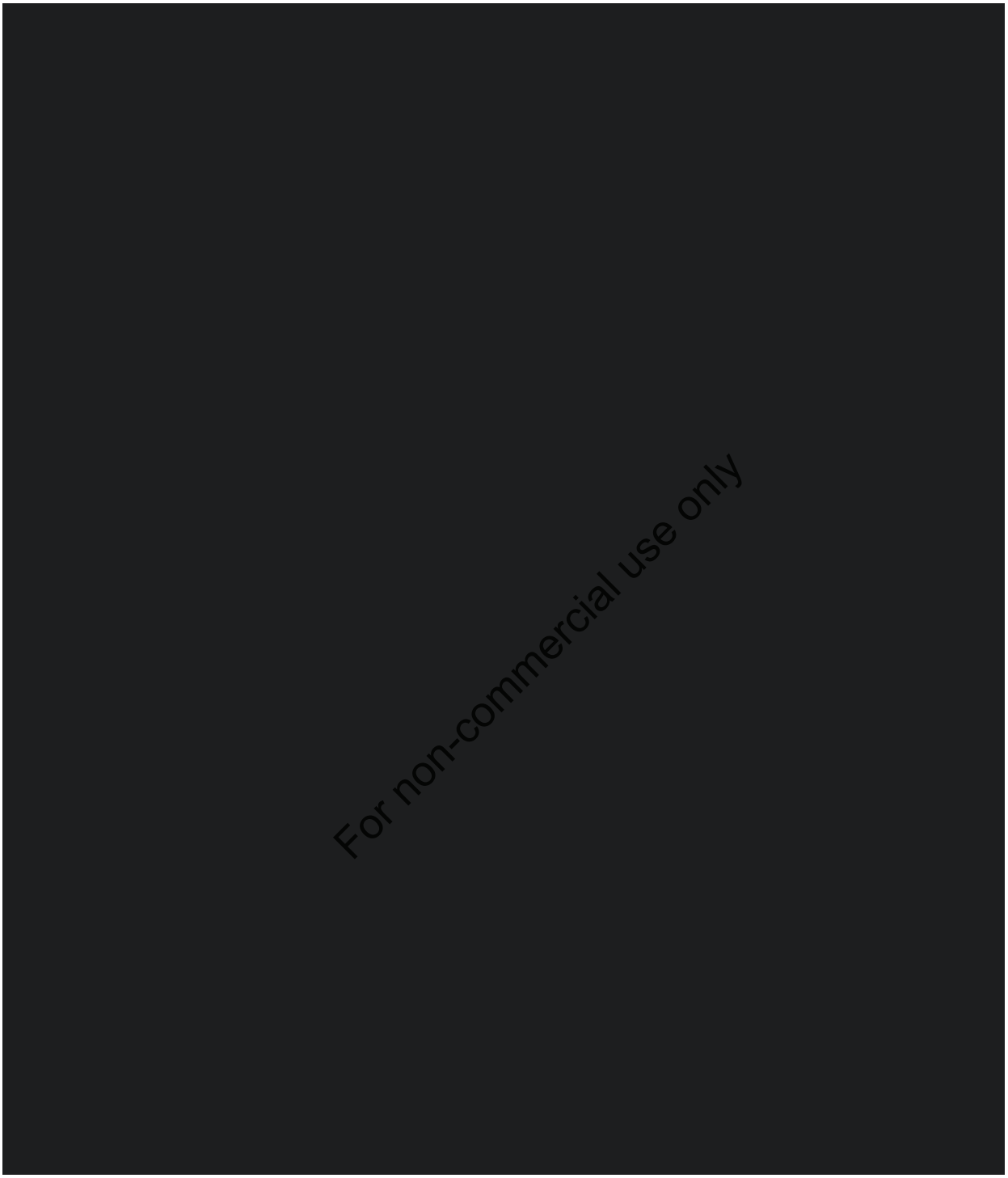
- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.
- Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:
- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

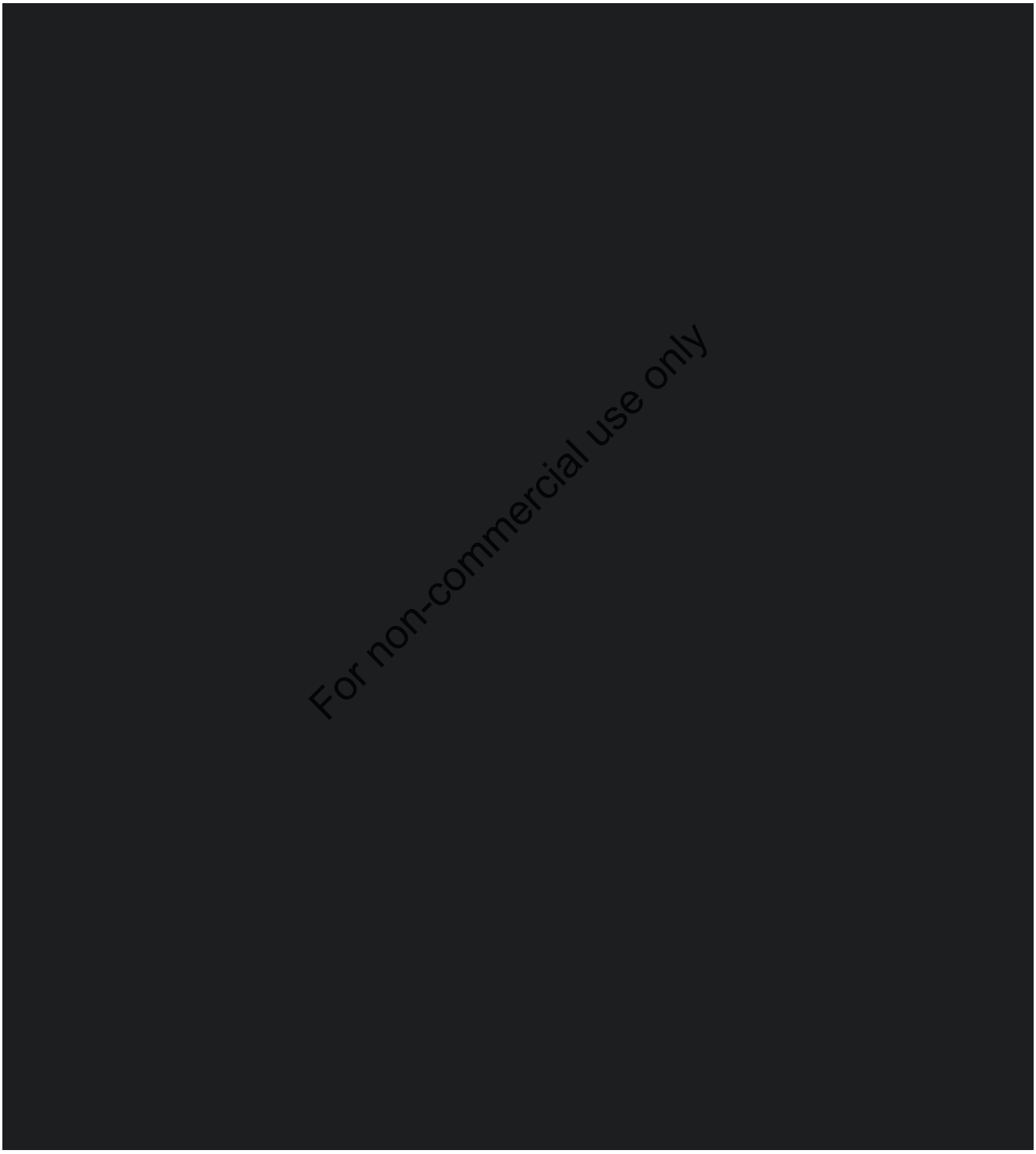
Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

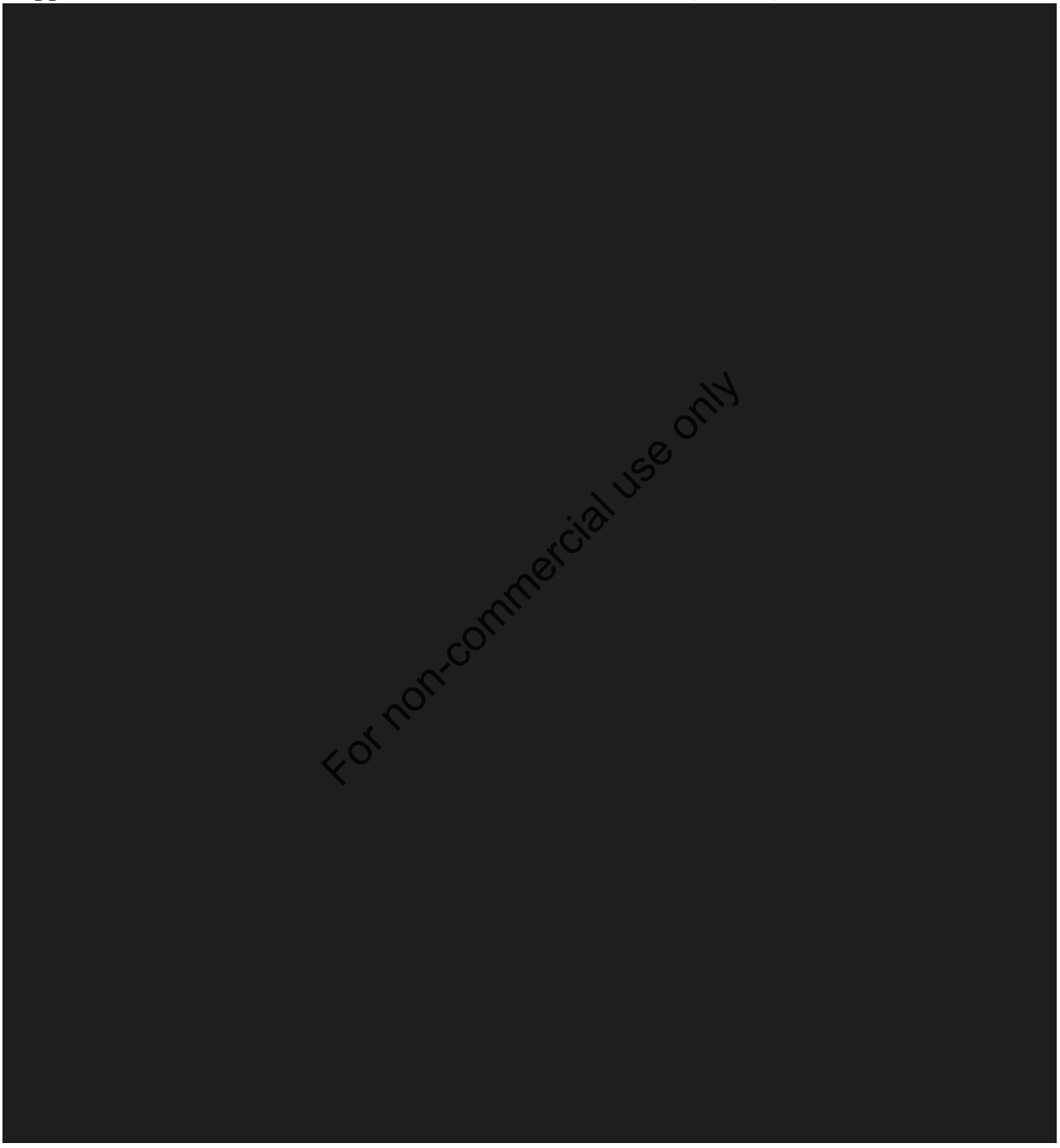
Appendix E Hunter Syndrome – Functional Outcomes For Clinical Understanding Scale (HS-FOCUS); Parent Completed Questionnaire (Shortened version)

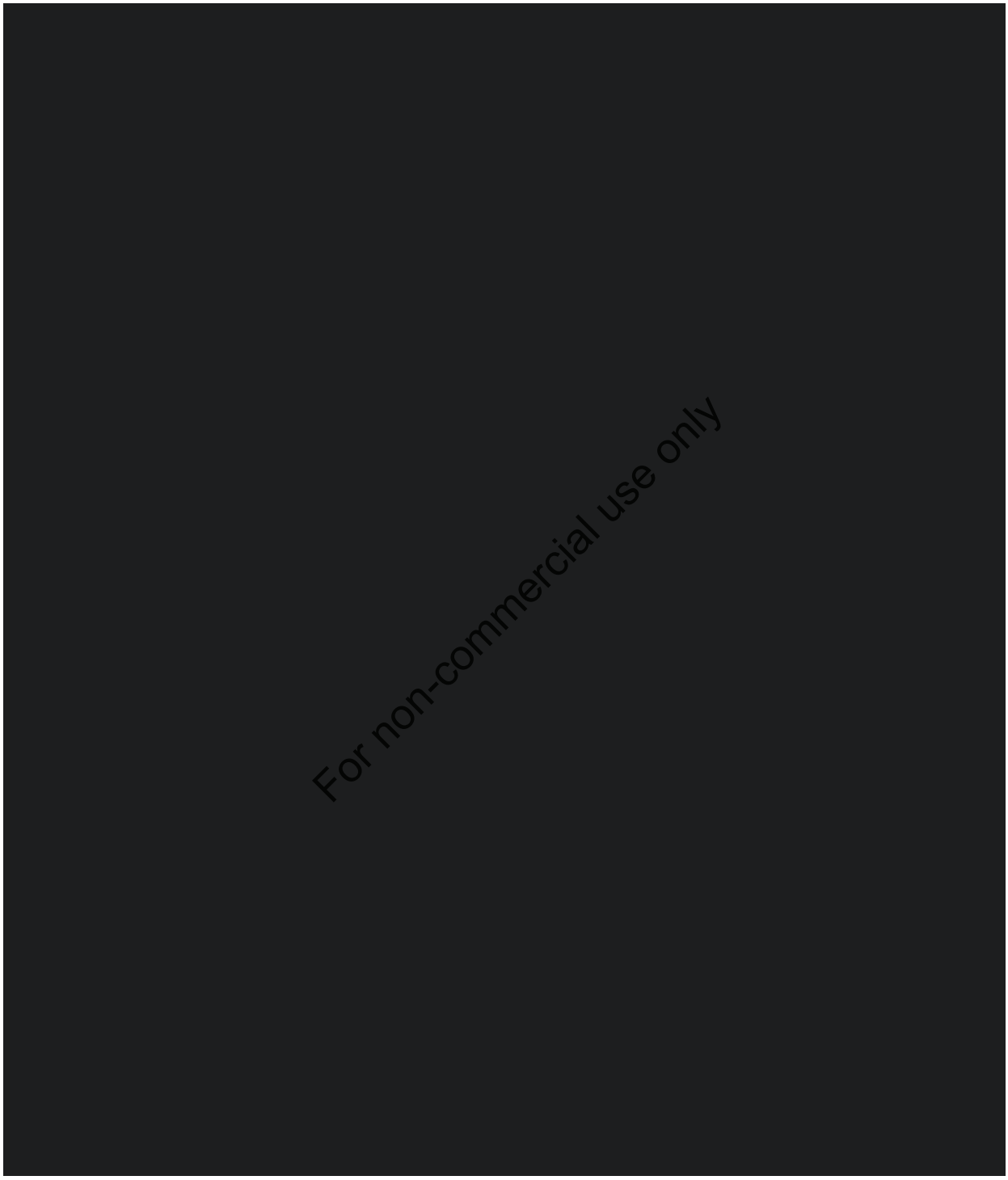



For non-commercial use only



Appendix F Childhood Health Assessment Questionniare (CHAQ)

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Appendix G Elaprase Package Insert for India

Appendix H Detailed Description of Amendments to Text

This is an original protocol.