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STATISTICAL ANALYSIS PLAN

Protocol Number: AGLU03707

An Exploratory Study of the Safety and Efficacy of Immune Tolerance Induction (ITI) in Patients with Pompe Disease Who Have Previously Received Myozyme

Author: [redacted]

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Abbreviations and Acronyms used in this Document

AEs	Adverse Events	IARs	Infusion-Associated Reactions to Myozyme
AIMS	Alberta Infantile Motor Scale	IgE	Immunoglobulin E
anti-rhGAA	anti-recombinant human acid α-glucosidase	IgG	Immunoglobulin G
BSA	Body Surface Area	LVM	Left Ventricular Mass
cm	Centimeters	LVMI	Left Ventricular Mass Index
CRIM	Cross-reacting immunologic material	LVMZ	Left Ventricular Mass Z-score
CS	Clinically Significant	MedDRA	Medical Dictionary for Regulatory Activities
ECG	Electrocardiogram	PEDI	Pediatric Evaluation of Disability Inventory
ECHO	Echocardiogram	PRAE	Prior Related Adverse Events
eCRF	Electronic Case Report Form	PT	Preferred Term (MedDRA)
ERT	Enzyme Replacement Therapy	PTAEs	Pre-Treatment Adverse Events
FA	Full Analysis	SAEs	Serious Adverse Events
GAA	Acid α-glucosidase	SAP	Statistical Analysis Plan
GMAE	Gross Motor Ability Estimator	SOC	System Organ Class (MedDRA)
GMFM-88	Gross Motor Function Measure-88	TEAEs	Treatment-Emergent Adverse Events

1 DESCRIPTION OF THE PROTOCOL

AGLU03707 is an exploratory, open-label study of patients of any age with Pompe disease to evaluate the efficacy, safety, and clinical benefit of 2 ITI regimens in combination with Myozyme in patients receiving Myozyme treatment. The objectives of the study are as follows:

1. To evaluate the efficacy of ITI regimens, as assessed by anti-recombinant human acid α-glucosidase (anti-rhGAA) antibody titers, and antibodies that inhibit the enzymatic activity and/or uptake of Myozyme;
2. To evaluate Pompe disease activity in patients receiving these regimens, as measured by overall survival, respiratory function, left ventricular mass index (LVMI), motor function, and disability index; and
3. To evaluate the safety of these regimens, as assessed by the incidence of adverse events (AEs), serious adverse events (SAEs), and clinical laboratory abnormalities.

Please refer to the protocol for additional details. The Schedule of Events from the protocol may be found in appendix 6.1 of this SAP.

1.1 Changes from Analyses Specified in the Protocol

No Applicable.

1.2 Changes from Analyses Specified in the Previous Version of the SAP

Not Applicable.

2 DEFINITIONS

2.1 Efficacy

2.1.1 Primary Endpoint(s)

Not applicable.

2.1.2 Secondary Endpoints

Not applicable.

2.1.3 Other Efficacy Endpoints

2.1.3.1 Routine Anti-rhGAA Immunoglobulin G (IgG) Antibody Testing

Serum samples for anti-rhGAA IgG antibody testing will be obtained prior to each Myozyme infusion at time points indicated in the Protocol Schedule of Assessments shown in 6.1.

2.1.3.2 Inhibitory Antibody Testing

In the event a patient becomes anti-rhGAA IgG positive during the course of the study, the presence of inhibitory antibody (enzyme activity and uptake) will be tested every 2 months using the serum samples collected for anti-rhGAA IgG antibody testing.

2.1.3.3 Echocardiogram (ECHO), Including LVMI

The primary cardiac outcome parameters (measured and derived) from the echocardiography to be collected include: LVM, LVM Z-score (LVMZ), LVMI, left ventricular posterior wall thickness, ejection fraction, and shortening fraction. (See protocol 9.3.3 for details.) LVMI is an index value created by normalizing LVM by body surface area (BSA), and will be recorded with the other ECHO parameters according to procedures outlined in the SOM and Cardiology Manual. Z-Scores provide an indicator of the number of standard deviations from the mean in a normal distribution. Values that are greater than 2 may indicate measurements that are outside of a normal range. The LVMZ and other derived variables will be provided by the central cardiologist.

2.1.3.4 Ventilator Use

A daily ventilator use diary will be completed by patients who at any time during the study require either invasive or non-invasive ventilator support. (See protocol 9.3.4 for details.)

2.1.3.5 Motor Development and Functional Assessments

2.1.3.5.1 Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI)

All patients will be administered the Pompe PEDI. The Pompe PEDI includes all items from the original PEDI, as well as additional items in the Functional Skills, Mobility, and Self-Care domains to reflect clinically relevant functional skills for children with Pompe disease. Results

are reported as raw score, normative standard score (with standard error), and scaled score (with standard error).

2.1.3.5.2 Gross Motor Function Measure-88 (GMFM-88)

The GMFM-88 will be used to evaluate changes in 5 categories of motor function:

- Lying and Rolling;
- Sitting;
- Crawling and Kneeling;
- Standing;
- Walking, Running, and Jumping.

Items on the questionnaire were selected to represent motor functions typically performed by children without motor impairments by 5 years of age. Each item is scored on a 4-point Likert scale (i.e., 0 = cannot do; 1 = initiates [< 10% of the task]; 2 = partially completes [10 to < 100 % of the task]; 3 = task completion, NT = not tested). The score for each dimension is expressed as a percentage of the maximum score for that dimension. The total score is obtained by adding the percentage scores for each dimension and dividing the sum by the total number of dimensions. Therefore, each dimension contributes equally to the total score. The Gross Motor Ability Estimator (GMAE), though mentioned in the protocol, will not be presented as it is not appropriate to use this scoring method that was validated with patients with cerebral palsy. It is an interval level measure where the subject is placed on an ability continuum from 0-100. The intervals are based on a movement analysis of children with cerebral palsy and we can't assume that the quality of movement or hierarchy of skill acquisition is similar for Pompe disease.

2.1.3.5.3 Alberta Infantile Motor Scale (AIMS)

AIMS measures normal motor development in infants from birth to 18 months of age. However, unless a child has successfully achieved the maximum total raw score of 58, indicating independent ambulation, the test can still be used to monitor the progress of a child. AIMS will be administered to all patients at study entry, provided they are at or below the highest level of age-equivalent performance for the test (i.e., independent walking), and the AIMS will continue to be administered to these patients until completion of the study to ascertain whether patients maintain any developmental gains achieved while on Myozyme therapy.

2.2 Safety

2.2.1 Adverse Events (AEs)

Adverse Events are defined in protocol section 9.6.1. The severity of AEs will be graded based on NCI/CTCAE, version 3.0, as described in protocol section 9.6.3.

2.2.1.1 Infusion-Associated Reactions (IARs)

Infusion-associated reactions are defined as AEs that occurred during either the infusion or the observation period following the infusion (i.e., ≤ 2 hours post-infusion) which were deemed by the investigator to be related (i.e., possibly, probably or definitely) to study drug. At the discretion of the Investigator, AEs that occurred after completion of the post-infusion observation period that were assessed as related could also be considered IARs. As part of the safety review for infusion reactions, analyses including all AEs that occurred during or up to 2 hours post-infusion, regardless of relationship, will be performed. To evaluate delayed onset infusion reactions, all post-infusion reactions occurring from 2 to 48 hours post-infusion, regardless of causality, will be classified by time period, e.g., reactions occurring 2 to 24 hours, 24 to 48 hours, and 2 to 48 hours overall post-infusion, and will then be subject to medical review to determine if the event was an infusion reaction. For further information, please refer to protocol section 9.6.4.

2.2.2 Vital Signs

Refer to protocol section 9.4.4 for details regarding collection of vital signs in this study.

2.2.3 Laboratory Assessments

Chemistry, urinalysis, and hematology laboratory parameters are described in section 9.4.2 of the protocol.

2.2.4 Other Safety Events of Special Interest

2.2.4.1 12-Lead Electrocardiogram (ECG)

The following standard 12-lead ECG parameters will be assessed according to the assessment schedule in Appendix 6.1: heart rate, rhythm, RR interval, PR interval, QRS complex, QT

interval, QTc interval, QRS axis, R voltage V6, S voltage V1, left ventricular hypertrophy criteria, right ventricular hypertrophy criteria, and repolarization changes. Refer to protocol section 9.4.3 for further details.

2.2.4.2 Continuous ECG Monitoring by Telemetry

Continuous ECG monitoring by telemetry will be performed on the days of cyclophosphamide infusions for patients on Regimen A who have cardiomegaly or hypertrophic cardiomyopathy, and on the days of rituximab infusions for all patients on Regimen B. Refer to protocol section 9.4.5 for further details.

2.2.4.3 Lymphocyte Subpopulation Counts

Refer to protocol section 9.4.6 for details regarding collection of blood samples for lymphocyte subpopulation counts in this study.

2.2.4.4 Immunoglobulin Panel

Refer to protocol section 9.4.7 for details regarding collection of blood samples for immunoglobulin panel.

2.2.4.5 Research Immunophenotyping

Refer to protocol section 9.5.1 for details regarding collection of blood samples for research immunophenotyping.

2.2.4.6 Functional T-Cell Assay

Refer to protocol section 9.5.2 for details regarding collection of blood samples for functional t-cell assay.

2.2.4.7 Anaphylaxis Reactions

A modified version of the Standardized MedDRA Query (SMQ) version 14.1 will be used as a tool to identify potential anaphylaxis/hypersensitivity reactions (See appendix 6.4). Patients with adverse event(s) coded to preferred term(s) satisfying the algorithm will be considered to have had potential anaphylaxis reactions. Other patients may also be considered to have had

anaphylaxis reaction based upon medical review within the Genzyme Global Safety Group & Risk Management.

2.2.4.8 Testing for Moderate, Severe, or Recurrent Infusion-Associated Reactions

In the event of moderate, severe, life-threatening, or recurrent IAR, additional blood samples will be collected and analyzed by Genzyme according to protocol section 9.5.3. In addition, at the request of Genzyme, after consultation with the Investigator, a plasma sample for complement activation testing, serum tryptase testing, and/or IgE testing may also be collected for patients with recurrent IARs to Myozyme suggestive of a hypersensitivity reaction.

2.2.4.8.1 Complement Activation Testing

Refer to protocol section 9.5.3.1 for further details.

2.2.4.8.2 Serum Tryptase Testing

Refer to protocol section 9.5.3.2 for further details.

2.2.4.8.3 Serum Anti-Recombinant Human Acid α-Glucosidase (anti-rhGAA) Immunoglobulin E (IgE) Antibody Testing

Refer to protocol section 9.5.3.3 for further details.

2.2.4.8.4 Skin Testing

Refer to protocol section 9.5.3.4 for further details.

2.2.4.8.5 Circulating Immune Complexes

Refer to protocol section 9.5.3.5 for further details.

3 DATA SETS ANALYZED (STUDY POPULATIONS)

3.1 Full Analysis (FA) Set

Patients who have signed informed consent, enrolled (i.e. completed all baseline assessments), and received at least one dose of Myozyme® (alglucosidase alfa) will be included in the full analysis (FA) set.

3.2 Per Protocol (PP) Set

A Per Protocol Set will not be defined for this study due to the small number of patients.

3.3 Safety Set

All patients who received at least one dose of Myozyme will be included in the Safety Set population.

4 STATISTICAL ANALYSIS

4.1 Study Patients

4.1.1 Disposition of Patients

A summary table of patient disposition will present the number of patients with signed informed consent, treated, and completed or withdrawn from the study (including death). A corresponding listing will be provided. A listing of reasons of treatment discontinuation and/or withdrawal from the study and a listing of reasons for patients who failed screening will also be provided.

4.1.2 Protocol Deviations

Protocol deviations will be tabulated in a listing. Major protocol deviations which may have impact on efficacy and safety conclusions will be discussed.

4.1.3 Demographics, Disease Characteristics, and History

All demographic and baseline characteristics information will be listed using the FA Set.

4.1.3.1 Demographics

The following demographic variables will be presented in a listing:

- Gender
- Ethnicity
- Race
- Date of birth
- Age (months) at enrollment
- Age (months) at first study infusion

4.1.3.2 Myozyme and Pompe History

The following Myozyme Pompe history variables will be presented in a listing:

- Age (months) at first infusion of Myozyme in the study
- Date of first symptoms of Pompe disease
- Date at diagnosis of Pompe disease
- Date at first commercial Myozyme infusion
- Whether Patients previously participated in another Genzyme sponsored ERT trial (Yes/No)
- If applicable, the protocol number of the previous trial and the associated patient number.
- Whether any related AEs were experienced while receiving Myozyme outside of a Genzyme-sponsored trial

4.1.3.3 Cross-Reacting Immunologic Material (CRIM) Status and Acid α-glucosidase (GAA) Activity

CRIM Status and GAA activity data collected at baseline will be presented in listings.

4.1.3.4 Pompe Medical History

Pompe medical history in the following body systems will be presented in listings:

- Ears, nose, throat
- Respiratory
- Cardiovascular
- Gastrointestinal
- Musculoskeletal

4.1.3.5 Baseline Ventilator Use

Baseline ventilator use data will be presented in a listing.

4.1.3.6 Medical / Surgical History

Current and non-current medical/surgical history will be presented in a listing.

4.1.4 Concomitant Medications / Therapies

From the time of informed consent through study completion, all medications and therapies (e.g., tube feeds) to treat AEs, for any long-term disease management, given as prophylaxis for this study, or administered as a pretreatment prior to infusion, will be recorded in the eCRFs. As patients enrolled in this study will have received commercial Myozyme, there will not be separate listings for medications administered prior and/or after receiving first infusion of Myozyme in the study. The recorded medications will be coded using the World Health Organization (WHO) Drug Q1 2007 or later version. Tables and listing will show all concomitant medications recorded during the study. Number and percentage of patients reporting any medication will be presented in the concomitant medication summary table, by WHO-DRUG Anatomical Therapeutic Classification (ATC) fourth level term and generic name. The table will be first sorted by most prevalent Drug Class (WHO ATC) based on total patients reporting any medication in that Drug Class, and then, by most prevalent Generic Name based on total patients reporting any medication in that Drug Class/Generic Name.

4.1.5 Genetic Mutation Analysis

A listing will be provided.

4.1.6 Optional Parental GAA Mutation Analysis

If any data are collected, a listing of the results will be provided.

4.2 Efficacy Analyses

All patients who receive Myozyme under this protocol will be presented in analyses.

All data will be presented in by-patient listings. Graphical displays will be presented as appropriate. Summary statistics will be produced as appropriate and meaningful. Continuous variables will be summarized using descriptive statistics (number [n], mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and percentages.

4.2.1 Primary Analysis

4.2.1.1 Anti-rhGAA IgG Antibody Testing

Summary of changes from baseline for Anti-rhGAA IgG antibody titers measured in the study will be presented. A corresponding by-patient listing will be provided.

4.2.1.2 Inhibitory Antibody Testing

Inhibitory antibody formation (activity and uptake) will be presented in a by-patient listing.

4.2.1.3 Pompe PEDI

Change from baseline in Pompe PEDI raw, normative standard, and scale scores will be presented in a summary table for the self-care, mobility, and social function domains in both the functional scale and the caregiver scale.

4.2.1.4 GMFM-88

Change from baseline in GMFM-88 raw and percent scores will be presented in a summary table by domain and total, for the lying and rolling, sitting, crawling and kneeling, standing, and walking, running & jumping domains.

4.2.1.5 AIMS

Change from baseline in AIMS scores (total raw scores, age-equivalent scores, and subscale scores) will be presented in a summary table. The subscale scores included scores for prone, supine, sitting, and standing positions.

4.2.1.6 ECHO, Including LVMI

Data from ECHO will be presented in a listing. Change from baseline in LVMI will be presented in a summary table.

4.2.1.7 Ventilator Use

A listing will present ventilator use start and stop dates, type of ventilation, reason(s) patients were put on ventilator support, reason(s) for stopping ventilator support, and patients' ventilator use status since last assessment.

4.2.2 Handling of Dropouts or Missing Data

Missing data will not be imputed using statistical methods.

4.2.3 Subgroup Analysis

No subgroup analysis is planned.

4.2.4 Multicenter Studies

Due to the small number of patients, efficacy results will not be tabulated for each center or state / country. The interaction between center and treatment cannot be explored when the centers have too small numbers of patients to make such analyses meaningful.

4.2.5 Hypothesis Testing and Significance Level

Due to the small sample size, no statistical testing will be conducted.

4.2.6 Sensitivity Analyses

No sensitivity analysis is planned.

4.2.7 Secondary Analyses

Not applicable.

4.2.8 Tertiary Analyses

Not applicable.

4.2.9 Other Efficacy Analyses

Not applicable.

4.2.10 Pharmacokinetic and Pharmacodynamic Analyses

Not applicable.

4.3 Safety Analyses

All safety data will be provided in patient listings. AEs will be coded in MedDRA 14.1 version and up and presented by MedDRA SOC and preferred term. No formal hypothesis testing is planned.

4.3.1 Study Duration, Treatment Compliance, and Exposure

Exposure to Myozyme, Cyclophosphamide, Rituximab, Methotrexate, and IVIG will be presented in listings. Number of Myozyme infusions administered, and duration of Myozyme infusions will be summarized.

4.3.2 Adverse Events (AEs)

Adverse Events (AEs) will be determined as occurring prior to treatment or as on or after first treatment (treatment-emergent) of Myozyme as described in appendix 6.4. Analyses on Prior Related Adverse Events (PRAE), Pre-Treatment Adverse Events (PTAEs) and Treatment-Emergent Adverse Events (TEAEs) will be tabulated and presented separately. Study displays are described below; additional details are outlined in appendix 6.4.

AEs will be presented by regimen and total and will include the displays described in the following sub-sections.

4.3.2.1 Treatment-Emergent Adverse Events (TEAEs)

All TEAEs will be presented using summary statistics. Number of patients will be presented. Due to the small number of patients enrolled in the study, percentages of patients in each category will not be presented. Frequency of events will also be presented in a select number of tables.

An overall summary table of TEAE information will be presented that will summarize the number of patients in each regimen and total who:

- Experienced any AE,
- Discontinued Myozyme due to an AE,
- Discontinued Cyclophosphamide due to an AE,
- Discontinued Methotrexate due to an AE,
- Discontinued Rituximab due to an AE,

- Discontinued IVIG due to an AE,
- Discontinued Plasmapheresis due to an AE,
- Died (CTCAE grade 5),
- Experienced an AE related to Myozyme,
- Experienced an AE related to Cyclophosphamide,
- Experienced an AE related to Methotrexate,
- Experienced an AE related to Rituximab,
- Experienced an AE related to IVIG,
- Experienced an AE related to Plasmapheresis,
- Experienced a serious AE (including CTCAE grade 4 AEs),
- Experienced a CTCAE grade 3 AE,
- Experienced a CTCAE grade 4 AE, or
- Experienced an AE assessed as an infusion-associated reaction (IAR).

A listing of all TEAEs leading to discontinued Myozyme treatment will also be provided.

4.3.2.2 TEAEs by System Organ Class (SOC) and Preferred Term (PT)

The number of TEAEs and the number of patients with events will be presented by SOC and PT for each regimen and total. Patients are counted once in each SOC and PT. SOCs and PTs will be listed in descending order of frequency of occurrence.

4.3.2.3 TEAEs by Severity and Relationship

Summaries of TEAEs by severity (based on CTCAE grades) and relationship to treatment will also be provided. If a patient has more than one occurrence of an AE, the most severe occurrence (highest CTCAE grade) of the AE will be used in the severity summary table and the strongest relationship to study treatment will be used in the relationship to treatment summary table.

In addition, summary tables of treatment-emergent SAEs (including CTCAE grade 4 and 5), and related AEs will be presented by SOC and preferred term. Summary of SAEs by severity and relationship to treatment (Myozyme, Cyclophosphamide, Methotrexate, Rituximab, IVIG, Plasmapheresis) will also be provided.

Detailed listings of patients who experience AEs, SAEs, related AEs, and anaphylaxis/hypersensitivity reactions will be presented. Detailed listings will include severity

(according to CTCAE grades) and relationship to treatment (Myozyme, Cyclophosphamide, Methotrexate, Rituximab, IVIG, Plasmapheresis), as well as action taken regarding study treatment (Myozyme, Cyclophosphamide, Methotrexate, Rituximab, IVIG, Plasmapheresis), other action taken, and patient outcome.

4.3.2.4 Deaths, Other SAEs, and Other Significant Adverse Events

4.3.2.4.1 Deaths

A listing of patients who died during the study will be provided.

4.3.2.4.2 Infusion Associated Reactions (IARs)

A summary table of treatment-emergent IARs, i.e., IARs occurred on or after treatment of Myozyme, will be presented by SOC and preferred term. All TEAEs occurring during infusion and up to 48 hours post-infusion, regardless of causality, will be summarized by time period: during infusion, 0 to 2 hours post-infusion, 2 to 24 hours post-infusion, 24 to 48 hours post-infusion, and 2 to 48 hours overall post-infusion. A by-patient listing of IARs will be presented.

4.3.3 Other Safety

4.3.3.1 Analyses for Laboratory Tests

Chemistry, urinalysis, and hematology laboratory parameters described in section 9.4.2 of the protocol will be presented in by-patient listings. Laboratory values that were marked as clinically significant or change from baseline will also be presented. All laboratory values will be classified as normal, below normal, or above normal based on normal ranges supplied by the central laboratory. For purposes of analyses, laboratory results based upon conventional units will be used.

By-patient figures will be provided for numerical laboratory values over time.

4.3.3.2 Vital Signs

A listing of vital signs will be presented by regimen, patient, visit, and measured vital sign values.

4.3.3.3 Physical Examinations

Results of physical examinations will be presented in a listing.

4.3.3.4 Other Safety Parameters of Special Interest

4.3.3.4.1 12-Lead ECG

ECG data will be presented in a listing.

4.3.3.4.2 Continuous ECG Monitoring by Telemetry

Data collected from telemetry will be presented in a listing.

4.3.3.4.3 Lymphocyte Subpopulation Counts

Lymphocyte subpopulation counts will be presented in a listing.

4.3.3.4.4 Immunoglobulin Panel

Data collected from the immunoglobulin panel will be presented in a listing.

4.3.3.4.5 Research Immunophenotyping

Data collected from research immunophenotyping will be presented in a listing.

4.3.3.4.6 Functional T-Cell Assay

Data collected from functional T-cell assay, if any, will be presented in a listing.

4.3.3.4.7 Testing for Moderate, Severe, or Recurrent Infusion-Associated Reactions

4.3.3.4.7.1 Complement Activation Testing

If any complement activation testing was performed and results collected, the data will be presented in a listing.

4.3.3.4.7.2 Serum Tryptase Testing

If any serum tryptase testing was performed and results collected, the data will be presented in a listing.

4.3.3.4.7.3 Serum Anti- rhGAA IgE Antibody Testing

If any IgE testing was performed and results collected, the data will be presented in a listing.

4.3.3.4.7.4 Skin Testing

If any skin testing was performed and results collected, the data will be presented in a listing.

4.3.3.4.7.5 Circulating Immune Complexes

If any circulating immune complexes testing was performed and results collected, the data will be presented in a listing.

5 REFERENCES

Not applicable.

6 APPENDICES

6.1 Protocol Schedule of Assessments

Table 6-1 Schedule of Assessments – Regimen A ITI Treatment Module (Months 1 through 6)

	Month 1									Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4				W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 20	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
Informed Consent	X																												
Confirmation of Inclusion/Exclusion Criteria[1]	X																												
Demographics	X																												
Medical/Surgical/ Pompe Disease History[2]	X																												
Genetic Mutation Analysis[3]	X																												
Optional Parental GAA Mutation Analysis[3]	X																												
Pregnancy testing[4]	X		X							X				X				X				X				X			
Optional Porta-Catheter Placement	X																												

	Month 1									Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4				W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 20	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
Physical Examination[5]	X	X	X		X	X		X		X		X		X		X		X		X		X		X		X		X	
Research Immunophenotyping		X			X	X		X										X								X			
Lymphocyte Subpopulation Counts		X			X	X		X										X								X			
Functional T cell Assay (ELISPOT)		X			X	X		X				X						X								X			
Immunoglobulin Panel[6]		X						X				X		X				X				X				X			

Table 6-1 Schedule of Assessments – Regimen A ITI Treatment Module (Months 1 through 6) (continued)

	Month 1									Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4				W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 20	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
CBC with Differential[6]	X	X	X		X	X		X		X		X		X		X		X		X		X		X		X		X	
Chemistry, CK and CK-MB[6]	X	X	X		X	X		X		X		X		X		X		X		X		X		X		X		X	
Urinalysis[6]	X	X	X		X	X		X		X		X		X		X		X		X		X		X		X		X	
Anti-rhGAA Antibody (IgG) Titers/Inhibitory Antibody Monitoring[7]		X				X				X		X		X				X				X				X			
ECG	X	X	X		X	X		X		X				X				X				X				X			
ECHO	X					X				X				X				X				X				X			
Vital Sign Monitoring		X	X		X	X		X		X		X		X		X		X		X		X		X		X		X	
Telemetry Monitoring[8]			X							X				X				X				X				X			
Cyclophosphamide[9]			X							X				X				X				X				X			
Myozyme Infusion			X			X				X		X		X		X		X		X		X		X		X		X	
Pompe PEDI[10]	X																	X								X			

	Month 1									Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4				W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 20	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
GMFM-88[10]	X																	X								X			
AIMS[10]	X																	X								X			
Ventilator Use Assessment	Continuous Monitoring																												

Table 6-1 Schedule of Assessments – Regimen A ITI Treatment Module (Months 1 through 6) (continued)

	Month 1									Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4				W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 20	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
Concomitant Medication Monitoring[11]	Continuous Monitoring																												
Concomitant Therapy Monitoring[11]	Continuous Monitoring																												
Adverse Event Monitoring[2]	Continuous Monitoring																												

[1] Includes, but is not limited to, confirmation of CRIM status, documentation of GAA enzyme deficiency, and anti-rhGAA titer levels (see Protocol Section 7.1).
[2] At screening/baseline, medical history will include an evaluation of retrospective, related AEs occurring while the patient was receiving Myozyme treatment prior to study entry (Protocol Section 9.6).
[3] Blood sample for patient gene mutation analysis must be obtained at baseline. Testing performed prior to informed consent is allowed, provided that written results are provided to the site. If consent is provided, samples also will be obtained from the biological parent(s) at baseline.
[4] Pregnancy testing for female patients of childbearing potential will be repeated on Day 0 if this occurs >14 days after the baseline test. Pregnancy test results must be obtained prior to starting the ITI regimen, and patients with positive test results will be excluded (or withdrawn) from the study.
[5] In addition to the scheduled physical examinations, brief, physical assessments should also be performed prior to the administration of any study medications (Myozyme and cyclophosphamide) to specifically ensure that the patient is clinically stable and can tolerate administration of these agents.
[6] Results of the most recent laboratory tests (obtained on the day of the infusion) should be reviewed by Investigators prior to dosing with cyclophosphamide. Results of the most recent immunoglobulin panel should also be reviewed prior to dosing.
[7] If a patient becomes anti-rhGAA (IgG) positive during the course of the study, he/she will also be tested every 2 months for the presence of inhibitory antibodies to Myozyme.
[8] Patients with cardiomegaly or hypertrophic cardiomyopathy will be admitted to the hospital for all cyclophosphamide infusions and will remain in the hospital for a minimum of 24 hours post-infusion.
[9] Patients should be well-hydrated prior to cyclophosphamide administration, but the patients' cardiac status should be taken into account when determining appropriate amount of hydration.
[10] A visit window of ±7 days will be permitted for the Pompe PEDI, GMFM-88, and AIMS. All remaining study assessments should be conducted at the indicated study visit during the ITI treatment module. Eligible CRIM-negative patients will be followed for a minimum of 18 months on treatment or, if a patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.
[11] All concomitant medications and therapies, including those given as prophylaxis or prior to an infusion, will be recorded in the eCRF.

Note: It is recommended that the Investigator monitor a patient's immunoglobulin levels and consider IVIG administration at a dose of 400 mg/kg, regardless of age, if indicated per the individual Investigator's clinical discretion.

Key: AIMS=Alberta Infantile Motor Scale; BL=baseline/screening; CBC=complete blood count; CK=creatine kinase; CK-MB=creatine kinase – myocardial band; CRIM=cross-reacting immunologic material; D=day; ECG= electrocardiogram; ECHO; echocardiogram; ELISPOT=enzyme-linked mmunosorbent spot [assay]; GAA=acid α-glucosidase; GMFM-88=Gross Motor Function Measure-88; IgG=immunoglobulin G; IVIG=intravenous immunoglobulin; PEDI=Pediatric Evaluation of Disability Inventory; rhGAA=Recombinant human acid α-glucosidase; W=week

Table 6-2 Schedule of Assessments – Regimen B ITI Treatment Module (Months 1 through 6)

	Month 1								Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4			W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
Informed Consent	X																											
Confirmation of Inclusion/Exclusion Criteria[1]	X																											
Demographics	X																											
Medical/Surgical/ Pompe Disease History[2]	X																											
Genetic Mutation Analysis[3]	X																											
Optional Parental GAA Mutation Analysis	X																											
Pregnancy testing[4]	X		X						X				X				X				X				X			
Optional Porta-Catheter Placement	X																											
Physical Examination[5]	X	X	X		X	X		X	X		X		X		X		X		X		X		X		X		X	

	Month 1								Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4			W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
Research Immunophenotyping		X			X	X		X									X								X			
Lymphocyte Subpopulation Counts		X			X	X		X									X								X			
Functional T cell Assay (ELISPOT)		X			X	X		X			X						X								X			
Immunoglobulin Panel[6]		X						X			X		X				X				X				X			

Table 6-2 Schedule of Assessments – Regimen B ITI Treatment Module (Months 1 through 6) (continued)

	Month 1								Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4			W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
CBC with Differential[6]	X	X	X		X	X		X	X		X		X		X		X		X		X		X		X		X	
Chemistry, CK and CK-MB[6]	X	X	X		X	X		X	X		X		X		X		X		X		X		X		X		X	
Urinalysis[6]	X	X	X		X	X		X	X		X		X		X		X		X		X		X		X		X	
Anti-rhGAA Antibody (IgG) Titers/Inhibitory Antibody Monitoring[7]		X				X			X		X		X				X				X				X			
ECG	X	X	X	X	X	X			X				X				X				X				X			
ECHO	X					X			X		X		X				X				X				X			
Vital Sign Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telemetry Monitoring[8]				X	X		X	X																				
Myozyme Infusion			X			X			X		X		X		X		X		X		X		X		X		X	
Rituximab[9,10,11,]				X	X		X	X																				
Methotrexate[12,13]				X			X			X		X		X		X		X		X		X		X		X		X
Pompe PEDI[14]	X																X								X			

	Month 1								Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4			W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
GMFM-88[14]	X																X								X			
AIMS[14]	X																X								X			
Ventilator Use Assessment	Continuous Monitoring																											

Table 6-2 Schedule of Assessments – Regimen B ITI Treatment Module (Months 1 through 6) (continued)

	Month 1								Month 2				Month 3				Month 4				Month 5				Month 6			
	W0		W1		W2	Weeks 3 and 4			W5		W7		W9		W11		W13		W15		W17		W19		W21		W23	
	BL	D -1	D 0	D 1	D 8	D 14	D 15	D 22	D 28	D 29	D 42	D 43	D 56	D 57	D 70	D 71	D 84	D 85	D 98	D 99	D 112	D 113	D 126	D 127	D 140	D 141	D 154	D 155
Concomitant Medication Monitoring[15]	Continuous Monitoring																											
Concomitant Therapy Monitoring[15]	Continuous Monitoring																											
Adverse Event Monitoring[2]	Continuous Monitoring																											

[1] Includes, but is not limited to, confirmation of CRIM status, documentation of GAA enzyme deficiency, and anti-rhGAA titer levels (see Protocol Section 7.1)
[2] At screening/baseline, medical history will include an evaluation of retrospective, related Aes occurring while the patient was receiving Myozyme treatment prior to study entry (**Protocol Section 9.6**)
[3] Blood sample for patient gene mutation analysis must be obtained at baseline. Testing performed prior to informed consent is allowed, provided that written results are provided to the site. If consent is provided, samples also will be obtained from the biological parent(s) at baseline.
[4] Pregnancy testing for female patients of childbearing potential will be repeated on Day 0 if this occurs >14 days after the baseline test. Pregnancy test results must be obtained prior to starting the ITI regimen, and patients with positive test results will be excluded (or withdrawn) from the study.
[5] In addition to the scheduled physical examinations, brief, physical assessments should also be performed prior to the administration of any study medications (Myozyme, methotrexate, or rituximab) to ensure that the patient is clinically stable and can tolerate administration of these agents.
[6] Results for the most recent laboratory tests (obtained the preceding day prior to initiating the Myozyme infusion) should be reviewed by Investigators prior to dosing with rituximab and methotrexate. Results of the most recent immunoglobulin panel should also be reviewed prior to dosing.
[7] If a patient becomes anti-rhGAA (IgG) positive during the course of the study, he/she will also be tested every 2 months for the presence of inhibitory antibodies to Myozyme.
[8] Patients with cardiomegaly or hypertrophic cardiomyopathy will be admitted to the hospital for all cyclophosphamide infusions and will remain in the hospital for a minimum of 24 hours post-infusion.
[9] Patients will be admitted to the hospital for all rituximab infusions and will remain in the hospital for a minimum of 24 hours post-infusion. Telemetry will be performed during all rituximab infusions from at least 10 minutes prior to the start of the infusion until at least 2 hours post-infusion.
[10] An optional, additional 4-week cycle of rituximab (up to 4 additional doses) may be administered as described in Protocol Section 8.1. This additional cycle must be completed within the first 6 months of the study.
[11] Pre-infusion medication may be given as per rituximab treatment guidelines.
[12] Patients should be well-hydrated prior to methotrexate administration, but the patients' cardiac status should be taken into account when determining appropriate amount of hydration.
[13] Folinic acid supplementation may be given at the discretion of the Investigator beginning 24 hours after the dose of methotrexate.
[14] A visit window of ±7 days will be permitted for the Pompe PEDI, GMFM-66, and AIMS. All remaining study assessments should be conducted at the indicated study visit during the ITI treatment module. Eligible CRIM-negative patients will be followed for a minimum of 18 months on treatment or, if a patient is <6 months of age at the time of enrollment, until the patient is 2 years of age.
[15] All concomitant medications and therapies, including those given as prophylaxis or prior to an infusion, will be recorded in the eCRF.

Note: It is recommended that the Investigator monitor a patient's immunoglobulin levels and consider IVIG administration at a dose of 400 mg/kg, regardless of age, if indicated per the individual

Investigator's clinical discretion.

Key: AIMS=Alberta Infantile Motor Scale; BL=baseline/screening; CBC=complete blood count; CK=creatine kinase; CK-MB=creatine kinase – myocardial band; CRIM=cross-reacting immunologic material; D=day; ECG= electrocardiogram; ECHO; echocardiogram; ELISPOT=enzyme-linked mmunosorbent spot [assay]; GAA=acid α-glucosidase; GMFM-88=Gross Motor Function Measure-88; IgG=immunoglobulin G; IVIG=intravenous immunoglobulin; PEDI=Pediatric Evaluation of Disability Inventory; rhGAA=Recombinant human acid α-glucosidase; W=week

Table 6-3 Schedule of Assessments – Follow-up Module (Months 7 through 18)

	Month 7[1]		Month 8[1]		Month 9[1]		Month 10[1]		Month 11[1]		Month 12[1]		Month 13[1]		Month 14[1]		Month 15[1]		Month 16[1]		Month 17[1]		Month 18[1]		EOS[1]	
	W25	W27	W29	W31	W33	W35	W37	W39	W41	W43	W45	W47	W49	W51	W53	W55	W57	W59	W61	W63	W65	W67	W69	W71	W73[2]	W75
	D168	D182	D196	D210	D224	D238	D252	D266	D280	D294	D308	D322	D336	D350	D364	D378	D392	D406	D420	D434	D448	D462	D476	D490	D504	D518
Physical Examination[3]	X		X		X		X		X		X		X		X		X		X		X		X			X
Pregnancy Testing[4]	X		X		X		X		X		X		X		X		X		X		X		X			X
Vital Sign Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Myozyme Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Research Immunophenotyping	X				X				X				X				X				X					X
Lymphocyte Subpopulation Counts	X				X				X				X				X				X					X
Functional T cell Assay (ELISPOT)	X				X				X				X				X				X					X
Immunoglobulin Panel	X				X				X				X				X				X					X
CBC with Differential	X		X		X		X		X		X		X		X		X		X		X		X			X
Chemistry, CK and CK-MB	X		X		X		X		X		X		X		X		X		X		X		X			X
Urinalysis	X		X		X		X		X		X		X		X		X		X		X		X			X
Anti-rhGAA Antibody (IgG) Titers/Inhibitory Antibody Monitoring[5]	X		X		X		X		X		X		X		X		X		X		X		X			X

	Month 7[1]		Month 8[1]		Month 9[1]		Month 10[1]		Month 11[1]		Month 12[1]		Month 13[1]		Month 14[1]		Month 15[1]		Month 16[1]		Month 17[1]		Month 18[1]		EOS[1]	
	W25	W27	W29	W31	W33	W35	W37	W39	W41	W43	W45	W47	W49	W51	W53	W55	W57	W59	W61	W63	W65	W67	W69	W71	W73[2]	W75
	D168	D182	D196	D210	D224	D238	D252	D266	D280	D294	D308	D322	D336	D350	D364	D378	D392	D406	D420	D434	D448	D462	D476	D490	D504	D518
ECG	X						X						X						X							X
ECHO	X						X						X						X							X

Table 6-3 Schedule of Assessments – Follow-up Module (Months 7 through 18) (continued)

	Month 7[1]		Month 8[1]		Month 9[1]		Month 10[1]		Month 11[1]		Month 12[1]		Month 13[1]		Month 14[1]		Month 15[1]		Month 16[1]		Month 17[1]		Month 18[1]		EOS[1]	
	W25	W27	W29	W31	W33	W35	W37	W39	W41	W43	W45	W47	W49	W51	W53	W55	W57	W59	W61	W63	W65	W67	W69	W71	W73[2]	W75
	D168	D182	D196	D210	D224	D238	D252	D266	D280	D294	D308	D322	D336	D350	D364	D378	D392	D406	D420	D434	D448	D462	D476	D490	D504	D518
Pompe PEDI							X						X						X							X
GMFM-88							X						X						X							X
AIMS							X						X						X							X
Ventilator Use Monitoring	Continuous Monitoring																									
Concomitant Medication Monitoring	Continuous Monitoring																									
Concomitant Therapy Monitoring	Continuous Monitoring																									
Adverse Event Monitoring	Continuous Monitoring																									

[1] A visit window of ±2 weeks will be permitted for all study assessments during the follow-up module. For Myozyme infusions, the visit window is ±1 week.
[2] Patients who are <2 years of age at their W73 visit should continue in the study until they reach their second (i.e., 2 years of age) birthday. Therefore, these patients should repeat the Schedule of Assessments at W25 and continue following the protocol until they reach this birthday (W75 visit will mimic W25 assessments, W77 visit will mimic W27 assessments, etc.). At the patient's second birthday visit, all End-of-Study (EOS) assessments should be performed for study completion. See Protocol Appendix 14.6. For further details.
[3] In addition to the scheduled physical examinations, brief, physical assessments should also be performed prior to the administration of any study medications (Myozyme) to ensure that the patient is clinically stable and can tolerate administration of these agents.
[4] Pregnancy testing will be performed monthly for female patients of childbearing potential, and patients with positive test results will be withdrawn from the study.
[5] If a patient becomes anti-rhGAA (IgG) positive during the course of the study, he/she will also be tested every 2 months for the presence of inhibitory antibodies to Myozyme.

Key: AIMS=Alberta Infantile Motor Scale; CBC=complete blood count; CK=creatine kinase; CK-MB=creatine kinase – myocardial band; D=day; ECG=electrocardiogram; ECHO; echocardiogram; ELISPOT=enzyme-linked mmunosorbent spot [assay]; EOS=End-of-Study; GMFM-88=Gross Motor Function Measure-88; IgG=immunoglobulin G; IVIG=intravenous immunoglobulin; PEDI=Pediatric Evaluation and Disability Inventory; rhGAA=Recombinant human acid α-glucosidase; W=week

6.2 Changes from Analyses Specified in the Previous Version of the SAP

Not applicable.

6.3 Sample Size, Power, and Randomization

Neither statistical sample size calculations nor power calculations were performed for this study. The sample size was chosen based solely on clinical considerations, as the number of Pompe patients satisfying the inclusion/exclusion criteria is very small. This is an open label study. Patients were not randomized; rather, specific criteria (see Section 6.1 of Protocol) were used in determining the regimen the patients should receive.

6.4 Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

Age

Age will be presented as the number of years between date of birth and the reference date. The following ages may be computed, with reference dates indicated:

AGE	REFERENCE DATE
Age at Enrollment	Date of Signing Informed Consent Form
Age at First Infusion of Myozyme in the Study	Date of First Infusion of Myozyme in the Study

Missing or partial dates will not be imputed.

Disease Duration

Disease duration will be presented as the number of years between date of first study infusion and date of first symptom. Missing dates will not be imputed.

Definition of Baseline Values

The baseline is defined as the value collected on the scheduled visit prior to or on the day of first study drug infusion.

Change from Baseline

Change from baseline will be calculated as (Observed value at the particular visit – baseline value).

Adverse Events

The analysis of Adverse Events is described in detail in section 4.3.2.

Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first study drug dose. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study drug dose, then the AE is treatment-emergent; else,
- If the start year is the same as the year of the first study drug dose and
    - the start month is missing, then the AE is treatment emergent; else if
    - the start month is present and is the same or after the month of the first study drug dose, then the AE is treatment-emergent; else,
- If the start date is completely missing, then the AE is treatment-emergent.

All other AEs, except prior related AEs (PRAEs), are considered Pre-Treatment Adverse Events (PTAEs).

Patient percentages are based on the total number of treated patients in the particular regimen or total.

Related AEs are defined as possible, probable or definitely related. Unrelated AEs are defined as unlikely or not related.

6.5 Additional details on Statistical Methods

Not applicable.