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Proposal for Managed Access Protocol for Lamzede (velmanase alfa) in the Netherlands

Summary
Lamzede (velmanase alfa) has received marketing authorization in the EU as an orphan drug for the treatment of non-neurological manifestations in patients with mild to moderate alfa-mannosidosis. Early results of treatment show a positive biochemical response (reduction in serum oligosaccharides), but variable clinical effects. There is no evidence for velmanase alfa on neurocognitive deficits in patients with alfa-mannosidosis, a feature that is invariably present in patients. Some improvement in motor function and lung function resulting from velmanase alfa treatment are suggested, but it is so far unclear which patients would benefit from therapy, since long term outcomes and validation of prognostic biomarkers is still the subject of studies. This protocol is intended to assist in evidence based decision making for initiation, monitoring an cessation of expensive treatment with Lamzede in the Netherlands.

Background
Alfa-mannosidosis is a very rare lysosomal storage disorder caused by deficiency of lysosomal alpha-mannosidase (MAN2B1) (E.C. 3.2.1.24). The birth prevalence is around 1 in 500.000 (Meikle et al 1999). Based on this estimation 20-30 patients might be expected to live in the Netherlands. The true clinical prevalence, however, is lower with 7-8 living patients currently identified in the Netherlands.
Establishing a deficiency of alpha-mannosidase enzyme activity in leukocytes or fibroblasts is the gold standard for the diagnosis. Molecular genetic testing of *MAN2B1* and the identification of two disease-causing alleles can confirm the diagnosis. Detection of a genetic variant in the *MAN2B1* gene should always be followed by biochemical testing for enzyme activity to confirm pathogenicity. There is no clear genotype/phenotype correlation, which hampers prediction of clinical outcome.

Phenotypes
The clinical expression of the disease varies widely, as is almost always the case for lysosomal storage disorders. While the phenotypes should be viewed as part of a continuum, there are roughly three clinical types (mild, moderate, and severe) that can be distinguished [Chester et al 1982, Malm & Nilssen 2008]. Most patients fit into the moderate type. (ref: Malm D. and Nilssen Ø Alpha-Mannosidosis; Synonym: Lysosomal Alpha-D-Mannosidase Deficiency, Gene Reviews 2012)

- Type 1. Mild form: clinically recognized after the age of ten years, with myopathy, slow progression, and absence of skeletal abnormalities

- Type 2. Moderate form: clinically recognized before age ten years, with myopathy, slow progression, and presence of skeletal abnormalities

- Type 3. Severe form: with obvious progression, leading to early death from primary central nervous system involvement or infection

General features of the disease are typical appearance of a storage disorder (as in the mucopolysaccharidoses) with coarse facial features, a relatively large head and frontal bossing. Hearing loss is frequently observed. Frequent infections may be partially explained by immunological disturbances, which are incompletely understood.
Skeletal disease also resembles the mucopolysaccharidoses with evidence of dysostosis multiplex leading to skeletal complications such as osteonecrosis. Osteoporosis may also occur. The neurological and psychiatric features are the most debilitating of the disorder: these affect cognition (patients all have intellectual disabilities) and speech. Development of motor function is frequently delayed or, after initial development of milestones, deteriorates. Patients frequently suffer from hypotonia. This further impacts their mobility. A large proportion of patients exhibit psychiatric symptoms, ranging from psychotic episodes to autistic behavior and depression. Finally, frequent infections (primarily pulmonary) have been reported in alfa-mannosidosis patients. The natural disease progression is variable. Patients can remain stable for very long periods of time, although systematic large cohort studies are lacking.

Treatment
Supportive care is the cornerstone of treatment: orthopedic interventions, antibiotics for infections, physical therapy and use of hearing aids or wheelchairs etc, as well as psychiatric support are all important. Families may need support as well, as the multisystemic impairment of patients may pose a heavy burden on family life.

Early studies have tried hematopoietic stem cell transplants (HSCT) as a therapeutic option with variable results. In general, patients cannot be cured, but HSCT may allow better mental development although scientific evidence in large studies is currently lacking.

Lamzede
The EMA recently authorized Lamzede as treatment for long-term enzyme replacement therapy in patients with alpha-mannosidosis (marketing authorisation under exceptional circumstances to Lamzede on 25 January 2018).
Lamzede is indicated for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis.

The pharmaceutical company (Chiesi Farmaceutici S.p.A.) performed several clinical studies to evaluate the safety and efficacy of recombinant alpha-mannosidase at different doses.

The final dose was 1 mg/kg of body weight administered once every week by intravenous infusion.
The studies all showed a significant effect of velmanase-alpha on the serum concentration of oligosaccharides. The results for the functional outcomes, however, did not reach statistical significance. In summary:

Phase II study:
A decrease in serum oligosaccharides after 18 months of therapy (mean percentage change –89.9%, P < 0.001) was observed and achievement of an average improvement of 39 steps in the 3-Minute Stair Climb Test (3MSCT; P = 0.004)

Phase III multicentre,double-blind, randomised, placebo-controlled trial:
Patients with alpha-mannosidosis were treated with 1 mg/kg velmanase-alpha per week (n = 15) or placebo (n = 10) for 52 weeks. Co-primary endpoints were changes in serum oligosaccharide levels and in the 3-minute stair climb test (3MSCT).
Efficacy was defined as a statistically significant reduction in serum oligosaccharides (P < 0.025) and a trend for improvement in the 3MSCT and one of the prioritized secondary endpoints (changes from baseline to week 52 in the 6-Minute Walk Test (6MWT) and in FVC % at the 52-week analysis).
Significant reductions in serum oligosaccharide concentrations were found for velmanase alfa treatment versus placebo, but no significant clinical effects were observed.

Phase III extension: combined cohort from phase I, II and III studies
Thirty-three patients (14 adults, 19 pediatric) were included; mean (SD) treatment exposure was 29.3 (15.2) months. Serum oligosaccharide levels were significantly reduced in the overall population at 12 months (mean change: – 72.7%, P < 0.001) and remained statistically significant at last observation (–62.8%, P <0.001). A mean improvement of +9.3% in 3MSCT was observed at 12 months (P = 0.013), which also remained statistically significant at last observation (+13.8%, P = 0.004).

The effects on motor function were variable and most clear in pediatric patients. However, results may also have been influenced by growth and aging. The small groups, variable responses, lack of clear clinical benefit hampers a definite conclusion on efficacy of this treatment.

Post marketing requirements
EMA issued a specific obligation to complete post-authorization measures for the marketing authorization under exceptional circumstances (pursuant to Article 14(8) of Regulation(EC) No 726/2004)

1. In order to obtain long term data on effectiveness and safety of treatment with Lamzede and to characterize the entire alpha-mannosidosis population, including variability of clinical manifestation, progression and natural history, the MAH is requested to submit the results of a study based on adequate source of data deriving from a registry of patients with alpha-mannosidosis.
Annual reports to be submitted as part of the annual reassessment
2. Paediatric Study rhLAMAN-08. A 24 month multi-center, open label phase II trial investigating the safety and efficacy of repeated velmanase alfa (recombinant human alpha mannosidase) treatment in paediatric patients <6 years of age with
Final Study report: November 2020. This study is not open in the Netherlands.

AMC and ErasmusMC
The Amsterdam UMC and ErasmusMC are the lysosomal expert centers in the Netherlands. Both centers are involved in the diagnosis and follow-up of patients with alfa-mannosidosis. Registry.

Experts from both centers concluded that based on the results from the clinical studies and experience with enzyme replacement therapy in other lysosomal storage disorders, the current opinion is that most patients will not benefit from treatment. However, therapy could be tried in children with mild to moderate disease at an early stage of disease. Evidence for treatment in adults is currently insufficient: the natural disease progression in those with very mild disease will probably not be changed by velmanase alfa treatment and those with neurological and/or skeletal symptoms will probably have irreversible disease. The expert opinion can be revised based upon new data and insights.

Purpose of the proposed protocol:
The protocol aims to provide conditional access to treatment with Lamzede for Dutch patients with alfa-mannosidosis for at least 5 years. Conditions are:

1. Patients in the Netherlands will only be treated with velmanase alfa following the strict start and stop criteria as laid down in this protocol.
2. An indication committee will be responsible for decisions concerning start or stop of treatment as well as monitoring
3. ErasmusMC and Amsterdam UMC will act as the center of excellence for diagnosis, follow-up and treatment of alfa-mannosidosis patients. One of the physicians (van den Hout, ErasmusMC) will take part in the Registry and act as coordinator
4. An agreement should be made between healthcare insurers and Chiesi on a substantially reduced price for velamanase alfa.
5. Chiesi will be asked to provide raw data from previous studies and the Registry for independent analysis of effectiveness.

Protocol
Each year, or every two years, depending on inclusions, the centers of expertise will perform an analysis of data on effectiveness and safety (i.e. data obtained from treated and untreated patients, as well as from available peer-reviewed publications). Criteria below will be re-evaluated based upon the updated information.

Untreated patients will be followed on a routine basis as well in agreement with ethics guidelines (patients should consent for participation in the local Dutch data acquisition). A more detailed flow-chart of follow-up measures will be developed, based upon the scheme below.

AMC and ErasmusMC will collaborate in an indication committee assessing all patients who might be treated with velmanase alfa and deciding on initiation of treatment, based on the criteria in this protocol. Interim follow-up and monitoring will also be performed through the committee. The committee exists of two experts from each center and two independent colleagues (e.g. a neurologist and pediatrician)

Methods:

1. Treatment of patients in the Netherlands

Eligibility

1. To receive treatment, patients, or legal representatives, must sign up to this Managed Access Protocol
2. Patients are required to attend their clinics at least 2-4 times a year for assessment.
3. Velmanase alfa will not be started if any of the following apply:
- The patient is diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit; or
- The patient has primarily neurological/psychiatric or skeletal symptoms leading to considerable handicap
- The patient has advanced disease * or has a poor performance status; or
- The patient is unwilling to comply with the associated monitoring criteria

** advanced disease will be defined on an individual basis: the complexity of the disease requires a case by case evaluation by the committee*

Start Criteria

All of the following are required before treatment is started:
- Only patients < 18 years of age with mild to moderate disease are eligible for treatment*
- All patients must have a confirmed diagnosis of alfa-mannosidosis with confirmed alfa-man enzyme deficiency and mutation analysis.
- There has to be unanimous agreement in the indication committee for start of treatment:
- Children eligible for treatment should have sufficient cognitive function for basic daily activities and communication, as assessed by the indication committee

*patients who started during childhood and have shown benefit of therapy may continue treatment after 18 years, when additional benefit is expected as assessed by the evaluation committee (e.g. achievement of peak bone mass, effect on pulmonary function)

Dosing: the dose will be 1 mg/kg/week. No dose adjustments are foreseen

Stop Criteria

Patients will cease enzyme therapy, based on assessment of all data by the indication committee, if any of the following applies:
- The patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 12 month period or missing of > 50% of infusions);
- The patient is unable to tolerate infusions due to infusion related severe adverse events that cannot be resolved.
- The presence of neutralising antibodies (assay to be set up)
- There is progressive skeletal or lung disease or neurological deterioration impacting* on basic daily activities and communication

** impact will be defined on an individual basis: the complexity of the disease requires a case by case evaluation by the committee*

Patients who are taken off treatment will continue to be monitored for disease course and supported with other clinical measures. These patients should continue to be assessed to allow gathering of important information.

Follow-up investigations (all tests will be age-appropriate)

First year baseline and thereafter every three months, the first year thereafter every 6 months:
- History, adverse events/side effects of infusions
- Vital signs, neurological and orthopedic evaluation,
- Routine chemistry and hematology
- Serum sample for antibodies and oligosaccharides
- Urine sample for oligosaccharides
- Physical therapy tests: Motor development, 6MWT

Yearly:
- Hearing test
- Speech skills
- Cognitive functioning
- Pulmonary tests/ sleepstudy

Every 2-4 years
- Skeletal X-rays

Analysis of data

Data will be collected as part of routine clinical care and recorded in an electronic file. Because of the low number of patients, no separate database will be launched. Data will be submitted to the Registry of the MAH.

The indication committee will discuss all patients on velmanase-alfa treatment at least on a yearly basis, focusing on treatment response. In individual cases interim analysis will be performed on request by the indication committee (e.g. in case of adverse events, deterioration at an earlier stage etc)