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Protocol No.: CLI-LMZYMAA1-12

NON-INTERVENTIONAL POST-AUTHORISATION STUDY PROTOCOL

THE ALPHA-MANNOSIDOSIS REGISTRY: A multi-centre, multi-country, non-interventional, prospective cohort, in alpha-mannosidosis patients

Version No: 8.0
Date: 01 February 2019

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma - Italy

GENERAL INFORMATION

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INVESTIGATOR (or Coordinating Investigator)	Prof. Julia B. Hennermann, Leiterin Villa Metabolica Universitatsmedizin, Mainz, Germany
MONITORING CONTRACT RESEARCH ORGANISATION	*name, address and telephone number (TBD)* <<WRITE HERE>>

VERSIONS' HISTORY

Version	Date	Change History
1.0	*13 October 2017*	*First version*
2.0	*06 December 2017*	*Second version according to EMA request*
3.0	*13 December 2017*	*Third version according to EMA request*
4.0	*02 March 2018*	*Fourth version for PRAC evaluation according to EMA request*
5.0	*09 July 2018*	*Fifth version following PRAC evaluation according to EMA request*
6.0	*15 November 2018*	*Sixth version following PRAC evaluation of the protocol*
7.0	*25 January 2019*	*Seventh version following EMA request on 9.2.6 paragraph*
8.0	*01 February*	*Eighth version following further EMA request to be added on 9.2.6 paragraph*

PAES/PASS INFORMATION

Title	THE ALPHA-MANNOSIDOSIS REGISTRY: A multi-centre, multi-country, non-interventional, prospective cohort, in alpha-mannosidosis patients
Protocol version identifier	Version 8.0
Date of last version of protocol	01 February 2019
European Union electronic register of post-authorisation studies (EU PAS register) number	Registration in the EU PAS register will be performed before the first is patient included.
Active substance	Velmanase alfa (recombinant form of human alpha-mannosidase) Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes ACT code: A16AB15
Medicinal product	Lamzede 10 mg powder for solution for infusion
Product reference	EU/1/17/1258
Procedure number	EMEA/H/C/003922
Marketing authorisation holder	Chiesi Farmaceutici S.p.A.
Joint PASS	No
Research question and objectives	The Alpha Mannosidosis Registry objectives are as follows: *Primary Objective* • To assess the long-term effectiveness and safety of treatment with Lamzede under conditions of routine clinical care. • In terms of effectiveness, the primary focus of the registry is to estimate the Global Treatment Response rate as percentage of patients qualified as responders by aggregately assessing oligosaccharides in serum (umol/L) (GTR-Pharmacodynamic Domain), 3MSCT (step/min), 6MWT (mt), FVC (% of predicted) (GTR-Functional Domain) and QoL based on CHAQ VAS-Pain and CHAQ- Disability Index (GTR-QoL Domain). • In terms of safety, the rate of AEs (including ADA, IRRs and Hypersensitivity as identified risks) in the treated patients will be the main research of the study.. *Secondary Objectives* • To characterize the alpha-mannosidosis population, including clinical manifestation, progression and natural history. • In particular, oligosaccharides in serum (umol/L), endurance based on 3MSCT (step/min), 6MWT (m) and 2MWT (m) assessment, respiratory function through FVC (as litre and as percentage of predicted), hearing function with PTA, length and rate of infections (requiring or not antibiotics), rate of psychotic events, immunological status as per serum IgG, IgA and IgM, and QoL assessed by EQ-5D-5L, Zarit Burden Interview, CHAQ, Behavior Checklists (prescholar, scholar, adult and older adult) will be adopted for characterizing the alpha-mannosidosis population • Rate of incidence of acute renal failure and loss of consciousness (as potential risks under Lamzede treatment), change in vital signs (SBP, DBP), laboratory tests (haematology and chemistry), physical examination and ECG will also be monitored.
Countries of study	It is foreseen that approximately 40 suitable centres in the European Union (EU) will be involved and additional sites may be added, as required. The final list of countries and sites will depend on the Lamzede authorisation and capability of the site to administer the treatment. Indicatively, the following countries will be involved: Germany, Denmark, Sweden, Norway, The Netherlands, Austria, Spain, France, UK, Italy, Belgium and Poland.
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MARKETING AUTHORISATION HOLDER

Marketing authorisation holder (MAH)	Chiesi Farmaceutici S.p.A., Via Palermo 26/A, 43122 Parma - Italy
MAH contact person	Giovanna Lasagna Chiesi Farmaceutici S.p.A., Via Palermo 26/A, 43122 Parma - Italy Tel.: +39 0521 279711 E-mail: g.lasagna@chiesi.com

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ABCL/ASR	Adult Behaviour Checklist/Adult Self reporting
ADA	anti-velmanase alfa-IgG antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency–2nd Edition
CBCL	Child Behaviour Checklist
CHAQ	Childhood Health Assessment Questionnaire
CRO	Contract Research Organisation
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D-5L	European Quality of Life Five Dimension Five Level Scale
EQ visual analogue scale	European Quality of Life visual analogue scale
ERT	enzyme replacement therapy
EU	European Union
EU PAS register	European Union electronic register of post-authorisation studies
FPFV	First Patient First Visit
FPLV	First Patient Last Visit
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GRT	Global Response to Treatment
GVP	Good pharmacovigilance practices
ICH	International Council for Harmonisation
Ig	immunoglobulin
IRRs	Infusion Related Reactions
LPLV	Last Patient Last Visit
MAA	Marketing Authorization Application
MAH	Marketing Authorisation Holder
MAN2B1	Mannosidase alpha class 2B member 1
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
OBCL/OASR	Older Adult Behaviour Checklist/Older Adult Self reporting
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PTA	Pure Tone Audiometry
Registry	Alpha Mannosidosis Registry
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T	time
VAS	Visual Analogue Scale
3MSCT	3-minute stair climb test

2MWT	2-minute walk test
6MWT	6-minute walk test

3. RESPONSIBLE PARTIES

The responsible parties involved in the conduct of the Alpha-mannosidosis Registry (henceforth referred to as Registry) are as follows:

- Principal or Coordinating Investigator (s): Prof. Julia B. Hennermann, Leiterin Villa Metabolica Universitatsmedizin, Mainz, Germany.
- Marketing Authorisation Holder (MAH): Chiesi Farmaceutici S.p.A., Via Palermo 26/A - 43122 Parma, Italy

4. ABSTRACT

Title:	THE ALPHA-MANNOSIDOSIS REGISTRY: A multi-centre, multi-country, non-interventional, prospective cohort, in alpha-mannosidosis patients
Protocol Number:	CLI-LMZYMAA1-12
Protocol Version:	Final 8.0
Protocol Date:	01 February 2019
Rationale and Background:	**Rationale and Background:** This Registry is being conducted to gather additional data in the context of post-marketing surveillance. Lamzede received Orphan Drug Designation in both the EU and the United States, and the marketing authorisation approval in the EU is sought under exceptional circumstances. In connection of Lamzede marketing authorization and its Risk Management Plan, the Alpha-mannosidosis registry is requested to obtain long term data on effectiveness and safety; furthermore, the Registry will expand the current understanding of alpha-mannosidosis by collecting additional data on natural history in alpha-mannosidosis patients despite the therapeutic treatment they are receiving.
	Alpha-mannosidosis: Human alpha-mannosidosis is a rare genetic disorder, caused by lack of the lysosomal enzyme alpha-mannosidase, resulting in mental retardation, skeletal changes, hearing loss and recurrent infections. The lack of alpha-mannosidase causes a disorder of glycoprotein catabolism associated with abnormal levels and excretion of small mannose-rich oligosaccharides. The epidemiology of alpha-mannosidosis is poorly understood and characterised in terms of its incidence and prevalence; although it belongs to a group of lysosomal storage disorders that includes more than 50 different diseases, with a cumulative frequency of about 1:10,000 worldwide. The incidence of alpha-mannosidase disease ranges from 1 in 500,000-1:1,000,000 worldwide. The disease is not specific to any ethnic groups. The life expectancy in alpha-

	mannosidosis is highly variable. Individuals with early onset severe disease often do not survive beyond childhood, whereas those with milder disorders may survive well into adulthood. Clinical expression of alpha-mannosidosis varies from a few symptoms to death. There is a broad phenotypic variation of manifestations, including intellectual disabilities, hearing impairment, motor function disturbances, facial coarsening, musculoskeletal abnormalities and immune deficiency. Alpha-mannosidosis always seems to have its onset before the age of two years, mostly at birth. Children are often born apparently normal, and their condition develops progressively, without any possibility to prevent this evolution. It is frequently associated with corneal opacities, hearing loss, aseptic destructive arthritis, metabolic myopathy and immune deficiency. Neurological findings, mental retardation, skeletal deformations and hearing impairment are foremost leading to the initiation of a diagnostic process in patients with alpha-mannosidosis. The long-term prognosis of the disorder is poor, although some patients can reach over 50 years of age. Neuromuscular and skeletal deterioration can occur over several decades. Lamzede is the only authorised treatment for alpha-mannosidosis in the EU. Prior to its approval, were available treatment focused on the relief of symptoms, and prevention of complications and impairments, with treatments and procedures designed individually based on symptoms and age. Bone marrow transplantation has been used as a therapeutic strategy for alpha-mannosidosis, but comes with a risk of mortality and morbidity. Palliative treatments include physiotherapy, respiratory physiotherapy or antibiotic treatment for recurrent infections. Prevention of the disease is restricted to prenatal diagnosis and carrier identification.
Research Question and Objectives:	The Registry objectives are as follows: *Primary Objective* • To assess the long-term effectiveness and safety of treatment with Lamzede under conditions of routine clinical care. • In terms of effectiveness, the primary focus of the registry is to estimate the Global Treatment Response rate as percentage of patients qualified as responders by aggregately assessing oligosaccharides in serum (umol/L), (GTR-Pharmacodynamic Domain), 3MSCT (step/min), 6MWT (mt), FVC (% of predicted) (GTR-Functional Domain) and QoL based on CHAQ VAS-Pain and CHAQ- Disability Index (GTR-QoL Domain). • In terms of safety, the rate of AEs (including ADA, IRRs and Hypersensitivity as identified risks) in the treated patients will be the main research of the study. *Secondary Objectives* • To characterize the alpha-mannosidosis population, including clinical manifestation, progression and natural history.

	• In particular, oligosaccharides in serum (umol/L), endurance based on 3MSCT (step/min), 6MWT (m) and 2MWT (m) assessment, respiratory function through FVC (as litre and as percentage of predicted), hearing function with PTA, length and rate of infections (requiring or not antibiotics), rate of psychotic events, immunological status as per serum IgG, IgA and IgM, and QoL assessed by EQ-5D-5L, Zarit Burden Interview, CHAQ, Behavior Checklists (prescholar, scholar, adult and older adult) will be adopted for characterizing the alpha-mannosidosis population. Rate of incidence of acute renal failure and loss of consciousness (as potential risks under Lamzede treatment), change in vital signs (SBP, DBP), laboratory tests (haematology and chemistry), physical examination and ECG will also be monitored.
Study Design:	The Registry is a multi-centre, multi-country, non-interventional, prospective cohort, in alpha-mannosidosis patients. The enrolment for participation in the Registry will occur during an indefinite timeframe. The duration of the observation period for each patient will be of 15 years. Patients with alpha-mannosidosis receiving and not receiving treatment with Lamzede will be enrolled. The study population will be characterized by distinct clinical features and/ or a short follow-up duration. This does not permit the definition of a control group and a direct, formal determined *a-priori* between-group comparison, allowing for a descriptive, explorative between-groups comparison only. If applicable in accordance with routine clinical practice, the following schedule of assessments is recommended: • Registry Inclusion Visit, at the time of enrolment into the Registry with the signature of the informed consent; • Registry Baseline Visit, corresponding to the time in which the observational period will start; • Six-month and Yearly follow-up visits for all patients included in the registry; • Unscheduled follow-up visits, such as but not limited to, three months after Lamzede treatment start, or whenever deemed appropriate according to treating physician's judgement for patients that start the Lamzede treatment within one year priori to Registry participation. As patients can start Lamzede treatment at any time during the course of their participation to the Registry, if applicable in accordance with routine clinical practice, a baseline visit is recommendedto be repeated before Lamzede administration starts and unscheduled visits are recommended as detailed in the setting of patients starting Lamzede treatment within one year prior to inclusion in the Registry. On the other hand, the patients can also terminate the Lamzede treatment at any time

	during the course of their participation to the Registry, and will be allowed completing in any case the 15-year follow-up period. This Registry will be conducted under conditions of routine clinical care, without mandatory diagnostic procedures and assessments that can be considered as outside of routine clinical care. Data collection will coincide with routine care visits only according to the judgement of the treating physician's. Data collection including retrospective data will be allowed. Since this is an observational study capturing only the outcomes of routine clinical practice, participation in the Registry will not change the patient/physician relation, nor influence the physician's drug prescription or therapeutic or other management of the patient. It is foreseen that approximately 40 suitable centres in the European Union (EU) will be involved and additional sites may be added, as required. The final list of countries and sites will depend on the Lamzede authorisation and capability of the site to administer the treatment. Indicatively, the following countries will be involved: Germany, Denmark, Sweden, Norway, The Netherlands, Austria, Spain, France, UK, Italy, Belgium and Poland.
Population:	The eligible patient population for this Registry includes any patient in the EU with alpha-mannosidosis who is willing to participate, and who meets the inclusion criteria for this Registry. Patients will be offered the Registry participation over a 15-year follow-up period. Due to the observational nature of the present Registry study, patients can start or stop Lamzede treatment at any time during this 15-year observational period. Eligibility criteria for the Registry are as follows: **Inclusion Criteria** Patients must meet all of the following inclusion criteria to be eligible for enrolment in the Registry: 1. Evidence of a personally signed and dated informed consent form indicating that the patient (or parents or a legally acceptable representative according to local regulation) has been informed of all pertinent aspects of the Registry and confirms the willingness to participate to the present observational study and to permit the investigator to enter assessment data recorded prior to Registry entry if available in the patient's medical records. 2. Diagnosis of alpha-mannosidosis (based on historical or current diagnosis). **Exclusion Criteria** There are no exclusion criteria for the Registry. Moreover, patients participating in other clinical trials of any placebo, drug or biological substance conducted under the provisions of a

	protocol will not be prevented to participate to the Registry at the discretion of the Investigator.
Variables:	**Effectiveness Variables** Effectiveness will be assessed by: • Oligosaccharides in serum (µmol/L) • 3-Minute Stair Climb Test (3MSCT) (step/min) • 6-Minute Walk Test (6MWT) (m) • 2-Minute Walk Test (2MWT) (m) • Forced Vital Capacity (FVC) (as litre and as percentage of predicted) • EQ-5D-5L • Zarit Burden Interview • Childhood Health Assessment Questionnaire (CHAQ) • Rate and length of infection (requiring or not antibiotic) • Serum IgG, IgA and IgM • Rate of psychotic events • Behaviour Checklists (Childhood, Adult and Older Adult) In patients below 4 years of age, 3MSCT, 2MWT and FVC % of predicted will be proposed upon the judgment of the treating physician. Since alpha-mannosidosis presents as a multi-systemic disease, characterized by many clinical manifestations, a Global Treatment Response (GTR) will be evaluated by aggregating single endpoints in 3 disease relevant domains: pharmacodynamics (reduction of serum oligosaccharides), functional (3MSCT, 6MWT and FVC % of predicted) and quality of life (improvement in CHAQ Disability Index and VAS pain). Clinically significant response assigned to each domain when at least one parameter of the domain will be improving beyond the proposed Minimal Clinical Important Difference (MCID) established for each endpoint from proxy diseases. Patients will then be qualified as a GTR-responder if the response criteria was reached in at least two domains. Global Treatment Response rate after 3 years of Lamzede treatment in naïve patients able to perform the functional tests will be evaluated. **Safety Variables** Safety will be assessed by: • Adverse Events (AEs) including non-serious and Serious AEs, including non-serious and serious adverse drug reactions (ADRs), AEs leading to treatment discontinuation and AEs leading to death at any time they become available. • anti-velmanase alfa-IgG antibody (ADA), infusion related reactions (IRRs) and hypersensitivity (as identified risks)

<table>
<tr><td></td><td>

Acute renal failure, loss of consciousness and medication errors (as potential risks)
Vital signs: systolic (SBP) and diastolic blood pressure(DBP), pulse rate (PR)
Electrocardiogram (ECG)
Laboratory tests (haematology and chemistry)
Physical Examination

Other Variables
In addition the following other variables will be presented:

Height, weight, Body Mass Index (BMI) and rate of growth
Hearing test (Pure Tone Audiometry)
Concomitant procedures and medications

</td></tr>
<tr><td>Data Sources:</td><td>Data sources will include patient medical records and any other records of clinical findings or observations collected as part of routine clinical practice. Retrospective data collection for any relevant measurement present in the patient's clinical records prior to the inclusion in the study will be allowed. The source data will be collected by the investigator in the patient file and captured in the electronic Case Report Form (eCRF).</td></tr>
<tr><td>Study Size:</td><td>All patients with alpha-mannosidosis who are willing to participate will be included in the Registry.
The size of the registry study is not based on the power to demonstrate a formal statistical hypothesis. However, some scenarios are presented in the table below, considering different proportions of GTR in naïve patients able to perform the functional tests after 3 years of treatment. The proportion of responders, the corresponding expected 95% confidence interval and the confidence width are shown below, assuming that at least 70 treated patients will be enrolled.
In this case, it is expected that an exact (Clopper-Pearson) two-sided 95% confidence interval (CI) might be provided with a width ranging from 0.239 (worst case) to 0.199 (best case) assuming GTR of 0.60 or more. Of note, in all scenarios the lower limit of 95% CI is always greater than 45% which is considered a clinical relevant result.
<table>
<tr><th>Expected Proportion</th><th>95% CI Lower Limit</th><th>95% CI Upper Limit</th><th>95% CI Actual width</th></tr>
<tr><td>0.60</td><td>0.476</td><td>0.715</td><td>0.239</td></tr>
<tr><td>0.65</td><td>0.527</td><td>0.760</td><td>0.234</td></tr>
<tr><td>0.70</td><td>0.579</td><td>0.804</td><td>0.225</td></tr>
<tr><td>0.75</td><td>0.632</td><td>0.846</td><td>0.214</td></tr>
<tr><td>0.80</td><td>0.687</td><td>0.886</td><td>0.199</td></tr>
</table>
</td></tr>
<tr><td>Data Analysis:</td><td>Categorical variables will be described by means of absolute and relative frequencies, while continuous variables by means of mean, standard deviation, quartiles, min and max.</td></tr>
</table>

	Analysis will consider data collected at available observational point, according to clinical practice and clinical judgment. In order to summarise data by time point (e.g. one year after baseline, two years after baseline, etc.), the nearest available evaluation/measurement will be considered (acceptable range). **Effectiveness of Lamzede** All effectiveness variables will be summarised by means of descriptive statistics or frequency distribution, as appropriate. All variables (actual values and change from baseline, if applicable) will be presented by time point. In addition, mean and individual profiles by time will be produced. The proportion of responders (i.e. naïve patients able to perform the functional tests who achieve a GTR after 3 years of Lamzede treatment) and the corresponding exact (Clopper-Pearson) two-sided 95% confidence interval (CI) will be presented. Effects of baseline characteristics will be evaluated by means of regression/logistic models including: • age subgroup (<18 years, ≥18 years), • gender (male, female) • genotype by subcellular localization of the protein (Genotype Group 1, Genotype Group 2, Genotype Group 3, as defined by Borgwardt et all., 2015) • baseline residual enzymatic activity (<10 nmol/h/mg, 10 to <15 nmol/h/mg, ≥15 nmol/h/mg) • baseline CHAQ Disability Index (0|-|1, 1-|2, 2-|3) as covariates. Comparison with control group will be done descriptively, provided that a minimum number of non-treated patients with adequate data will be enrolled. **Safety of Lamzede** The proportion of patients experiencing at least one AE, non-serious and serious AEs, non-serious and serious ADRs, AE leading to treatment discontinuation and AEs leading to death will be provided. The above category of AEs will be summarized in terms of frequency of patients with at least one AE and in terms of number of events. These results will be provided by year from the baseline. The proportion of patients experiencing at least one AE will be calculated as the ratio between the number of patients experiencing at least one AE during the reference period and number of patients at risk (population at risk). In addition, incidence rates per person-time will be calculated as appropriate. The same approach will be followed also for identified and potential risks. The duration of follow-up will be described.

<table>
<tr><td></td><td>The proportion of patients developing immunogenicity (as Anti-velmanase alfa-immunoglobulin G antibody in serum) will be also presented.</td></tr>
<tr><td>Milestones:</td><td>
<table>
<tr><td>Milestone</td><td>Planned Date</td><td>Planned date calendar time</td></tr>
<tr><td>Start of data collection</td><td>7-8 months from CHMP/PRAC Protocol Approval</td><td>30/09/2019</td></tr>
<tr><td>End of data collection</td><td>Not applicable, as an indefinite enrolment period is foreseen</td><td>Not applicable</td></tr>
<tr><td>Interim report</td><td>Yearly, as part of annual re-assessment</td><td>By March 23rd of each year</td></tr>
<tr><td>Registration in the EU PAS register</td><td>Registration in the EU PAS register will be performed before the first patient is included</td><td>31/03/2019</td></tr>
<tr><td>Final report of study results</td><td>Within 6 months from End of data collection</td><td>Not applicable</td></tr>
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5. AMENDMENTS AND UPDATES

None. Updated version 2.0 dated 06 December 2017 according to the D195 Joint Rapporteurs Assessment Report. Afterwards updated version 3.0 dated 13 December 2017 according to additional Rapporteurs indication. Additional afterwards version 4.0 dated 02 March 2018 and version 5.0 dated 09 July 2018 have been issues according to PRAC evaluation according to EMA request. A further version 6.0 has been issued after PRAC subsequent evaluation. The version 7.0 has been issued after EMA request. The version 8.0 has been issued after EMA further request to be added to par. 9.2.6.

6. MILESTONES

Milestone	Planned date	Planned date calendar time
Registration in the EU PAS register	Registration in the EU PAS register will be performed before the first patient is included	31/03/2019
Start of data collection	7-8 months from CHMP/PRAC Protocol Approval	30/09/2019
Interim report	Yearly, as part of annual re-assessment	By March 23rd of each year
End of data collection	Not applicable, as an indefinite enrolment period is foreseen	Not applicable
Final report of study results	Within 6 months from End of data collection when it will be defined	Not applicable

EU PAS register=European Union electronic register of post-authorisation studies

7. RATIONALE AND BACKGROUND

7.1 Background

Alpha-mannosidosis is rare lysosomal storage disorder caused by deficiency of alpha-mannosidase, a lysosomal enzyme involved in the catabolism of glycoproteins [1]. The main effect of this deficiency is the accumulation of mannose-rich oligosaccharides in the tissues. Alpha-mannosidosis is caused by mutations in the *MAN2B1* (mannosidase alpha class 2B member 1) protein-coding gene, leading to the production of a dysfunctional or non-functional alpha-mannosidase. Deficiency in alpha-mannosidase is inherited in an autosomal recessive manner. The clinical variability of alpha-mannosidosis is considerable, encompassing a continuum ranging from mild to severe. There is a broad phenotypic variation of manifestations, including intellectual disabilities, hearing impairment, motor function disturbances, facial coarsening, musculoskeletal abnormalities, immune deficiency, corneal opacities, psychiatric symptoms, aseptic destructive arthritis and metabolic myopathy. At birth, alpha-mannosidosis patients appear normal, but their condition progresses over several decades, rendering most patients wheelchair-dependent over the course of adulthood. Neurological findings, mental retardation, skeletal deformations and hearing impairment are foremost leading to the initiation of a diagnostic process in patients with alpha-mannosidosis. Biochemical testing of alpha-mannosidase activity in leukocytes forms the basis of diagnosis, and detection of vacuoles in lymphocytes is seen in the peripheral blood of 90% of the patients [2]. Excretion of mannose-rich oligosaccharides in urine can also be demonstrated. Molecular genetic testing of

MAN2B1 and identification of two disease-causing mutations can contribute to establishing the diagnosis.

Lamzede (velmanase alfa, henceforth referred to as Lamzede) is a recombinant human lysosomal alpha-mannosidase product, developed as an intravenous enzyme replacement therapy (ERT) for the treatment of alpha-mannosidosis. The safety and efficacy of Lamzede in adults and children (≥6 years old) has been evaluated in 33 patients (20 males and 13 females; 19 children [paediatric group, aged younger than 18 years] and 14 adults; median age 17.1 years, range 6.0-35 years) in five clinical studies (three exploratory Phase I to IIb studies, one Phase III pivotal study and one Phase III long-term efficacy and safety evaluation (rhLAMAN-10) in all patients previously enrolled in clinical trials with under-treatment data for up to 48 months).

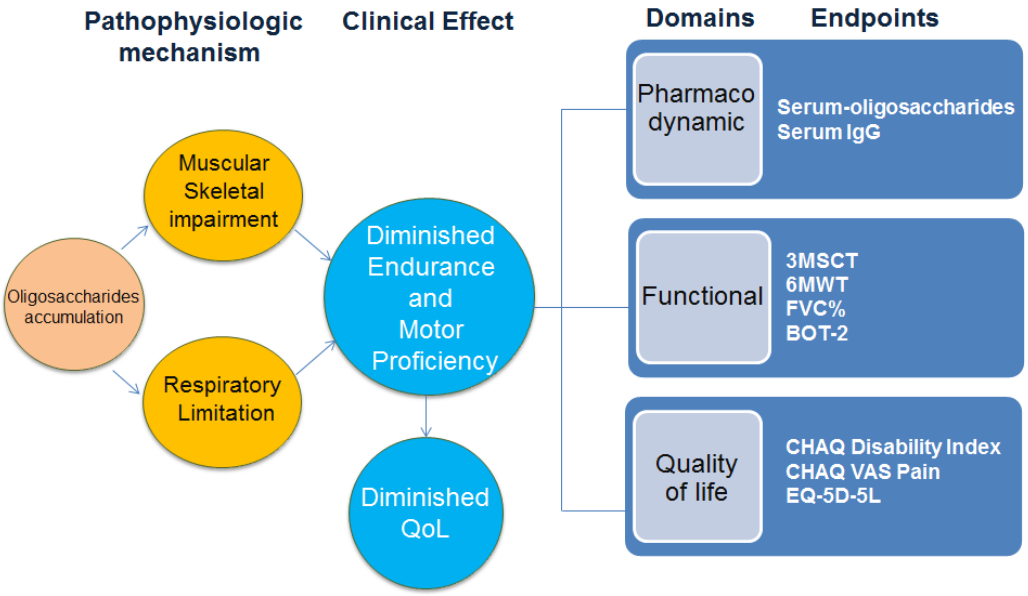
The rhLAMAN-10 open-label, uncontrolled, phase III study encompassed an integrated database created by pooling cumulative databases from all studies with Lamzede together with an additional long-term assessment endpoint. Statistically significant improvements were detected in serum oligosaccharide levels, 3-minute stair climb test (3MSCT) and pulmonary function over time, up to the last observation. The effects of Lamzede were more evident in patients younger than 18 years. Descriptive evidence of improvement was also documented in several additional clinical endpoints, including serum immunoglobulin G (IgG), Bruininks-Oseretsky Test Of Motor Proficiency–2nd Edition (BOT-2) subdomains and Childhood Health Assessment Questionnaire (CHAQ) Disability Index, CHAQ visual analogue scale (VAS) Pain, European Quality of Life Five Dimension Five Level Scale (EQ-5D-5L) Health Index. A progressive improvement from baseline was also evident in the 6-minute walk test (6MWT). For further details, refer to the Lamzede Summary of Product Characteristics (SmPC).

A multi-domain post-hoc responder analyses was conducted across the pharmacodynamics (serum oligosaccharide response only), functional (3MSCT, 6MWT and Forced Vital Capacity (FVC) % predicted) and quality of life (CHAQ disability index and CHAQ VAS pain) domains.

A clinically significant response for each domain was claimed when at least one parameter of the domain improved beyond the proposed MCID.

In the overall responder analysis, a patient was qualified as responder to treatment if response criteria was reached in at least two domains. The alpha-mannosidosis Response Model generated as part of this approach is depicted in Figure 1.

Figure 1 Alpha-Mannosidosis Treatment Response Models Treatment Response Model



Source: Provided by Chiesi

Based on the MCID-based Treatment Response Model, the Global Response to Treatment (GRT) of rhLAMAN-05 shows a discernible treatment difference between the two groups, with a clinical response in at least two domains at 12 months observed in 87% of patients treated with velmanase alfa compared to 30% in placebo. Moreover, 13% treated patients but none of the placebo patients reported a clinically-significant response in all three domains (Figure 3).

In the single-arm, integrated analysis from rhLAMAN-10 study, a remarkably similar proportion of 79% of patients showed a significant response in at least two domains at 12 months, 24% in all three. The proportion increases at Last Observation with a clinically meaningful response in at least two domains achieved in 88% patients (100% of paediatric patients and 71% of adult patients) and in at least three domains in 45% patients (53% of paediatric patients and 36% of adult patients) (Figure 2). The proposed domains are aligned with the representation of (a) the clinical burden, (b) the endpoints hierarchy defined with the CHMP, (c) the measurements of the benefit perceived by the patients (health-related QoL).

Figure 2 Global Response to Treatment in rhLAMAN-10 Study Integrated Analysis

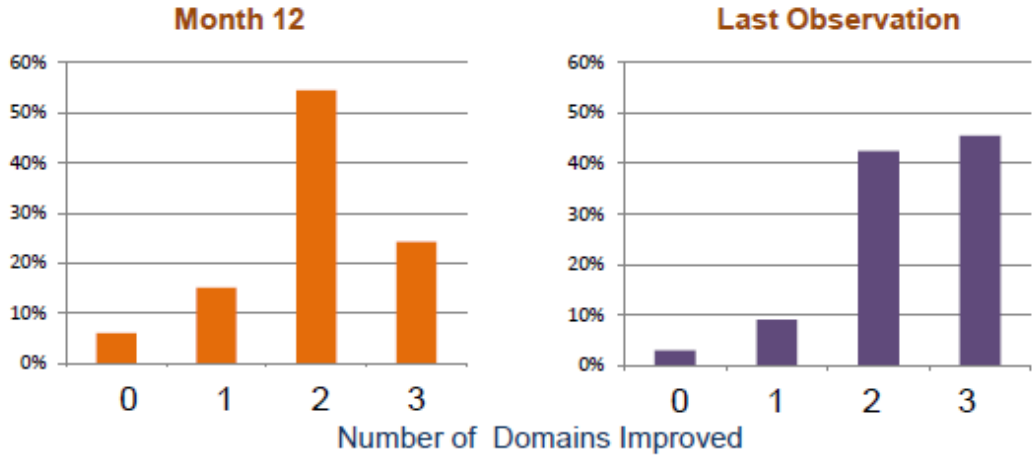
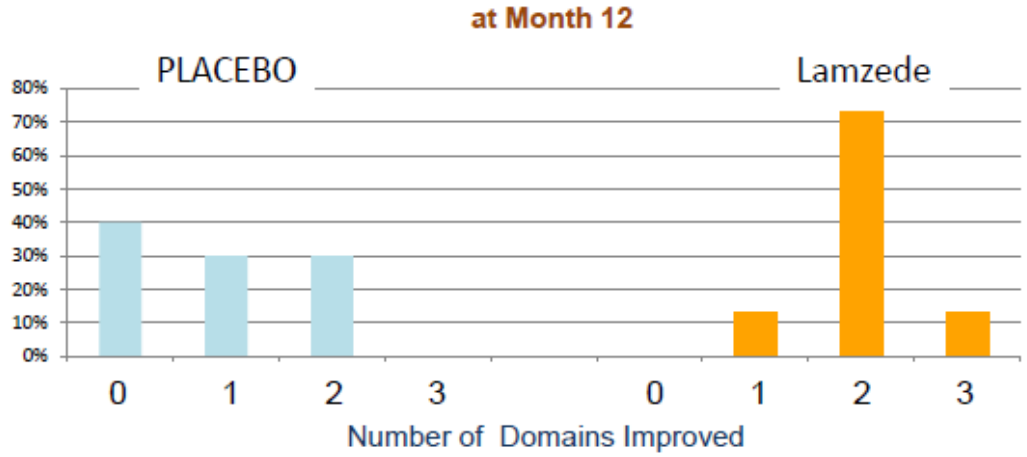


Figure 3 Global Response to Treatment at 12 Months in rhLAMAN-05 Placebo-controlled Study



The most common adverse reactions observed during treatment with Lamzede were weight increase (18%), infusion-related reactions (9%), diarrhoea (12%), headache (9%), arthralgia (9%), increased appetite (6%) and pain in the extremities (6%). A total of two serious adverse reactions (loss of consciousness in one patient and acute renal failure in one patient) considered possibly related to study treatment were observed; both cases recovered without sequelae. For further safety information, refer to the Lamzede SmPC.

Lamzede is indicated in patients with alpha-mannosidosis. The marketing authorisation in the EU was granted for Lamzede with European Commission implementing decision of 23rd March 2018. Lamzede is the only authorised treatment for alpha-mannosidosis in the European Union (EU). Prior to its approval, treatment focused on the relief of symptoms, and prevention of complications and impairments, with treatments and procedures designed individually based on symptoms and age. Bone marrow transplantation has been used as a therapeutic strategy for alpha-mannosidosis, but comes with a risk of mortality and morbidity. Palliative treatments include physiotherapy, respiratory physiotherapy or antibiotic treatment for recurrent infections. Prevention of the disease is restricted to prenatal diagnosis and carrier identification.

7.2 Rationale

The Registry is being conducted as an EU Risk Management Plan (EU-RMP) Additional Pharmacovigilance Activities. Lamzede received Orphan Drug Designation in both the EU and the United States, and the marketing authorisation approval in the EU is sought under exceptional circumstances. In connection to Lamzede marketing authorization and its Risk Management Plan, the Alpha-mannosidosis registry is requested to obtain long term data on effectiveness and safety of treatment with Lamzede; furthermore, the Registry will expand the current understanding of alpha-mannosidosis by collecting natural history data, disease modifiers and confounder factors in alpha-mannosidosis patients despite the therapeutic treatment they are receiving.

This study will be conducted in compliance with the Declaration of Helsinki (1964 and amendments), current International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) as far as applicable, in accordance with the obligation in the framework of a marketing authorisation granted

under exceptional circumstances (category 2 of studies in Good pharmacovigilance practices [GVP] Module V) and all other applicable laws and regulations.

8. RESEARCH QUESTION AND OBJECTIVES

Primary Objective

- To assess the long-term effectiveness and safety of treatment with Lamzede under conditions of routine clinical care.
- In terms of effectiveness, the primary focus of the registry is to estimate the Global Treatment Response rate as percentage of patients qualified as responders by aggregately assessing oligosaccharides in serum (umol/L), (GTR-Pharmacodynamic Domain), 3MSCT (step/min), 6MWT (mt), FVC (% of predicted) (GTR-Functional Domain) and QoL based on CHAQ VAS-Pain and CHAQ- Disability Index (GTR-QoL Domain).
- In terms of safety, the rate of AEs (including ADA, IRRs and Hypersensitivity as identified risks) in the treated patients will be the main research of the study.

Secondary Objectives

- To characterize the alpha-mannosidosis population, including clinical manifestation, progression and natural history.
- In particular, oligosaccharides in serum (umol/L), endurance based on 3MSCT (step/min), 6MWT (m) and 2MWT (m) assessment, respiratory function through FVC (as litre and as percentage of predicted), hearing function with PTA, length and rate of infections (requiring or not antibiotics), rate of psychotic events, immunological status as per serum IgG, IgA and IgM, and QoL assessed by EQ-5D-5L, Zarit Burden Interview, CHAQ, Behavior Checklists (prescholar, scholar, adult and older adult) will be adopted for characterizing the alpha-mannosidosis population
- Rate of incidence of acute renal failure and loss of consciousness (as potential risks under Lamzede treatment), change in vital signs (SBP, DBP), laboratory tests (haematology and chemistry), physical examination and ECG will also be monitored.

9. RESEARCH METHODS

9.1 Study Design

The Registry is a multi-centre, multi-country, non-interventional, prospective cohort including alpha-mannosidosis patients, despite any treatment they received or are receiving. The Registry will be conducted under conditions of routine clinical practice, without registry-mandatory assessments according to the treating physician and will include all eligible patients who agree to participate.
Within the Registry, a pool of patients with alpha-mannosidosis undergoing Lamzede therapy will be suitable to allow a further data collection revolved to the long-term safety and effectiveness of Lamzede therapy (see Section 9.7.4 for the study endpoints). In this group of patients, Lamzede has to be administered in accordance with the current Lamzede SmPC and in line with usual clinical practice. Patients with alpha-mannosidosis receiving and not receiving Lamzede will be also enrolled. It is expected that the pool of patients not receiving Lamzede will be limited in number and characterized by distinct clinical features and/ or a short follow-up duration. This does not permit the definition of a control group and a direct, formal determined *a-priori* between-group comparison, allowing for a descriptive, explorative between-groups comparison only.

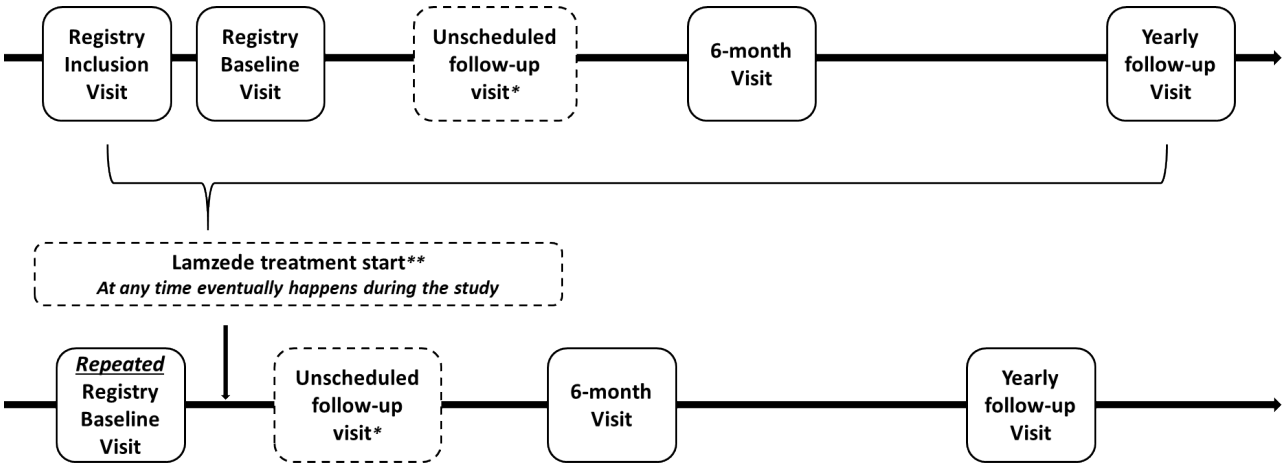
If applicable in accordance with routine clinical practice, the following schedule of visits is recommended:

- **Registry Inclusion Visit**, at the time of enrolment into the Registry approximately 7 days prior to the Registry Baseline visit. In order to check eligibility criteria and when the informed consent form could also be signed in case to patient willingness to participate to the study;
- **Registry Baseline Visit**, corresponding for all patients included, to the time in which the observational period will start (Time 0) and when the site can also evaluate to possibly start or continue the treatment with Lamzede according to clinical practice;
- **Six-month** and **Yearly follow-up** visits for all patients included in the registry;
- **Unscheduled follow-up visits**, such as but not limited to, three months after Lamzede treatment start, or whenever deemed appropriate, according to treating physician's judgement for patients that start Lamzede treatment within one year prior to Registry inclusion. During the following years, routine clinical visits are recommended to take place at least annually, for all patients.

As patients can start Lamzede treatment at any time during the course of their participation to the Registry, if applicable in accordance with routine clinical practice, a baseline visit is recommended to be repeated before Lamzede administration starts and unscheduled visits are recommended as detailed in the setting of patients that start Lamzede treatment within one year prior to Registry inclusion. On the other hand, the patients can also terminate the Lamzede treatment at any time during the course of their participation to the Registry, completing in any case the 15-year follow-up period.

A schematic diagram is reported in Figure 4.

Figure 4. Timetable (recommendation for the first year of the 15-year observational period)



* If applicable in accordance with routine clinical practice, unscheduled follow-up visits can be performed at, but not limited to, three months after Lamzede treatment start, or whenever deemed appropriate according to treating physician's judgement for patients that start Lamzede treatment within one year prior to Registry inclusion.

** Patients can start Lamzede treatment at any time during the course of their participation to the Registry, if applicable in accordance with routine clinical practice, a baseline visit is recommended to be repeated before Lamzede administration starts and unscheduled visits are recommended as reported in the schema above

The investigator will report data for study endpoint assessments during the data reporting periods outline in Table 1.

9.2 Setting

9.2.1 Subject Recruitment

The eligible patient population for this Registry includes any patient in the EU suffering from alpha-mannosidosis who is willing to participate, and who meets the inclusion criteria (see below) for this Registry. The recruitment period will be indefinite.

About 30 patients are foreseen as coming from previous Lamzede clinical trials. Each patient will be followed-up for 15 years.
Based on the current unmet medical need, patients can start Lamzede treatment independently from the Registry set up.

9.2.2 Inclusion Criteria

To be eligible for enrolment in the Registry, patients must fulfil all the following inclusion criteria:

1. Evidence of a personally signed and dated informed consent form indicating that the patient (or parents or a legally acceptable representative according to local regulation) has been informed of all pertinent aspects of the Registry and confirms the willingness to participate to the present observational study and permits the investigator to enter assessment data recorded prior to Registry entry if available in the patient's medical records.
2. Diagnosis of alpha-mannosidosis (based on historical or current diagnosis).

9.2.3 Exclusion Criteria

There are no exclusion criteria for the Registry.
Moreover, patients participating in other clinical trials of any placebo, drug or biological substance conducted under the provisions of a protocol will not be prevented to participate to the Registry at the discretion of the Investigator.

9.2.4 Patient Withdrawal

Patients may be discontinued from the study at any time for any of the following reasons:

- The patient is lost to follow-up.
- The patient withdraws consent and is unwilling to continue the registry participation.
- The sponsor or the regulatory authorities or the Ethics Committees (ECs), for any reason, terminates the entire study, or terminates the study for this study site or this particular patient.

It is understood by all concerned that an excessive rate of withdrawals can render the study not interpretable; therefore, unnecessary withdrawals of patients should be avoided.
However, should a patient discontinue the study, all efforts will be made to complete and report the observations as thoroughly as possible.
In case a patient is transferred to another continuing care site, the new treating site will be formally involved in the Registry study following a request of authorization submitted to the relevant Ethics

Committee and Regulatory Authority to complete the 15-year observational period following the patient and collecting all information as per study protocol.
In case of withdrawal, the investigator must fill in the "Study Termination" page in the electronic Case Report Form (eCRF), reporting the main reason for withdrawal.
In order to collect as complete as possible information in the clinical study database, all ADRs and SAEs ongoing at the time the patient's study participation ends should be evaluated up to 14 days after last Lamzede intake. After this period, all unresolved ADRs and SAEs will be reported as "ongoing" in the eCRF.
If a patient is withdrawn from the registry, after having started or continued the treatment with Lamzede, the investigator should report to the sponsor any post-discontinuation new serious adverse event causally related to Lamzede he/she may have knowledge of.
If a patient is withdrawn/drops-out of the study the patient study number should not be reassigned to another patient.

9.2.5 Study Place

Registry patients will be enrolled in the EU only. It is foreseen that approximately 40 suitable centres in the European Union (EU) will be involved and additional sites may be added, as required. The final list of countries will depend on the Lamzede authorisation and capability of the site to administer the treatment. Indicatively, the following countries will be involved: Germany, Denmark, Sweden, Norway, The Netherlands, Austria, Spain, France, UK, Italy, Belgium and Poland.

Study Duration
The overall duration of the study is not defined. The enrolment for participation in the Registry will occur for an indefinite period. The duration of the observational period for each patient will be of 15 years. The end of the study is defined as the last visit of the last patient in the study.

9.2.6 Study Plan

The Registry will be conducted under conditions of routine clinical practice, without Registry-mandated diagnostic procedures and assessments that can be considered as outside of routine clinical care by the treating physician. Data collection will coincide with routine care visits only according to the judgement of the treating physician. Patients' data collection including retrospective data will be performed.
If applicable in accordance with routine clinical practice, the following schedule of assessments is recommended, as presented in Table 1 and previously described in section 9.1 concerning study design.

Since this is an observational study capturing only the outcomes of routine clinical practice, participation in the Registry will not change the patient/physician relation, nor influence the physician's drug prescription or therapeutic or other management of the patient.
Lamzede has to be administered in accordance with the current Lamzede SmPC and in line with usual clinical practice.

If further medicinal products will be applied besides Lamzede® for the treatment of alpha mannosidosis all medicinal products have to be administered in accordance with their respective SmPCs and in line with usual clinical practice.

Table 1 Schedule of Assessments to be reported (Flow-Chart).

Procedure	Registry Inclusion visit (approx. -7 days)	Registry Baseline visit (Time 0)	Unscheduled Follow-up Routine Clinical Visits[1]	Six-month Follow-up Routine Clinical Visits[2]	Yearly Follow-up Routine Clinical Visits
Administrative					
Informed consent form	X	X[3]			
Inclusion/exclusion criteria	X	X[3]			
Medical and disease history (including disease onset, residual enzymatic activity, genotype mutations, bone marrow transplantation) and concomitant illnesses	X	X[3-4]			
Previous and concomitant medications, including Lamzede in hospital or home infusion setting		X[4]	X	X	X
Concomitant procedures	X	X	X	X	X
Physical examination[5] (Vital signs and anthropometric measurements, including rate of growth)		X	X	X	X
Demographics	X	X[3]			
Administration of medication					
Lamzede therapy, in hospital or home infusion setting[6]		X	X	X	X
Assessments[7]					
Anti-velmanase alfa-IgG antibody (ADA) [7a]		X	X		X
Standard haematological tests[8a]		X	X		X
Laboratory chemistry[8b]		X	X		X
Oligosaccharides in serum [7a]		X	X		X

Procedure	Registry Inclusion visit (approx. -7 days)	Registry Baseline visit (Time 0)	Unscheduled Follow-up Routine Clinical Visits[1]	Six-month Follow-up Routine Clinical Visits[2]	Yearly Follow-up Routine Clinical Visits
Serum Immunoglobulin class G, A, M [7a]		X	X		X
Three-minute stair climbing test (3MSCT)[9], when applicable		X			X
Six-minute walk test (6MWT)[9], when applicable		X			X
Two-minutes walk test (2MWT)[10], when applicable		X			X
Forced vital capacity (L and % of predicted)		X	X		X
Electrocardiogram		X	X		X
Hearing test (PTA)		X	X		
Infections (including length and antibiotics requirement)		X	X		X
Psychotic events		X	X		X
Adverse Events /Adverse Drug Reactions[11]	X	X	X	X	X
Health Assessment Questionnaires					
EQ-5D-5L		X			X
Zarit Burden Interview		X			X
CHAQ		X			X
Behavior Checklists[12]		X			X

Abbreviations: ADA, anti-velmanase alfa-immunoglobulin G (IgG) antibody; CHAQ, Childhood Health Assessment Questionnaire; EQ-5D-5L, European Quality of Life Five Dimension Five Level Scale; L, litre; PTA, pure tone audiometry

1. Unscheduled follow-up visits can be performed at, but not limited to, three months after Lamzede treatment start, or whenever deemed appropriate according to treating physician's judgement for patients that start Lamzede treatment within one year prior to Registry inclusion.
2. Additional follow-up visit after six months is highly recommended for patients that start Lamzede treatment within one year prior to Registry inclusion.
3. If not taken or collected at Registry Inclusion visit.
4. Patients' retrospective data may be collected at the time of Registry enrolment if available. Baseline visits are recommended to be repeated for those patients who will start Lamzede therapy during the course of the study, before therapy is initiated.
5. Physical examination to collect vital signs, anthropometric measurements like height, weight, rate of growth and the ability to perform the endurance test at the study visit.
6. If applicable, information regarding weekly Lamzede therapy received by the patient need to be recorded within all the Registry duration

7. All assessments mentioned in the above table will be collected only if considered necessary and available as part of routine clinical practice by the treating physician and no additional tests specific to the Registry will be done.
   7a. The markers (oligosaccharides in serum, IgG, IgA and ADA) will not be evaluated by a central laboratory for German patients only, while markers testing will take place according to local routine clinical practice in Germany.

The markers oligosaccharides in serum, IgG, IgA and ADA) will be evaluated through a central laboratory in EU countries other than Germany.

8. Standardtest for haematology and chemistry assessed by local laboratory if available per clinical practice of the site:
   a. Haemoglobin, haematocrit, platelet count, red blood cells, white blood cells with differential count (band forms, segment forms, neutrophils, eosinophils, basophils, monocytes, lymphocytes) (all expressed in % as well as in absolute numbers). Blood smear for leukocytes detection by electronic microscopy may be done at the treating physician's discretion.
   b. Biochemistry: Serum electrolytes (sodium, potassium, calcium, inorganic phosphate), creatinine, creatine-kinase, amylase, AST, ALT, ALP, albumin, bilirubin (total and direct), LDH.
9. In patients *from* 4 years of age and when applicable according to the judgment of treating physician.
10. In patients *below* 4 years of age and when applicable according to the judgment of treating physician.
11. Adverse Events /Adverse Drug Reactions based on all risk categories associated with Lamzede EU RMP, including infusion related reactions (IRRs) and hypersensitivity (as identified risks), acute renal failure, loss of consciousness and medication errors (as potential risks). Data on pregnancy and lactation (as missing information) will be also collected if available.
12. One of the Behavior Checklists (CBCL prescholar-scholar, ABCL/ASR (self-reporting), OABCL) will be used to the applicable age and according to the judgment of treating physician.

9.3 Variables

Only available evaluations as decided by the treating physician based on local routine clinical practice will be collected in the Registry. Patients' retrospective data may be collected if available. Where there are no data to report, this will be indicated in the applicable section(s) of the eCRF. See Table 1 for the schedule of assessments to be reported.

9.3.1 Demographic and Baseline Characteristics

After the patient, or parents or a legally acceptable representative according to local regulation, has provided signed informed consent and the patient has been included in the Registry, the following information will be reported in the eCRF for the baseline visit.

- Demographics (ethnicity, age, gender).
- Medical and disease history and concomitant illnesses – includes collection of time to diagnosis and manifestations, infections/fractures (if any), blood genotype results, serum/leukocyte determination of disease activity level, residual enzymatic activity, occurrence of bone marrow transplantation and outcome, hepatic or renal insufficiency.
- Previous and concomitant medications, including Lamzede received in hospital or home infusion setting*.
- Previous and concomitant procedures.
- Physical examination (including ability to perform the endurance test).
- Vital signs [systolic (SBP) and diastolic blood pressure (DBP), pulse rate (PR)] and anthropometric measurements (weight, height, head circumference with rate of growth by gender and age when applicable).

**all available information regarding therapies received by the patient before inclusion in the current study*

9.3.2 Administration of Medication

The Registry is an observational study and for this reason no treatment will be administered per protocol requirement. Information concerning administration of medication will be collected from the practice of the routine clinical care. Details of weekly Lamzede therapy and concomitant therapies received by the patient either in hospital or in home infusion settings, where allowed per local practice, will be collected at baseline and within the overall duration of the study. Setting of treatment administration will be collected as well.

9.3.3 Assessments

For the baseline visit and each follow-up routine clinical visit the following information will be reported in the eCRF if considered necessary and available as part of routine clinical practice by the treating physician:

- Genetic mutations testing, residual enzymatic activity (at Baseline only).
- Anti-velmanase alfa-IgG antibody (ADA) test in serum*. Only for patients receiving Lamzede treatment, at Baseline for patients about to start Lamzede therapy. Additional measurements will follow the judgment of the treating physicians.
- Laboratory chemistry and standard haematological if available per clinical practice:
  - Hemoglobin, hematocrit, platelet count, red blood cells, white blood cells with differential count (band forms, segment forms, neutrophils, eosinophils, basophils, monocytes, lymphocytes) (all expressed in % as well as in absolute numbers). Blood smear for leukocytes detection by electronic microscopy may be done at the treating physician's discretion.
  - Biochemistry: Serum electrolytes (sodium, potassium, calcium, inorganic phosphate), creatinine, creatine-kinase, amylase, AST, ALT, ALP, albumin, bilirubin (total and direct), LDH.
- Oligosaccharides in serum*
- 3MSCT (annually, see Section 9.3.3.3 for further details of the 3MSCT), when applicable.
- 6MWT (annually, see Section 9.3.3.3 for further details of the 6MWT), when applicable.
- 2MWT (annually, see Section 9.3.3.3 for further details of the 6MWT), when applicable
- FVC, as litre and as percentage of predicted, annually, when applicable.
- Serum IgG and IgA*
- Serum IgM.
- Electrocardiogram (ECG) (annually; more frequently in treatment-naive patients if considered necessary by the treating physician).
- Hearing test (by pure tone audiometry [PTA]) (annually).
- Occurrence of infections, antibiotic treatment requirement and length of treatment.
- Occurrence of psychotic events.
- Occurrence of all AEs/ADRs based on all risk categories associated with Lamzede EU RMP, including non-serious and Serious AEs, ADRs, AEs leading to treatment discontinuation and AEs leading to death at any time they become available.

Functional tests included in the Global Treatment Response (GTR) (namely 3MSCT, 6MWT, EQ-5D-5L and FVC are considered not doable in very young paediatric patients (i.e. < 4 years), due to the subject's inability to adequately execute the tests. Therefore, pre-treatment data will not be collected in this population (limited to these tests) in the infrequent case of patients starting treatment

before 4 years Concerning the 2MWT will be eventually performed according to the judgment of the treating physician For non-treated patients who are enrolled at such young age, but start treatment later, it will be strongly advised to the treating physician to take care of the fact that at least one pre-treatment battery of motor function tests is performed.

*Serum oligosaccharides, serum IgG, IgM and IgA, anti-velmanase alfa-IgG antibody (ADA) will be assessed by a centralised and specialised laboratory. In Germany these markers will not be evaluated by the central laboratory, but theywill be evaluated for German patients only locally in accordance to German requirements as part of routine clinical practice.
This centralised evaluation is needed to perform the quantitative detection by validated and consistent methods of the mentioned biochemical parameters, as specialised laboratories in these specific determination might be not locally available yet or some variability among different laboratories might introduce at certain extent limits in results' comparability. The MAH reassures that patients will not be undergoing additional or other than routine testing based on inclusion into the registry and that the testing within the Registry will only take place as part of routine clinical practice.
On the other hand, the MAH is not in the position, as per current rules, to offer the collection of serum samples for the testing of serum oligosaccharides, IgG, IgM and IgA and ADA as part of general clinical practice to patients treated with velmanase alfa who are not willing to participate in the registry and who are not signing the relevant informed consent form prior to any study related procedures and data collection.
The MAH acknowledges that according to German local rules and specific requirement the above markers will not be evaluated by the central laboratory for German patients only, so that markers testing will take place locally in Germany as part of routine clinical practice.

9.3.3.1 Serum oligosaccharides

Oligosaccharides can be detected quantitatively by a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS)) analyses of serum. The oligosaccharide content in serum of subjects before and after ERT is used as an important biomarker to assess the efficacy of Lamzede in alpha-mannosidosis subjects. The assessment is recommended as per If further medicinal products will be applied besides Lamzede® for the treatment of alpha mannosidosis all medicinal products have to be administered in accordance with their respective SmPCs and in line with usual clinical practice.

Table 1.

9.3.3.2 Development of Antibodies to velmanase alfa (ADA) Antibody Testing

Serum samples for anti-velmanase alfa antibody (ADA) testing will be obtained as per If further medicinal products will be applied besides Lamzede® for the treatment of alpha mannosidosis all medicinal products have to be administered in accordance with their respective SmPCs and in line with usual clinical practice.

Table 1.

9.3.3.3 Endurance: 3-Minute Stair Climb Test (3MSCT), 6-Minute Walk Test (6MWT) and 2-Minute Walk Test

The 3MSCT and 6MWT will be administered by a certified physiotherapist when applicable according to the judgment of the treating physician.
The 2MWT will be administered in paediatric subjects below 4 years of age, or when applicable according to the judgment of the treating physician.

In all cases, the investigator will enter data into the eCRF. Each battery of 3MSCT, 6MWT and 2MWT will include two assessments on different days. The best value will be evaluated for effectiveness. A time frame of maximum 3 weeks is applicable for test repetition.

The 3MSCT measures limiting factors between multiple systems such as the musculoskeletal, neurological and cardiovascular systems. Stair climbing also provides a functional measure that is commonly performed in daily life and relates to level of the independence and community participation. Skeletal abnormalities and myopathy are common disease manifestations in alpha-mannosidosis and the stair climbing test is associated with measures of lower limb strength and power. Stair climbing also requires a greater range of motion from the joints of the lower limbs and greater strength than level walking [3]; [4]. The test measures the number of steps climbed up in 3 minutes and it will be performed in accordance with the test guidelines.
The 6MWT is a frequently-used indicator of functional exercise capacity. The test measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units and muscle metabolism. The test will be performed in accordance with the American Thoracic Society standards [5].
The 2MWT measures sub-maximal cardiovascular endurance by recording the distance that the participant is able to walk in 2 minutes and is considered a pragmatic alternative for the 'gold standard' 6MWT. This shorter test has been validated for the assessment of exercise capacity and is sensitive to detect response in patients with moderate-severe COPD, interventions in lower limb amputations, the elderly, neuromuscular diseases and chronic heart diseases [6]; [7].

9.3.3.4 Health Assessment Questionnaires

The Quality of Life questionnaires are not mandated by the Registry. For the baseline visit and each annual follow-up routine clinical visit the results from the following health assessment questionnaires will be reported, if available, in the eCRF:

- EQ-5D-5L.
- Zarit Burden Interview.
- CHAQ.
- Behavior Checklists: CBCL prescholar (1.5-5) and scholar (6-18); Adult Behavior Checklist (19-59)/ASR, Older Adult Behavior Checklist (60-and above).

Euro Quality of Life-5 Dimensions (EQ-5D-5L)

The EQ-5D-5L is a validated and standardised measure of health status developed by the EuroQol Group to provide a simple generic measure of health status for clinical and economic evaluation (http://www.euroqol.org/). EQ-5D-5L is filled in by patients; from a cognitive point of view it is easy, since it only takes few minutes to complete the questionnaire. The EQ-5D-5L essentially consists of 2 pages - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labelled "best imaginable health state" and "worst imaginable health state" (http://www.euroqol.org/). The VAS responses can be used as a quantitative measure of health as judged by the individual patients. The questionnaire will be provided in the country main language. Being self-administered, patients able to tick in the boxes and to indicate their self-rated health on the VAS will fill in the questionnaire.

Zarit Burden Interview

The Zarit Burden Interview was developed to measure subjective burden among caregivers. Items were generated based on clinical experience with caregivers and prior studies resulting in a 22-item self-report inventory that examines burden associated with functional/behavioural impairments and the home care situation. The items are worded subjectively, focusing on the affective response of the caregiver.
Scoring/Interpretation: each question is scored on a 5 point Likert scale ranging from 'never' to 'nearly always present'. Total scores range from 0 (low burden) to 88 (high burden).

Childhood Health Assessment Questionnaire (CHAQ)

The custodial parent(s) of all patients will be asked to complete the CHAQ. From the CHAQ the following topics are displayed: dressing and personal care, getting up, eating, walking, hygiene, reach, grip, activities, pain (from VAS), and general evaluation (from VAS).
The score for each question in the CHAQ is based on the following validated scoring system: without any difficulty (0), with some difficulty (1), with much difficulty (2), unable to do (3). For each category, the 2-5 items within the category is averaged for the summary tabulation. Even though this questionnaire is meant for children, the expected low equivalent age of the patients in this study makes the entire study population suitable for the questionnaire. Disability Index, VAS general and VAS pain will be evaluated.

Behavior Checklists and self-administered forms

The Child Behavior Checklist (CBCL) is a parent-report questionnaire on which the child is rated on various behavioural and emotional problems [9]. The preschool forms and profiles span ages 1½-5 years. The forms are completed by the parent/caretaker who spends the most time with the child on problem items plus descriptions of problems, disabilities, what concerns respondents most about the child, and the best things about the child
The school forms and profiles span ages 6-18 years and is completed by the parents or surrogates, and covers like the pre scholar form various behavioural and emotional problems.
The Adult forms (ABCL completed by a partner or surrogates) and ASR (for self-reporting) include normed scales for adaptive functioning, personal strengths, empirically based syndromes, substance use, internalizing, externalizing, and total problems. In addition, the ASR and ABCL profiles feature DSM-oriented scales consisting of items that experts from many cultures identified as being very consistent with DSM-5 categories.
The Older Adult forms/OASR (self-reported) allow assessments in a variety of contexts, including psychiatric and psychological evaluations; medical care; assessments following significant life changes, such as loss of a loved one or a move to an assisted living environment; and evaluations before and after planned changes and interventions.

9.3.3.5 Serum IgG, IgA, IgM and rate of infections

Serum samples for IgG, IgA, IgM testing will be obtained as per Table 1. Occurrence of infections, length of the episode, antibiotics requirements will be also traced according to Table 1. IgM information will be collected if available in clinical practice as per local laboratory.

9.3.3.6 Rate of psychotic events

Anecdotic reductions of the number of psychosis have been reported by the treating physicians. The observation is considered attributable to the general improvement of the physical conditions following treatment with velmanase alfa, while physical changes (i.e. increased pain, somatic complains, unfavourable physical events, physical trauma) might trigger psychotic events to occur or recur. Occurrence and rate of psychotic events will be therefore monitored as per Table 1.

9.3.3.7 Pure Tone Audiometry

A pure tone audiometry (PTA) will be administered to all subjects as per Table 1. PTA will be performed without hearing aids and will be carried out using audiometer earphones in a sound-proof room. Air-conduction and bone conduction will be measured.

9.4 Data Sources

Data sources will include patient medical records and any other records of clinical findings or observations collected as part of routine clinical practice. Retrospective data collection for any relevant measurement present in the patient's clinical records prior to the inclusion in the study will be allowed. The source data will be collected by the investigator in the patient file and captured in the eCRF.

In case a patient is transferred to another continuing care site during the 15-year observational period, the new treating site will be formally involved in the Registry study following a request of authorization submitted to the relevant Ethics Committee and Regulatory Authority to complete the 15-year observational period following the patient and collecting all information as per study protocol.

9.5 Study Size

All patients with alpha-mannosidosis who is willing to participate will be included in the Registry. The size of the registry study is not based on the power to demonstrate a formal statistical hypothesis. However, some scenarios are presented in the table below, considering different proportions of GTR in naïve patients able to perform the functional tests after 3 years of treatment. The proportion of responders, the corresponding expected 95% confidence interval and the confidence width are shown below, assuming at least 70 treated patients will be enrolled.

In this case, it is expected that an exact (Clopper-Pearson) two-sided 95% confidence interval (CI) might be provided with a width ranging from 0.239 (worst case) to 0.199 (best case) assuming GTR of 0.60 or more. Of note, in all scenarios the lower limit of 95% CI is always greater than 45% which is considered a clinical relevant result.

Expected Proportion	95% CI Lower Limit	95% CI Upper Limit	95% CI Actual width
0.60	0.476	0.715	0.239
0.65	0.527	0.760	0.234
0.70	0.579	0.804	0.225
0.75	0.632	0.846	0.214
0.80	0.687	0.886	0.199

9.6 Data Management

An eCRF will be filled-in by the investigator and/or his/her representative designee.
Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.
Questionnaires will be collected on paper and data will be entered in the database by the allocated Contract Research Organisation (CRO).
Medical history, AEs and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary; medications will be coded using the World Health Organization Drug dictionary and Anatomical Therapeutic Chemical classification.
The dictionary version to be use will be the most current version at the time the data collection starts.
Considering the long duration of the study, the versions could be updated during the trial by re-coding all terms already entered in database according to the new dictionary version. Re-coded terms will be reviewed by Chiesi for approval.
The detailed process and the coding tools will be specified in the Data Management Plan once the CRO will be selected.
External data (i.e. laboratory data) will be processed centrally[a] and results will be sent electronically to the designated CRO.
Access to electronic systems used for data collection will be granted to the study personnel only after appropriate training.
The data checks will be created by a CRO according to its own relevant SOPs. The CRO will be request to produce a Data Validation Plan (DVP). This document is envisaged to describe all online data validation checks and the manual checks, which will be programmed for data cleaning proposal.
The DVP online checks will be executed directly after the data entry procedure by saving a single eCRF page. Queries resulting from this process will be automatically posted into the eCRF on an ongoing basis.
The DVP will also detail both consistency and medical checks which will be performed by a CRO personnel (Data Manager, Medical Monitor), leveraging listings generated in SAS based on data extracted from the eCRF.The source data will be collected by the on-site personnel, then transcripted in the eCRF.
The eCRF access will be managed by the CRO, according to its own relevant SOPs.

The access to eCRF will be granted to the CRO, Chiesi and On-site personnel after appropriated training is attended.
Each user will receive a personal account and specific privileges based on the role, and will be able to reset his/her own password in the system.
On-site personnel account will be linked to a single site, enabling to access only the data of the patients enrolled at that specific site; on the contrary, the CRO and Chiesi personnel will be entitled to see all sites data in read-only mode.
The CRO personnel will have also the possibility to issue and manage queries in the system.
An appropriate documentation will be prepared to describe the user account creation and management, roles and corresponding privileges, and training on eCRF system as soon as the CRO will be appointed for the study set-up and conduction.

The CRA appointed by the CRO will be in charge to reconciliate any potential discrepancy between data collected in the source document and data reported in the eCRF. In case of discrepancies intercepted during the source data verification or other monitoring activities, the CRA will create a query in the eCRF to be sent to the investigator at the site. The investigator is expected to review each query and evaluate the best option to handle it.

Questionnaires will be managed through a paper process only. Two copies are foreseen to be available: the original form will be shipped to the CRO for entering the data in the study database and the second copy will be archived in the Investigator's Site File at the site.
The original copy will then be collected in the main Trial Master.

After the completion of data collection and cleaning, a review meeting will be held to determine the occurrence of any protocol violation and to define the patient populations for the analysis. Once the database has been declared to be complete and accurate, it will be locked, and the planned statistical analysis will be performed.
If the database is unlocked after the initial lock, the process must be carefully controlled and documented; updates to the study data must be authorised by Chiesi.
At the study conclusion, a complete copy of the study data will be created for archival purposes at Chiesi. The investigators will receive copies of the patient data for retention at the investigational sites.

[a] Local laboratory will be used in Germany as per local clinical practice. Central laboratory will be adopted in extra-German sites.

9.7 Data Analysis

The following describes the statistical analysis as it is foreseen at the time of planning the trial. Detailed methodology for the summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP).

9.7.1 Populations for Analysis

The following analysis sets will be defined:

- The Lamzede Safety analysis set (L-SAF) will contain all enrolled patients fulfilling inclusion criteria who have, at some time, received Lamzede treatment. This will include all patients entering the study currently taking Lamzede and all patients not taking Lamzede on entry to the study, but who begin doing so during the study. The latter group (those not taking Lamzede on entry to the study, but who begin doing so during the study) will only be classed as in the L-SAF from the time that they begin taking Lamzede. As is common practice, patients who have taken any amount of Lamzede, even if only one dose, will be included in the safety analyses. With regards to L-SAF definition, a minimum individual follow up of 1 month after last dose taken will be proposed. A consequence of this approach, where patients can be in the L-SAF for very varying amounts of time is that adverse event (and adverse reaction) rates will be presented based on person-years at risk, and not simply based on the total number of patients who are ever in the L-SAF.
- The Lamzede Effectiveness analysis set (L-FAS) will contain patients included in the Lamzede Safety analysis set – at the times when they have been taking Lamzede, and for 12 months thereafter – excluding patients without any valid measurement and those with major protocol deviations affecting the effectiveness evaluations. The consequence of this is that

"baseline" will be clearly defined for each patient – namely the time they started to take Lamzede, not necessarily the time they enter the study. So a patient can be excluded from the L-FAS for some of their time in the study, and then join the L-FAS. In such cases, their "baseline" would be the time when they started.

- The No-Lamzede Safety analysis set (NL-SAF) will include patients only for the time when they are not (and have not within 1 month) been taking Lamzede.
- The No-Lamzede Effectiveness analysis set (NL-FAS) will include patients only for the time when they are not (and have not within the 12 months) been taking Lamzede.

Exact definitions of major Protocol deviations will be discussed by the clinical team case by case during the Data Review Meeting and described in the Data Review Document.
A summary table reporting the reason for exclusion from analysis sets will be presented.

The primary objective of the study (i.e. to assess the long-term effectiveness and safety of treatment with Lamzede) will be based on the Lamzede Safety analysis set (L-SAF) for safety variables and on the Lamzede Effectiveness analysis set (L-FAS) for effectiveness and other variables.
The secondary objectives of the study will be based on the No-Lamzede Safety analysis set (NL-SAF) for safety variables and on the No-Lamzede Effectiveness analysis set (NL-FAS) for effectiveness and other variables.

9.7.2 Descriptive Statistics

Categorical variables will be described by means of absolute and relative frequencies, while continuous variables by means of mean, standard deviation, quartiles, min and max.
Analysis will consider data collected at available observational point, according to clinical practice and clinical judgment. In order to summarise data by time point (e.g. one year after baseline, two years after baseline, etc.), the nearest available evaluation/measurement will be considered (acceptable range).
The clinical features of all patients who switch on-to, or off, Lamzede treatment will be described, including outcomes (efficacy and harms) before switching, reasons for switching, and outcomes (efficacy and harms) after switching. Any patients who switch multiple times will have each switching episode described individually, as well as an overview of that patient's whole experiences.

9.7.3 Patient Demographics and Baseline characteristics

Demographic and baseline characteristics will be summarized by means of descriptive statistics and frequency distributions, as appropriate. The following variables will be presented: age, gender, ethnicity, height, weight, head circumference, rate of growth, Body Mass Index (BMI), alpha-mannosidosis history (time to diagnosis, time to manifestations, previous infections/fractures, blood genotype results, serum/leukocyte determination of disease activity level, residual enzymatic activity, occurrence of bone marrow transplantation and outcome, hepatic or renal insufficiency), medical history, concomitant disease, previous and concomitant medications including Lamzede received in hospital or home infusion settings, previous and concomitant procedures.

9.7.4 Effectiveness Variables

Effectiveness will be assessed by:

- Oligosaccharides in serum (µmol/L)

- 3MSCT (step/min)
- 6MWT (m)
- 2MWT (m)
- FVC (as litre and as percentage of predicted)
- EQ-5D-5L
- Zarit Burden Interview
- CHAQ
- Rate and length of infections (requiring or not antibiotic)
- Serum IgG, IgA and IgM
- Rate of psychotic events
- Behavior Checklists: CBCL prescholar (1.5-5) and scholar (6-18); Adult Behavior Checklist (19-59)/ASR, Older Adult Behavior Checklist (60-and above).

All effectiveness variables will be summarised by means of descriptive statistics or frequency distribution, as appropriate. All variables (actual values and change from baseline, if applicable) will be presented by time point. In addition, mean and individual profiles by time will be produced.

Since alpha-mannosidosis presents as a multi-systemic disease, characterized by many clinical manifestations, a Global Treatment Response (GTR) will be evaluated by aggregating single endpoints in 3 disease relevant domains: pharmacodynamics (reduction of serum oligosaccharides), functional (3MSCT, 6MWT and FVC % of predicted) and quality of life (improvement in CHAQ Disability Index and VAS pain). Patients will be considered responders in one domain if the Minimal Clinical Important Difference (MCID) established for each endpoint from proxy diseases will exceeded in at least one endpoint of the domain; GTR will be reached by patients responding in at least 2 domains.
At the time of planning this registry, adopted MCID are: oligosaccharides below 4 umol/L, increase of 7 steps/minute for 3MSCT (proxy: MPS IV A), increase of 30 meters for 6MWT (proxy: Pompe disease), increase of 10% for FVC (proxy: Pompe disease), decrease of 0.13 for CHAQ DI (proxy: Juvenile Arthritis) and of 8.2% for CHAQ pain (as in paediatric rheumatology). However, taking into account the length of this registry and the disease characteristics, if new scientific factors (i.e. knowledge about alpha-mannosidosis, clinical guidance) emerge the criteria used to establish the GTR may be reviewed and additional criteria may be added (like, but not limited to, EQ-5D-5L and serum IgG). The Global Treatment Response rate after 3 years of Lamzede treatment in naïve patients able to perform the functional tests will be evaluated. The proportion of responders and the corresponding exact (Clopper-Pearson) two-sided 95% confidence interval (CI) will be presented.

Effects of baseline characteristics will be evaluated by means of regression/logistic models including:

- age subgroup (<18 years, ≥18 years),
- gender (male, female),
- genotype by subcellular localization of the protein (Genotype Group 1, Genotype Group 2, Genotype Group 3, as defined by Borgwardt et all., 2015)
- baseline residual enzymatic activity (<10 nmol/h/mg, 10 to <15 nmol/h/mg, ≥15 nmol/h/mg)
- baseline CHAQ Disability Index (0|-|1, 1-|2, 2-|3)

as covariates.

Comparison with control group will be done descriptively, provided that a minimum number of non-treated patients with adequate data will be enrolled. If data will allow, Global Treatment Response after 3 year will be analysed comparing the two groups using propensity score (PS) analysis. The PS will be calculated as the predicted probability of Lamzede-treated vs non-treated patients from a logistic regression. This score represents the "propensity" for an observation to be in a treatment group or the other. The logistic regression model will include the following confounding factors as explanatory variables:

- age subgroup (<18 years, ≥18 years),
- gender (male, female),
- genotype by subcellular localization of the protein (Genotype Group 1, Genotype Group 2, Genotype Group 3, as defined by Borgwardt et all., 2015)
- baseline residual enzymatic activity (<10 nmol/h/mg, 10 to <15 nmol/h/mg, ≥15 nmol/h/mg)
- baseline CHAQ Disability Index (0-1, 1-2, 2-3)

The distributions of each confounding factor as well as of the calculated PSs (Lamzede-treated vs non-treated) will be displayed graphically for both groups and their similarity evaluated.

In addition, depending on the outcome of interest and available sample size, subgroup analyses may be performed and results will be presented and regarded as descriptive. Further exploratory analyses will be developed as necessary and fully described in the SAP.

9.7.5 Safety Variables

Safety will be assessed by:

- Adverse Events (AEs) including non-serious and Serious AEs, non-serious and Serious ADRs, AEs leading to treatment discontinuation and AEs leading to death at any time they become available.
- ADA, IRRs and Hypersensitivity (as identified risks)
- Acute renal failure, loss of consciousness and medication error (as potential risks)
- Vital signs (SBP, DBP, PR)
- Physical Examination
- Laboratory tests (haematology and chemistry)
- ECG

The proportion of patients experiencing at least one AE, non-serious and serious AEs, non-serious and serious ADRs, AE leading to treatment discontinuation and AEs leading to death will be provided. The above category of AEs will be summarized in terms of frequency of patients with at least one AE and in terms of number of events. These results will be provided by year from the baseline. The proportion of patients experiencing at least one AE will be calculated as the ratio between the number of patients experiencing at least one AE during the reference period and number of patients at risk (population at risk). In addition, incidence rates per person-time will be calculated as appropriate. Adverse events will be summarized by System Organ Class and Preferred Term using the MedDRA dictionary. The same approach will be followed also for identified and potential risks (see Section 11.1 for definition). For all the analyses outlined above, patients withdrawn from the study will be included: if they did not experience any events until their withdrawal they will be considered with no events for the examined period.
The duration of follow-up will be described.

The proportion of patients developing immunogenicity (as Anti-velmanase alfa-immunoglobulin G antibody in serum) will be also presented.

Vital Signs (SBP, DBP, PR) will be summarised by means of descriptive statistics. All variables (actual values and change from baseline, if applicable) will be presented by time point. In addition, the proportion of patients with substantial changes from baseline (i.e. >20mmHg for SBP and >10mmHg > for DBP) will be presented.
Physical examination (anthropometric measurements like height, weight, rate of growth and the ability to perform the endurance test) will be summarised by means of descriptive statistics. All variables (actual values and change from baseline, if applicable) will be presented by time point. The number and percentage of subjects able and not able to perform the endurance test will be produced.

Quantitative laboratory tests (haematology and chemistry) will be summarised by means of descriptive statistics. All variables (actual values and change from baseline, if applicable) will be presented by time point. All relevant clinical laboratory tests will be classified as Low NCS (non clinically significant)/Low CS (clinically significant), Normal, High NCS/High CS, or Normal/Abnormal NCS/Abnormal CS according to the normal ranges and investigator assessment. The number and percentage of subjects with values in each category will be produced.

ECG interpretations will be classified as Normal, Abnormal NCS and Abnormal CS. The number and percentage of subjects with values in each category will be produced.

9.7.6 Other Variables

In addition the following other variables will be presented:

- Height, weight, BMI and rate of growth
- Hearing test (Pure Tone Audiometry)
- Concomitant procedures and medications

Other variables will be summarised by means of descriptive statistics or frequency distribution, as appropriate. All variables (actual values and change from baseline, if applicable) will be presented by time point.

9.7.7 Missing Data

Patients with missing values will not be excluded from the analysis, but their data will not be replaced. Further details on dealing with missing data, along with the handling of possible outliers, will be described in the SAP. Other critical missing data, if any, will be discussed during the Data Review Meeting. Decisions will be fully documented in the Data Review Document.

9.8 Quality Control

9.8.1 Direct Access to Source Documents/Data

The investigators must permit study-related monitoring, audits, EC review or regulatory inspection, providing direct access to source data/documents.

9.8.2 Study Monitoring

Monitoring will be performed by *(please enter the CRO's name)* who has been designated by Chiesi. It is understood that the monitor(s) will contact and visit the investigator/centre before the study, regularly throughout the study and after the study had been completed, and that they will be permitted to inspect the various study records: eCRF, investigator study file and source data (source data is any data that is recorded elsewhere to the case report forms), provided that patient confidentiality is respected.

The purposes of these visits are:

- To assess the progress of the study.
- To review the compliance with the study protocol.
- To discuss any emergent problem.
- To check the eCRFs for accuracy and completeness.
- To validate the contents of the eCRFs against the source documents.
- Prior to each monitoring visit, the investigator or staff will record all data generated since the last visit on the eCRFs. The investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.
- To ensure that all the patients included in the registry are performing all visits planned in the study protocol, if not highlight any missing data either during Monitoring Visits on site either regular phone calls and proper actions defined.
- It is possible that the investigator site may be audited by sponsor personnel or regulatory national and/or international regulatory agencies during and after the study has been completed.

9.8.3 Quality Assurance

The R&D Quality Assurance Department of Chiesi may perform an audit at any time according to the sponsor's Standard Operating Procedures, in order to verify whether the study is being conducted in agreement with GCP and this protocol.

9.8.4 Confidentiality

All study documents are provided by the sponsor in confidence to the investigator and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the study without written permission from Chiesi.

The investigator must assure the patient's anonymity will be maintained. The investigator will keep a separate list with at least the initials, the patient's study numbers, names. The investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Chiesi.

9.8.5 Record Retention

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file.

The essential documents should be retained for at least five years after completion of the study. It is the responsibility of the sponsor to inform the investigator of when these documents can be destroyed. The investigator must contact Chiesi before destroying any study-related documentation. In addition, all patients' medical records and other source documentation will be kept for the maximum time permitted by the institution.

9.9 Limitations of the Research Methods

The Registry is a multi-centre, multi-country, non-interventional, prospective cohort in alpha-mannosidosis patients. The Registry will be conducted under conditions of routine clinical care and will include all eligible patients with alpha-mannosidosis who agree to participate. The decision to start treatment with Lamzede can be taken at any time during the course of the Registry. Based on the current unmet medical need patients can start the treatment independently from the Registry set up.

The study will involve collection of primary data directly from healthcare professionals. The data collected are expected to provide evidence of the long-term safety and effectiveness of Lamzede in the treatment of alpha-mannosidosis in patients under conditions of routine clinical care; moreover, the data collected on the natural history of the disease are expected to expand the knowledge on the pathology itself. Only available evaluations as decided by the investigator and based on local clinical practice will be collected. Where there are no data to report there will be no information recorded in the applicable section(s) of the eCRF. Therefore, the assessments performed and data provided from different study sites may vary depending on local clinical practice. Assessments will generally be interpreted locally by the investigators, rather than centrally, therefore there may be differences between sites for the outcomes of evaluations.

In case a patient is transferred to another continuing care site during the 15-year observational period, the new treating site will be formally involved in the Registry study following a request of authorization submitted to the relevant Ethics Committee and Regulatory Authority to complete the 15-year observational period following the patient and collecting all information as per study protocol Data will be collected prospectively after enrolment in the Registry. However, retrospective data may be collected. The availability and quality of these retrospective data may be variable.

It is acknowledged that patient self-selection into a study of this nature is inevitable as due to the willingness of the patients to participate and, without a randomised control arm, such selection could introduce bias. Such bias, however, will always be of unknown size and direction. All reports and publications from the study will clearly describe these potential limitations.

9.10 Other Aspects

The archiving process at the end of the study is defined by Chiesi Standard Operating Procedure.

Archiving of the datasets and related documentation (e.g. Define.xml, annotated CRF) and of all programs used, including statistical programming to generate the results, should be done, as soon as the final version is available, and at the latest when the CSR is finalized, in a validated Chiesi Archive Area.

All data and related documentation saved will remain available as originally stored for at least 25 years after finalization.

The area is in “read only” access; only IT personnel upon authorization by the Head of Statistics and Data Management has the permission to apply changes to this area. In case of changes, appropriate documentation will be prepared to support the new archiving process.

Changes can be related to technical reasons (e.g. mistakes in naming and/or creating folder, failure in copying the files) or to other reasons (e.g. database unlock leading to updated data to be archived).

In case of update, the initial archive folder won’t be overwritten but a new folder will be created to guarantee the traceability.

As per the Sponsor procedure, the qualification of the central[a] lab will be documented by collecting qualification certificates released by recognized Institution and archived in the study Trial Master File (TMF).

Shipment of samples from the study sites to the central[a] laboratory will be overviewed by the Clinical Research Organization staff in charge of the study and the process will be fully described and documented in corresponding Lab manuals. Samples receipt to the lab will be tracked and also shipment temperature recorded and controlled, all documents will be filed in the relevant section of the study TMF.

[a] Local laboratory will be used in Germany as per local clinical practice. Central laboratory will be adopted in extra-German sites.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Ethical and Regulatory Considerations

This study was designed and shall be implemented and reported in accordance with the Guide on Methodological Standards in Pharmacoepidemiology (Revision 3, July 2014) of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, with the ethical principles laid down in the Declaration of Helsinki (1964 and amendments) and with the laws and regulations of each country in which the research is carried out. The study will be conducted in full conformance with the principles of the Declaration of Helsinki, current ICH E6 GCP as far as applicable, the Guidelines on GVP: Module VIII – PASS (Rev 2. European Medicines Agency EMA/813938/2011 from 04 August 2016) or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection of the individual. Scientific guidance on post-authorisation efficacy studies (12 October 2016EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015)
The study proposal will be submitted to the EC in accordance with the requirements of each country.
Before the study commences, the EC shall give its opinion in writing, clearly identifying the study number, study title and informed consent form approved.
A copy of all communications with the EC will be provided to the sponsor.
The investigator should provide written reports to the EC annually or more frequently if requested on any changes significantly affecting the conduct of the study and/or increasing risk to the patients (according to the requirements of each country).
The study will be notified to the Health Authorities (or authorised by) according to the legal requirements in each participating country.
Selection of the patients will not start before the approval of the EC has been obtained and the study notified to Health Authorities (or authorised by).
This study does not include treatments or diagnostic examinations other than those prescribed in the ordinary clinical practice, therefore no insurance agreements are applicable unless specifically required by local law.

10.2 Informed Consent

It is the responsibility of the investigator to obtain written consent from each patient or from the patient's legal representative prior to the collection of any data from the patient's records.

If the patient and his/her legal representative are unable to read, the informed consent will be obtained in the presence of an impartial witness, e.g., a person independent of the study who will read the informed consent form and the written information for the patient.
Consent must be documented by the patient's dated signature. The signature confirms that the consent is based on information that has been understood. Moreover, the investigator must sign and date the informed consent form.
Each patient's signed informed consent must be kept on file by the investigator. One copy must be given to the patient.
Whenever appropriate, the minor should participate in the (informed) consent process together with the parents. The information about the clinical study needs to be provided to the minors according to their level of understanding and maturity. When possible, the minor's response should be documented.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Definitions

An **Adverse Event** is "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment"
An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
An **Adverse Drug Reaction** is an "untoward and unintended responses to an investigational medicinal product related to any dose administered".
All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there are facts (evidence) or arguments meant to suggest a causal relationship.
The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.
A **Serious Adverse Event/Serious Adverse Drug Reaction** is any untoward medical occurrence or effect that at any dose falls in one or more of the following categories:

- **Results in death**

Death is not an AE but an outcome. It is the cause of death that should be regarded as the AE. The only exception to this rule is "sudden death" where no cause has been established; in this latter instance, "sudden death" should be regarded as the AE and "fatal" as its reason for being serious.

- **Is life-threatening**

Life-threatening refers to an event in which the patient was at risk of death at the time of the event (e.g., aplastic anaemia, acute renal failure, and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it were more severe.

- **Requires hospitalisation or prolongation of existing hospitalisation**

Hospitalisation refers to a situation whereby an AE is associated with unplanned overnight admission into hospital, usually for purpose of investigating and/or treating the AE. Hospitalisation for the treatment of a medical condition that occurs on an "elective" or "scheduled" basis or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as an AE.

Complications that occur during the hospitalisation are AEs. If a complication prolongs hospitalisation, the event is an SAE.

- **Results in persistent or significant disability or incapacity**

The term significant disability should be viewed as any situation whereby an AE has a clinically important effect on the patient's physical or psychological well-being to the extent that the patient is unable to function normally.

- **Is a congenital anomaly or birth defect**
- **Is a medically significant AE**

This criterion allows for any situations in which important AEs/adverse reactions that are not immediately life-threatening or do not result in death or hospitalisation may jeopardise the patient's health or may require intervention to prevent one of the above outcomes.

Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether an event is serious because medically significant.

A **Non-Serious AE/Non-Serious ADR** is an AE or ADR that does not meet the criteria listed above for a SAE/serious ADR.

11.2 Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable product information (investigator's Brochure for an unauthorised investigational product or SmPC or approved Package Insert for an authorised product), otherwise it is considered unexpected.

Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered as "unexpected". Examples of such events are: (a) acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

In the event an exacerbation is interpreted as due to lack of efficacy, it should not be classified as drug related.

11.3 Intensity of Adverse Event

Each AE must be rated on a 3-point scale of increasing intensity:

- **Mild:** The event causes a minor discomfort, or does not interfere with daily activity of the patient, or does not lead to either modification of test treatment dosage or establishment of a correcting treatment.
- **Moderate:** The event perturbs the usual activity of the patient and is of a sufficient severity to make the patient uncomfortable. The event leads to a diminution of dosage of the test treatment, or a temporary interruption of its administration or to the establishment of a correcting treatment.
- **Severe:** The event prevents any usual routine activity of the patient and causes severe discomfort. It may be of such severity to cause the definitive interruption of test treatment.

11.4 Causality Assessment

The following "binary" decision choice will be used by the investigator to describe the causality assessment:

- Reasonable possibility of a relatedness.
- No reasonable possibility of relatedness.

The expression "reasonable possibility of relatedness" is meant to convey, in general, that there are facts (evidence) or arguments meant to suggest a causal relationship.

The investigator will be asked to consider the following before reaching a decision on causality assessment:

- Time relationship between study drug intake and event's onset.
- Dechallenge (did the event abate after stopping drug?).
- Rechallenge (did the event reappear after reintroduction?).
- Medical history.
- Study treatment(s).
- Mechanism of action of the study drug.
- Class effects.
- Other concomitant or previous treatments.
- Withdrawal of study treatment(s).
- Lack of efficacy/worsening of existing condition.
- Erroneous treatment with study medication (or concomitant).
- Protocol related process.

11.5 Action taken with the study drug

- Study drug dose not changed.
- Study drug permanently withdrawn.
- Study drug temporarily interrupted.
- Study drug dose reduced.
- Study drug dose increased.
- Unknown.
- Not applicable.

11.6 Other actions taken

- Specific therapy/medication.
- Concomitant Procedure.

11.7 Outcome

Each AE must be rated by choosing among:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal.
- Unknown.

11.8 Recording of Adverse Events

All AEs occurring during the course of the study must be documented in the AE page of the eCRF. Moreover, if the AE is related to the study drug, the AE form must be also completed.
It is responsibility of the investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of patients, by observation and by routine open questionings.
The recording period for AEs is the period starting from the Informed Consent signature until the patient's study participation ends.
If a clinically significant abnormal laboratory finding or other abnormal assessment meets the definition of an AE, then the AE eCRF page must be completed, as appropriate. A diagnosis, if known, or clinical signs and symptoms if diagnosis is unknown, rather than the clinically significant abnormal laboratory finding, should be reported on AE eCRF page. If no diagnosis is known and clinical signs and symptoms are not present, then the abnormal finding should be recorded.
In order to collect as complete as possible information in the clinical study database, all ADRs and SAEs ongoing at the time the patient's study participation ends should be evaluated up to 14 days after last study drug intake. After this period, all unresolved ADRs and SAEs will be reported as "ongoing" in the eCRF.
For pharmacovigilance purposes, all SAEs should be followed-up in order to elucidate as completely and practically as possible their nature and/or causality until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, stable condition is reached or the patient is lost to follow-up. Follow-up may therefore continue until after the patient has left the study up to 30 days after his/her discontinuation from the study for unrelated SAEs, and without timelines for related SAEs.

11.9 Reporting Serious Adverse Events to Chiesi

The investigator must report all SAEs to the <CRO> Safety Contact listed below within 24 hours of awareness. The information must be sent by faxing the completed SAE form. At a later date, the <CRO> Safety Contact will report all information to Chiesi Global Pharmacovigilance (GPV), the Clinical Project Manager and the Clinical Research Physician.

Name and Title	Telephone no.	Mobile no.	Fax no.	E-mail
<CRO> Safety Contact				
Chiesi Safety Contact	-	-		

- Reporting of SAEs from the investigator site is from the time of patient's signature of informed consent and until the patient's study participation ends. All new SAEs occurring beyond this time frame and coming to the attention of the investigator must be recorded only if they are considered [in the opinion of the investigator] causally-related to the study drug.
- Up to the closure of the site, AE reports should be reported to the <CRO> Safety Contact. All new related AEs occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

The collected safety report should be as complete as possible. In any case, the initial safety report should at least refer the following minimum information, and then followed-up to obtain a complete safety report:

- An identifiable healthcare professional reporter (the reporter can be identified by either name or initials, or address or qualification, e.g., physician, dentist, pharmacist, nurse).
- An identifiable patient (at least one among patient initials, patient number, date of birth or age or age group, gender).
- At least one suspected active substance/medicinal product.
- At least one suspected AE/adverse reaction.

11.10 Reporting Adverse Drug Reactions to Regulatory Authorities/Ethics Committees

All ADRs occurring during the study must be reported to the Authorities according to the applicable laws. The reporting treating physician is also recommended to report all ADRs to the relevant MAH in the involved medicinal products.
If an AE occurred and it is considered to have at least a possibly suspected relationship with Lamzede, it is considered an ADR and, therefore, it is to be managed as reportable.
Additionally, it should be also reported conditions of use outside the marketing authorisation of the medicinal products (i.e. off-label or medication errors) or from occupational exposure, as well as cases of suspected drug interaction, pregnancy, breast-feeding exposure and lack of efficacy.
The management and reporting to Competent Health Authorities of any adverse reactions will be in line with the GVP module VI.

11.11 Pregnancy

Any occurrence of a pregnancy in a patient on Lamzede must be reported to Chiesi/concerned CRO within 24 hours upon learning of the patient's condition.
The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.
Pregnancies should be recorded on a Pregnancy Form and reported to Chiesi/concerned CRO by the treating physician or other health care professional involved. Pregnancy follow-up should be recorded on the same form and should include assessment of the possible relationship to Lamzede of any pregnancy outcome. Any AE experienced during pregnancy must be reported in the AE Report Form.

11.12 General Notes

- In case of death, a comprehensive narrative report of the case should be prepared by the investigator and sent to the <CRO/Chiesi> Safety Contact by fax together with the AE form, retaining a copy on site with the case report form.
- If an autopsy is performed, copy of autopsy report should be actively sought by the investigator and sent to the <CRO/Chiesi> Safety Contact as soon as available, retaining a copy on site with the case report form.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The clinical study report, including the statistical and clinical evaluations, shall be prepared and sent to Co-ordinating Investigator's for agreement and signature.

Study progress reports may be requested by a national Competent Authority. They may also be requested by the Pharmacovigilance Risk Assessment Committee, since Lamzede follows the centrally-authorised procedure rules.
Upon request, progress reports shall be submitted to the competent authorities of the Member States in which the study is conducted and to the European Medicines Agency for PASS.
Study progress should also be reported in any periodic safety reports (see Module VII) and RMP updated (see Module V), where applicable.
At the end of the study a summary of the clinical study report will be provided to all ECs, to the Competent Authority of the EU Member State concerned and to investigators.
Chiesi is entitled to publish and/or present any results of this study at scientific meetings, and to submit the clinical study data to national and international Regulatory Authorities. Chiesi furthermore reserves the right to use such data for industrial purposes.
In the absence of a Study Steering Committee, investigators will inform Chiesi before using the results of the study for publication or presentation, and agree to provide the sponsor with a copy of the proposed presentation. Data from individual study sites must not be published separately, or the Sponsor need to be informed in advance and receive a copy of the communication
Negative as well as positive results should be published or otherwise made publicly available.

13. REFERENCES

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[8]Achenbach, T.M., & Rescorla, L.A. (2001). Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Protocol Signature Page Sponsor		
2	Protocol Signature page Investigators		
3	List of sites		

THE ALPHA-MANNOSIDOSIS REGISTRY: A multi-centre, multi-country, non-interventional, prospective cohort, in alpha-mannosidosis patients

Product: Lamzede 10 mg powder for solution for infusion

Approval of the Post-Authorisation Efficacy and Safety Study Protocol by the Sponsor's Representative:

Clinical Program Leader _____ Date:_____
(Federica Cattaneo, MD)

EU Qualified Person for Pharmacovigilance _____ Date:_____
(Gian Nicola Castiglione, MD)

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma – Italy

THE ALPHA-MANNOSIDOSIS REGISTRY: A multi-centre, multi-country, non-interventional, prospective cohort, in alpha-mannosidosis patients

Product: Lamzede 10 mg powder for solution for infusion

Approval of Post-Authorisation Efficacy and Safety Study Protocol by the Investigator:

I have carefully read this protocol and I agree that it contains all the necessary information required to conduct the study and I agree to conduct it as described.

I understand that this study will not be initiated without Ethics Committee approvals and that the administrative requirements of the governing body of the institution will be fully complied with.

Informed written consent will be obtained from all participating patients and appropriately documented, prior to their enrolment in the study.

The undersigned agrees that the study will be carried out in conformity with the Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), current International Council for Harmonisation (ICH) E6 Good Clinical Practice as far as applicable and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in patients.

Investigator's Name: _____,MD

Centre No. :_____

_____ _____
Signature Date

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma - Italy

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

THE ALPHA-MANNOSIDOSIS REGISTRY: A multi-centre, multi-country, non-interventional, prospective cohort, in alpha-mannosidosis patients

Study reference number:

CLI-LMZYMAA1-12

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6.0
1.1.2 End of data collection[2]	☐	☐	☒	N/A
1.1.3 Study progress report(s)	☒	☐	☐	6.0
1.1.4 Interim progress report(s)	☒	☐	☐	6.0
1.1.5 Registration in the EU PAS register	☒	☐	☐	6.0
1.1.6 Final report of study results.	☒	☐	☐	6.0

Comments:

To be completed once the Authorities (EMA and PRAC) approval process will be completed

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	N/A

Comments:

This is a descriptive study with no *a priori* hypothesis.

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2, 9.3, 9.4, 9.9
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	N/A
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

This is a descriptive study therefore no formal statistical testing is planned and the analyses will be descriptive.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.6
4.2.2 Age and sex?	☒	☐	☐	9.2.1, 9.2.2
4.2.3 Country of origin?	☐	☒	☐	9.2.5
4.2.4 Disease/indication?	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.2.6
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.

Comments:

It is foreseen that approximately 40 suitable centres in the European Union (EU) will be involved and additional sites may be added, as required. The final list of countries and sites will depend on the Lamzede authorisation and capability of the site to administer the treatment. Indicatively, the following countries will be involved: Germany, Denmark, Sweden, Norway, The Netherlands, Austria, Spain, France, UK, Italy, Belgium and Poland.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	N/A
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	N/A
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	N/A

Comments:

The study will report the use of Lamzede in routine clinical care with descriptive results only

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3, 9.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.1, 9.2
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3, 9.7

Comments:

N/A

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	7.2
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	7.2
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.1, 9.2
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	N/A

Comments:

Possible disease modifiers and confounder factors information will be collected

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	N/A

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.3
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.6, 9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.6, 9.7
9.3.3 Covariates?	☐	☐	☒	NA
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Covariates do not apply to this study.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☐	☐	☒	N/A
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	N/A
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

This study will report descriptive results only

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6, 9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	N/A

Comments:

There is no plan for an independent review of the study results.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	N/A
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	N/A
13.3 Have data protection requirements been described?	☒	☐	☐	9.8

Comments:

There have been no ethical review applications to date.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

N/A

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

N/A

Name of the main author of the protocol: Federica Cattaneo

Date: / /

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

None.