Statistical Analysis Plan

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 1.0, 21 May 2024

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STATISTICAL ANALYSIS PLAN

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Phase: IV

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JSS Sign off			
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Approver	**Designation**		**Date**

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
NA	NA	NA

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ABBREVIATIONS

Abbreviation	Definition
AE(s)	Adverse event(s)
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATP	Adenosine Triphosphate
BUN	Blood Urea Nitrogen
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EOS	End of Study
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
ICH-GCP	International Council on Harmonization-Good Clinical Practice
ICF	Informed Consent Form
EC	Ethics Committee
LAR	Legally Acceptable Representative
ITT	Intent to Treat
LOCF	Last Observation Carry Forward
MedDRA	Medical Dictionary for Regulatory Activities
JSS India	JSS Medical Research Asia Pacific Private Limited
PI	Principal Investigator
PP	Per Protocol
PPS	Per Protocol Set
RBC	Red Blood Cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TLGs	Tables, Listings and Graphs
WBC	White Blood Cell
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

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

1.1.2 Secondary Objective(s)

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

1.2 Endpoints

1.2.1 Primary Endpoint(s)

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.

1.2.2 Secondary Endpoint(s)

1. Change from baseline in percentage Forced Vital Capacity (%FVC) as a measure of respiratory function at Weeks 27 and 53.
2. Change from baseline in 6 Minute Walk Test (6MWT) as a measure of physical functional capacity at Weeks 27 and 53.
3. Change from baseline in Cardiac Left Ventricular Mass Index (LVMI) and Ejection Fraction at Weeks 27 and 53.
4. Change from baseline in liver volume at Weeks 27 and 53.
5. Change from baseline in spleen volume at Weeks 27 and 53.
6. Change from baseline in normalized urine GAG (uGAG) levels at Weeks 14, 27, 40, and 53.
7. Change from baseline in Global Joint Range of Motion (JROM) score at Weeks 27 and 53.
8. Changes from baseline in anthropometric parameters including height in subjects <18 years at baseline and weight in all subjects at Weeks 27 and 53.

9. 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.

1.3 Estimand(s)

Not Applicable

2.0 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 based on study inclusion and exclusion criteria in Indian Pediatric and Adult Population patients.

Eligible patients will be administered a 0.5 mg/kg dose 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

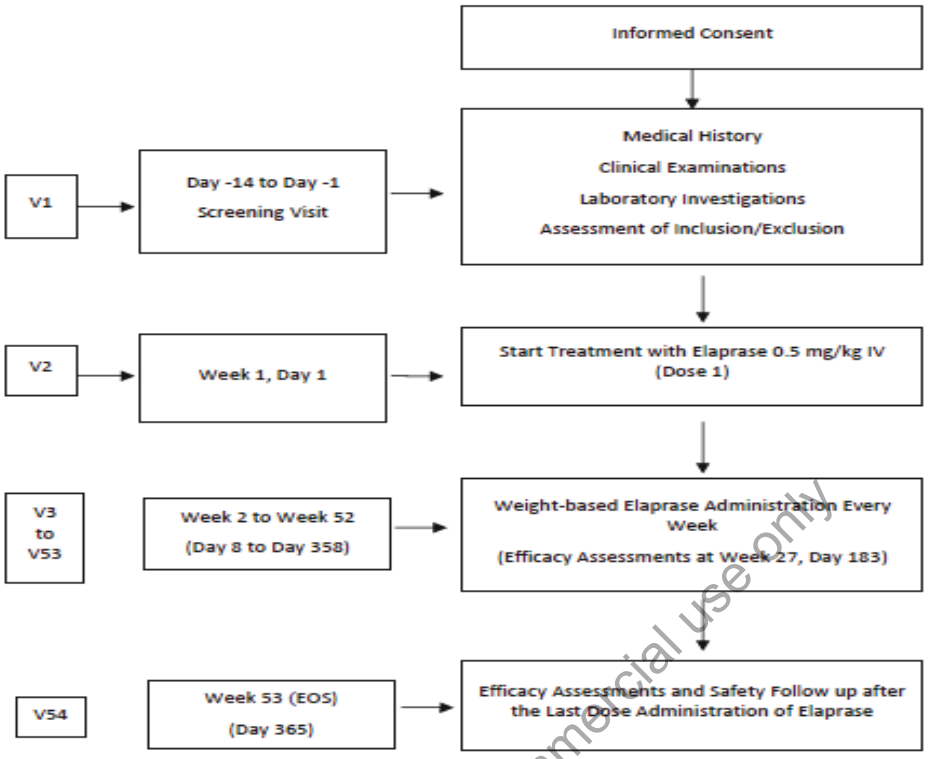
The total duration of the study for each subject will be up to 55 weeks for an individual patient spread over three phases in following sequence:

- Screening period (Days 14 to -1) consists of 14 days.
- Study treatment period consists of 52-weeks (Week 1 to Week 52)
- Follow-up period consists of 1 week (Week 53) followed 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.

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.



Schedule of Visits and 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

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[i,j] (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	
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

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).

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

No hypothesis will be tested in this study.

3.1 Statistical Hypotheses

Not Applicable.

3.2 Statistical Decision Rules

Not Applicable.

3.3 Multiplicity Adjustment

Not Applicable.

4.0 SAMPLE-SIZE DETERMINATION

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.

5.0 ANALYSIS SETS

Following analysis set will be used for efficacy and safety data analysis.

5.1 Safety Analysis Set

The Safety Analysis Set will comprise all subjects who received at least one dose of study drug at any time during trial.

5.2 Full Analysis Set

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.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Safety Analysis set (SAF) will be used for the primary safety analyses and Full Analysis set (FAS) will be used for secondary efficacy analyses. For all the safety analysis, Safety Analysis set (SAF) will be the primary approach for analysis.

Depending on the study population, data compiled up to the point of discontinuation will be used for analysis. Patients who are withdrawn prematurely from the study treatment will be included in all analyses (up to the date of withdrawal), regardless of the duration of treatment.

Descriptive statistics including number of non-missing observations (n), mean, standard deviation (SD), median, P_{10}, P_{90}, minimum, and maximum (range) will be presented for continuous variables. For categorical data, the descriptive statistics will be presented with number of exposed patients and number (n) with percentage of observations in the various categories of the endpoint, where percentage will be based on the exposed patients.

All data will be summarized using descriptive statistics and presented in subject data listings. All the statistical tests will be carried out as two-sided on 5 % level of significance unless otherwise stated.

6.1.1 Handling of Treatment Misallocations

This is a single arm study. All subjects will be administered Elaprase.

6.2 Disposition of Subjects

The summary for study disposition will be prepared on All Screened population and its include number of subjects screened, number of screen failures, number and percentage of subjects enrolled, reason of screen failure, the number and percentage of subjects who are in each analysis set, who complete the study, and who withdraw early from the study which will be provided using frequencies and percentages.

A listing will be presented to describe dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each patient.
A listing and table of inclusion/exclusion criteria responses will also be provided.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Demographic variables will be summarized descriptively. The variables will include age, gender, race, weight, height and BMI. Variables that are measured on a categorical scale will be summarized using frequencies and percentages.

For variables that are measured on a continuous scale, such as the age**,** weight**,** height and BMI etc., the number of non-missing observations (n), mean, median, SD, P_{10}, P_{90}, minimum, and maximum will be presented.

6.3.2 Medical History

Medical history will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). The frequency and percentage of subjects will be summarized according to the coded terms of system organ class and preferred and the corresponding subject data listing will also be provided. . Analysis of medical history will be presented on Safety Analysis population(SAF).

6.4 Prior Medications and Concomitant Medications

Prior medications will include any medication started and discontinued prior to the first study treatment dose. Prior/ Concomitant medications will include those which started prior to the first study treatment date and continued past that date. Also, concomitant medications will include all the medications which started after the first study treatment date.
All prior and concomitant and prior/ concomitant medications will be presented on Safety Analysis Population (SAF) and coded and summarized using frequencies and percentages, by Therapeutic class and generic name by treatment and overall using the most recent version of the WHO drug classification.

6.5 Efficacy Analysis

The secondary efficacy analysis will be performed on the Full Analysis Set (FAS). Descriptive statistics for continuous variables will be presented with number (n) of non-missing observations, mean, standard deviation, median, and P_{10}, P_{90}, minimum and maximum. For categorical data, the descriptive statistics will be presented with number of exposed patients and number (n) with percentage of observations in various categories of the variable, where percentage will be based on exposed patients. Descriptive analyses will also include graphical presentations of data, wherever appropriate. Individual data listings will also be provided.

6.5.1 Primary Endpoint(s) Analysis

Not applicable. There is no primary efficacy endpoint.

6.5.2 Secondary Endpoint(s) Analysis

For analysis of secondary endpoints, all subjects in Full Analysis Set will be used.

- **Change from baseline in percentage Forced Vital Capacity (%FVC) as a measure of respiratory function at Weeks 27 and 53.**

  Forced vital capacity (FVC) is the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.

Subjects who answered," Was Spirometry assessment performed?" as "Yes" with non-missing "FVC (%)" from the dataset SPIROMETRY will be considered.

Mean change in the Forced vital capacity (%FVC) from baseline to week 27 will be summarized using number of patients (n), mean, SD, range, minimum and maximum and 90% CI.

The same analysis will be performed to analyze the mean change from baseline to week 53.

- **Change from baseline in 6 Minute Walk Test (6MWT) as a measure of physical functional capacity at Weeks 27 and 53**

Six-minute walk test (6MWT) is the distance covered over a time of 6 minutes.

Subjects who answered," Was 6 Minutes Walk Test performed?" as "Yes" with non-missing "Distance covered in meters" from the dataset "SIX MINUTES WALK TEST" will be considered.
Mean change in the six-minute walk test (6MWT) from baseline to week 27 will be summarized using number of patients (n), mean, SD, range, minimum and maximum and 90% CI.

The same analysis will be performed to analyze the mean change from baseline to week 53.

- **Change from baseline in Cardiac Left Ventricular Mass Index (LVMI) and Ejection Fraction at Weeks 27 and 53.**

Left ventricular (LV) mass is the weight of the left ventricle, typically estimated using echocardiography, and is thought to represent the cumulative effect of blood pressure on the heart. Left ventricular mass index (LVMI) is a surrogate of left ventricular hypertrophy and a predictor of cardiac morbidity and mortality.

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 (m2).
Cardiac LVMI (in gram per square meter [g/m2]) =LVM /BSA.

Subjects who answered," Was 2D Echocardiography assessment performed?" as "Yes" with non-missing "Left Ventricular Mass LVM" from the dataset 2D ECHOCADIOGRAHY will be considered.

Mean change in the Left Ventricular Mass Index (LVMI) from baseline to week 27 will be summarized using number of patients (n), mean, SD, minimum and maximum and 90% CI.

Cardiac LVMI (in gram per square meter [g/m2]) =LVM /BSA.

The same analysis will be performed to analyze the mean change from baseline to week 53 for LVMI.

And

Subjects who answered," Was 2D Echocardiography assessment performed?" as "Yes"" and non-missing "Ejection Fraction" from the dataset 2D ECHOCADIOGRAHY will be considered.
Ejection fraction measures your heart's ability to pump oxygen-rich blood out to your body. In a healthy heart, the fraction is a higher number. A low number means that the heart has difficulty keeping up with your body's needs.

Mean change in the Ejection fraction from baseline to week 27 will be summarized using number of patients (n), mean, SD, range, minimum and maximum and 90% CI.

The same analysis will be performed to analyze the mean change from baseline to week 53 for Ejection fraction.

- **Change from baseline in liver volume at Weeks 27 and 53.**

Subjects who answered," Was USG for liver and spleen performed?" as "Yes" with non-missing "Liver Volume" from the data set "ULTRASONOGRAPHY OF LIVER AND SPLEEN" will be considered.
Mean change in the liver volume from baseline to week 27 will be summarized using number of patients (n), mean, SD, minimum, maximum and 90% CI.
The same analysis will be performed to analyze the mean change from baseline to week 53 for liver volume.

- **Change from baseline in spleen volume at Weeks 27 and 53.**

Subjects who answered," Was USG for liver and spleen performed?" as "Yes" with non-missing "Spleen Volume" from the data set "ULTRASONOGRAPHY OF LIVER AND SPLEEN" will be considered.
Mean change in the spleen volume from baseline to week 27 will be summarized using number of patients (n), mean, SD, minimum, maximum and 90% CI.

The same analysis will be performed to analyze the mean change from baseline to week 53 for spleen volume.

- **Change from baseline in normalized urine GAG (uGAG) levels at Weeks 14, 27, 40, and 53.**

  Subjects who answered," Was the urine sample collected? as "Yes" with non-missing "Spleen Volume" from the data set "CLINICAL LABORATORY TEST FOR GAG" will be considered.

  Mean change in the normalized urine GAG (uGAG) levels from baseline to week 14 will be summarized using number of patients (n), mean, SD, minimum, maximum and 90% CI,

  The same analysis will be performed to analyze the mean change from baseline to week 27, 40 and 53 for spleen volume**.**

- **Change from baseline in Global Joint Range of Motion (JROM) score at Weeks 27 and 53**

  Subjects who answered," Was Global JROM assessment performed? as "Yes" with non-missing "Global JROM" from the data set "GLOBAL JOINT RANGE OF MOTION (JROM)" will be considered.

  Mean change in the Global Joint Range of Motion (JROM) from baseline to week 27 will be summarized using number of patients (n), mean, SD, minimum, maximum and 90% CI,

  The same analysis will be performed to analyze the mean change from baseline to week 53 for JROM**.**

- **Changes from baseline in anthropometric parameters including height in subjects <18 years at baseline and weight in all subjects at Weeks 27 and 53.**

  Subjects who have non-missing "Height" for height parameter and non-missing "Weight" for weight parameter from the dataset "VITAL SIGNS AND ARTHROPOMETRY will be considered.
  Mean change in the height in subjects <18 years from baseline to week 27 will be summarized using number of patients (n), mean, SD, minimum, maximum and 90% CI,

  The same analysis will be performed to analyze the mean change from baseline to week 53 for height in subjects <18 years and the mean change from baseline to week 27 and 53 for weight in all the subjects**.**

- **Change from baseline in the health-related quality of life (HRQoL) based on Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS in all subjects and Childhood Health Assessment Questionnaire (CHAQ) in subjects between age of ≥1 year to ≤18 years at Weeks 27 and 53.**

  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 questionnaire has 5 function domains (walking/standing, grip/reach, school/work, activities, and breathing).

  The scale of the 5 function domains ranges from 0 to 3 i.e.

  - 0 score indicates "With No Difficulty"
  - 1 score indicates "With Some Difficulty"
  - 2 score indicates "With Much Difficulty"
  - 3 score indicates "Unable To Do"

  The 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.

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

  Domain score=Σ $item\ scores\ within\ domain$ / $No.\ of\ items\ completed\ within\ domain.$

  The HRQoL assessment based on HS-FOCUS will be performed in all subjects at screening, Weeks 27 and 53.

  Mean change in the domain score from baseline to week 27 will be summarized using number of patients (n), mean, SD and 90% CI.

  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 represent 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 analysis of impact of illness on ability to function in daily life will be performed from study baseline for the Prospective Efficacy Population utilizing the CHAQ. Results will be presented in tabular format, as well as in a by-patient listing.

The CHAQ includes 30 items measured on a scale of 0 to 3:

0=Without any difficulty

1=With some difficulty

2=With much difficulty

3=Unable to do

Missing: Does not apply

The highest scoring item in each category determines the CHAQ Score for that category.

Disability Index Score: The mean score for the 8 subscales (dressing, hygiene, arising, eating, walking, reach, grip and activities) is the Disability Index Score.

The same analysis will be performed to analyze the mean change from baseline to week 27 and 53 for CHAQ score and the mean change from baseline to week 27 and 53 disability index will be performed for subjects between age of ≥1 year to ≤18 years.

6.6 Safety Analysis

6.6.1 Primary Endpoint(s) Analysis

- **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.**

Where Infusion related reaction defined as the adverse event that occurs to the subjects after the administration of medication and must be related to the study medication. i.e. Injury, poisoning and procedural complications.

The frequency and percentage of subjects with 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 will be presented. 90% CI of proportion calculated by using Clopper-Pearson method.

The proportion of patients experiencing an adverse event during 53 weeks of study duration after the initiation of Elaprase will be calculated and 90% confidence intervals will be constructed.

A subject level listing will also be prepared for AEs. Furthermore, a separate listing of SAEs and AEs that lead to withdrawal will be provided.

AE and 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.

All AEs, all SAEs, all TEAEs, all TEAEs by severity, by relationship to study treatment, related to study treatment, related to study treatment by severity, all TEAEs leading to death, all TEAEs leading to discontinuation from study.
All serious AEs, serious TEAEs by relatedness and severity, Infusion-related reactions, ADRs and Unexpected ADRs
AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA).

6.6.2 Other Safety Analysis

6.6.2.1 Laboratory assessments

The laboratory evaluations include hematology tests and clinical chemistry tests, and analysis will be presented on Safety Analysis population (SAF).

The laboratory data with different units from various laboratories will be converted into System International (SI) units.

Hematology

All continuous variables (results) will be summarized descriptively, using the number of non-missing observations (n), mean, median, SD, P_{10}, P_{90} minimum, maximum (range) and frequencies and percentages for categorical variables (done/not done and normal/abnormal CS/

abnormal NCS), at screening, Weeks 14, 27, 40, and 53 for overall subjects in the available treatment arm. Hematology data which includes (Hemoglobin, hematocrit, platelet count, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC), RBC count, WBC count, differential count (neutrophils, eosinophils, lymphocytes, basophils, monocytes will be analyzed using the values of change from baseline to each post baseline visits.
A subject level listing will also be prepared for hematology.

Clinical Chemistry: All continuous variables (results) will be summarized descriptively, using the number of non-missing observations (n), mean, median, SD, P_{10}, P90, minimum, maximum (range), frequencies and percentages for categorical variables (done/not done and normal/abnormal CS/ abnormal NCS), at screening, Weeks 14, 27, 40, and 53 for overall subjects in the available treatment arm. Clinical chemistry data which includes (AST, ALT, total bilirubin, Alkaline Phosphatase, H.D.L., L.D.L., Triglyceride, Total Cholesterol, Blood Urea Nitrogen (BUN), Serum Creatinine, Random Blood Glucose (RBG), Albumin, Globulin, Total Protein, Gamma-Glutamyl Transferase (GGT), Sodium, Potassium, Chloride, Bicarbonate and Urea. These variables will be analyzed using the values of change from baseline to each post baseline visit.
A subject level listing will also be prepared for Clinical Chemistry.

6.6.2.2 Physical Examinations

All the categorical variables will be summarized using frequencies and percentages. Safety Analysis Population (SAF) will be use in physical examination analysis. The number (%) of subjects will be reported at each scheduled visit for overall, for normal and abnormal. The same will be extended to 'If Abnormal- CS and NCS' for categorical variables of physical examination data, which includes

- Head and Neck
- Eyes, Ears, Nose and Throat
- Skin and Appendages
- Renal
- Cardiovascular
- Pulmonary
- Gastrointestinal
- Endocrine
- Genitourinary
- Neurologic
- Musculoskeletal
- Lymph Nodes
- Other, if any

A listing of all physical examination assessments will be provided.

6.6.2.3 Vital signs

The vital signs include body temperature (°C), pulse rate (beats/min), respiratory rate (breaths/min), and blood pressure (mmHg).
Descriptive statistics will be presented for all subjects in the available treatment arm at each visit will be reported, using number (n) of non-missing observations, mean, SD, median, minimum, maximum (range), P_{10} and P_{90} for continuous variables and frequencies and n and percentages for categorical variables.

6.6.3 Extent of Exposure and Compliance

Duration of treatment exposure is defined as the time the subjects will be on treatment during the study. i.e., from Day 1(week 1) to Day 365 (week 53).

Duration of treatment exposure: number of days between the last dose date of Elaprase and the first dose date of Elaprase + 1 i.e., date of last dose -date of first dose +1.

Analysis will be on Safety Analysis population (SAF).

Compliance

Compliance (%) = [(Total duration of actual study drug administration in days) x100 / (Total duration of planned study drug administration in days)].

6.7 Interim Analyses

There is no planned interim analysis in this study.

6.8 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

There is no planned DSMB in this study.

7.0 REFERENCES

- ICH E3: Structure and content of Clinical Study Reports, November 1995 (Step 5), CPMP.
- ICH E9: Statistical Principles for Clinical Trials, February 1998 (Step 5), CPMP.
- TAK-665-4001 Takeda ELAPRASE Protocol v2.1 dated 23APR2021
- TAK-665-4001 Takeda ELAPRASE CRF v1.0 dated 06OCT2021

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

There is no change in the planned analysis.

9.0 APPENDIX

9.1 Changes from the Previous Version of the SAP

Not Applicable

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Reporting of Numeric Values

All raw data will be presented to the original number of decimal places. The mean, median and quartiles will be presented with 1 decimal place more than raw data. The standard deviation (SD), and Confidence Interval (CI) of mean will be presented with 1 decimal place more than mean. The range (minimum and maximum) will be presented as per the raw data Percentages will be presented in xx.x% format. P_{10} and P_{90} will be presented to two decimal place. All categories of variables will be presented even if there is no data.

Precision of p-values will be 4 decimal places. p-values less than 0.0001 will be presented as <0.0001 and if equal to 1 then ≥ 0.9999.

Output (Tables, Listings and Graphs) Considerations

The default Tables, Listings and Graphs (TLG) layout will be as follows.

Orientation	All pages should preferably be landscape.
Paper Size	Legal size
Margins	Top: 1.25 in Bottom: 1 in Left: 1 in Right: 1 in
Font	Font style (preferably Times New Roman) of the Text
Headers	**Titles of Table/Listing will be center** **Left** Sponsor: Study Name: Protocol No:
Footers	**Left** Analyst Initials: Program Name: Program Run date: time: **Right** Datasets Used:

	Page XXX of YYY

The margin may be reduced as necessary to allow additional rows to be presented, but not at the expense of clarity. In addition, the orientation may be changed to portrait if appropriate. The date format for all presentations will be 'DDMMMYYYY'.

9.2.2 Definition of Baseline

Baseline value is defined as the last non-missing assessment prior to the first study treatment exposure (including unscheduled assessments). If the data are not measured at randomization/treatment administration visit, the screening observations will be considered as baseline measurements. In this study the baseline visit will be Baseline(Visit 2)/(Day 1).
If the data are measured at screening, randomization/treatment administration visit (Day 1), the latest observations will be considered as baseline measurements.

In this study, all the events having the last non-missing assessment at day 1 will have their baseline value as the value of day 1, for e.g., Physical examination and vital signs. While for those events which are having last non-missing assessment at screening then their screening value will be used as baseline value, for e.g., FVC, 6MWT, Cardiac LVMI and Ejection Fraction etc.

9.2.3 Change from Baseline

Value of change from baseline at any post baseline visit will be defined as the difference of the non-missing baseline value to the non-missing post baseline value i.e.

Change from baseline (Δ) = post-baseline value at visit X - baseline value, where both values are non-missing.

Percent change from baseline will be calculated as:

(Assessment value at post-baseline visit X – baseline value) / baseline value * 100.

9.3 Analysis Software

All the statistical analyses including summary Tables, Listings, and Figures (TLFs) will be generated using a customized reporting SAS® Version 9.4 (SAS Institute Inc., Cary, NC).