University of Minnesota
Blood and Marrow Transplantation Program

Study of Administration of Intravenous Naglazyme® Following Allogeneic Transplantation for Maroteaux-Lamy Syndrome MT2014-08R

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Revision History

Revision Number	Version Date	Summary of Changes	Consent change?
	03/17/2014	original to CPRC	
	04/17/2014	revision to CPRC	
	05/05/2014	original version to IRB section 7.2 – designate research related testing with an R schema and section 3.1: correct time from transplant as > 2 years not within 2 years cover page: remove administrative personnel throughout document: Sara Johnson as study coordinator/contact person	n/a
1	12/04/2015	schema and section 3 – update inclusion/exclusion criteria • Add pre-screening details • Permit enrollment of patients who are receiving or previously received Naglazyme • Clarify proof of engraftment must be within previous year schema, synopsis and sections 4, 5.1 and 7.1 – update to include pre-screening plan section 4 – require enrollment within 6 months of initial enrollment (previously 1 year) section 7 – add pre-screening section, edits to evaluations during treatment, and correct section 7.4 section header as no assessments are required at the local medical facility section 8 – update to current language, delete reference to infusion form in appendix I as this will be a separate document. replace appendix I with an eligibility checklist update to current template language especially sections 8 and 9.4 other minor edits and clarifications update title page with current investigators (add Drs. Peirpont, and Miller, delete Drs Shapiro and Polgreen), indicate which co-I's will not consent subjects.	yes plus new screening consent

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Protocol Synopsis

Study of Administration of Intravenous Naglazyme® Following Allogeneic Transplantation for Maroteaux-Lamy Syndrome

Study Design: This is a single center study in which Naglazyme® will be given weekly for two years in patients with Maroteaux-Lamy syndrome, also known as mucopolysaccharide VI (MPS VI), who have previously been treated with an allogeneic transplant.

Primary Objective: The primary objective of this study is to evaluate the efficacy of weekly Naglazyme given for 2 years to patients with Maroteaux-Lamy syndrome after allogeneic transplantation as measured by the change in urinary GAG excretion; the change in endurance and mobility as measured by the 6-minute walk test and standard tests of range of motion and mobility; and the change in neurocognitive ability.

Secondary Objectives: The secondary objectives of this study are:

- to measure the development of antibodies, including neutralizing antibodies, associated with weekly Naglazyme® infusion in this patient population;
- to evaluate the impact of these antibodies on cardiorespiratory and skeletal parameters as measured by the 6-minute walk test and standard tests of range of motion and mobility, and the change in neurocognitive ability

Inclusion Criteria:

- Mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome) treated with a prior allogeneic transplant >2 years previously
- Persons who have received or are currently receiving Naglazyme may be considered for enrollment
- >10% engraftment based on most recent testing (within previous year)
- Willing to commit to traveling to the University of Minnesota every 6 months for 2 years
- Written informed consent with parent/guardian consent for children < 18 years of age or persons unable to consent with minor assent if appropriate

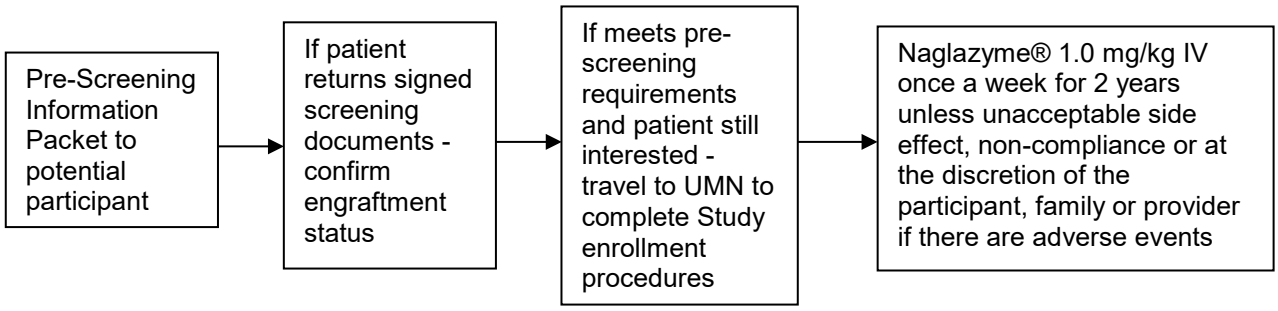
Exclusion Criteria:

- Pregnant or breastfeeding
- Any condition that, in the view of the investigator, places the patient at high risk of poor treatment compliance or of not completing the study

Accrual Objective: 10 evaluable patients

Schema

Patient Population: Mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome) treated with an allogeneic transplant more than 2 years prior to study enrollment and > 10% engraftment on most recent testing (patients need not have been transplanted at the University of Minnesota)



Disease specific testing will be performed per section 7.3.

Non-local patients will be treated with Naglazyme at a medical facility close to their home with mandatory visits to the University of Minnesota every 6 months
Arrangements will be made with the patient for the shipping urine to UMN for urine GAG testing for the 1st 30 days of enzyme and at months 3, 9, 15 and 21.

1 Objectives

1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of weekly Naglazyme given for 2 years to patients with Maroteaux-Lamy syndrome after allogeneic transplantation as measured by the change in urinary GAG excretion; the change in endurance and mobility as measured by the 6-minute walk test and standard tests of range of motion and mobility; and the change in neurocognitive ability.

1.2 Secondary Objectives

The secondary objectives of this study are:

- to measure the development of antibodies, including neutralizing antibodies, associated with weekly Naglazyme® infusion in this patient population
- to evaluate the impact of these antibodies on cardiorespiratory and skeletal parameters as measured by the 6-minute walk test, pulmonary, function test and standard tests of range of motion and mobility

2 Background and Study Rationale

2.1 Overview of MPS VI

Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome, OMIM 253200) is an inherited lysosomal storage disease resulting from the deficiency of functional enzyme N-galactosamine 4-sulfatase (arylsulfatase B, ARSB) (Neufeld and Muenzer, 2001). This enzyme is responsible for the degradation of dermatan sulfate, an essential glycosaminoglycan (GAG) found within the extracellular matrix of connective tissue. Accumulation of dermatan sulfate in MPS VI results in the clinical picture of small stature, dysostosis multiplex, joint pain and stiffness, coarsened facial features, corneal clouding, conductive hearing losses, macroglossia, upper airway obstruction, restrictive pulmonary disease, cardiac valve disease and cervical cord compression from dural thickening and atlantoaxial instability. Urinary GAG excretion >200µg/mg creatinine is associated with an accelerated clinical course while urinary GAG levels below 100µg/mg creatinine appears to predict longer survival and a milder phenotype (Swiedler, 2005).

2.2 Hematopoietic Cell Transplantation (HCT) for MPS VI

The first HCT for MPS VI was performed on a 12 year old girl in 1983 at the University of Minnesota and thereafter was performed regularly in several centers from 1984 until ~2000 (Krivit, 1984; Herskhovitz, 1999). Because cognitive decline was not considered to be present in MPS VI (in contrast to severe MPS I) and

because the reported long-term HCT-associated mortality has been estimated to be 30-35%, recent treatment guidelines have recommended HCT for MPS VI only if ERT fails (Giugliani, 2007; Prasad, 2010). Thus, due to small numbers of widely-dispersed recipients (Turbeville, 2011), the long-term benefits of HCT in MPS VI have remained limited to isolated case reports without a systematic review of benefits.

2.2.1 Demographics of patients undergoing HCT for MPS VI

Turbeville et al (2011) have summarized the survival outcome of HCT for MPS VI for 45 patients (24M, 21F) whose data has been recorded with the Center for International Blood and Marrow Transplant Research (CIBMTR) from 1982-2007. Diagnosis had been made at a median age of 1 year (range <1-9 years) with HCT occurring only at a median age of 5 years (range 1-22 years). This much older age at transplant is in marked contrast to HCT performed for severe MPS I (performed as early as possible in infancy and – unless extenuating circumstances exist – before 2 years of age) and may account for part of the post-HCT findings noted below. Two-thirds of the transplants occurred between 1982 and 2000. Patient country of origin was United States (60%), followed by Saudi Arabia (18%) with 5 countries (Australia, Brazil, China, England, Japan) accounting for the remaining 22% of patients. Detailed information on urinary GAG excretion, enzyme level and mutation were not included in this work thus precluding an assessment of severity of disease.

2.2.2 HCT procedure and survival for MPS VI

Two-thirds of the patients (N=30) underwent conditioning with cyclophosphamide and busulfan; total body irradiation was part of conditioning in an additional 13%. Bone marrow was the most common graft source (74%) with cord (24%) or peripheral (1%) accounting for the remainder. Unrelated-donors accounted for 60% and HLA-identical sibling or other related donor for the remaining 40% of transplant source (Turbeville). Information on the enzyme level of the donor (normal or heterozygous) was not included.

Overall survival for these 45 patients was 78% (range 65-89%) at one year, and 66% (range 52-79%) at three years after transplant. Survival was better in transplants performed before 1995 (79% 3 year survival), suggesting that those transplanted in larger centers may have fared better. With HCT, hepatosplenomegaly (HSM) quickly resolved, skin coarseness lessened, nasal secretions decreased and upper airway obstruction improved (Table 1). Cognition remained intact and usually within the normal range (Ahmed, 2013). Despite these favorable findings, multiple organ systems remain un- or partially-corrected after HCT.

2.2.3 Systems remaining abnormal after HCT in MPS VI

2.2.3.1 Urinary GAG excretion remains abnormal. It has been repeatedly shown that urinary GAG excretion after HCT, although improved from baseline values, may not achieve normal values (Table 1). Hershkovitz (1999) has found this in 4 transplanted MPS patients after 1-9 years of follow-up; Whitley and Utz (2010) showed that urinary GAG was elevated in a single patient despite 20 years of successful engraftment; and finally Sohn (2012) showed it in a single patient 10 years after HCT.

2.2.3.2 Growth and endocrine function remain impaired. Despite successful engraftment small stature is consistently found long-term after HCT for MPS VI with heights as much as 10 standard deviations below normal for age reported (Table 1). A relationship to age at transplant has not yet been studied. Endocrine abnormalities are not routinely sought but appear to be common. Primary ovarian failure, hypogonadotrophic hypogonadism and elevated IGF-1 have all been reported after HCT in MPS VI. These findings are very similar to the endocrine and growth data of 48 children with MPS IH treated with HCT reported by Polgreen et al (2008) between 1983 and 2002, who had survived more than 1 year after HCT. In this study there was a very high prevalence of short stature (71% at last evaluation) and endocrinopathy (27% subclinical or clinical hypothyroidism, 7-40% GH deficiency) in children with MPS IH after HCT.

This growth failure is likely multifactorial, due to hormonal deficiencies, i.e. - high prevalence of thyroid disease and growth hormone (GH) deficiency, and mechanical abnormalities , i.e. - known progression of skeletal disease after HCT (Oussoren, 2011), local accumulation of GAG, and abnormalities in the growth plate in MPS likely causing local GH resistance and impaired bone growth. Although not significantly associated with short stature in this study, the use of irradiation in the bone marrow transplant preparative regimen is thought to cause resistance to GH and insulin-like growth factor-1 (IGF-1) (Brauner, 1997).

2.2.3.3 Mobility is improved but skeletal manifestations (dysostosis multiplex) and contractures persist. Mobility is reported to be improved in the majority of MPS VI HCT recipients who have been observed to ‘run better’, ‘walk long distances’, and swim. Despite this improvement, joint contractures of the elbows and knees have been reported and carpal tunnel surgery is often required (Table 1). Dysostosis multiplex- the radiographic constellation of characteristic bone abnormalities including kyphosis and scoliosis with anterior beaking of vertebrae, hip dysplasia, and genu valgum- is characteristic of MPS VI

(Garcia, 2010; White, 2013). These changes persist and progress after successful HCT in MPS VI; surgical correction has been required for hips and knees and lumbar fractures have been noted. Low whole body bone mineral density measured by DXA is present in individuals with MPS I, II and VI (Polgreen 2013).

The etiology of these bony abnormalities, compounded by frequent joint contractures, has yet to be determined for any MPS syndrome. Animal model studies have indicated abnormalities in osteoclasts (responsible for bone resorption), osteoblasts (bone formation), and chondrocytes (Oussoren, 2011). Studies of the growth plates in both human and animal models of MPS have shown vacuolated chondrocytes due to GAG accumulation and a loss of the usual columnar architecture of the growth plate. HCT has also been associated with abnormalities of bone density (Mosstoufi-Moab, 2012).

2.2.3.4 Obstructive sleep apnea and pulmonary function – mixed results after HCT. Obstructive sleep apnea has been found to occur commonly in individuals with MPS VI with more severe hypoxemia and more sleep disruption occurring in pubertal or post-pubertal individuals (Lin, 2010). Lin speculated that macroglossia, adenotonsillar hypertrophy, excessive GAG deposition in the tracheobronchial mucosa, restrictive lung disease and decreased abdominal dimension due to lumbar hyperlordosis and hepatosplenomegaly all contributed the progressive nature of this finding. After HCT obstructive sleep apnea was reported resolved or improved in 4 patients with MPS VI; snoring was decreased in one patient; CPAP pressure lowered in another; and a final patient who previously had been a mouth breather became a nose breather with engraftment. The patient in whom CPAP pressure had been decreased had only 6 months of follow-up but had undergone HCT at 12 years of age for progressive airway obstruction with severe obstructive sleep apnea and desaturation, and extreme airway narrowing documented by CT with concern for future total airway obstruction.

Table 1. Summary of findings after HCT in patients with MPS VI.

Parameter / Study	McGovern (1986)	Imaizumi (1994)	Alvaro (1998)	Hershkovitz (1999)	Lee (2000)	Wang (2008)	Do Cormo (2010)	Whitley (2010)	Sillence (2011)	Sohn (2012)
Age at transplant	13 yr (F)	13.75 yr	12 yr (M)	3-9.5 yrs (2M, 2F)	5.8 yr (M)	10 yr (F)	22 months (M)	1.5 yr(M)	3 yr (F)	5 yr ( )F
Years follow-up	3.25 yr	4 yr	0.5 yr	1-9 yrs	15 months	12 yrs	13 yrs	20 yrs	1 yr	10 yrs
Urine GAG/cr ratio	'Normal values'	Decreased	No data	7—8[1]; 15,22[2]	No data	'normal'	No data	7-8.5[3]	Normal	92.2[4]
Growth	No change - short stature	Improved	No data	<3 centile	Some growth	'Slow'	Short stature	Short stature	'growing and developing well'	-10 SD < nl
Mobility	Improved	Walked >200 meters compared to 50 M before transplant	No data	Improved in all pts	Runs better and can walk long distances	Walks, bikes on own	Swims	No data	Improved but delayed	425.6 feet/12 minutes
Skeletal system	No change noted	No change	No data	Less lordosis; dysostosis multiplex persists in all; progressive hip changes – surgery in 2 pts	Knee contractures remain; no resolution skeletal deformities	No change	Large head, 'skeletal alterations'	No data	Minimal progression gibbus and metatarsus adductus	Deformities present including lumbar vertebral fractures
Upper extremities	Improved ROM	Improved	No data	Carpal tunnel surgery	Fingers less stiff; contractures of elbows remain	Bathes on own	Articular limitation	No data	No data	Contractures persist
Respiratory	Resolution OSA	No data	↓CPAP	↓OSA- 1 pt;	Now a nose breather, not mouth breather	↓snoring, ↓URI ↓SOB with exercise	Mouth breather	No OSA	Resolution OSA*	No data
Cardiac	Improved cor pulmonale	No progression of cardiac and valvular dysfunctions	No data	Myocardium improved; valves unchanged	No data	No significant change	Heart murmur	Normal function	No change – mitral regurgitation, normal LV function	Moderate aortic and mitral insufficiency unchanged
ENT	No data	No data	↓otorrhea	Conductive hearing loss – 3 pts; Sensorineural hearing loss – 1 pt Resolution dysphonia and hoarseness – 2 pts	↓suppurative middle ear effusion	No data	Macroglossia, gingival hyperplasia present Abnormal teeth	No data	Some improved hearing; resolution tonsillar and adenoid hypertrophy*	No data
Ophthalmologic	Subjective improvement	No improvement	No data	Continued corneal clouding	Continued corneal clouding	No data	Glaucoma, corneal opacity	Corneal clouding	No data	Corneal opacity present
Spinal cord	No data	No data	No data	No cervical cord compression or atlantoaxial instability	No data	No data	Odontoid hypoplasia present	No data	No data	None stated
Skin	Remains coarse	Less tight	↓coarseness	↓coarseness	↓coarseness	No data	Hypertrichosis	No data	↓coarseness*	↓coarseness
Liver/spleen	Normalized	↓hepatomegaly	↓HSM	No data	Resolution HSM	No data	No data	No data	Resolution HSM*	No HSM
Endocrine	No data		No data	Abnormalities present	No data	No data	No data	None found	No data	↑IGF-1 present
Neuropsych	normal			Uncertain	In school	University	In school	No data	No data	No data

1. Range GAG/cr ratio 1-5; 2. Range GAG/cr ratio 2-15;
3. Normal <6.5 mgGAG/mmol cr; 4. Normal <85 Unit CPC/g cr
*Resolution of tonsillar and adenoid hypertrophy, HSM, OSA and cutaneous features occurred during ERT before HCT

Pulmonary function testing, reported in 6 untreated MPS VI patients aged 7.6-17.4 years of age, has shown that restrictive pulmonary disease was present in 4 of them (Lin, 2013). Abnormalities of pulmonary function increased with age with virtually all post-pubertal MPS patients showing evidence of dysfunction. Post-HCT formal pulmonary function testing has been reported in only one patient (Sohn, 2012), a 15 year old recipient who showed decreased FEV1 and FVC (65% and 55% predicted, respectively) some 10 years after HCT. Since no pulmonary function testing had been performed prior to HCT, the effect of HCT in this single patient cannot be judged although the findings suggest continued moderate to severe restrictive pulmonary disease, perhaps due to the continued skeletal abnormalities.

2.2.3.5 Cardiac function remains normal but valves continue to be abnormal. While myocardial performance is usually normal, thickened, regurgitant and/or stenotic valves, as well as ventricular hypertrophy, are a common finding in untreated MPS VI (Braunlin, 2013). After successful HCT, ventricular function has been reported to continue to be normal in MPS VI (Table 1) – just as has been reported after HCT for severe MPS I (Braunlin, 2003). Similarly, just as in post-HCT severe MPS I, cardiac valves in MPS VI do not appear to benefit from HCT. Thickened and regurgitant mitral and aortic valves remain present despite long-term successful engraftment. It is speculated that the avascular nature of cardiac valve tissue precludes population of this tissue by normal donor cells.

2.2.3.6 ENT function is partially corrected by HCT. The ENT manifestations of MPS include otitis media with effusion, mixed conductive and sensorineural hearing loss, macroglossia, mandibular abnormalities, abnormalities of dentition and bite, and adenotonsillar hypertrophy (Simmons, 2005). Decreased otorrhea and suppurative middle ear effusions have been reported after HCT. Although some improvement in hearing has been reported after HCT, continued conductive hearing loss and a new finding of sensorineural hearing loss have been reported despite engraftment (Table 1). Macroglossia and abnormal dentition have persisted late after HCT in at least one individual. Adenotonsillar hypertrophy, dysphonia and hoarseness, by contrast, appear to have resolved in 2 others after HCT for MPS VI.

2.2.3.7 Ophthalmologic abnormalities persist. Corneal clouding, glaucoma and optic nerve abnormalities from GAG deposition within ocular tissue, surrounding tissues or the brain have all been described in untreated MPS VI (Fahnehjelm, 2012). Despite successful

engraftment, corneal clouding and glaucoma continue to persist after HCT in MPS VI (Table 1).

2.2.3.8 Thoracic, but not cervical, cord abnormalities have been reported after HCT. Cervical cord compression, one of the most common and serious complications of untreated MPS VI, is thought to be due to dysplasia of the odontoid process, diffuse thickening of the dura and extradural tissues from GAG deposition and atlantoaxial instability (Jurecka 2012). A review of the literature showed that spastic tetraparesis and hyperreflexia was the most common presentation. Surgical decompression was performed in the majority of these patients and all procedures resulted in improvement. No case of cervical cord compression in MPS VI has been reported after HCT (Table 1) although Ahmed and colleagues (2013) did find one MPS VI patient who required thoracic (T11-12) cord decompression after HCT.

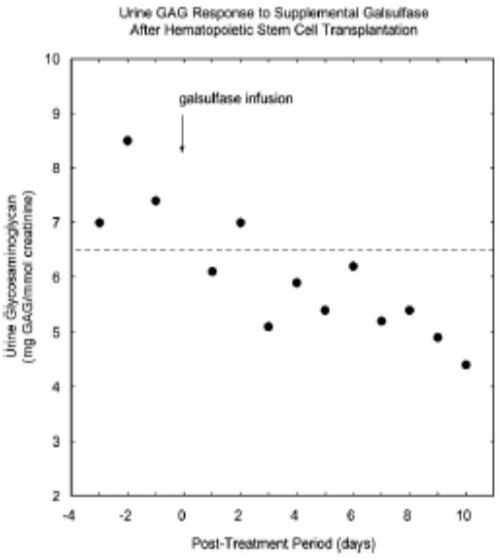
2.2.3.9 Neurocognitive complications. Abnormalities are frequently found in the brain MRI of children with MPS VI (Azevedo, 2013) with more than 90% of those studied showing the presence of dilated perivascular spaces, 76% having white matter lesions, 66% with hydrocephalus and 47% with cerebral atrophy. Correlations were found between age and both normalized white matter lesion load and normalized cerebral volume supporting the progressive nature of the disease. Normalized IQs did not correlate with MRI findings. After HCT a preliminary report (Ahmed, 2013) shows that ventricular size appears smaller in a small group of MPS VI subjects when compared to those receiving ERT; intervention for hydrocephalus has not been reported after HCT (Table 1). A comprehensive evaluation of the brain MRI findings and correlation to cervical cord issues has not been reported.

2.2.3.10 Summary of outcome after HCT for MPS VI. HCT clearly improves the health of patients with MPS VI by decreasing GAG accumulation within organs where tissue-specific donor hematopoietic cells reside. However, it is undeniable that significant morbidity of the disease persists in these patients despite a “successful” transplant. Globally, these complications may include continued corneal clouding, hearing deficits, cardiac and pulmonary difficulties. Importantly, despite “successful” transplantation, many of the MPS VI patients continue to have abnormal urinary GAG excretion, develop significant orthopedic difficulties, including spinal changes, limitations of range of motion, shoulder, knee and hip changes, as well as carpal tunnel syndrome and “trigger digits”. Many of these changes limit function, cause discomfort, and may require surgical intervention.

Quality of life is significantly impacted for children with MPS due to the persistence of skeletal abnormalities, contractures, and severe short stature. These patients, despite a successful transplant procedure, often require multiple orthopedic surgeries, frequently need to wear a brace for abnormal spine curvatures, and live with significant pain, typically on a daily basis. In part due to this bone disease, their short stature can be quite severe, frequently -3 to -6 standard deviations below the mean height for age and gender. Short stature this severe limits activities of daily living, and can negatively impact social development, socio-economic status, and career advancement.

2.3 The Case for Use of Intravenous Administration of Enzyme after HCT

Whitley and Utz (2010) have provided evidence that ERT improves the metabolic correction provided by HCT. Urinary GAG levels, which had remained slightly greater than normal 20 years after successful HCT in a 22 year old male with MPS VI, progressively declined below the age specific normal range after administration of a single dose of Naglazyme® (see Figure). Urinary GAG levels continued to decline for the entire study period of 10 days. This not only raises the possibility that intravenous enzyme reaches sanctuaries inaccessible to the effects of HCT but also suggests that ERT dosing schedules may need to be individualized.

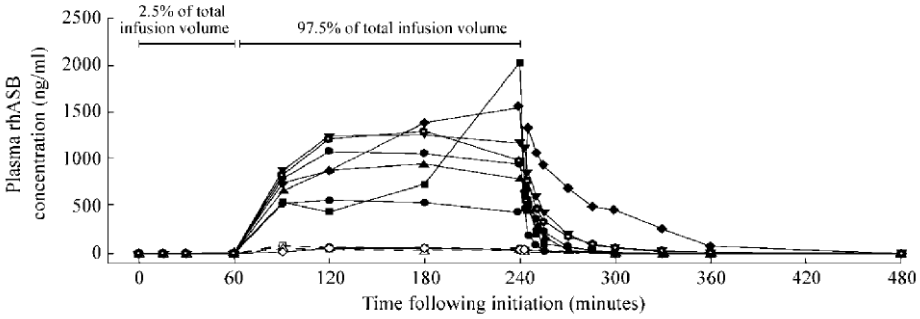


Long-term administration of ERT after HCT has been reported (Sohn, 2012) in a single 15 year old female patient with MPS VI who had undergone successful HCT 10 years previously. Weekly infusions of Naglazyme® over 18 months resulted in an increased growth velocity from 2cm/year to 4.5 cm/year; 70% increase in the 12-minute walk test; improvement in range of motion of several upper and lower extremity joints; ~30% improvement in the 3-minute stair climb and improvement in facial features. Increased distance travelled in the 12-minute walk test was not only sustained, but continued to improve during the 18 month follow-up period. Urinary GAG declined by 50% and reached the normal range. It was hypothesized by the authors that the increased joint mobility and growth accounted for the remarkable increase in 12-minute walk test.

HCT provides a continuous, but not necessarily equal, metabolic correction for each patient undergoing the process as has been documented in a study of MPS

I post-HCT recipients (Church, 2007). In these MPS I patients, post-HCT enzyme levels as well as residual substrate (as determined by urinary GAG) not only depended upon the recipient status (genotype, age, peri-transplant complications) but also upon the donor and whether full donor chimerism occurred after transplantation. In Church's MPS I patients activity of post-HCT leukocyte α-L-iduronidase level varied widely ranging from 7.1μmol/g/h in mixed chimerism recipients who had a heterozygous donor to 24.8μmol/g/h in full donor chimerism recipients who had a donor with normal enzyme levels. Residual substrate was tightly and inversely related to enzyme activity. It is clear that these same factors exist for individuals with MPS VI undergoing HCT and can lead to a considerable variability in metabolic correction.

By contrast, the delivery and distribution of enzyme with ERT differs from HCT. In MPS VI, Naglazyme®, delivered by weekly infusion, has a peak plasma concentration that occurs at between 120 and 240 minutes into the infusion but is not



measureable in the plasma within 10 minutes following completion of the infusion (see figure above, Harmatz, 2005). In humans the mean elimination half-life in patients during initial week of infusion ranges from 6 to 21 minutes (Package insert). The AUC_{o-t} of Naglazyme® increased from the 1 to the 2nd infusion but remained stable thereafter. Urinary GAG excretion dropped by ~75% from baseline values but did not normalize during the 96 weeks in which it was measured (Harmatz, 2005). Anti-rASB antibodies developed and the regressed during this time but did not appear to affect GAG excretion. Despite the lack of urinary GAG normalization, the administration of intravenous Naglazyme® significantly decreased urinary GAG, led to improvement in the 6 and 12 minute walk tests and 3 minute stair climb, as well as a significant increase in growth rate and height (Harmatz, 2008).

As recombinant galsulfase (Naglazyme®) is FDA approved for MPS VI, we hypothesize that the addition of intermittent intravenous dosing of Naglazyme® may benefit patients following transplantation. The primary objective of this study will include measurements that have been previously been shown to improve in single patients with MPS VI after HCT: namely, urinary GAG excretion,

endurance and mobility. However, it is possible that adverse effects or toxicity may be observed in patients with MPS VI who have previously undergone transplantation, as the use of Naglazyme® has been tested long term in only one patient within this population (Sohn, 2012). We therefore propose a study with to determine if antibody formation is observed and to gather information regarding the effect of antibody formation on outcome parameters, with the intent of ultimate long-term administration of ERT to MPS VI HCT recipients.

2.4 Potential Assessments of Patient Response

2.4.1 Orthopedic Parameters of Response to Therapy: Methods of Bone Assessment. Given the rapid change in bone size and shape during growth, along with the tremendous individual variability in maturity and growth rates, non-invasive assessment of bone mass and density, such as dual energy x-ray absorptiometry (DXA) in pediatric populations presents numerous challenges, even in healthy populations (Baim, 2008). Those challenges are magnified in clinical populations such as MPS where the bone is uniquely shaped and growth rates are even more varied than in healthy children (Polgreen 2013). Despite these challenges, peripheral quantitative computed tomography (pQCT) presents a feasible way to assess important components of bone density, geometry and strength in this population as well as detect earlier changes in bone in response to treatment compared to CXA... This is discussed in detail as follows.

Peripheral quantitative computer tomography (pQCT). Peripheral quantitative computed tomography (pQCT) provides a 3-dimensional image of peripheral bones (tibia, radius and distal femur) thus reducing size-related errors. Testing by pQCT also has a higher resolution than DXA and is able to assess cortical and trabecular bone volumetric density (vBMD, mg/mm^3) separately (Zemel, 2008, 2011). This is particularly important in clinical trials as the trabecular bone may be earlier and disproportionately affected by disease or pharmaceutical intervention. In addition to cortical and trabecular density, pQCT provides measures of bone geometry (total and cortical bone area) and estimates of bone strength (section modulus and strength strain index) (Zemel, 2011). A study using pQCT has assessed bone density, geometry and strength in long-term survivors of HCT (Moustafi-Moab, 2012) where significant deficits in trabecular volumetric bone mineral density, cortical geometry and muscle area were found years after transplantation. In this study both total body irradiation and growth hormone deficiency were significant risk factors for musculoskeletal defects. These factors may play a role in MPS VI HCT recipients and deserve investigation.

2.4.1.1 Use of pQCT: We have collected tibia and radius pQCT scans on more than 50 children with MPS and found abnormal bone geometry and relatively thin cortical bone (Figure 2). We were able to successfully scan at least one limb in most children. We use a flexible arm holder that

allows for better and more comfortable positioning, as movement based on discomfort can interfere with the imaging.

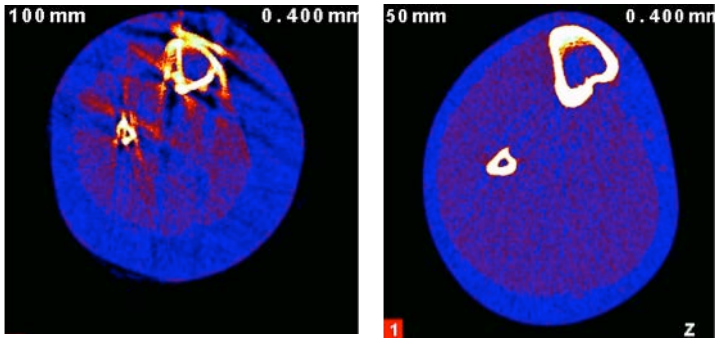


Figure 2. Image of tibia scan with excessive movement (A) in MPS I patient (female, age 11 yrs), and (B) a good scan at the same site in MPS II patient (male, age 13 yrs).

2.4.1.2. Markers of Bone Turnover: Biomarkers of bone turnover have been used in adult populations to predict fracture risk (Miller, 2005), to monitor the treatment effect of bisphosphonate therapy (Bonnick, 2006), and to monitor metastatic disease (Hannon, 2006). Decreased osteocalcin has been reported in 50% of adults with Gaucher disease, a lysosomal storage disease associated with low bone density and bone complications (Van Dussen, 2011).

2.4.1.3. Radiographic Assessment of Spine and Lower Extremity Changes: Anterior hypoplasia of the lumbar vertebrae causing lumbar gibbus and progressive lordosis, hip dysplasia and luxation, progressive genu valgum are common findings in MPS VI (Garcia, 2010). To evaluate these parameters, X-rays with local read will be performed for changes in the spine (scoliosis series) and for lower extremity abnormalities with X-rays of the knees and hips.

2.4.2 Assessment of Joint Mobility and Dexterity. Untreated MPS VI patients exhibit the most severe limitations in shoulder flexion, followed by knee extension and elbow flexion (Cardoso-Santos, 2008). Hand grip strength was compromised in all patients in this study and pinch strength showed a positive correlation with age. Limitation of shoulder flexion occurred early and was not associated with age suggesting it may be an important clinical diagnostic element. Limitation of elbow flexion interferes with activities of daily life such as brushing teeth, combing hair, self-care after toilet.

Physical and occupational therapists skilled in the assessment patients with MPS will see the enrolled patients, and assess the range of motion/flexibility at the designated time points. Dexterity will be evaluated by timed testing using the 9-block peg (Reuben, 2013).

2.4.3 Endurance Testing and Gait Analysis: To determine if enzyme infusion provides benefit leading to the potential for increased activity, the standard-12 minute walk test will be performed in accordance with published standards (Solway, 2001). This test has been extensively utilized in determining the effect of ERT in improving ambulation in subjects with MPS VI (Harmatz, 2008) and will provide the most comparable measure of change for subjects after HCT who receive ERT.

The assessment of gait involves more than measuring the distance walked. The kinematic gait analysis is a quantitative method. It describes movements of the major joints and gait components of the lower extremity through wearable sensors mounted on the lower extremity. Quantitative gait analysis provides information about velocity, cadence, step length, and base of support. Slower gait speed and shorter step length have been documented in MPS disorders. In addition gait kinematics provides key information about angular displacements of lower limb joints. It is of particular interest in MPS as joint disease causing joint stiffness is one of major factors affecting gait pattern. Another advantage of wearable kinematic sensors is low cost and good portability. Gait analysis can be a sensitive measure of disease severity and treatment response.

2.4.4 Cardiac Function: Enrolled patients will have clinical evaluations including physical examination, an ECHO and EKG to monitor cardiac changes.

2.4.5 Neurocognitive Imaging and Testing: We have previously studied 41 children with MPS IH who were treated with HCT at the University of Minnesota (Bjoraker, 2006) and found that treatment of MPS IH with HCT resulted in an overall improvement in neuropsychological functioning compared to historical controls not treated with HCT. However, there continued to be limitations in the development of 4 measured domains that constitute adaptive functioning: communication, daily living skills, socialization, and motor skills, even after HCT treatment. Preliminary neurocognitive testing in subjects with MPS VI have been reported by us (Ahmed, 2013). While IQ is normal in MPS VI patients whether treated with HCT or ERT, attention span is below average for both. We have also determined that volumetric findings on MRI are consistent with functional findings (Kovac, 2013) with gray matter volumes not different from normal controls, but white matter volumes, especially corpus callosum, significantly smaller than normal controls, which likely affects function as seen functionally by poor attentional deployment. Enrolled subjects (n=6), who are ERT naïve, will undergo brain and cervical spine MRI as well as neurocognitive testing, to define

parameters as indicated above, at baseline and annually during the proposed trial.

2.5 Dosing Rational and Assessments of Potential Toxicity

The use of Naglazyme® has been assessed in an open-labeled Phase I/II study (Harmatz, 2004) and in a placebo-controlled, double-blind Phase III study with extension to 260 weeks (Harmatz, 2006; Harmatz, 2008). Weekly infusion dosage of 1mg/kg was determined to be well tolerated and to provide rapid decline in urinary GAG levels as well as rapid improvement in endurance in patients with rapidly progressing disease in Phase I/II studies (Harmatz, 2004). This is the standard dosing of drug stated in the package insert for Naglazyme®. In the open-labeled Phase I/II study (Harmatz, 2004), there were 7 serious adverse events (SAEs) during the first 48 weeks of treatment. Two of these events were deemed unrelated to infusion: mild desaturation during sleep in one patient that did not vary from baseline findings, and development of brain glioma and adenocarcinoma occurring approximately 10 months after the patient withdrew from the trial due to an unrelated genetic mutation. None of the remaining five SAEs (hypoxia during routine tracheostomy change, vasovagal syncope during intravenous line insertion, paratracheal skin hypertrophy, worsening Eustachian tube dysfunction, and bilateral carpal tunnel syndrome) were deemed related to study drug. There were no reports of allergic reactions (urticarial, angioedema). Thirty-one AEs occurred during drug infusion: all were assessed as mild and all resolved. Events deemed related to drug infusion included hypotension, tachypnea, skin irritation on neck and chest, pain at IV insertion site and a 3-second run of ventricular tachycardia. During the first 48 weeks of treatment, 126 AEs were reported with the following assessed as possibly related to drug infusion: lethargy (2), hypotension (1), itching (4), rash/skin irritation (4) and intermittent joint popping (1).

In the placebo controlled Phase III trial the incidence of total AEs, severe AEs and serious AEs in subjects allocated to Naglazyme® was similar to that of subjects receiving placebo (Harmatz, 2010). Although all patients experienced AEs during this 260 week study, only 560 (14%) of AEs were related to treatment. The majority of AEs were mild to moderate in nature; 83 of the total AEs (2%) and 10 of 560 were treatment-related AEs were described as severe. Two severe AEs occurring during infusion included one subject who, at Week 18 of treatment, experienced ‘apnea’ requiring intubation 75 minutes into the infusion, likely related to diphenhydramine premedication; the second who, at Week 167 of treatment, developed laryngeal edema, facial edema and urticarial responding to interruption of treatment, additional antihistamine and corticosteroid treatment. Non-severe events included respiratory distress, fever, mild angioedema with anaphylactoid reaction, and exacerbation of asthma several hours after infusion. All cases responded to decreasing the infusion rate

and administering additional medications. Treatment was not discontinued because of these reactions.

Package insert for Naglazyme® indicates that anaphylaxis and severe allergic reactions have been seen in patient during, and up to 24 hours after, infusion. Type III immune-mediated reactions, including membranous glomerulonephritis in a single patient (who was successfully re-challenged) have been reported. MPS patients are susceptible to fluid volume overload and a risk of cardiorespiratory failure is present in such patients. It is advised that patients using supplemental oxygen or CPAP should have this support readily available during infusion in the event of an infusion related reaction or drowsiness from pre-treatment with antihistamines.

Infusion related reactions, some severe, occurred frequently despite pretreatment with antihistamine and, in some cases, antipyretic. Serious reactions included laryngeal edema, apnea, pyrexia, urticarial, respiratory distress and anaphylactoid reaction. Sever adverse reactions included urticarial, chest pain, rash, dyspnea, apnea, laryngeal edema and conjunctivitis. The most common drug-related infusion reactions were pyrexia, chills, rash, urticarial, dyspnea, nausea, vomiting, abdominal pain, hypertension and headache. Infusion related reactions were seen as early as Week 1 and as late as Week 146; 70% of patients experienced recurrent infusion reactions during the course of the infusions.

Interestingly, nearly all of the subjects developed IgG antibodies against Naglazyme® (Harmatz, 2004; Harmatz, 2010) by 30 weeks of treatment. Despite the presence of antibody, subjects (with rare exception) still experienced positive clinical benefit and GAG excretion. There appeared to be no constant predictive relationship between antibody titer, neutralizing or IgE antibodies, infusion-associated reactions, urinary GAG or endurance measures. Antibody development was not associated with significant complement depletion during infusion but the majority of patients who experienced infusion-associated reactions (IARs) had high antibody titers although there were many exceptions (Harmatz, 2006).

3 Patient Selection

Patients will be referred from other health care providers or self-referred for consideration in this protocol. While there will be every effort to seek out minority patients, the patient population is dependent upon the referral pattern. It is expected that this study will enroll patients from throughout North America. Costs associated with travel to and housing during studies at the University will be borne by the funder per negotiated budget.

Potential participants will be mailed a study information packet which will include two copies of the screening consent/a release of information form and the current treatment consent. After reviewing the packet information and if still interested the participant will be asked to sign and return the screening consent and the release of information form to permit pre-screening to occur (primarily confirm donor engraftment). If the participant meets engraftment criteria, arrangements will be made for travel to the University of Minnesota for a multi-day baseline visit which will include review and formal written consent to the study using the current treatment form.

3.1 Inclusion Criteria

- Mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome) treated with an allogeneic transplant more than 2 years prior to enrollment – patients need not have been transplanted at the University of Minnesota
- Persons who have received or are currently receiving Naglazyme may be considered for enrollment
- >10% engraftment based on most recent testing (within previous year) – confirmed during pre-screening
- If female of child-bearing age, willing to defer pregnancy for the duration of the trial
- Willing to commit to traveling to the University of Minnesota every 6 months for the duration of the trial (2 years)
- Written informed consent prior to the performance of any study related procedures with parent/guardian consent for children < 18 years of age or persons unable to consent with minor assent if appropriate.

3.2 Exclusion Criteria

- Is pregnant or breastfeeding at screening or baseline, or planning to become pregnant (self or partner) at any time during the study. Pregnancy Category B: Adequate and well-controlled studies have not been conducted with Naglazyme in pregnant women. Patients who become pregnant will be discontinued from study.
- Any condition that, in the view of the investigator, places the patient at high risk of poor treatment compliance or of not completing the study

4 Patient Registration

4.1 Registration with the Masonic Cancer Center Clinical Trials Office

Potential patients will initially be registered in OnCore upon receipt of a signed screening consent. If the patient later signs the treatment consent and completes the study screen/baseline visit, the registration in OnCore will be updated. Otherwise the patient will be considered a screen failure and OnCore will be updated to reflect this status.

4.2 Patients Who Are Registered and Do Not Receive Study Treatment

Patients will have 6 months to enroll into the study after the initial evaluation at the University of Minnesota. If a patient is registered to the study, and is later found not able to begin the study treatment, for whatever reason, the patient will be removed from study and treated at the physician's discretion. The Study Coordinator or designee will update OnCore of the patient's non-treatment status and notify the Principal Investigator. Study data will be collected until the time the patient is off study. The reason for removal from study will be clearly document in OnCore. The patient will be replaced, if possible.

5 Treatment Plan

5.1 Baseline Assessment/Identification of a Local Medical Facility

All potential patients will be assessed at the University of Minnesota according to the schedule of assessments in section 7.2 after completion of an initial screening per section 3..

It is expected that this study will enroll patients from throughout North America. During the baseline assessment, arrangements will be made with an appropriate medical facility close to the family's home for administration of some or all of the weekly treatments between the required minimum every 6 month visit at the University of Minnesota.

5.2 Dosage and Administration

It is anticipated the vast majority of Naglazyme administration will take place at a medical facility close the family's home. Medical oversight, decision to treat or not, and drug administration/monitoring will be based on the clinical judgment of the local medical team with consideration of the following standard of care guidelines.

The recommended dosage regimen of Naglazyme is 1 mg per kg of body weight administered once weekly as an intravenous infusion. Weekly is defined as once during a calendar week with a +/- 1 day window permitted.

There are no recommended dose modifications, only dose delays and infusion time adjustment as detailed below.

Pre-treatment Assessment/Dose Delay: Patients should be briefly assessed prior to each dose for general health status. Treatment may be delayed weekly if medically indicated or at the patient's family request (i.e. illness, travel); however, a break of more than 4 weeks between Naglazyme doses will result in removal from study.

Consider delaying Naglazyme infusions in patients who present with an acute febrile or respiratory illness because of the possibility of acute respiratory compromise during infusion of Naglazyme. Refer to section 6.6.4 for additional information.

Pre-medication Guidelines: Patients should be treated approximately 30 minutes to one hour prior to each infusion with non-sedating antihistamines such as citrazine or loratadine. Antipyretics may be administered at the discretion of the investigator. If a patient has a history of infusion reactions or other risk factors (e.g., history of allergies), a sedating antihistamine such a diphenylhydramine may be administered, and premedication with additional agents such as steroids maybe considered. Refer to section 6.6.5 for additional information.

The total volume of the infusion should be delivered over a period of time of no less than 4 hours. Naglazyme should be diluted with 0.9% Sodium Chloride Injection, USP, to a final volume of 250 mL and delivered by controlled intravenous infusion using an infusion pump. The initial infusion rate should be 6 mL per hour for the first hour. If the infusion is well tolerated, the rate of infusion may be increased to 80 mL per hour for the remaining 3 hours. The infusion time can be extended up to 20 hours if infusion reactions occur.

For patients 20 kg and under or those who are susceptible to fluid volume overload, physicians may consider diluting Naglazyme in a volume of 100 mL *[see Warnings and Precautions (section 6.6 and specifically section 6.6.3)]*. The infusion rate (mL per hour) should be decreased so that the total infusion duration remains no less than 4 hours.

5.3 Duration of Therapy

Naglazyme® every week, based on the schedule of the patient and potential confounding factors (illness, travel, etc.), will continue for 2 years unless one of the following occurs. The decision to stop therapy may be based on the following:

- Unacceptable side effects
- A change in therapy is felt to be in the best interest of the patient
- More than 4 week break between Naglazyme® doses
- Patient/parent withdraws consent
- Patient/parent preference

At the conclusion of the study, subjects may elect to continue receiving Naglazyme® under the care of their local providers although no further evaluations will be supported by BioMarin as part of this study after the first two

years of therapy. The feasibility of continued therapy may of course be dependent on continued insurance coverage, and is therefore not assured.

5.4 Duration of Study Participation

Study participation will be for 2 years with the 24 month visit at the University of Minnesota the final study related visit. If treatment is discontinued earlier, a final study visit to the University of Minnesota will be scheduled.

6 Naglazyme Preparation, Administration, Availability and Expected Side Effects

Refer to the prescribing information for Naglazyme available through www.**naglazyme**.com/

6.1 Dosage Forms and Strengths

Injection; 5 mL vials (5 mg per 5 mL).

6.2 Preparation for Administration

Each vial of Naglazyme provides 5 mg of galsulfase (expressed as protein content) in 5 mL of solution and is intended for single use only. Do not use the vial more than one time.

The concentrated solution for infusion must be diluted with 0.9% Sodium Chloride Injection, USP, using aseptic techniques. Prepare Naglazyme using low-protein-binding containers and administer the diluted Naglazyme solution to patients using a low-protein-binding infusion set equipped with a low-protein-binding 0.2 µm in-line filter. There is no information on the compatibility of diluted Naglazyme with glass containers.

Instructions for Use

Prepare and use Naglazyme according to the following steps. Use aseptic techniques.

a. Determine the number of vials to be used based on the patient's weight and the recommended dose of 1 mg per kg:
   - Patient's weight (kg) × 1 mL/kg of NAGLAZYME = Total number of nL of NAGLAZYME
   - Total number of Nl of NAGLAZYME ÷ 5 mL per vial = Total number of vials
   - Round up to the next whole vial. Remove the required number of vials from the refrigerator to allow them to reach room temperature. Do not allow vials to remain at room temperature longer than 24 hours prior to dilution. Do not heat of microwave vials.

b. Before withdrawing the NAGLAZYME solution from the vial, visually inspect each vial for particulate matter and discoloration. The NAGLAZYME solution should be clear to slightly opalescent and colorless to pale yellow. Some translucency may be present in the solution. Do not use if the solution is discolored or it there is particulate matter in the solution.

c. From a 250 mL infusion bag of 0.9% Sodium Chloride Injection, USP, withdraw and discard a volume equal to the volume of NAGLAZYME solution to be added. If using a 100 mL infusion bag, this step is not necessary.

d. Slowly withdraw the calculated volume of NAGLAZYME from the appropriate number of vials using caution to avoid excessive agitation. Do not use a filter needle, as this may cause agitation. Agitation may denature NAGLAZYME, rendering it biologically inactive.

e. Slowly add the NAGLAZYME solution to the 0.9% Sodium Chloride Injection, USP, using care to avoid agitation of the solutions. Do not use a filter needle.

f. Gently rotate the infusion bag to ensure proper distribution of NAGLAZYME. Do not shake the solution. Administer the diluted NAGLAZYME solution to patients using a low-protein-binding infusion set equipped with a low-protein-binding 0.2 µm in-line filter.

NAGLAZYME does not contain preservatives; therefore, after dilution with saline, the infusion bags should be used immediately. If immediate use is not possible, the diluted solution must be stored refrigerated at 2°C to 8°C (36°F to 48°F) and administered within 48 hours from the time of dilution to completion of administration. Other than during infusion, do not store the diluted NAGLAZYME solution at room temperature. Any unused product or waste material must be discarded and disposed of in accordance with local requirements.

NAGLAZYME must not be infused with other products in the infusion tubing. The compatibility of NAGLAZYME in solution with other products has not been evaluated.

6.3 Premedication

After pre-infusion assessments, all patients should be treated approximately 30 minutes to one hour prior to each infusion with non-sedating antihistamines such as citrazine or loratadine. Antipyretics may be administered at the discretion of the investigator. If a patient has a history of infusion reactions or other risk factors (e.g., history of allergies), a sedating antihistamine such a diphenylhydramine may be administered,

and premedication with additional agents such as steroids maybe considered.

6.4 Drug Procurement

NAGLAZYME is commercially available. The cost of the drug will be billed to the patient's health insurance/health plan.

During the baseline assessment, arrangements will be made with an appropriate medical facility close to the family's home for administration of some or all of the weekly treatments between the required minimum every 6 month visit at the University of Minnesota.

While at the University of Minnesota and with BioMarin Patient & Physician Support (BPPS), insurance coverage will be verified.

In addition, if the local medical facility cannot or prefer not to oversee the administration of weekly Naglazyme, Fairview Home Infusion (FHI) will facilitate arrangement of local administration of the drug.

6.5 Contraindications

None.

6.6 Warnings and Precautions

6.6.1 Anaphylaxis and Allergic Reactions

Anaphylaxis and severe allergic reactions have been observed in patients during and up to 24 hours after NAGLAZYME infusion. Some of the reactions were life-threatening and included anaphylaxis, shock, respiratory distress, dyspnea, bronchospasm, laryngeal edema, and hypotension. If anaphylaxis or other severe allergic reactions occur, NAGLAZYME should be immediately discontinued, and appropriate medical treatment should be initiated. In patients who have experience anaphylaxis or other severe allergic reactions during infusion with NAGLAZYME, caution should be exercised upon rechallenge; appropriately trained personnel and equipment for emergency resuscitation(including epinephrine) should be available during infusion.

6.6.2 Immune-Mediated Reactions

Type III immune complex-mediated reactions, including membranous glomerulonephritis have been observed with NAGLAZYME, as with other enzyme replacement therapies. If immune-mediated reactions occur, discontinuation of the administration of NAGLAZYME should be considered, and appropriate medical treatment initiated. The risks and benefits of re-administering NAGLAZYME following an Immune-mediated reaction should be considered. Some patients have successfully been rechallenged and have

continued to receive NAGLAZYME under close clinical supervision [*see Adverse Reactions*].

6.6.3 Risk of Acute Cardiorespiratory Failure

Caution should be exercised when administering NAGLAZYME to patients susceptible to fluid volume overload; such as in patients weighing 20 kg or less, patients with acute underlying respiratory illness, or patients with compromised cardiac and/or respiratory function, because congestive heart failure may result. Appropriate medical support and monitoring measures should be readily available during NAGLAZYME infusion, and some patients may require prolonged observation times that should be based on the individual needs of the patient. [*see Adverse Reactions*].

6.6.4 Acute Respiratory Complications Associated with Administration

Sleep apnea is common in MPS VI patients and antihistamine pretreatment may increase the risk of apneic episodes. Evaluation of airway patency should be considered prior to initiation of treatment. Patients using supplemental oxygen or continuous positive airway pressure (CPAP) during sleep should have these treatments readily available during infusion in the event of an infusion reaction, or extreme drowsiness/sleep induced by antihistamine use.

Consider delaying NAGLAZYME infusions in patients who present with an acute febrile or respiratory illness because of the possibility of acute respiratory compromise during infusion of NAGLAZYME.

6.6.5 Infusion Reactions

Because of the potential for infusion reactions, patients should receive antihistamines with or without antipyretics prior to infusion. Despite routine pretreatment with antihistamines, infusion reactions, some severe, occurred in 33 of 59 (56%) patients treated with NAGLAZYME. Serious adverse reactions during infusion included laryngeal edema, apnea, pyrexia, urticarial, respiratory distress, angioedema, and anaphylactoid reaction. Severe adverse reactions included urticarial, chest pain, rash, dyspnea, apnea, laryngeal edema, and conjunctivitis.

The most common symptoms of drug-related infusion reactions were pyrexia, chills, rash, urticaria, dyspnea, nausea, vomiting, pruritus, erythema, abdominal pain, hypertension, and headache. Respiratory distress, chest pain, hypotension, angioedema, conjunctivitis, tremor, and cough were also reported. Infusion reactions began as early as Week 1 and as late as Week 146 of NAGLAZYME treatment. Twenty-three of 33 patients (70%) experienced recurrent infusion reactions during multiple infusions though not always in consecutive weeks.

Symptoms typically abated with slowing or temporary interruption of the infusion and administration of additional antihistamines, antipyretics, and occasionally corticosteroids. Most patients were able to complete their infusions. Subsequent infusions were managed with a slower rate of NAGLAZYME administration, treatment with additional prophylactic antihistamines, and in the event of a more severe reaction, treatment with prophylactic corticosteroids.

If severe infusion reactions occur, immediately discontinue the infusion of NAGLAZYME and initiate appropriate treatment. The risk and benefits of re-administering NAGLAZYME following a severe reaction should be considered.

No factors were identified that predisposed patients to infusion reactions. There was no association between severity of infusion reactions and titer of anti-galsulfase antibodies

6.7 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates observed in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

NAGLAZYME was studied in a randomized, double-blind, placebo-controlled trial in which 19 patients received weekly infusions of 1 mg/kg NAGLAZYME and 20 patients received placebo; of the 39 patients 66% were female, and 62% were White, non-Hispanic. Patients were aged 5 years to 29 years. NAGLAZYME-treated patients were approximately 3 years older than placebo-treated patients (mean age 13.7 years versus 10.7 years, respectively).

Serious adverse reactions experienced in this trial include apnea, pyrexia, and respiratory distress. Severe adverse reactions include chest pain, dyspnea, laryngeal edema, and conjunctivitis. The most common adverse reactions requiring interventions were infusion reactions.

Table 2 from package insert (PI) summarizes the adverse reactions that occurred in the placebo-controlled trial in at least 2 patients more in the NAGLAZYME-treated group than in the placebo-treated group.

PI Table 2: Adverse Reactions that Occurred in the Placebo-Controlled Trial in at least 2 Patients More in the NAGLAZYME Group than in the Placebo Group

MedDRA Preferred Term	NAGLAZYME (n = 19)	PLACEBO (n = 20*)
	No. Patients (%)	No. Patients (%)
All	19 (100)	20 (100)
Abdominal Pain	9 (47)	7 (35)
Ear Pain	8 (42)	4 (20)
Arthralgia	8 (42)	5 (25)
Pain	6 (32)	1 (5)
Conjunctivitis	4 (21)	0
Dyspnea	4 (21)	2 (10)
Rash	4 (21)	2 (10)
Chills	4 (21)	0
Chest Pain	3 (16)	1 (5)
Pharyngitis	2 (11)	0
Areflexia	2 (11)	0
Corneal opacity	2 (11)	0
Gastroenteritis	2 (11)	0
Hypertension	2 (11)	0
Malaise	2 (11)	0
Nasal congestion	2 (11)	0
Umbilical Hernia	2 (11)	0
Hearing Impairment	2 (11)	0
*One of the 20 patients in the placebo group dropped out after Week 4 infusion		

Four open-label clinical trials were conducted in MPS VI patients aged 3 months to 29 years with NAGLAZYME administered at doses of 0.2 mg/kg (n=2), 1 mg/kg (n=55), and 2 mg/kg (n=2). The mean exposure to the recommended dose of NAGLAZYME (1 mg/kg) was 138 weeks (range 54 to 261 weeks). Two infants (12.1 months and 12.7 months) were exposed to 2 mg/kg of NAGLAZYME for 105 and 81 weeks, respectively.

In addition to those listed in Table 2, common adverse reactions observed in the open-label trials include pruritus, urticaria, pyrexia, headache, nausea, and vomiting. The most common adverse reactions requiring interventions were infusion reactions. Serious adverse reactions included laryngeal edema,

urticaria, angioedema, and other allergic reactions. Severe adverse reactions included urticaria, rash, and abdominal pain.

Observed adverse events in four open-label studies (up to 261 weeks treatment) were not different in nature or severity to those observed in the placebo-controlled study. No patients discontinued during open-label treatment with NAGLAZYME due to adverse events.

6.8 Immunogenicity

Ninety-eight percent (53/54) of patients treated with NAGLAZYME and evaluable for the presence of antibodies to galsulfase developed anti-galsulfase IgG antibodies within 4 to 8 weeks of treatment (in four clinical studies). In 19 patients treated with NAGLAZYME from the placebo-controlled study, serum samples were evaluated for a potential relationship of anti-galsulfase antibody development to clinical outcome measures. All 19 patients treated with NAGLAZYME developed antibodies specific to galsulfase; however, the analysis revealed no consistent predictive relationship between total antibody titer, neutralizing or IgE antibodies, and infusion-associated reactions, urinary glycosaminoglycan (GAG) levels, or endurance measures. Antibodies were assessed for the ability in inhibit enzymatic activity but not cellular uptake.

The data reflect the percentage of patients whose test results were considered positive for antibodies to galsulfase using specific assays and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to galsulfase with the incidence of antibodies to other products may be misleading.

6.9 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of NAGLAZYME. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In addition to infusion reactions reported in clinical trials, serious reactions which occurred during NAGLAZYME infusion in the worldwide marketing experience include anaphylaxis, shock, hypotension, bronchospasm, and respiratory failure.

Additional infusion reactions included pyrexia, erythema, pallor, bradycardia, tachycardia, hypoxia, cyanosis, tachypnea, and paresthesia.

During postmarketing surveillance, there has been a single case of membranous nephropathy and rare cases of thrombocytopenia reported. In the case of membranous nephropathy, renal biopsy revealed galsulfase-immunoglobulin complexes in the glomeruli. With both membranous nephropathy and thrombocytopenia, patients have been successfully rechallenged and have continued to receive NAGLAZYME.

6.10 Use in Specific Populations

6.10.1 Pediatric Use

Clinical studies with NAGLAZYME were conducted in 56 patients, ages 5 to 29 years, with the majority of these patients in the pediatric age group *[see Clinical Studies]*. In addition, an open-label study was conducted in four infants (3 months to 12.7 months) treated with 1 mg/kg (n=2) or 2 mg/kg (n=2) of NAGLAZYME. Safety results in infants were consistent with results observed in patients 5 to 29 years old [*see Adverse Reactions*].

6.10.2 Geriatric Use

Clinical studies of NAGLAZYME did not include patients older than 29 years of age. It is not known whether older patients respond differently from younger patients.

6.11 Use in Pregnancy

Pregnancy Category B: Adequate and well-controlled studies have not been conducted with Naglazyme in pregnant women. Patients who become pregnant will be discontinued from study.

7 Required Observations/Testing

7.1 Pre-Screening (after signing pre-screening consent)

Confirm diagnosis, transplant date (must be at least 2 years post for study enrollment) and meets > 10% donor engraftment after receipt of a signed pre-screening consent.

7.2 Assessments to Be Performed at the University of Minnesota

Assessment	**Baseline**	**Every 6 months**	**Final study visit (24 month visit)**
Consent	x		
Demographics	x		
Medical History	x	x	x
Medication history	x	x	x
Monitor signs and symptoms spinal cord compression	x	x	x
Monitor for adverse events	x	x	x
Physical Exam	x	x	x
Height	x		x
Weight	x	x	x
Specific Disease Related Evaluations	Refer to section 7.3		

7.3 Specific Disease Related Evaluations

R = Research

Evaluation Performed / **Month on Study**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**
1. Metabolic and Biomarker Testing									
• Full metabolic panel	X		X		X		X		X
• Total and non-HDL cholesterol; Troponin, BNP	X				X				X
• Pregnancy testing for post-menarche females	X				X				X
• Urine and plasma GAG quantitative	R		R		R		R		R
• Quantitative urine GAG 3 times prior to initial infusion, and then daily for the first 30 days after infusion[1]	X								
• Urine GAG every 3 months[1]		X	X	X	X	X	X	X	X
2. Endocrine Assessment									
• IGF-1, IGF-BP3, TSH, free T4	X				X				X
• LH-ICMA, FSH, ultrasensitive estradiol or total testosterone for girls ≥ 8 yrs and boys ≥ 9 yrs	X				X				X
• 25-OH Vitamin D	X				X				X
3. Inflammatory/immunology[2]									
• Anti-Naglazyme antibody	R		R		R		R		R
• Anti-Naglazyme inhibiting antibody	R		R		R		R		R

Evaluation Performed / Month on Study	0	3	6	9	12	15	18	21	24
4. Transplant testing									
• Engraftment[3](perform more frequently if clinically indicated)	X	X	X		X		X		X
• Mutation analysis	X								
5. Ophthalmologic evaluation									
• Consultation	X				X				X
6. Audiology testing	X				X				X
7. Cardiology									
• Consultation	X		R		X		R		X
• EKG	X		R		X		R		X
• ECHO	X		R		X		R		X
8. Pulmonary testing									
• Pulmonary function testing	X		R		X		R		X
9. Neurologic testing									
• Neuropsychology evaluation	X		R[4]		X		R[4]		X
• Pain assessment	R		R		R		R		R
• QOL SF36 (>18) or CHQ (<18 years of age) , HAQ	R		R		R		R		R
• MRI of brain and C-spine with read (CMRR site)	R				R				R
10. Orthopedic Assessment									
• Peripheral Quantitative CT (pQCT) done at DCRU/CTSI	R				R				R
• Scoliosis series with read	X								X
• X-ray for genu valgum, hip dysplasia with read	X								X
• Bone Age – L hand and wrist (< 21 years only)	X								
• Gait assessment (including goniometry, ROM measurements on lower limbs)	R				R				R
• Formation testing (bone specific alkaline phosphatase, osteocalcin)	R				R				R
• Resorption testing (C-telopeptide, deoxypyridoline)	R				R				R
11. Ortho Functional Assessments									
• 6-minute walk test, Sitting/standing height, Arm span (PT)	R		R		R		R		R
• Upper extremity muscle strength (hand dynamometer) and ROM	R		R		R		R		R
• Lower extremity muscle strength (Biodex)	R		R		R		R		R
• Upper extremity dexterity testing (PT)	R		R		R		R		R

1. For visits performed at a local medical facility, each subject will store daily urine specimens in a small freezer, purchased by the study with funds budgeted by BioMarin, and will ship specimens with pre-paid shipping label to the University of Minnesota Send-out Lab. U of MN staff will ship to Mayo for testing.
2. Performed by BioMarin

3. Applies only to patients transplanted at UMN; for non-UMN transplants - results will be requested from the transplant center (done as part of SOC follow-up). In these cases, time points in the protocol cannot be adhered to and will not constitute a deviation.
4. Abbreviated evaluation to include attention and adaptive skills

7.4 Treatment at Local Medical Facility and Collection of Urine GAG

A Study Start-Up packet will be provided at the time a local medical facility is identified.

For treatments that occur at the patient's local medical facility, arrangements will be made with the study coordinator to communicate all pertinent assessments and treatment information.

For days 1 to 30 for the first month and at months 3, 9, 15 and 21 all patient specimens will be sent by overnight service to the University of Minnesota using the provided FedEx shipping/billing label. No protocol required laboratory tests will be run at the local facility.

Daily morning urine GAG will be collected by the subject and stored in a small freezer (provided by the study). Urine specimens will be couriered weekly on dry ice by scheduled pick-up to the University of Minnesota using the provided pre-paid shipping/billing label. The specimens will be inspected, repackaged and sent to Mayo Laboratories for measurement of quantitative urinary GAG.

7.5 Description of Study Assessments

Anthropometry

Standard anthropometric measurements will be taken: standing and sitting height, weight, arm span, lower segment length. Height will be measured standing without shoes and sitting on a stool and the average of three measurements by the same observer using identical technique with a wall mounted stadiometer. Each subject will be repositioned between each measurement. Height SDS will be calculated based on the National Center for Health Statistics 2000 data as provided by the Center for Disease Control. Weight to be measured once with subject in light clothing or dressing gown with shoes removed. Arm span is measured between the ends of each middle finger. Lower segment is measured from the pubic symphysis to the floor.

Physical examination and vitals

Pubertal staging will be determined by physical examination of breast or testicular volume (by orchiometer) and pubic hair as described by Tanner.

Medical history

A general medical history will be obtained including concurrent illnesses and medications. Ongoing evaluations will be performed by Pharmacology (Jeanine

Utz, PharmD) to determine potential drug interactions and to educate the subjects and their families about the delivery of the enzyme as well as the importance of the collection of the initial daily urinary GAG.

Laboratory evaluations

Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) are both produced in the liver in response to GH and thus reflect the level of GH secretion.

Thyroid stimulating hormone (TSH) is the pituitary hormone which stimulates the thyroid gland to produce thyroid hormones, including thyroxine (T4). Low free T4 and elevated TSH indicates primary hypothyroidism, low free T4 and low TSH is secondary (central) hypothyroidism, and normal free T4 with an elevated TSH is subclinical hypothyroidism.

Pubertal stage is assessed by physical examination. Evaluation of the pituitary-gonadal axis is done through laboratory testing of luteinizing hormone (LH) and follicle stimulating hormone (FSH) which are produced in the pituitary and stimulate the gonads to produce testosterone or estradiol.

All endocrinology lab tests will be done by the Fairview University Laboratory, Minneapolis, MN, except for LH-ICMA which will be sent to Esoterix and markers of bone turnover which will be performed by the University of Minnesota Cytokine Laboratory.

Pulmonary function tests

Routine pulmonary function testing will include spirometry, and pulse oximetry. It is recognized that some very young children (younger than 5 or 6 years) may not be able to complete all of the testing requirements. In these situations, documentation should be placed in the medical record and it will not be considered a protocol deviation.

Peripheral quantitative computed tomography (pQCT)

Detailed measures of bone mass and strength will be assessed using pQCT (XCT-3000, Orthometrix Inc., White Plains, NY). PQCT is a non-invasive technique that allows for 3-dimensional assessment of bone volumetric density, bone geometry and estimates of bone strength. Images will be taken at the 34, 38, and 66% sites of the left tibia and the 34 and 38% sites of the non-dominant radius measured from the proximal end of the distal growth plate. Standardized procedures for participant positioning and data analysis will be used for all scans. Image processing and calculation of bone parameters will be completed using the manufacturer's software (version 5.5) and thresholds established in the literature and in our previous work.

Bone outcomes will include measurements of the mass and tissue density (BMC, mg and vBMD, mg/cm^3) for both cortical and trabecular bone compartments. Total bone cross sectional area (CSA, mm^2) and cortical thickness (mm) provide meaningful measures of bone geometry at cortical sites, and structural estimates of bone bending strength will be calculated using the cross-sectional moment of inertia (CSMI, mm^4) and section modulus (Z, mm^3) as outcomes.

Bone age

Plain radiographs of the left hand and wrist for individuals <21 years of age will be taken for bone age evaluation and interpreted by a University of Minnesota Pediatric Radiologist.

Markers of bone turnover/biomarkers

Blood samples will be obtained for serum osteocalcin (OC), bone-specific alkaline phosphatase (BSAP), carboxyterminal telopeptide α1 chain of type I collagen (CTX)], and urine for deoxypyridinoline and pyridinoline and compared to normative data from healthy children obtained for a separate study. The University of Minnesota Cytokine Research Laboratory will be performing the bone marker assays. Samples will be analyzed at the end of the study to eliminate inter-assay variability.

Radiographs

Data from radiographs of the spine and lower extremities will be collected and, to ensure patient safety, will undergo a formal read by radiology at the University of Minnesota. These will include a scoliosis series and xrays for genu valgum and hip dysplasia.

Brain and cervical spine MRI

Cervical cord compression is a common, potentially lethal, abnormality in individuals with MPS VI. Increased mobility, as has been found with the administration of ERT, has increased the risk of symptomatic cord compression in individuals with MPS VI (Horovitz, 2011; Jurecka, 2012) and has been prominently displayed in the package insert. Subjects will undergo cervical spine MRI with read prior to initiation of ERT and annually thereafter. Similarly, as hydrocephalus is a known finding in MPS VI, subjects will undergo brain MRI with read prior to initiation of ERT and annually thereafter. Real-time interpretation of both cervical and brain MRI are required for patient safety. In addition, as developed by the University of Minnesota group, volumetric assessment of brain (quantifying white matter, gray matter, ventricle, hippocampus, corpus callosum volumes) and diffusion tensor imaging, (quantifying connectivity in the brain using the corpus callosum as the region of interest) may be performed.

Cardiac Echo

Mitral and aortic valve regurgitation and stenosis as well as ventricular hypertrophy are common findings in MPS VI (Braunlin, 2013). Case reports after HCT suggest that valve findings are not improved despite engraftment (Table 1). Definition of the cardiac valve findings in any of the MPS syndromes requires careful and reproducible evaluation. Sonographers at the University of Minnesota have extensive experience producing reliable and useful imaging of the cardiac findings in the MPS syndromes. Subjects will undergo cardiac ultrasound at the University prior to initiation of ERT and annually thereafter.

Table 4. Echo parameters to be obtained in MPS VI subjects undergoing Naglazyme infusion after HCT.

Echo Imaging Parameter	M-mode	2-dimension	Doppler
LV chamber dimension	X	X	
LV wall thicknesses	X	X	
Aortic root diameter	X	X	
LV function	X	X	
RV pressure			X
Aortic stenosis/regurgitation			X
Mitral stenosis/regurgitation			X
Pulmonary stenosis/regurgitation			X
Tricuspid stenosis/regurgitation			X
Other abnormalities	X	X	X

Neuropsychological testing

Subjects will undergo full neuropsychological testing annually and abbreviated testing for attention and adaptive skills at the six-month interval visits (Section 7.3). Subjects will complete a Medical Outcomes Questionnaire annually. This questionnaire is designed to provide an overall assessment of clinical health and allows comparison of scores between treatment groups (Ahmed, 2013).

Table 5. Neuropsychological tests to be performed on MPS VI subjects receiving weekly Naglazyme infusions after HCT

TEST ADMINISTERED (total testing time 2-3 hours)
INTELLIGENCE
Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II)
ATTENTION/EXECUTIVE FUNCTION
Test of Variables of Attention (TOVA)
LEARNING & MEMORY
California Verbal Learning Test, Children's Version (CVLT-C) ≤16yrs
California Verbal Learning Test, Second Edition (CVLT-II) >17yrs
Behavior Rating Inventory of Executive Function, Adult form (BRIEF)
Quality of Life and Social-Emotional: SF-36
Vineland Adaptive Behavior Scales-II (Parent/Caregiver Rating Form)
Brief Symptom Inventory (BSI) >13yrs

Motor function, endurance and dexterity measurements

Impaired joint mobility and upper extremity dexterity remain significant co-morbidities despite successful HCT in MPS VI (see Table 1). In this respect, the outcome of HCT is comparable to that found in MPS I HCT recipients. A recent systematic literature survey of orthopedic issues affecting MPS I HCT recipients found that motor functioning was hampered by reduced joint mobility, decreased hand dexterity, delayed motor development and longitudinal growth (van der Linder, 2011). In MPS I HCT recipients' development of independent walking was often delayed due to hospitalization for HCT and due to orthopedic issues. Once developed, the quality of gait was abnormal – reduced walking speed, shortened step length and increased energy expenditure early in life – but this normalized by 4 years of age. Importantly, 25% of HCT recipients lost independent unaided gait at an average of 6 years after HCT due to orthopedic issues of hip dislocation and genu valgum. While many fewer individuals with MPS VI have undergone HCT, dysostosis multiplex, impaired joint mobility and the need for hip surgery have all been reported as long-term findings after successful HCT (Table 1). The 6 minute walk has served as the standard measure of mobility and overall cardiopulmonary fitness in all clinical trials of ERT in MPS VI (Harmatz, 2008) and will be employed annually in the MPS VI HCT recipients. This measure is well validated for adults and children (Reuben, 2013) and is routinely performed by respiratory therapists by standardized protocols in our institution. Marked improvement in one MPS VI post-HCT subject has been reported by Sohn (2012).

Manual dexterity is a critical component necessary for independence in the activities of daily living: the ability to dress one's self, perform daily rituals of washing and toileting, eat with standard utensils, open and close doors, turn

pages of a book, type on a keyboard – all require a measurement of manual dexterity. Dexterity will be tested by timed completion of the Roylan 9-hole pegboard test (Reuben, 2013). This validated test is being used in ongoing clinical trials with MPS IV (Morquio) subjects (A. Jester, unpublished communication, 2013).

Hand grip strength will be measured in both hands with a mechanical hand held dynamometer with the subject in a seated position. The shoulder will be in a neutral position, the elbow flexed to 90 degrees midway between pronation and supination and the forearm supported on the arm of the chair. The grip size of the dynamometer will be adjusted for the comfort of the participant 91. Each participant will squeeze the hand held dynamometer three times with each hand. All three values will be recorded. Dominant hand will be noted.

8 Adverse Event Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE). A copy of the CTCAE can be downloaded from the CTEP home page http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

8.1 Definitions

BioMarin Standard Language for Adverse Event Reporting: IST Program, Naglazyme

Adverse Events

According to the ICH definition, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational product.

This definition includes intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions. Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

Adverse event information will be collected in an ongoing fashion through patient reporting AEs to their physician or health care provider. Seriousness and relatedness will be assessed by the treating physician, with appropriate reporting.

A designated primary contact person based at the treatment center will be responsible for the collection and reporting of AEs for patients participating in the program.

Serious Adverse Events

A serious adverse event (SAE) is defined as any AE that:

- Results in death
- Is life threatening, that is, places the subject at immediate risk of death from the event as it occurred. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death
- Requires in-patient hospitalization or prolongation of an existing in-patient hospitalization. Admission of a subject to the hospital as an in-patient as a result of an AE, even if the subject is released on the same day, qualifies as hospitalization
- Results in persistent or significant disability or incapacity. An event qualifies as resulting in a persistent or significant disability or incapacity if it involves a substantial disruption of the subject's ability to carry out usual life functions. This definition is not intended to include experiences of relatively minor or temporary medical significance.
- Is a congenital anomaly or birth defect, that is, an AE that occurs in the child or fetus of a subject exposed to Naglazyme prior to conception or during pregnancy
- Is an important medical event that does not meet any of the above criteria, but may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed above.

More than one of the above criteria may apply to any specific event.

8.2 Adverse Event Documentation

For the purposes of this study, targeted adverse events and unexpected events will be collected by the local health care provider completing the targeted toxicity form at baseline just prior to each Naglazyme infusion and again 1 hour after the infusion end (+/- 15 minutes) as part of the drug log. Refer to the form for specific details.

8.3 Required Expedited Reporting: Local Medical Facilities to MCC Study Coordinator

Expedited reporting by the local treating medical facility/staff within 1 working day of knowledge to the MCC Study Coordinator is required for the following situations:

Event	Form to Use
Any event that meets the definition of serious (defined in section 8.1) regardless of relationship	MCC SAE reporting form
Any grade 3 or 4 infusion related reaction (per section 10.4)	Stopping Rule Event Form (in addition to SAE form if it meets the definition of serious)
Pregnancy	MCC SAE reporting form

All toxicity assessments are based on the Common Terminology Criteria for Adverse Events (CTCAE) available as a pdf download at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf or as a smart phone app from the app store. The grading is also reflected in the targeted toxicity forms.

Local medical staff should not wait to collect additional information that fully documents the event before notifying the MCC Study Coordinator. Additional information may be submitted as it becomes available as follow-up reports. In the event of pregnancy, every effort should be made to follow the patient through resolution of the pregnancy (termination or delivery) and report the resolution to the MCC Study Coordinator.

The MCC research staff will be responsible for forwarding all events meeting the definition for expedited reporting in section 8.4 to BioMarin and the University of Minnesota Institutional Review Board.

Local medical facilities are responsible for adhering to all local reporting requirements (if applicable).

8.4 Required Reporting: MCC to U of MN IRB, BioMarin, and MCC SAE Coordinator

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/fax numbers	Copy AE to:
U of MN IRB	Events requiring prompt reporting including, but not limited to unanticipated death of a locally enrolled subject(s); new or increased risk; any adverse event that require a change to the protocol or consent form or any protocol deviation that resulting in harm refer to http://www.research.umn.edu/irb/guidance/ae.html#.VC7xraI0-sh	Within 5 business days of event discovery	Report Form	irb@umn.edu	SAE Coordinator mcc-saes@umn.edu
Bio Marin (refer to sections 8.4.1 and 8.4.2)	Any event that is serious regardless of relationship Any infusion related reaction regardless of seriousness Pregnancy	Upon knowledge with an annual summary of all SAE's	MCC SAE or FDA 3500A	BioMarin Pharmaceutical Inc 105 digital Drive Novato, CA 94949 Phone: 415-506-6179 Fax: 415-532-3144 Email: drugsafety@bmrn.com	
MCC SAE Coordinator	Any stopping rule event	upon reporting	stopping rule form	SAE Coordinator mcc-saes@umn.edu	Not applicable

8.4.1 Pregnancy

Pregnancy in a subject being treated with the product should be reported immediately (within 24 hours of becoming aware of the pregnancy) to BioMarin Pharmacovigilance by using the MCC SAE form or FDA 3500A (MedWatch Form). Every effort should be made to follow the patient through resolution of the pregnancy (termination or delivery) and report the resolution of the MCC SAE form or FDA 3500A (MedWatch Form) to BioMarin Pharmacovigilance.

8.4.2 SAE and Pregnancy Reporting – IND exempt studies

All serious, adverse events (SAEs) and pregnancy reports whether or not considered drug-related should be reported to BioMarin Pharmacovigilance (contact information below) within 24 hours of receipt by investigator/sponsor by using the MCC SAE form or FDA 3500A (MedWatch From).

Clinicians should not wait to collect additional information that fully documents the event before notifying BioMarin's Drug Safety Department of an SAE or pregnancy. BioMarin may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that clinicians submit additional information requested by BioMarin as soon as it becomes available.

Reporting of SAEs to the IRB will be done in compliance with the standard operating procedures and policies of the IRB and with applicable regulatory requirements.

Contact information for BioMarin's Drug Safety Department is as follows:
BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949
Phone: (415) 506-6179
Fax: (415) 532-3144
Email: drugsafety@bmrn.com

The SAE Coordinator will provide the Masonic Cancer Center's Data and Safety Monitoring Council (DSMC) with the SAE in an appropriate format depending on the individual SAE (as reported or in a summary format).

9 Study Data Collection and Monitoring

9.1 Data Management

This study will report clinical data using The Online Enterprise Research Management Environment (OnCore™), a web based Oracle® database utilizing study specific electronic case report forms. Key study personnel at the University of Minnesota are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore.

9.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRF) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and one of the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRF based on the patient specific calendar, and updating the patient record until the end of study participation. Source data will be sent to the University Of Minnesota Study Coordinator from local medical facilities for entry into OnCore.

9.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at: http://www.cancer.umn.edu/prod/groups/ahc/@pub/@ahc/@mcc/documents/content/ahc_content_487799.pdf

For the purposes of data and safety monitoring, this study is classified as high risk (local investigator initiated study). Therefore the following requirements will be fulfilled:

- The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the study's progress at least quarterly.
- The PI will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in section 8.4 to the Masonic Cancer Center's SAE Coordinator and the University of Minnesota IRB.

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

9.4 Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the sponsor-investigator and/or sponsor/investigator designee, IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

Local medical facilities will not be subject to study related monitoring but will be required to provide relevant infusion related clinical notes and targeted toxicity forms to serve as source documentation.

9.5 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at 6 years after the study file is closed with the IRB.

In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the CTO before destroying any study related records.

10 Statistical Considerations

This is a study with a known small number of available subjects designed for the purpose evaluating safety and efficacy of administration of Naglazyme after hematopoietic cell transplantation (HCT).

10.1 Statistical Endpoints

The primary endpoints listed below will be monitored as used to decide whether Naglazyme can be recommended after successful HCT.

- Change in urinary GAG excretion
- Change in distance traveled in 6 minute walk and standard tests of range of motion and mobility
- Change in neurocognitive ability

The secondary endpoints will be the development of antibodies including neutralizing antibodies with weekly Naglazyme therapy and the impact of these antibodies on cardiorespiratory and skeletal parameters as measured by the 6-minute walk test and standard tests of range of motion and mobility, and the change in neurocognitive ability

10.2 Statistical Analysis

Simple descriptive statistics such as proportions, means, standard deviations, medians and ranges will be used to estimate the various parameters in this study. The estimate with 95% confidence interval will be calculated for the primary endpoints.

10.3 Sample Size Justification

Since the number of known MPS VI subjects who have received HCT is known to be 45 worldwide, a sample size of ten patients will be employed to estimate the study parameters.

10.4 Monitoring Guidelines: Stopping Rules

Early stopping rule will be used to monitor the excess toxicity. Stopping rules were developed using Pocock stopping boundaries (Ivanova 2005).

Grade III-IV infusion related reaction will be monitored so that the study will stop and the protocol will be re-evaluated if the toxicity rate exceeds the boundary. Given a hypothesized toxicity rate of 10%, a maximum tolerated rate of 20% and

a sample size of 10 patients, the upper stopping boundary for toxicity is 2 out of 2, 3 out of 4, 4 out 8 and 5 at any time. If the true toxicity rate is as high as 50% then the chance of early stopping is 72% and the expected sample size is 6.4.

11 Ethical Considerations

11.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study treatment/procedures. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

11.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

11.3 Institutional Board Review (IRB)

Before the initiation of this study, this protocol will have been reviewed and approved by the Human Subjects Committees at the University of Minnesota, as defined by FDA regulations (21 CFR Part 56).

IRB approval of any future modifications of the protocol or consent form for this study will be given in writing. Unanticipated adverse effects must be reported to the IRB. The IRB will receive notification of the completion of the study. The investigators will maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

11.4 Informed Consent

The principles of informed consent described in FDA Regulations (21 CFR Part 50) will be followed to comply with Food and Drug Administration regulations. A patient will give written consent prior to study participation which must be signed and dated before the conduct of any study related procedures. The original consent will be retained by the investigator as part of the study records. A copy of the consent form will be given to the patient.

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Appendix I – Eligibility Checklist

Study of Administration of Intravenous Naglazyme® Following Allogeneic Transplantation for Maroteaux-Lamy Syndrome (MT2014-08R)

Eligibility Checklist – page 1 of 1

Patient initials ☐☐☐☐ Patient ID☐☐☐☐

1st 2 initials of first name + 1st 2 initials of last name Seq # (i.e. 01, 02, 03, etc.)

INCLUSION CRITERIA

A "NO" response to any of the following disqualifies the patient from study entry.

		Yes	No
1.	Mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome) treated with an allogeneic transplant more than 2 years prior to enrollment – patients need not have been transplanted at the University of Minnesota	☐	☐
2.	Persons who have received or are currently receiving Naglazyme may be considered for enrollment	☐	☐
3.	>10% engraftment based on most recent testing (within previous year) – confirmed during pre-screening	☐	☐
4.	If female of child-bearing age, willing to defer pregnancy for the duration of the trial	☐	☐
5.	Willing to commit to traveling to the University of Minnesota every 6 months for the duration of the trial (2 years)	☐	☐
6.	Written informed consent prior to the performance of any study related procedures with parent/guardian consent for children < 18 years of age or persons unable to consent with minor assent if appropriate	☐	☐

EXCLUSION CRITERIA

A "YES" response to any of the following disqualifies the patient from study entry.

		Yes	No
7.	Is pregnant or breastfeeding at screening or baseline, or planning to become pregnant (self or partner) at any time during the study.	☐	☐
8.	Any condition that, in the view of the investigator, places the patient at high risk of poor treatment compliance or of not completing the study	☐	☐

Date consent form signed: _____

Having obtained consent and reviewed each of the inclusion/exclusion criteria, I verify that this patient is:

☐ Eligible ☐ Ineligible Date registered _____

_____ _____

Signature of person verifying eligibility Date