Protocol Title: An extension study of intrathecal enzyme replacement for cognitive decline in mucopolysaccharidosis I

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Protocol Title

Study Number MIRC-002 (100)

An extension study of intrathecal enzyme replacement for cognitive decline in mucopolysaccharidosis I

RDCRN Protocol #6728

HSC Review History

Version 2.6

Principal Investigator

Agnes Chen, MD

1. Objectives

Safety

To evaluate the long-term safety of intrathecal recombinant human α-L-iduronidase (rhIDU), approved as Aldurazyme® [laronidase] for the treatment of cognitive impairment in patients with mucopolysaccharidosis I (MPS I).

- Evaluate the long-term safety of administering rhIDU intrathecally in MPS I subjects
- Evaluate the presence and effect of an immune response to the administered rhIDU
- Determine whether there are any other unexpected effects of rhIDU on the safety of MPS I subjects

Outcome

To evaluate the long-term effects of a limited number of intrathecal injections of rhIDU to stabilize or reverse neuropsychological deficits in non-transplanted MPS I patients.

- Neuropsychological: through an established battery of outcome measures
- Clinical: including subject reported changes, neurologic examination and walk testing ability
- Radiologic: including 3 Tesla brain MRI and diffusion tensor imaging to look at volumes, morphology, diffusion abnormalities and white matter fiber tracking.
- Biochemical: measures of GAG storage within the CSF

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The primary outcome measure will be the mean intra-subject change in memory score on the Hopkins Verbal Learning Test between baseline/screening for MIRC-002 and the subject's final visit of the extension study.

2. Background

Mucopolysaccharidosis I (MPS I) is an inherited lysosomal storage disease due to deficiency of α-L-iduronidase. Deficiency or absence of α-L-iduronidase causes accumulation of glycosaminoglycans (GAG) throughout the body. Excess GAG storage causes joint pain and stiffness, difficulty breathing, valvular heart disease, and other problems leading to progressive disability and often death.

MPS I is a heterogeneous disease with several clinical phenotypes ranging from the most severe, Hurler syndrome, to the attenuated forms, Hurler-Scheie and Scheie. Patients with all forms of MPS I suffer from central nervous system disease, including cognitive decline, hydrocephalus, spinal cord compression, hearing loss, and vision difficulties. Patients with the most severe form of MPS I develop slowing in cognitive development that usually appears after age one and thereafter accelerates. By age 3 years, most of these children fall into the range of mental retardation as defined by standard intelligence tests (Shapiro and Balthazar 2000).

Although patients with milder forms of MPS I may not have grossly observable problems with cognition, these patients do have learning difficulties that are apparent in school and with neuropsychological testing. In a series of 29 attenuated MPS I patients, 34% manifested problems in speech/language development by clinical report (Vijay and Wraith, 2005). In a case study of three siblings with Hurler-Scheie, decline of cognitive function was seen on neuropsychological testing, specifically with problems encoding new information and spatial ability (Fig. 1, Bjoraker et al., 2005, 2006). In a study comparing Hurler patients after hematopoietic stem cell transplantation (HSCT) and Hurler-Scheie patients on intravenous enzyme replacement therapy (ERT), Hurler-Scheie patients did comparatively worse in memory and spatial testing (Shapiro et al., 2006).

An ongoing pilot study of hematopoietic stem cell transplantation (HSCT)-treated Hurler patients and ERT-treated attenuated MPS I patients (Hurler-Scheie and Scheie) is examining brain structure and function (Shapiro et al., 2007). Along with extensive neuropsychological testing, this study is employing a 3 Tesla MRI to look at volumetrics of the hippocampus compared to other regions, as well as diffusion tensor imaging and tractography to examine white matter connectivity of afferent and efferent pathways from the hippocampus to the rest of the brain. Preliminary results on neuropsychological testing support previously described findings of decline in learning and spatial ability. In attenuated MPS I patients, IQ, recognition memory and spatial working memory (controlled for IQ) correlated

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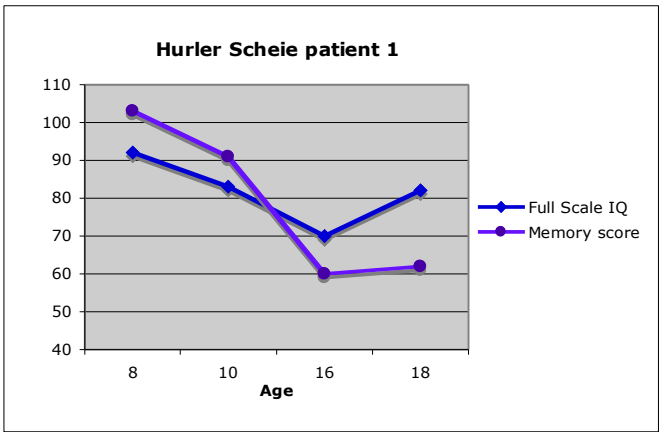
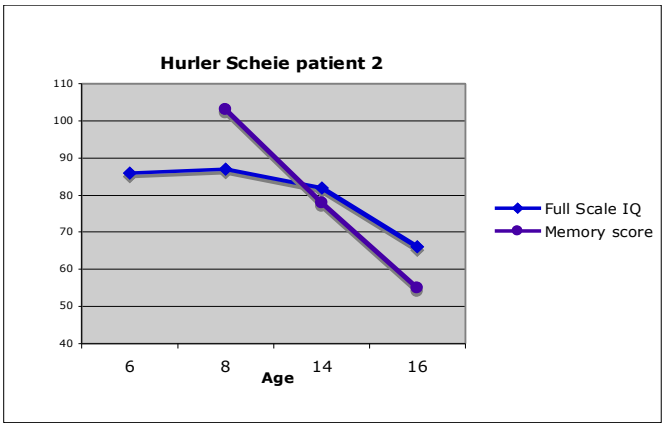
with age, with older patients being more impaired. Attenuated MPS I patients were more impaired than HSCT-treated severe MPS I patients on the California Verbal Learning Test (CVLT), a test of memory encoding and spatial working memory. In addition, preliminary MRI findings demonstrate that patients with attenuated MPS I have statistically significant smaller hippocampal volumes than patients with Hurler syndrome treated with HSCT and that these hippocampal volumes correlate with functional deficit in memory. In addition, abnormal patterns of white matter diffusion have been found in both groups, with more abnormal patterns seen in the severe than the attenuated group (Shapiro et al., 2007).





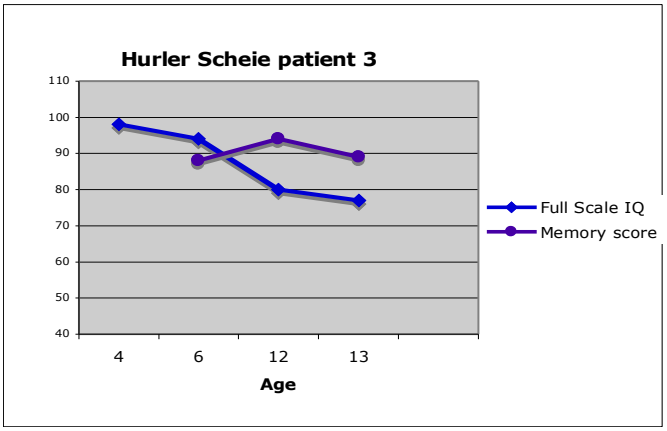


Fig. 1: Memory and intelligence quotient testing in three siblings with Hurler-Scheie form of MPS I receiving intravenous rhIDU. Average decline is 2 points per year. Courtesy of K Bjoraker and E Shapiro.

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Most patients with MPS I develop hydrocephalus, which is thought to be due to GAG storage in the arachnoid granulations affecting CSF reabsorption (Neufeld and Muenzer, 2001). Hydrocephalus can cause chronic, painful headaches, and may require a ventriculoperitoneal shunt to relieve pressure in the brain. In most cases, it is not the primary cause of the serious cognitive deterioration.

Hematopoietic stem cell transplantation is available to treat the brain and spinal cord as well as the physical aspects of the disease (Peters et al., 1998). However, HSCT has high rates of mortality and morbidity. A recent series of transplanted Hurler patients demonstrated a mortality of 14% related to initial transplant and 56% morbidity, which comprised acute and chronic graft versus host disease, veno-occlusive disease, and pulmonary complications (Boelens et al., 2007). HSCT is also not generally used for patients with the attenuated (Hurler-Scheie and Scheie) forms of MPS I, **even those with demonstrated cognitive defects, because little benefit for cognitive impairment has been shown in MPS I patients transplanted after age 2 years** (Whitley et al., 1993). Thus, alternative treatments for central nervous system (CNS) disease in MPS I are needed for patients who have no suitable donor, are unwilling to risk the transplant, do not qualify for HSCT, or are not completely disease-free following the procedure.

Enzyme replacement therapy given intrathecally has been shown to achieve high levels of iduronidase and reduce GAG storage in the brain, spinal cord and spinal meninges in the canine model (Kakkis et al., 2004; Dickson et al., 2007). In the brain, GAG storage levels became normal in all nineteen treated MPS I dogs (Fig. 2). When intrathecal enzyme replacement was stretched out to monthly and quarterly (every 3 months) dosing, there was no significant difference between iduronidase levels and quantitative reduction of GAG storage in the brain compared to weekly dosing.

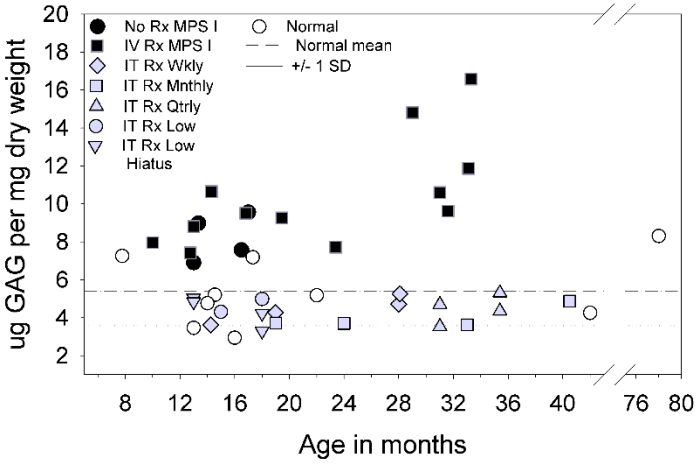

Fig. 2: Quantitative glycosaminoglycan (GAG) storage in brain of normal dogs, untreated MPS I dogs, and MPS I dogs treated with IT rhIDU. Brain GAG levels in the IT-treated dogs reached normal levels regardless of age or treatment regimen (Dickson et al., 2007).

MPS I patients have been treated with intrathecal rhIDU for spinal cord compression as part of an earlier clinical trial (MIRC-001, BB IND 12561,

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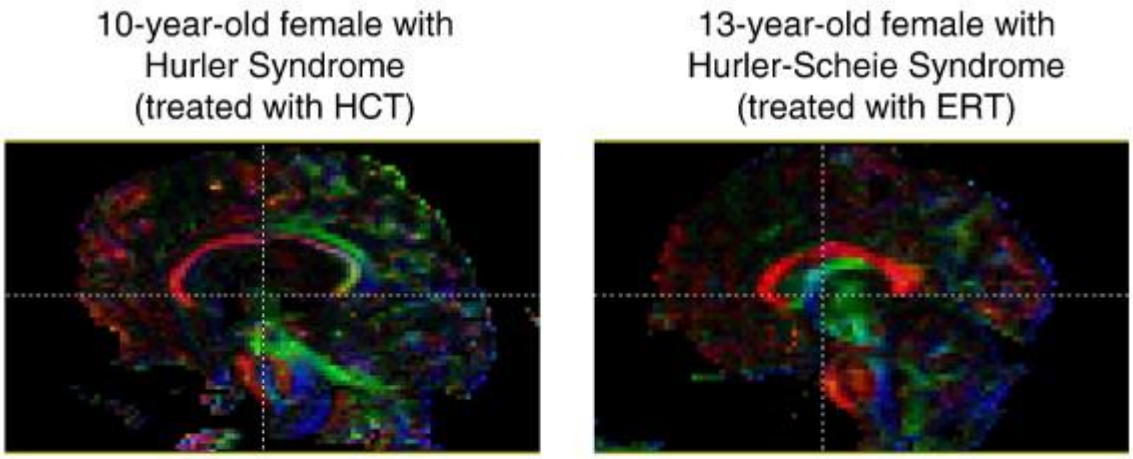
NCT00215527). Three adult subjects have completed the study. In addition, one adult and three children with MPS I have been treated worldwide with intrathecal rhIDU off-study for cord or brainstem compression. Subjective improvement was noted in all 3 of the patients for whom data are available in at least 3 major CNS symptoms. These included ability to move legs, reduced pain in the legs, back and/or neck, bladder/bowel incontinence, restless legs, numbness/tingling of the feet, fatigue, and improved hand use. Improvement in neurologic examination occurred in all three patients as measured by pain/temperature asymmetries, strength, deep tendon reflexes, and range of motion. In addition, one eight-year old, wheelchair-bound patient gained the ability to walk with support during treatment (Giugliani et al., 2007). Monthly intrathecal rhIDU injections have been well tolerated. Adverse events with >1 occurrence included headache, pain in buttocks, back pain, neck pain, pneumonia, low platelet count, anemia, and sore throat. One subject developed CSF pleocytosis which responded to a short course of oral steroids. Two subjects with hydrocephalus and implanted shunts at study entry developed apparently transient elevated CSF opening pressure. Serious adverse events have included one death, two episodes of pneumonia, one episode of hypoxia with respiratory distress following anesthesia, and one corneal transplantation. All were judged unrelated to study drug.

This study is an extension of the current ongoing clinical trial of intrathecal enzyme replacement for cognitive decline in MPS I (MIRC-002, NCT00852358). Thus far, there have been no serious adverse events related to study drug. The AEs possibly related to study drug include back, neck, buttock and groin pain, transient blurry vision and headache and mild CSF pleocytosis.

We propose an extension of our study to examine the long-term effects of intrathecal enzyme replacement on cognition. In order to document improvement with intrathecal ERT, neuropsychological testing, clinical testing, and imaging modalities will be employed. Multiple cognitive domains will be tested with an established battery of neuropsychological tests that have documented validity in patients with storage diseases (Shapiro et al., 2006). Magnetic resonance imaging of the brain will be used to document abnormalities and changes in volume and morphology. In addition, brain diffusion tensor imaging (DTI) will be employed to characterize diffusion abnormalities and perform fiber tracking. DTI and fiber tracking register diffusion patterns of water to follow axonal transport in the brain. Preliminary results in attenuated MPS I patients show DTI and fiber tracking to be abnormal in some patients (Fig. 3, Shapiro et al., 2012). DTI has been used to quantify improvement following hematopoietic stem cell transplantation in the lysosomal storage disorder, Krabbe disease (Provenzale et al., 2005).

Fig. 3: FA maps for MPS IH and MPS IA participants matched for age and gender. The figures below show the assigned colors for FA in the white matter tracts for the following directions: red = medio-lateral (left–right), green = anterior–posterior (front–back) and blue = superior–inferior (up–down). Data below the figure are from these two participants. (Shapiro et al., Mol Genet Metab 2012)



	10 year old Hurler	13 year old Hurler-Scheie
IQ (normal 100±15)	72	77
D prime (attention) (normal 100±15)	62	80
FA	0.46	0.66
MD	1.15	0.82

To summarize, many people with mild and moderate forms of MPS I suffer from cognitive decline, poor performance in school, and behavior difficulties. There is essentially no treatment for these problems. These patients are not candidates for hematopoietic stem cell transplantation, and intravenous enzyme replacement therapy does not treat these central nervous system symptoms. Data from the canine model of MPS I show that intrathecal rhIDU can penetrate the brain, spinal cord, and meninges, reducing GAG storage to normal levels. Data from human subjects have shown that intrathecal therapy is safe, and that it leads to clinical improvement in spinal cord compression symptoms and signs on neurologic examination. In this study, we plan to extend the evaluation of IT rhIDU to the stabilization or reversal of cognitive decline in MPS I patients.

3. Setting of the Human Research

The study will be conducted at the Los Angeles Biomedical Research Institute at Harbor-UCLA (LAB-HUCLA), Children's Hospital Oakland Research Institute

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(CHORI) and the University of Minnesota (UMN). Additional study sites may be added as subjects are identified. Specific details are below:

- Recruitment: Subjects will be recruited from participants in the MIRC-002 study at LAB-HUCLA and CHORI.
- Procedures: Procedures will be performed at LAB-HUCLA, CHORI, and additional study sites that are added as subjects are recruited to the study. The addition of any new study site will be contingent upon approval by their local institutional review board (IRB), and the IRB at LAB-HUCLA. Neuropsychological testing will be performed at UMN.
- Regulations: The IRBs at CHORI and UMN will oversee the research at these respective sites, with LAB-HUCLA the primary site responsible.

4. Resources Available to Conduct the Human Research

Since subjects will be recruited from among participants enrolled in the pilot (MIRC-002) study:

- All participants are accessible for recruitment
- 67% are anticipated to be enrolled in the proposed study
- Study staff have previously been involved with participants and their families through the pilot study, so are familiar with local culture and attitudes toward clinical research.

Time requirement for the Principal Investigator to conduct and complete the proposed study within the agreed trial period is projected to be 8 hours per week.

Site study staff at the LAB-HUCLA include six members: two co-Primary Investigators, two pharmacists, one Study Coordinator, and one laboratory staff. Study staff at the CHORI site include three members: one site PI, one pharmacist and one study coordinator. Study staff at the UMN include two members: one site PI and one study coordinator. All study staff have completed appropriate training regarding protection of human research subjects, Good Clinical Practices, and HIPAA, and have previously participated in other clinical research trials.

Inpatient study treatments are conducted at the hospital in an area designated for clinical research and study evaluations are completed in separate outpatient clinical research facilities. Principal Investigators have hospital privileges at their respective sites and non-study staff resources are available at each hospital should study participants require medical or psychological support as a result of an anticipated consequence of the research study.

A site initiation meeting will be scheduled to discuss the study overview and protocol with all study staff, and to review regulatory issues, study procedures including study drug preparation, administration and accountability logging, documentation and investigators' responsibilities. As all study staff participated in the pilot (MIRC-002) clinical trial, site initiation visits will not be undertaken.

5. Prior Approvals

This study will require the following approvals prior to initiation at LAB-HUCLA:

- NIH
- IRB
- UCLA CTSI

In addition, the protocol will be filed to the Investigational New Drug Application (IND) for MIRC-002 (BB IND 104,354) at least thirty days prior to the initiation of the study.

6. Study Design

6.1. Recruitment Methods

Subjects will be recruited from participants in the pilot (MIRC-002) study. Recruitment will take place after the subject has completed the end-study visit and the investigator has deemed that the subject meets criteria for screening (see Inclusion and Exclusion criteria). Therefore, no study advertisements will be utilized for recruitment.

Subjects will be informed that financial compensation is not available and that their participation in this study is entirely voluntary.

6.2. Inclusion and Exclusion Criteria

6.2.1. Inclusion criteria

1. The subject has completed the MIRC-002 study of intrathecal enzyme replacement therapy for cognitive decline in mucopolysaccharidosis I
2. Age six years or older.
3. Subject and/or guardian willing and able to provide written informed consent.
4. Negative urine pregnancy test at screening (non-sterile females of child-bearing potential only)

5. Currently using two acceptable methods of birth control as determined by the investigator and willing to continue to use acceptable birth control during their participation in the study (non-sterile females of child-bearing potential who are sexually active only)
6. Willing and able to comply with study procedures. For example, the subjects must be able to complete written and computer-based testing. The subjects must be able to lie still in the MRI scanner for at least 40 minutes without sedation.

6.1.1. Exclusion criteria

1. The subject has undergone hematopoietic stem cell transplantation
2. Recent initiation of intravenous Aldurazyme® therapy with less than 6 months of therapy. Subjects who have been receiving Aldurazyme® therapy for more than 6 months, and those who have never received Aldurazyme® therapy, will be allowed to enroll
3. Pregnant or lactating, or considering pregnancy
4. Receipt of an investigational drug or procedure other than intrathecal Aldurazyme® within 30 days of enrollment
5. A condition, medical or other, that prevents participation in the study, including severe auditory or visual impairment, significant lumbar pathology, lumbar catheter, or recent major surgery within 6 weeks that would preclude their ability to participate.
6. Infusion reactions to intravenous or intrathecal Aldurazyme® therapy that are life-threatening or require emergent intervention such as epinephrine, cardiopulmonary resuscitation, or hospitalization
7. The subject has severely impaired spinal CSF flow, demonstrated by failure of appearance of radionuclide in the basal cisterns by 4 hours after intra-lumbar administration.
8. The subject has a coagulopathy, as identified by a platelet count of less than 50,000, an INR of 1.5 or greater, or a PTT that is 1.5 times the upper limit of normal for the laboratory from which it was drawn.

6.2. Local Number of Subjects

We expect to recruit subjects who have completed the MIRC-002 study. The total number of expected subjects in MIRC-002 is 6 subjects. Up to 6 subjects will be screened and up to 6 subjects will be enrolled in the MIRC-002(100) extension study at all sites.

6.3. Study-Wide Number of Subjects

We expect to recruit subjects who have completed the MIRC-002 study. The total number of expected subjects in MIRC-002 is 6 subjects. Up to 6 subjects will be

screened and up to 6 subjects will be enrolled in the MIRC-002(100) extension study at all sites.

6.4. Study Timelines

The duration of each subject's participation in the study is expected to be five years. We anticipate enrolling these subjects over a 4-year period. The estimated date of completion of the study is 10 years following the onset of the study.

7. Procedures Involved in the Human Research

This study is a five-year open-label, prospective trial in 6 MPS I subjects age six years or greater who have completed a 24-month open label study (MIRC-002). Potentially eligible subjects who (or, if appropriate whose parents or guardians) have provided signed, written informed consent will first participate in a baseline screening phase. This will occur at least six months after subjects have completed the MIRC002 pilot study. During baseline screening, the subjects will receive the baseline evaluations outlined below, and their eligibility will be determined. Every three months, subjects will receive intrathecal recombinant human α-L-iduronidase (IT rhIDU) approved as Aldurazyme® [laronidase] for the treatment of cognitive impairment in patients with mucopolysaccharidosis I (MPS I). Neuropsychological testing and MRI will be performed at baseline and at one year intervals. Safety will be monitored continuously throughout the subject's study participation through recording all adverse events (AEs) and periodically performing clinical and laboratory evaluations.

Study subjects will receive intrathecal enzyme therapy only during the study; intrathecal enzyme therapy will not be administered at the end of the five-year period. If further intrathecal enzyme is desired, the subject may enroll in further intrathecal research if another study is available.

To assure that subjects enrolling in the trial have maximum access to alternative therapy, subjects will be asked to receive counseling regarding other available appropriate medical and surgical alternatives prior to enrollment in this trial.

7.1. Study Rationale

In MPS I, GAG storage in the brain can cause substantial neurologic morbidity. In its most severe form, Hurler syndrome, patients are mentally retarded, but evidence of progressive cognitive decline can also be seen in patients with less severe forms of MPS I, Scheie and Hurler-Scheie syndromes. GAG storage can also obstruct CSF reabsorption with resultant hydrocephalus, which can also contribute to mental decline, in addition to causing debilitating headaches. Treatment of the hydrocephalus often requires implanting a ventricular-peritoneal shunt to relieve CSF pressure. Currently there is no treatment for cognitive

decline in MPS I, except for early HSCT that is offered to young Hurler patients only. Essentially, patients with Scheie or Hurler-Scheie syndromes have no treatment available for cognitive decline. Intrathecal rhIDU may provide benefit for these patients for whom HSCT was not an option. It may also provide an alternative non-surgical treatment for the hydrocephalus that results from GAG storage at CSF reabsorption sites.

This study is limited to patients six years and older with milder forms of MPS I because the older and less severely affected subjects will be able to comply with the examinations and will therefore be more accurately assessed.

Neuropsychological evaluations in children younger than age six would require a different battery of tests, and therefore, the data would not be compatible. Younger children would also require general anesthesia for all of the procedures, increasing the risk to patients participating in the study. In addition, older subjects do not have HSCT as a therapeutic option. Finally, less affected MPS I patients make some enzyme on their own and may be less likely to have an immune reaction to rhIDU. For these reasons, we have selected a study population of mild to moderate MPS I patients, age six or above, with documented cognitive decline that is attributable to their disease.

7.2. Schedule of Study Evaluations

After obtaining informed consent, the investigator will conduct the study as outlined in the following sections. Table 1 summarizes the nature of the assessments and treatments and their timelines. Refer to Study Operations Manual for guidelines regarding test assessments and procedures for handling/shipment of all central laboratory samples.

Table 1 Schedule of study assessments and treatments

Month Number	Baseline	Visit 1/Odd Numbered Visits	Visit 2/Even Numbered Visits	End Study
Neuropsychological testing	X		yearly	
MRI of brain	X		yearly	
Clinical tests				
History and Physical examination	X	X	X	X
Neurologic examination	X	X	X	X
Photography and video (optional)	X	X	X	X
Six-minute walk test	X	X	X	X
Subjective response of clinical symptoms	X	X	X	X
FIM scoring	X	X	X	X

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Laboratory tests (CSF)				
Protein, glucose, cell count		X	X	
GAG levels		X	X	
Anti-rhIDU antibody		X	X	
CSF iduronidase assay		X	X	
Laboratory tests (blood)				
Anti-rhIDU antibody	X	X	X	X
CBC, Chem panel 20, Coagulation studies	X	X	X	X
Neurophysiologic test				
CSF flow study	X			
Investigator Global Assessment	X	X	X	X
Treatments Intrathecal rhIDU		X	X	

Visits occur at three-month intervals starting from Visit One. There may be a variable period between Baseline/Screening and Visit One from five days to three months. If the period between Baseline/Screening and Visit One is less than one week, then all of the other assessments do not need to be repeated for Visit One.

7.3. Screening and qualification

A variable length screening phase will begin with a history and physical and neuropsychological evaluation to assess the patient for entry criteria. Patients meeting enrollment criteria will enter the study; patients not meeting enrollment criteria will not be enrolled.

7.4. Pregnancy testing

Female subjects of child-bearing potential will be required to submit a urine pregnancy test (urine beta-hCG) at baseline and at each study visit. Subjects testing positive will be withdrawn from the study. Sexually-active subjects of child-bearing potential will be required to use two acceptable methods of birth control (as determined by the investigator) during the study period.

7.5. Dose Selection

Based on the canine studies, 1 mg of rhIDU in a 20 kg dog with about 20cc of CSF (approximately 1 cc of CSF per kg body weight) resulted in 300 fold normal levels of enzyme in the meninges (the target tissue of this study), which are far above the levels necessary for effectively treatment. This dose is 0.05 mg/kg body weight, and 0.05 mg/cc CSF. Meningeal GAG reduction ranged from 57-70%, and pathologic studies showed that the majority of storage in cells is reduced or eliminated. This dose appears to be sufficient to achieve substantial reduction. At the lower 0.3 mg dose (0.015 mg/kg body weight or 0.015 mg/cc

CSF), substantial levels were also observed in the normal dogs in the brain suggesting that even at this dose meningeal levels would be far above required levels for treatment.

For an MPS I patient of 60 kg, there is about 120 cc of CSF. To obtain the same concentration as the 1 mg dose in dogs requires 6 mg of enzyme. Given the large fold excess (300 fold normal) achieved in the meninges at this dose, and since this is the first treatment in humans, a lower 1.74 mg dose (volume 3 cc) approximates the human dose comparable to the lower 0.3 mg dose studied in the dogs (0.029 mg/kg body weight, or 0.0145 mg/cc CSF) Higher doses could be considered in the future, if the data from this study suggest that higher doses are needed and safety is demonstrated at the lower dose.

By using 3 cc of enzyme with 6 cc of Elliotts B® solution in a 9 cc total injection volume, the enzyme is diluted 3 fold to reduce the impact of the high phosphate buffer and low pH of the drug formulation. The Elliotts B® solution is approved in the US and has been used routinely for the purpose of reducing the acidity of chemotherapy drugs during intrathecal administration.

7.6. Intrathecal enzyme replacement

The subject will be taken to a procedure room and placed on continuous pulse oximetry. Vital signs (pulse, respirations, blood pressure, pulse oximetry) will be recorded every 15 minutes. Temperature will be recorded before the procedure, then after the procedure on an every 4 hour schedule as described below. Equipment and medications necessary for resuscitation will be in the room, along with qualified personnel. A peripheral intravenous catheter will be placed in a superficial vein, usually an arm, for administration of medication. The subject will receive 5 mg of midazolam (or as determined to be patient-appropriate for conscious sedation) with a normal saline flush. Depending on the hospital situation and local practice, general anesthesia may be preferred and is up to the discretion of the investigator with the consent of the subject, and approval of the local IRB or ethics committee.

A local anesthetic (lidocaine dose as appropriate) will be administered in the skin and underlying tissue above the chosen interspace. A small spinal needle will be inserted under sterile conditions into the lumbar spinal sac. A small amount of CSF (roughly 6-10 mL) will be collected for laboratory evaluations (refer to Section 7.7.4.1 below).

A dose of 3 ml of Aldurazyme (0.58mg/ml) or about 1.74 mg of recombinant α-L-iduronidase will be combined slowly and gently in a syringe with 6 cc Elliotts B® (or other equivalent solution as described below in Section 22.1) for a total volume of 9 mL. The syringe should be slowly inverted to mix, taking care to avoid creating small bubbles, shaking or shear in the solution. Dilution of the enzyme in Elliotts B® should be mixed immediately prior to injection. The Elliotts

B®-Aldurazyme® mixture should be administered as soon as possible and not later than 2 hours following mixing.

The diluted enzyme will be administered via lumbar puncture and given slowly over 2-3 minutes. The subject will be watched closely during enzyme administration for any adverse clinical reactions. After enzyme administration, the subject will lie supine in Trendelenberg (head below the level of the legs) for a period of one hour with monitoring continued. If the subject is unable to tolerate the Trendelenberg position, he or she may lie down in a position of comfort. The subject should be observed for another 3 hours supine or lying down in an alternative position of comfort. Subjects will remain hospitalized for a minimum of 24 hours from the time of the intrathecal injection. During hospitalization, vital signs, including pulse, respiration, blood pressure, pulse oximetry, and temperature will be checked every 4 hours. Neuro checks, including assessment of level of consciousness, sensation and movement, will be done q15 minutes during the first hour post-procedure, then hourly for the next 3 hours, and q4 hours thereafter during the 24 hour inpatient monitoring period. Discharge may not occur if any headache or pain greater than baseline for the subject are present. New narcotic analgesics may not be administered on an outpatient basis to study subjects. Family members will be provided clear instructions regarding the post discharge monitoring of the subject for anticipated adverse events. The day following discharge from the inpatient unit, the subject will return for an outpatient visit. A physical and neurologic examination and interim history will be performed. Re-hospitalization will occur if new neurologic symptoms, signs, or pain (greater than the subject's baseline) are present at this follow up visit. The above procedure will be followed for all subjects for all treatment visits.

Radiologically-guided lumbar puncture may be required in certain individuals due to body habitus or other factors. This will be performed under fluoroscopy or ultrasound guidance at the discretion of the investigator.

7.7. Other Study Procedures

7.7.1. Cognition

Neuropsychological testing will be performed at baseline and yearly using the following tests:

- CANTAB - the Cambridge Neuropsychological Test Assessment Battery (a sensitive and precise computerized non-language assessment battery that captures changes in cognitive performance on tests sensitive to frontal and temporal lobe functions [touch sensitive hardware and software required]),
- WASI - Wechsler Abbreviated Scale of Intelligence (4 subtest form - brief IQ measure),

- Hopkins Verbal Learning Test (measure of verbal declarative memory – multiple forms available for repeat testing), this is the primary outcome variable
- Brief Visual-spatial Learning Test (measure of visual declarative memory – multiple forms available for repeat testing), and
- TOVA (Test of Variables of Attention – computerized test of attention [hardware and software are needed])

7.7.2. Magnetic resonance imaging

MRI of the brain will be performed on a 3T MR scanner at baseline and yearly. MRI will be used to document changes in the following:

- Volumes: Whole brain, white matter, gray matter, hippocampal, caudate and ventricular volumes will be calculated using specialized software. Volumetric studies will use T1-weighted high-resolution structural MRI images, converted into 176 slices with a resolution of 1 mm isotropic voxels. As efforts to obtain a precise and reliable automated program have not been successful, manual measurement is needed for hippocampal structures, using the Image J v1.38 or later software. Reliability will be ensured within and across raters.
- White matter changes and Virchow-Robin spaces: assessed using the methodology in Matheus et al. 2004. See Appendix C.
- Diffusion Tensor Imaging and Tractography to examine white matter structure and function will use 12 directional diffusion weighted imaging to calculate fractional anisotropy (FA) with the corpus callosum measure on the midsagittal section as the Region of Interest (ROI). We will also examine connectivity of the afferent and efferent pathways from the hippocampus to the rest of the brain using the fornix as the ROI if possible.

If a subject has a programmable ventriculoperitoneal shunt, it may need to be reprogrammed after the MRI. This should be supervised by a neurosurgeon or physician trained to analyze and reset the programmable shunt. The analysis and reprogramming of the shunt may require up to three plain x-rays of the shunt.

The neuropsychological tests and brain MRI may be done as part of a separate study being conducted at the University of Minnesota. If these tests have been performed within 60 days of enrollment in MIRC-002, then this data may be used as baseline data for this extension study.

7.7.3. Clinical evaluations

Clinical evaluations as described below will be completed at the study site and documented on Case Report Forms.

7.7.3.1. History and Physical Examination

A history and physical examination will be performed at each visit. A detailed and thorough medical history will be obtained at screening. Specific information relating to any prior or existing medical conditions/surgical procedures involving the following systems: Infectious Diseases, Allergy, Metabolic/Endocrine/Nutritional, Hematopoietic, Musculoskeletal, Dermatologic, HEENT (Head, Ears, Eyes, Nose, and Throat), Breasts, Respiratory (including supplemental O_2, presence/absence of tracheostomy, mechanical ventilation requirement), Cardiovascular, Gastrointestinal/Hepatic, Genitourinary/Renal, Neurologic (ambulatory status), and Psychiatric/Psychosocial. An interim history will be obtained at each subsequent visit.

Each physical examination will include the following physical observations: General Appearance, Skin, HEENT, Lymph Nodes, Heart, Chest, Abdomen (including degree of Hepatosplenomegaly), Extremities/Joints. A Snellen test will be performed at each visit by a standard, age or intellect-appropriate eye chart 20 feet from the subject in a well-lighted, indoor space, with each eye examined individually while the opposite eye is covered.

If clinically significant worsening from the baseline medical status or vital signs status is noted, the change will be documented as an AE on the appropriate data collection sheet and will be followed as an adverse event consistent with the procedure outlined in Section 11.3. Clinical significance is defined as any variation in physical findings, which has medical relevance resulting in an alteration in medical care.

7.7.3.2. Neurologic examination

A neurologic examination including mental status, cranial nerves, motor, sensory, associated motor, and reflexes will be conducted at each visit. Mental status exam will include assessment of level of consciousness and the Mini-Mental State Examination (MMSE). Although more commonly used as a screening exam in adults, the MMSE has been studied in children as young as age four, and has been shown to correlate with chronologic and mental age (Ouvrier et al.,1993). We will use the minor modifications to the MMSE as detailed in the Ouvrier paper (Appendix A).

7.7.3.3. Photography and Video

Photographs and/or video of the subjects may be taken at baseline and each visit to record the subject's appearance, posture, gait, physical and neurologic findings, and document any changes occurring in the subjects with time. Photography and video is optional at the discretion of the investigator and willing participation of the subject.

7.7.3.4. Six minute walk test

The subject will be given a six-minute walk test according to American Thoracic Society guidelines (ATS statement, 2002), except that the course distance will be 15 meters.

7.7.3.5. Subjective response of clinical symptoms

The subject will be asked at baseline to verify if they have the following symptoms: headache, memory loss, difficulty concentrating, decreased ability to function at work or school or in their daily life. Also, the subject may identify additional CNS symptoms that concern them. At each subsequent visit, the symptoms should be scored by the subject as no change (score 0), slightly better (+1), moderately better (+2), much better (+3), slightly worse (-1), moderately worse (-2) or much worse (-3).

7.7.3.6. Independence of functioning scale

A modified Functional Independence Measure (FIM) score will be determined (Maynard et al., 1997). The modified FIM will evaluate the following areas of functioning: self-care, sphincter control, mobility, and locomotion. The subject will be asked to assign a score to each item in these areas. A parent or guardian may assist the subject in completion of the FIM score. Further description of the FIM score is detailed in Appendix B.

7.7.4. Laboratory tests

The following laboratory tests will be performed as described with test reports forwarded to the designated study staff.

7.7.4.1. CSF analyses

7.7.4.1.1. CSF chemistry and cell counts

Approximately 6-10 mL of CSF, roughly equivalent to the injection volume, will be withdrawn from each subject at each lumbar puncture for all CSF evaluations. A portion of this sample (~ 1 cc) will be used for determination of glucose, protein, and cell counts. Specimens will be collected and processed at each study site in a laboratory conforming to the local standards and regulations. The subject's levels will be compared to age-matched normative controls from that laboratory.

7.7.4.1.2. CSF GAG content

A portion of the CSF (~1cc) will be frozen and shipped on dry ice to a specialty laboratory for subsequent glycosaminoglycan analysis. Sulfated glysocaminoglycans will be assayed using a modification of the dimethylene blue dye method as published (Whitley et al., 1989). The GAG quantities will be determined by comparison to standards of dermatan sulfate.

7.7.4.1.3. CSF Iduronidase Assay

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A portion of the CSF (~2-4 cc) will be frozen and, if applicable, shipped on dry ice to the Harbor-UCLA laboratory for subsequent assay of iduronidase activity by fluorometric assay. 25 µl CSF will be incubated at 37º C for 1 h with 25 µl of 6mM 4-methylumbilliferyl α-L iduronide substrate. The reaction will be stopped with 1 ml glycine carbonate buffer (400 mM, ph 10). Samples will be read by spectrofluorometer, wavelength 365 excitation/440 emission. Iduronidase activity is expressed in nmol of converted substrate per hour per ml CSF.

7.7.4.1.4. CSF ELISA for α-L-iduronidase specific antibodies

A portion of the CSF (~ 2-4 cc) collected will be frozen and shipped on dry ice to a specialty laboratory for subsequent anti-iduronidase antibody analysis. Antibodies specific for iduronidase are detected by standard ELISA protocol using anti-human IgG labeled with alkaline phosphatase as the secondary antibody.

7.7.4.1.5. Additional CSF

The remainder of the CSF collected (~ 2-6 cc) may be frozen and stored at the LAB-HUCLA for future studies.

7.7.4.2. Serum analyses

7.7.4.2.1. Serum ELISA for α-L-iduronidase specific antibodies

Blood samples are collected from each subject in a serum separator tube at baseline and at three month intervals. Approximately 2.5-5 cc of blood will be collected. These samples spun down and the serum quick frozen, then shipped on dry ice to Harbor-UCLA Medical Center (Torrance, CA) for subsequent anti-iduronidase antibody analysis. Antibodies specific for iduronidase are detected by standard ELISA protocol using anti-human IgG labeled with alkaline phosphatase as the secondary antibody.

7.7.4.2.2. Complete blood count (CBC) and serum chemistries

Standard blood specimens for CBC and comprehensive metabolic panel chemistries will be collected in the institution-specific tube and analyzed by the local laboratory. The serum chemistries will evaluate electrolytes (sodium, potassium, chloride, calcium), bicarbonate, glucose, BUN, creatinine, magnesium, phosphate, hepatic enzymes (AST and ALT), total protein, albumin, bilirubin, and alkaline phosphatase. Other chemistries may be obtained if clinically indicated in the opinion of the investigator.

7.7.4.2.3. Coagulation studies

Standard blood specimens for prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) will be collected in the institution-specific tube and analyzed by the local laboratory.

7.7.5. Neurophysiologic evaluation

7.7.5.1. CSF flow study

At baseline screening, the subject will undergo a CSF flow study. This study is performed by injecting radionuclide (e.g. ^{99m}Technetium-DTPA) into the lumbar cistern. Access to the lumbar cistern may require fluoroscopic-guided assistance due to body habitus or disease-related changes to the lumbar bony and ligamentous structures. Images will be obtained using a scintillation camera as the radionuclide flows caudally. Time to appearance of the radionuclide to specific CSF compartments will be compared to established norms (Chamberlain 1998). This study will guide our decision as to whether a lumbar approach for the intrathecal injection can be performed.

7.7.6. Investigator global assessment

At each study assessment, the Principal Investigator will use data from the clinical assessments, laboratory studies, neurophysiologic assessments, and imaging studies to assign a global assessment score to each subject. Each score will be assessed in comparison to the subject's baseline. Scoring will be done as follows:

+3 – Marked improvement

+2 – Moderate improvement

+1 – Mild improvement

0 – No change

-1 – Mild decline

-2 – Moderate decline

-3 – Marked decline

The Principal Investigator will be asked to justify the decision in a comment section on the CRF.

7.8. Safety and Outcome Endpoints

Safety will be monitored continuously throughout the subject's study participation through recording all adverse events (AEs) and periodically performing clinical and laboratory evaluations. Also refer to Section 11.6 for a description of a Data

and Safety Monitoring Board for additional evaluation of the endpoints described below.

7.8.1. Safety Endpoints

7.8.1.1. History and Physical Examination

A detailed and thorough medical history will be obtained at screening as described in the methods. Data will be qualitative.

A detailed and thorough physical examination will be performed at each visit as described in the methods. Data will be qualitative.

If clinically significant worsening from the baseline medical status or vital signs status is noted, the change will be documented as an AE on the appropriate data collection sheet and will be followed as an adverse event consistent with the procedure outlined in Section 11.3. Clinically significant worsening is defined as variation decline in physical findings that has medical relevance and results in an alteration in medical care.

7.8.1.2. Laboratory Evaluations

7.8.1.2.1. CSF chemistry and cell counts

Glucose, protein, and cell counts will be recorded in their standard units. The subject's levels will be compared to age-matched normative controls from that laboratory. Data will be kept as quantitative, continuous variables, and each subject assessed for change over the study period.

7.8.1.2.2. Complete blood count and chemistries

Blood for a complete blood count and serum chemistries (including basic chemistries, liver function tests, renal function tests) will be performed according to the schedule above. Analyses will be performed at a local clinical laboratory. Age-appropriate normal values for the laboratory will be used for comparison.

The investigator must score all abnormal laboratory values as either clinically significant (CS) or not clinically significant (NCS). Some laboratory values may be outside of the normal value range because of the underlying disease. As in routine practice the investigator should use clinical judgment when considering clinical significance. Clinical significant worsening is defined as any variation in laboratory parameters that has medical relevance and results in an alteration in medical care.

If clinically significant laboratory worsening from baseline is noted, the changes will be documented on the appropriate adverse event form and will be followed as an adverse event consistent with the procedure outlined in Sections 11.1,

11.2, and 11.3. The investigator will also assess the relationship of all clinically significant abnormal values to program drug as being none, remote, possible, probable, or definite.

7.8.2. Outcome Endpoints

7.8.2.1. Neuropsychological evaluations

Neuropsychological testing will be performed at baseline and yearly as described in Section 7.7.1. Data will be quantitative. The primary outcome variable is the score on the Hopkins Verbal Learning Test.

7.8.2.2. MRI of Brain

MRI will be performed at baseline and yearly as described in Section 7.7.2. Volumetric data and scoring for white matter changes and perivascular spaces will be quantitative. Diffusion tensor imaging and tractography data will be quantitative. Analysis of MRI results will be performed at the end of the study; however, if there are incidental findings of clinical significance found during the study, these will be reported to the PI.

7.8.2.3. Clinical Evaluations

7.8.2.3.1. History and Physical Examination

A detailed and thorough medical history will be obtained at screening as described in the methods. Data will be qualitative.

A detailed and thorough physical examination will be performed at each visit as described in the methods. Data will be qualitative.

Any clinically significant worsening from the baseline medical status and vital signs status will be documented as an AE on the appropriate data collection sheet and will be followed as an adverse event consistent with the procedure outlined in Section 11.3. Clinical significance is defined as any variation in physical findings that has medical relevance and results in an alteration in medical care.

7.8.2.3.2. Neurologic examinations

A full neurologic examination including mental status, cranial nerves, motor, sensory, associated motor, and reflexes will be conducted at each visit throughout the study period (refer to Section 7.7.3.2 for further information). Data will be qualitative.

7.8.2.3.3. Six minute walk test

The six minute walk test will be performed at each visit. Borg scale results for before and after the test will be kept as ordinal variables for each subject at each

visit. Before and after results will be compared at each visit to determine change over time.

The distance walked and laps walked will be continuous variables. Means and standard deviations for the changes made by the subjects over the study period will be calculated.

7.8.2.3.4. Subjective improvement

Subjective accounts will be recorded and kept as qualitative data.

7.8.2.3.5. Independence of functioning scale

Functional Independence Measure (FIM) score will be performed at each visit (Maynard et al., 1997). The FIM score is calculated as described in Appendix B. Change in the FIM score for each subject with time will be calculated.

7.8.2.4. Laboratory tests

CSF GAG content

At the each lumbar puncture, a portion of CSF will be quick frozen for subsequent glycosaminoglycan analysis. Sulfated glysocaminoglycans will be assayed using a modification of the Alcian Blue method of Bjornsson as published (Whitley et al., 1989). The GAG quantities will be determined by comparison to standards of dermatan sulfate.

7.8.2.4.1. CSF ELISA for α-L-iduronidase specific antibodies

CSF antibody levels will be performed according to the schedule above. Titers will be recorded as OD units/mL. An antibody titer > 20 OD units/mL is considered positive. Data will be kept as quantitative, continuous variables, and each subject assessed for change over the study period. A mean and standard deviation for the pre and post-treatment antibody levels may be calculated. Titers will be sent for analysis every six months.

7.8.2.4.2. Serum ELISA for α-L-iduronidase specific antibodies

Serum antibody levels will be performed according to the schedule above. Titers will be recorded as OD units/mL. An antibody titer > 20 OD units/mL is considered positive. Data will be kept as quantitative, continuous variables, and each subject assessed for change over the study period. A mean and standard deviation for the pre and post-treatment antibody levels may be calculated. Titers will be sent for analysis every six months.

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8. Data and Specimen Banking

CSF and serum specimens will be stored at -20 degrees C without identifiers at Los Angeles Biomedical Research Institute for at least 11 years. Specimens will be accessed for study tests by qualified laboratory personnel. Access to specimens by other investigators will be granted contingent upon IRB approval and informed consent of study participants.

The clinical information collected for this study will be stored at the Data Management and Coordinating Center at the University of South Florida in Tampa, FL and also sent to a Federal data repository. All retrospective data (from the beginning of the study) and all ongoing prospective data will be collected. The data management center uses several layers of protection for the clinical data stored there. It meets all of the local and federal security requirements for research datacenters. Information is stored only using a study ID.

While the study is active, access to the stored data and specimens will be limited to approved study staff. After the study is closed, local access will be limited to the site's Principal Investigator(s). Authorized study staff with access to stored specimens and/or data have completed training that included GCP, HIPAA, and if applicable, an overview of the study database. Access to the data by other investigators will be granted contingent upon IRB approval and informed consent of study participants

Data to be stored for each study participant include:

- Medical history and physical
- Neurologic examination including mental status, cranial nerves, motor, sensory, associated motor, and reflexes
- Standard blood CBC and comprehensive metabolic panel chemistries
- Blood serum chemistries, including electrolytes (sodium, potassium, chloride, calcium), bicarbonate, glucose, BUN, creatinine, magnesium, phosphate, hepatic enzymes (AST and ALT), total protein, albumin, bilirubin, and alkaline phosphatase. Other chemistries may be obtained if clinically indicated in the opinion of the investigator.
- Coagulation studies, including prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR)
- CSF glucose, protein, and cell counts
- CSF opening pressure
- ELISA anti-IDU antibody
- Serum glycosaminoglycans (GAG) levels

- Brain MRI data, including white matter changes and Virchow-Robin spaces, volumes, diffusion tensor imaging and tractography
- Hopkins Verbal Learning Test
- Six minute walk test with Borg scale results
- Functional Independence Measure (FIM) score
- Subjects' subjective improvement scores
- Global assessment score based on subject's clinical assessments, laboratory studies, neurophysiologic assessments, and imaging studies

9. Data Management

9.1. Overview

This study will evaluate changes in neuropsychological, radiological, clinical, biochemical measures, and safety after 5 years of intrathecal injections of rhIDU in six MPS-I subjects. The statistical goal is estimation of the magnitude of these changes and their heterogeneity and calculation of rates of adverse events.

9.2. Study Size

A study size analysis was done for the pilot study. As this study is only open to subjects that have completed the pilot study, the maximum number of subjects available for this study is six.

9.3. Data analysis methods

A descriptive summary of subject characteristics at baseline will be made with frequencies and percentages for categorical variables, and with mean and standard deviation or median and quartiles, depending on statistical distribution, and range for continuous measurements. Some analyses specified below require that continuous observed or derived measures have statistical properties such as normal distributions. If there is evidence that statistical requirements are not met, transformations to achieve those requirements will be performed. If such transformations are not possible, non-parametric analogues to the proposed parametric methods will be substituted.

9.3.1. Analysis Populations

The safety population will include all subjects enrolled in the study.

The outcome population will include all subjects in the study that received at least one dose of study medication and have at least one post-baseline measurement.

The study population will be compared to available normative data for age, as well as data from age-matched MPS I subjects not receiving IT rhIDU.

9.3.2. Study Conduct

Information about the study conduct will be summarized. Specifically details about the number of subjects completing or discontinuing the study will be summarized along with the reason for discontinuation. In addition, information about duration of enrollment and number of intrathecal doses will be summarized.

9.3.3. Safety analyses

Four categories of measurements related to safety will be examined:

9.3.3.1. Laboratory evaluations: CSF and anti-IDU antibody

Absolute, percent, and reference range change in CSF glucose, protein, and cell counts from the month 0 visit to the subsequent month visits will be calculated for each subject, and summarized over subjects with means, standard deviations, and 95% confidence intervals. Frequency and percent of subjects with values outside their reference range will be reported.

Absolute and percent change ELISA anti-IDU antibody from the month 0 visit to the subsequent month visits will be calculated for each subject, and summarized over subjects with means, standard deviations, and 95% confidence intervals. Frequency and percent of subjects with values outside their reference range for the subject's age will be calculated.

9.3.3.2. History and physical examination

At each visit, each subject will be classified as experiencing an adverse event if clinically significant worsening from baseline medical status, as described in Section 7.8.1.1, has occurred. The frequency and percent of subjects experiencing such an event will be tabulated for each visit.

9.3.3.3. Standard CBC and Chemistry Measurements

At each visit, each subject will be classified as experiencing an adverse event if there is clinically significant CBC or chemistry panel worsening from baseline, as described in Section 7.8.1.2.4. The frequency and percent of subjects experiencing such an event will be tabulated for each visit.

9.3.3.4. Other Adverse Events

Other adverse events and unexpected adverse events from the time of injection to the time of subsequent injection will be recorded for each subject. The frequency and percent of subjects experiencing any such event will be tabulated for each post-injection interval, and for the entire month 0 to end study interval.

9.3.4. Primary outcome analyses

The outcome population will be used for all outcome analyses. The primary outcome analysis will assess cumulative outcome on the Hopkins Verbal Learning Test (the primary outcome variable) after multiple injections.

Secondary outcome analyses will examine additional outcomes and time points. Five categories of measurements related to outcome will be examined:

- Neuropsychological testing
- Brain MRI results
- Clinical signs and symptoms of cognitive decline
- Biochemical results

9.3.4.1. Primary outcome variable and analysis

The mean change from baseline for the Hopkins Verbal Learning Test will be presented over time. Changes will be analyzed through the 5-year study period. Summary statistics of mean changes, standard deviations, and 95% confidence intervals will be presented.

9.3.4.2. Secondary outcome variables and analyses

9.3.4.2.1. Neuropsychological testing

Other neuropsychological measures such as IQ will be analyzed using the same method as described for the primary analysis.

9.3.4.2.2. Brain MRI

Brain MRI data will be analyzed in three data sets:

- White matter changes and Virchow-Robin spaces will be assessed using the methodology in Matheus et al. 2004, see Appendix C. Absolute and percent change from the month 0 visit to the final study visit in each of the MRI scores will be calculated for each subject. Summary statistics of means, standard deviations, and 95% confidence intervals will be presented.
- Volumes: Whole brain, white matter, gray matter, hippocampal, caudate and ventricular volumes will be calculated. Absolute and percent change from the month 0 visit to the final study visit in each of the MRI scores will be calculated for each subject. Summary statistics of means, standard deviations, and 95% confidence intervals will be presented.
- Diffusion Tensor Imaging and Tractography: Fractional anisotropy values will be used to evaluate white matter structure and function. These variables will be analyzed using the same method as the MRI volume data above.

9.3.4.2.3. Clinical signs and symptoms of cognitive decline

Absolute and percent change from the month 0 visit to final study visit in (1) the MMSE, (2) the six-minute walk test, and (3) the FIM scale will be calculated for each subject, and summarized by presenting means, standard deviations, and 95% confidence intervals.

Each subject's total subjective improvement score from the day 0 visit to the final study visit will be calculated as the mean (of up to the five clinical areas) of the sum of all the subjective scores. These changes will be summarized by presenting means, standard deviations, and 95% confidence intervals.

9.3.4.2.4. Biochemical

Absolute and percent change from the month 0 visit to the final study visit in glycosaminoglycans (GAG), will be calculated for each subject, and summarized by presenting means, standard deviations, and 95% confidence intervals.

10. Confidentiality

Local transport of the Case Report Forms, source documents and specimens will be limited to the site's authorized staff. Study participants and/or respective guardians will be informed that information that identifies them or their child will be used only for the purpose of the study; this includes information that can help study personnel locate or contact them as well as information related to their or their child's medical condition (medical records, for example).

Data and specimens will be stored locally for at least 11 years as previously described. While the study is active, access to the stored data and specimens will be limited to approved study staff. After the study is closed, local access will be limited to the site's PI(s).

11.Certificate of Confidentiality

To help protect participant privacy, a Letter of Confidentiality has been obtained from the National Institutes of Health (NIH). With this Certificate, the researchers cannot be forced to disclose information that may identify a study participant, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify a participant, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

Even with the Certificate of Confidentiality, the investigators continue to have ethical obligations to report child abuse or neglect and to prevent an individual from carrying out any threats to do serious harm to themselves or others. If keeping information private would immediately put the study participant or someone else in danger, the investigators would release information to protect the participant or another person.

Department of Health and Human Services (DHHS) personnel may request identifying information for purposes of performing audits, carrying out investigations of DHHS grant recipients, or evaluating DHHS funded research projects.

12. Provisions to Monitor the Data to Ensure the Safety of subjects

12.1. Adverse Events

Subjects in this study will be closely monitored during the enzyme administration and for one hour afterward with frequent (every 15 minutes) vital signs and continuous pulse oximetry. The subject will be able to contact the investigator or other appropriate personnel to report adverse events occurring later. These will be treated with appropriate medical care where applicable. Adverse events that are unanticipated will be reported within 10 working days to the institutional review board.

An adverse event (AE) is any undesirable physical, psychological or behavioral effect (an unfavorable and unintended sign, symptom or disease) experienced by a subject during their participation in an investigational study whether or not product-related. This includes any untoward signs or symptoms experienced by the subject from the time of signing of the informed consent until completion of the study. Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient or subject and/or observed by the investigator or medical staff.
- Laboratory abnormalities of clinical significance.
- Disease signs, symptoms and/or laboratory abnormalities already existing prior to the use of the study medication are not considered adverse events after treatment unless they reoccur after the subject has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

All reportable AEs will be assigned a relationship to the study drug by the principal investigator. A drug-related AE is an event with a plausible time relationship to drug intake that cannot be explained by the disease or other drugs.

Any AEs experienced by the subject, from the time of signing the Informed Consent Form through the completion of study participation, will be reported as described (see Section 11.3) and recorded on the CRF. If AEs are present when the patient completes study participation, the subject will be re-evaluated within two weeks of completion and the results of this re-evaluation will be recorded on the CRF. If AEs are not resolved, additional follow-up will be performed as appropriate. All reportable AEs must be reported to the RDCRN within **20 working days** of the notification of the event or of the site becoming aware of the event.

Local institutional reporting requirements to IRBs, any CTSA oversight committee and the FDA, if appropriate, remain the responsibility of the site investigator and the Principal Investigator.

An unanticipated adverse event is defined as any adverse event, the specificity or severity of which is not consistent with the risks of information described in the protocol, and the event is related or possibly related to participation in the research, and suggests that the research places subjects or others at a greater risk or harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Expected adverse events are those that are known to be associated with or have the potential to arise as a consequence of participation in the study.

12.2. Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse event that results in any of the following outcomes:

- Death
- Life-threatening experience
- Required or prolonged inpatient hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defects

Life-threatening experience: Any adverse event that places the patient, in the view of the reporter, at immediate risk of death from the adverse event as it occurred, i.e., does not include an adverse event that had it occurred in a more severe form, might have caused death.

Persistent or significant disability/incapacity: The adverse event that resulted in a substantial disruption of a person's ability to conduct normal life functions.

Important medical events based upon appropriate medical judgment, that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above: Adverse events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they

may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
The investigator will be asked to assess the severity of the adverse drug/biologic experience using the following categories: mild, moderate and severe. This assessment is subjective and the investigator should use medical judgment to compare the reported adverse event to similar type events observed in clinical practice. Below are listed guidelines for severity assessment:

- Mild: Symptom(s) barely noticeable to the subject/patient or does not make the subject/patient uncomfortable. The adverse event does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
- Moderate: Symptom(s) of a sufficient severity to make the subject/patient uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
- Severe: Symptom(s) of a sufficient severity to cause the subject/patient severe discomfort. Severity may cause cessation of treatment with the study drug. Treatment for symptom(s) may be given.

12.3. Adverse Event and Serious Adverse Event Reporting

The necessity and time requirements for reporting of SAEs are as follows:

All SAEs and subject terminations will be reported to the Principal Investigator within 24 hours.

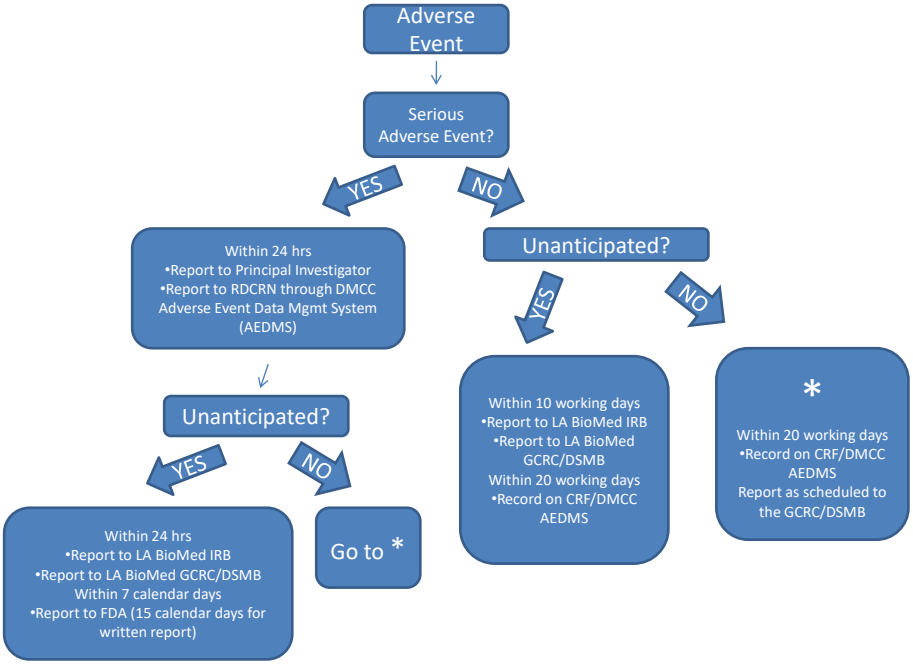
All SAEs will be reported to the Principal Investigator and to the RDCRN through the DMCC Adverse Event Data Management System within 24 hours of the investigator's first knowledge of the event, even if the experience does not appear to be related to the study drug. This also includes those events that are unexpected/unanticipated or is considered life-threatening/disabling or results in the death of a subject.

For all SAEs, a detailed written description that includes copies of relevant patient records, autopsy reports, and other documents will be collected.

Additionally, the IRB must be notified in writing of any events falling into these categories. It is the responsibility of the investigator to notify the IRB within **24 hours** if the event is unanticipated or is considered life-threatening/ disabling or results in the death of a subject. All other reportable SAEs must be reported within **5 working days** (of learning of the event).

All AEs and SAEs will be noted on the CRF, with a full description including the nature, date and time of onset and resolution, determination of seriousness, severity, corrective treatment, outcome, and relationship to study drug.

Flowchart for Adverse Event Reporting



12.4. Institutional Review Board

The study will be approved by the institutional review board (IRB) at each respective study site. All investigators must obtain IRB approval.

12.5. Food and Drug Administration Investigational New Drug Application

A new IND has been filed to the FDA [1,354]. The investigator and all study personnel will conduct the study according to FDA requirements.

12.6. Data and Safety Monitoring Board (DSMB)

The DSMB will review the research protocol, informed consent documents and plans for data safety and monitoring, evaluate the progress of the trial, including periodic assessments of data quality and timeliness, number of subjects screened, number enrolled, number dropped with reason for discontinuation, interim and cumulative data from all study sites, adverse events and serious adverse events, performance of the trial sites, and other factors that can affect study outcome. The establishment of a DSMB was recommended because of the inherent risks, the multicenter nature of the trial, and the significant financial

interest involved in this research. At the initial DSMB meeting, the DSMB will approve the study protocol and consider data elements to be included in the periodic reports to the DSMB. See DSMB Charter. During the initial meeting, the DSMB will also develop the Standard Operating Procedure of the DSMB. This SOP will be forwarded to the LABiomed IRB and GCRC for review.

The DSMB will provide the Sponsor-Investigator with the minutes from the open sessions of the DSMB meetings and summary report with any recommendations for future study conduct (continuation, modification or termination of the study). The Sponsor-Investigator will provide copies of the minutes, reports and recommendations to each site's co-investigators, the LABiomed IRB, and the GCRC Advisory Committee.

This study protocol will also be reviewed and approved by the National Institutes of Health (NIH). This is an interventional study that meets the federal definition of moderate risk.

The Principal Investigator has primary oversight of this clinical trial. The Principal Investigator and the Steering Committee will review accrual patterns, adverse events, data quality, and protocol compliance on an annual basis.

12.7. Local Reporting

The investigator will prepare a periodic report to include target, interval and cumulative data in a tabular format for subjects enrolled at Harbor-UCLA Medical Center and for the entire study as follows:

- Number of subjects screened
- Number of subjects enrolled
- Number of subjects not qualified for enrollment based on screening with reason for screen failure
- Dropout number with reason for dropout and stage of study at dropout.
- Completion number
- All adverse events with severity and attribution. During the period between the treatments and the follow-up period, the rates of adverse event related to underlying disease and routine illnesses (URI, headaches, muscle aches, etc.) and traumatic injuries are not expected to be different than usual and will not be reported as unexpected AEs but will be tracked and reported as AEs for the DSMB reports.
- For all serious adverse events (SAEs) and all unexpected adverse events (UAEs), the clinical summary will also be provided in a cumulative fashion. For SAEs and UAEs, IRB and GCRC policy on adverse event reporting will be followed.

To ensure subject confidentiality, all subjects will be identified by a numerical identifier only.

The primary monitor for this study is the DSMB. The data and safety monitoring board will be comprised of three persons: a statistician, a neurologist, and a pediatrician geneticist. All DSMB members will be external to the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, and shall have no financial interest in the institute, Aldurazyme, or in the companies that manufacture and distribute Aldurazyme (i.e. BioMarin Pharmaceutical, Inc. and Genzyme Corp.).

A separate DSMB charter will be drafted and approved by all board members prior to reviewing any data. The members of this DSMB should not have substantial conflicts of interest and have no substantive financial ties to the applicant or to the proposed research and will be required to submit an affidavit to these effects.

The board will convene every four months at the inception, during, and at the end of the study period. Due to the small number of subjects and the relatively small number of visits, every 4 months is recommended to allow review of relevant data. An emergency meeting of the DSMB may be called at any time by the DSMB Chairperson or the Sponsor-Investigator should question of subject safety arise.

12.8. RDCRN Adverse Event Data Management System (AEDMS)

Upon entry of a serious adverse event by a site investigator, the DMCC created Adverse Event Data Management System (AEDMS) will immediately notify the Principal Investigator. The Principal Investigator is responsible for notifying NINDS staff.

Serious adverse events: The site investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The DSMB will also review the SAE incident report.

The DSMB may request further information if necessary and possibly suggest changes to the protocol or consent form to the NINDS as a consequence of adverse events. A back-up notification system is in place so that any delays in review by the DSMB chair beyond a specified period of time are forwarded to a secondary reviewer. The Adverse Event Data Management System (AEDAMS) maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.

Non-serious expected adverse events Except those listed above as immediately reportable, non-serious expected adverse events that are reported to or observed by the investigator or a member of his/her research team will be

submitted to the DMCC in a timely fashion (within 20 working days). The events will be presented in tabular form and given to the DSMB on a quarterly basis or as requested. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DMCC will post aggregate reports of all adverse events (serious/not serious and expected, unexpected) for site investigators and IRBs.

All reported adverse events will be classified using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) developed and maintained by CTEP at National Cancer Institute.

12.9. Unanticipated Problem Reporting

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Per the definition, only a subset of adverse events would be characterized as unanticipated problems. There are other types of incidents, experiences, and outcomes that are not considered adverse events, but are characterized as unanticipated problems (e.g., breach of confidentiality or other incidents involving social or economic harm).

Incidents or events that meet the OHRP criteria for unanticipated problems are to be reported to the IRB, per local institutional reporting requirements. Local institutional reporting requirements to IRBs, any GCRC oversight committee and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

12.10. Discontinuation Guidelines

The participation of all study subjects will be halted pending review by the NIH, DSMB and IRB for the following reasons:

- WHO Grade 3 toxicity (such as a seizure or meningitis) is experienced by 2 or more subjects
- Death or WHO Grade 4 toxicity is experienced by 1 or more subjects

If one of the above conditions are met, the study will be placed on hold (no new enrollment, and a halt to all study procedures on enrolled subjects), and the PI will notify the NIH, IRB and DSMB within 24 hours.

This study may be also suspended or closed if:

- Accrual has been met
- The study objectives have been met
- The Study Chair / Study Investigators believe it is not safe for the study to continue
- The RDCRN DSMB suspends or closes the trial
- The NIH suspends or closes the trial
- The FDA suspends or closes the trial

13. Data Quality Assurance

All required data will be recorded on the CRF. All missing data will be explained. If a space is blank because the item was not done, the item will be marked "ND." If the item is unknown, item will be marked "UNK." If the item is not applicable to the individual case, the space will be marked with a "NA." If the item is not available, it will be marked with "NAV." All entries will be recorded in black ink. If an entry error has been made, a single straight line will be drawn through the wrong entry and the correct data will be entered above it and initialed and dated. ERRORS MAY NOT BE ERASED AND WHITEOUT MAY NOT BE USED.

The CRFs will be reviewed manually at the study site for completeness. All data will be entered into a study database for analysis and reporting. Any data captured electronically (e.g., laboratory data) will be electronically transferred to the database. Upon completion of data entry, the database will receive a quality assurance (QA) check to ensure acceptable accuracy and completeness.

13.1. Data Quality and Monitoring

As much as possible data quality is assessed at the data entry point using intelligent on-line forms. Data element constraints, whether independent range and/or format limitations or 'relative' referential integrity limitations, can be enforced by all methods employed for data input. QA reports assess data quality post-data entry. As we note, data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Of the more important quality assurance measures are the internal validity checks for reasonableness and consistency. In addition to those describes above, we propose to build these checks into the

initial tables and cross tabulations that should reveal any remaining data quality issues.

All study data will be collected via systems created in collaboration with the RDCRN Data Management and Coordinating Center and will comply with all applicable guidelines regarding subject confidentiality and data integrity.

- Data Monitoring: The RDCRN DMCC identifies missing or unclear data and generates a data query to the consortium administrator contact.
- Data Delinquency Tracking: The Data Management and Coordinating Center will monitor data delinquency on an ongoing basis.

13.2. Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. IRB approval for the protocol must be on file at the DMCC before accrual can occur from the clinical site.

The DMCC will use a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the registering site will have access to the linkage between this number and the personal identifier of the subject. When the participant is registered to participate in the study, using the DMCC provided web-based registration system, the system will assign a participant ID number. Thus each participant will have two codes: the local one that can be used by the registering site to obtain personal identifiers and a second code assigned by the DMCC. For all data transfers to the DMCC both numbers will be required to uniquely identify the subject. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a participant for data entry since the numbers should match to properly identify the participant.

13.3. Data Entry

Data will be collected on the Case Report Forms during the study visit and subsequently from source documents (laboratory and test reports). Data will then be entered into online electronic case report forms as previously described. Using encrypted communication links, on-line forms will be developed that contain the requisite data fields.

Refer to Section 11.6 regarding periodic evaluation of the data by a Data and Safety Monitoring Board.

13.4. Protocol Deviations

A protocol deviation is an unintentional departure from the approved protocol's procedures. If the deviation does not increase risk or decrease benefit or; does not have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data, these deviations will be reported as a note-to-file in the subject's binder.

If the deviation increases risk or decreases benefit, affects the subject's rights, safety, or welfare, or the integrity of the data, these deviations will be reported to the IRB as soon as reasonably possible after the deviation is discovered. Local Institutional guidelines and additional reporting requirements for protocol deviations should be followed.

14. Withdrawal of Subjects

14.1. Subject withdrawal

A subject (or the legal guardian acting on behalf of the subject) is free to withdraw consent and discontinue participation in the study at any time, and without prejudice to further treatment, according to standard clinical practice. A subject who decides to discontinue participation in the study should be contacted to obtain information about the reason(s) for discontinuation and collection of any potential AEs.

All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless a participant withdraws consent. A subject's participation in the study may be discontinued at any time at the discretion of the investigator. The following may be justifiable reasons for the investigator to remove a subject from the study:

- The subject is uncooperative or non-compliant with the protocol.
- The subject develops an exclusion criterion or concurrent disease.
- The subject develops a condition or adverse event that, in the opinion of the investigator, contraindicates the continuation of treatment.
- The subject desires a surgical procedure or other alternative treatment for cognitive decline.

The reason for withdrawal should be clearly described. Withdrawn subjects may not re-enter the study. Follow-up procedures will be required if the subject discontinues as a result of an adverse event. Follow-up may include completing the study assessments scheduled at the final visit. Every effort will be made to conduct a final study visit with the participant, and participants will be followed clinically until, if applicable, all adverse events resolve.

If a subject or the subject's legal guardian, acting on behalf of the subject, discontinues participation in the study, or the subject is discontinued by the

investigator, the Patient Completion/Discontinuation Case Report Form (CRF) describing the reason for discontinuation must be completed. Any AEs experienced up to the point of discontinuation must be documented on the AE CRF. If AEs are present when the subject withdraws from the study, the subject will be re-evaluated within two weeks of withdrawal. If AEs are not resolved, additional follow-up will be performed, as appropriate.

14.2. Termination of Subject Participation

The investigator may choose to terminate a subject's participation in the study at any time. Conditions that may warrant termination of study participation include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- Insufficient adherence to protocol requirements.

Subjects who withdraw or are withdrawn from the study will not receive further evaluations unless warranted by an ongoing adverse event.

15. Risks to Subjects

15.1. Human trials

In the current study, there have been no drug-related severe adverse events (SAEs). Due to the nature of the disease, MPS I subjects have had multiple disease-related SAEs. These include surgery for spinal cord compression, lumbar spine surgery, severe muscle cramping, worsening of previous psychiatric disease. One subject was diagnosed with prostate cancer during the study, but this is likely not drug nor disease-related.

In the spinal cord compression trial, no drug-related severe adverse events (SAEs) occurred; one subject experienced a non-drug-related SAE (pneumonia), one subject experienced several moderate adverse events due to systemic MPS disease, one subject died 2 days after receiving IT rhIDU. Autopsy results showed no evidence of central nervous system (CNS) abnormality, including no evidence of CNS inflammation.

15.2. Seizures

In early canine experiments with IT rhIDU, hyperventilation and/or brief seizures occurred in some dogs that received undiluted IT rhIDU. Seizures occurred in the immediate post-treatment (recovery) period; no seizure occurred between treatments. The problem was attributed to the formulation buffer. Dilution of 1:3 by volume in Elliotts B artificial CSF solution prevented these side effects in all subsequent animals. In addition, no seizure, hyperventilation, or posturing has been reported in the seven MPS I patients who have received IT rhIDU worldwide. If a seizure were to occur, intravenous midazolam or other benzodiazepine drug could be given to manage this short term complication.

15.3. Chemical irritation

The acidity (pH 5.5), phosphate concentration, osmolarity, and the presence of trace amounts of polysorbate 80 in the Aldurazyme® formulation could cause chemical irritation within the CSF space. By diluting the enzyme in Elliotts B®, the pH effect is blunted as it is for commonly used intrathecal chemotherapy agents such as methotrexate (pH 8.5) or cytarabine (pH 5). Dilution also lowers the phosphate concentration and osmolarity of the solution. Polysorbate 80, which is required to stabilize rhIDU in the formulation, is present at very low quantities (0.001%). Very low total dose amounts will be given (0.03 micrograms per dose). Polysorbate 80 is generally seen as a mild irritant and is present in various foods, drugs, and cosmetics. The every 3 month dosing schedule should provide sufficient time for recovery if modest irritation occurs.

15.4. Immune response and immune-mediated meningitis

The data in the MPS I dog suggest that an immune response can occur and results in a mild-moderate meningitis. One subject in the spinal cord compression trial had a CSF lymphocytosis up to 37, but did not have meningismus clinically. She was given a short course of oral steroids and subsequent CSF cell counts were normal. Human patients have tolerized over time to IV rhIDU administration unlike the dogs which do not tolerize without a special tolerance regimen (Kakavanos et al., 2003). Study subjects who have recently initiated intravenous Aldurazyme, with fewer than 6 months of enzyme treatment, will be excluded because increasing titers during the first 3 months might, in theory, increase the risk for immune-mediated meningitis. After 6 months, the titers have stabilized or begun to decline in most cases. Study subjects who have never received Aldurazyme prior to beginning this study are not thought to be at increased risk, and will be allowed to participate.

Any immune response will be monitored via clinical history, anti-iduronidase antibody titers, CSF cell counts and MRI scans. If a reaction were to occur, it could be managed by providing pretreatment with glucocorticoids such as methylprednisolone. The single subject who developed an increased CSF leukocyte count did respond to a short course of oral steroids and pretreatment with steroids for subsequent doses. For human patients with clinical reactions to intravenous rhIDU, pretreatment with steroids can prevent the acute infusion-associated reaction and minimize the clinical adverse impact.

15.5. Risks from study procedures

Spinal tap: Subjects may experience some discomfort from the spinal tap. This may include back pain, headache, lightheadedness and feeling faint. It is also possible and rare that a spinal headache may develop. More serious and rare

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side effects from a spinal tap include paralysis, nerve injury, spinal hematoma, spinal herniation, and death.

Sedation medicine given for the spinal tap may cause sleepiness, nausea, vomiting, blurry vision, light-headedness, chills, yawning, loss of balance, nervousness, confusion, hallucinations, anxiety, restlessness, sleep problems, nightmares, and feeling happy or unhappy. Subjects may also experience stomach discomfort, an acid taste, coughing, hiccoughs, excessive drooling, and/or throwing up. The chance of these side effects occurring is low, and they are usually temporary and not serious. Rarely, some people who receive the medicine have slurred speech, tingling or other sensation, rapid eye movements, and other movements including convulsion-type movements.

More serious side effects can occur from the sedation medication; these include difficulty breathing, not breathing, heart beating too slow or too fast, or an allergic reaction.

The numbing cream and the other medicine given to numb the subject's back may also cause side effects. These include shivering, nausea, numbness, light-headedness, nervousness, feeling scared**,** confusion, dizziness, drowsiness, ringing in the ears, blurred vision, seeing double, feeling hot or cold, twitching, shaking, convulsions, fainting, and feeling happy. The chance of these side effects occurring is low, and they are usually temporary and not serious. Some people who receive the medicines have pain, redness, or swelling on the spot on their body where the medicine is injected. These are also usually temporary and not serious.

More serious side effects can occur, including loss of consciousness, breathing too slow, not breathing, irregular heartbeat, and death. The chance of these serious side effects occurring is very low, and the study doctor and her staff will take every precaution to prevent them or treat them immediately.

Spinal tap using fluoroscopy: If the study doctor needs fluoroscopy to guide the spinal tap, the subject will receive a dose of radiation. The radiation dose is about 2500 millirads per minute of exposure time. The total dose for each procedure is expected to be between 2000 and 13,800 millirads, depending on how long the procedure takes and how difficult it is to insert the needle into the spinal canal. A millirad is a unit of measurement for radiation. No amount of radiation is considered safe.

Although each organ will receive a different dose, the amount of radiation exposure that subjects will receive from each of these procedures is equal to a whole body exposure of between 6 and 47 years of exposure to natural background radiation (radiation we receive every day from environment).

For the sake of comparison, other estimated doses of medical radiation are: chest x-ray (25 millirads), set of dental x-rays (750 millirads) and barium enema x-ray (2000 millirads). Non-medical doses are: natural radiation exposure living at sea level (100 millirads each year) and watching TV 1 hour each day (1 millirads each year).

Aldurazyme: Some people who receive Aldurazyme have a flu-like illness or rash. These are the most common side effects with Aldurazyme treatment and are not usually serious. Less common side effects include chest pain, numbness or tingling, jaundice, swelling of the face, arms, or legs, or increased reflexes. These are usually temporary and not usually serious, but may cause discomfort.

Some people may have pain, swelling, redness, or an infection in the area on the body where the Aldurazyme is injected. During the Aldurazyme treatment, some people experience flushing, fever, headache, rash, cough, difficulty breathing, itching, hives, and swelling of the lips, eyes, or throat.

More serious side effects include low blood pressure, an allergic reaction, bleeding, and difficulty breathing. Symptoms of an allergic reaction include rash, itching, swelling of the lips, face, or throat, difficulty breathing, and low blood pressure.

Aldurazyme given into the spinal fluid is a new treatment and has been given to a very small number of people (less than 20) in this manner. It may have side effects that are not known at this time. The following side effects may be possible: convulsions, rapid breathing, muscle twitching, pain, or meningitis. Meningitis is an irritation in the tissue surrounding the spinal cord and brain that may cause neck pain, stiffness, headache, back pain, difficulty sitting and walking, and other problems. It is not known whether these side effects will be temporary or permanent or what their likelihood will be.

<u>One study patient died 1 ½ days after receiving Aldurazyme treatment by injection into the spinal canal. Tests done to determine the cause of death showed no signs of meningitis (infection and/or inflammation of the brain). It was concluded that this patient's death was not directly related to treatment with Aldurazyme and that this patient died due to the underlying MPS disease.</u>

Aldurazyme contains a chemical named "polysorbate 80." This chemical is present in various foods, dyes, and other household products. It is generally thought to be safe. The effects of polysorbate 80 when put into the spinal fluid are not known, but it may possibly cause irritation of the tissues surrounding the spinal cord, or it may cause other problems that are not known. The polysorbate 80 may stay in the spinal tissues or brain for the rest of the subject's life. The amount of polysorbate 80 in Aldurazyme is extremely low, but it may accumulate over time with each dose. While polysorbate 80 is thought to be safe, it is not

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known whether this build up in the spinal tissues or brain may be potentially harmful.

As with any medical treatment, unexpected reactions or side effects can occur. Because they cannot all be predicted and because of the underlying MPS I disease, significant injury or even death could occur during this treatment.

***Insertion of a small tube/catheter into a vein*:** The effects of inserting a catheter into a vein are usually some pain, bleeding and/or a bruise where the catheter is inserted. Occasionally the area around the vein may swell. Serious complications such as a blood clot or infection may occur but these are rare. Some people feel faint when having needles or catheters inserted or blood drawn.

Magnetic resonance imaging (MRI): There are no known risks from the MRI. Because a strong magnet is used to do these measurements, no one with a pacemaker or other type of metallic implant should have the procedure done. Being in a tunnel-like enclosure may cause subjects with claustrophobia to become anxious.

Subjects who are very anxious about the MRI may receive sedation medicine. Risks of sedation medicine are the same as those reviewed above under risks of a spinal tap.

If the subject has a programmable ventriculoperitoneal shunt, it may need to be reprogrammed after the MRI. This may require up to three plain x-ray films to be taken of the shunt. If x-rays are performed, the subject will be exposed to a small amount of radiation exposure, about 7.3 millirads per x-ray. The x-rays are necessary to make sure that the shunt is reprogrammed correctly. Please see the above section “Spinal tap using fluoroscopy” and the below section “Spinal Fluid Flow Study” for more information on radiation doses.

If your programmable ventriculoperitoneal shunt is turned off by the MRI machine, there is a small risk that the subject could develop hydrocephalus. A specialist will evaluate the subject if this occurs and appropriate treatment will be given.

***Six-minute walk test*:** Subjects may feel discomfort during the six-minute walk test. Other risks include difficulty breathing, breathing fast, sweating, leg cramps, chest pain, lightheadedness, looking pale, or staggering. A subject could fall or otherwise become injured during the test. In some cases, these may be serious and require emergency medical treatment. Rarely, a person may have a heart attack and potentially die during the test. The chance of these serious side effects occurring is very low, and the study doctor and her staff will take every precaution to prevent them or treat them immediately.

***Pictures and Videotaping*:** For subjects who agree to being videotaped or having pictures of them taken, there is a possibility that his or her confidentiality might be breached and his or her identity might be revealed. Every effort will be made to protect subject's confidentiality.

Neuropsychological testing: There are no significant risks involved in neuropsychological testing; however, the subject may experience some anxiety or may become tired during the testing.

Spinal Fluid Flow study: This test involves a spinal tap which may cause some discomfort. This may include back pain, headache, lightheadedness and feeling faint. A spinal headache is also a rare, but possible risk of this procedure. The sections above discuss the risks of a spinal tap and spinal tap using fluoroscopy in detail. This flow study also involves injection of a small amount of radioactive material (radionuclide) into the spinal fluid.

Below is a table below that lists the estimated radiation dose for a 2 mCi injection of Tc-99m DTPA. Please note that 2mCi is the highest dose that an adult could receive in this study. The actual dose may be lower depending on the subject's weight.

Radiation Dose Based on a 2 mCi injection of Tc-99m DTPA

Organ	5 year old	10 year old	15 year old	Adult
Bone Surfaces(millirads)	56	38	30	24
Red Marrow(millirads)	37	25	20	16
Urinary Bladder Wall(millirads)	640	430	720	570
Ovaries(milirads)	67	45	51	41
Kidneys(millirads)	100	70	51	42
Testes(millirads)	57	36	38	28
Effective Dose Equivalent(millirem)	89	60	74	61

Note: the radiation doses in this table were based on the assumptions and models given in the document(s) entitled: "Radiation Dose Estimates to Adults and Children From Various Radiopharmaceuticals" (revised: 04/30/96) Radiation Internal Dose Information Center, Oak Ridge Institute for Science and Education.

For the sake of comparison, other estimated doses of medical radiation are: chest x-ray (25 millirads), set of dental x-rays (750 millirads) and barium enema x-ray (2000 millirads). Non-medical doses are: natural radiation exposure living at sea level (100 millirads each year) and watching TV 1 hour each day (1 millirad each year).

Reproductive Risks: There are unknown reproductive risks associated with Aldurazyme; therefore, pregnant subjects are excluded from this study.

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15.6. Unknown responses

The subjects will be monitored for a number of possible events using clinical laboratory studies and imaging studies to complement clinical evaluations. The Institutional Review Boards (IRBs) involved with this protocol would be notified of course if such events were to occur.

16. Potential Benefits to Subjects

The goal of this study is to evaluate whether IT rhIDU injections can stabilize or improve cognitive decline in human subjects with MPS I. Cognitive decline can be manifested by disturbances in memory, language, executive function, and visuospatial deficits. Such declines result in difficulties in school, work, activities of daily living, and interpersonal relationships. Given that no current treatment option is available for these problems, IT rhIDU may provide the only therapy for these damaging and progressive symptoms.

It is unclear what the expected magnitude and duration of these effects will be. We know from canine data that reduction in brain glycosaminoglycan storage after a single rhIDU intrathecal injection lasts at least 3 months; hence, the reason for q3month injections. In addition, it is possible that the IT rhIDU will also treat other central nervous system manisfestations of MPS I disease, including spinal cord compression, hydrocephalus, and headache.

17. Provisions to Protect the Privacy Interests of Subjects

The subject's privacy will be protected by performing all study procedures in a private room; this includes obtaining consent and medical history, performing exams, and tests. The only personnel that will be present will be the study investigator, study coordinator, and staff, such as nurses, who perform procedures under the direction of the study investigator. Any other persons will need explicit consent of the subject to be present. Subjects will be made to feel at ease by limiting the number of personnel present, and encouraging the subject to ask questions and notify the staff if he or she is uncomfortable in any way.

The Protected Health Information (PHI) Authorization details exactly what will happen to the subject's PHI, and who is allowed to view the PHI. Privacy of the subject's PHI will be maintained by never posting the subject's name in the outpatient clinic or the inpatient ward. The protocol number is used instead. The subject's medical record is kept out of view at the nursing station, and only the research team is allowed to access it. The research record is kept in a locked office, in a locked file cabinet, and only members of the research team have access to the office. Subjects will be made aware that their name or records will not be given out without their consent, unless required by law.

Privacy issues related to the research will be covered in the consent. These include the likelihood that the results of this research, including the subject's tests, photographs, videotapes, x-rays may be published to inform other physicians and scientists. Subjects will be made aware that their name or records will not be given out without their consent, unless required by law.

Subjects will be told that information that identifies them or their child will be used only for the purpose of the study. They will be told that this includes information that can help study personnel locate or contact them as well as information related to their or their child's medical condition (medical records, for example).

The following protected health information may be used or disclosed in connection with the research:

Personal information:

- Name
- Address (including ZIP code only)
- All elements of dates (except year) for dates directly related to an individual, e.g., birthday, date of death, date of hospitalization
- Medical record number
- Health plan beneficiary number
- Telephone number or Fax number
- Full face photographic image and any comparable image

Linked with the following medical information:

- Face Sheet
- Physician Attestation/ICD Codes
- Discharge Summary
- History & Physical
- Outpatient/Short Stay Record
- Operative/Procedure Report
- Emergency Room Records
- Progress Notes/Notes
- All Consultation Reports
- All Labs
- All EKGs
- Echocardiogram
- MRI/MRA Scan Reports
- CSF Flow Study Report
- Ankle-Arm Blood Pressures
- Lumbar Puncture Report
- All Pathology Reports
- Neuropsychological Testing Reports

The following people, organizations or other groups may use, disclose, or receive the subject's protected health information:

- The investigators at both sites (LA BioMed and the Children's Hospital Oakland Research Institute)
- The investigator's research staff at both sites
- The Institutional Review Board's at both sites
- LA BioMed and CHORI staff charged with protecting your safety
- Food and Drug Administration (FDA)
- National Institutes of Health (NIH)
- LA BioMed Accounting for purposes of paying for travel expenses
- Data Management and Coordination Center of the University of South Florida

Subjects' protected health information will be used for up to 11 years after the date they sign the protected health information authorization. Subjects or their guardians will be informed of their right to take back (revoke) this authorization at any time by signing a form available from the researcher, or by writing a note requesting this and then signing it. In some circumstances, however, they may not be able to have previously collected information removed from the study if the loss of this protected health information could stop the research from reaching a successful end, such as finding out whether a drug being tested is safe and effective or not.

Subjects will be informed of their rights, including the right to inspect or copy the protected health information they are authorizing the investigator to collect about you/your child.

They will be informed that if the research involves disclosure of their protected health information to someone or some organization that is not covered by the privacy laws, then their information might not be protected.

18. Compensation for Research-Related Injury

Subjects will be told of the availability of emergency care should they become injured, but it will not necessarily be free of charge.

19. Economic Burden to Subjects

Subjects may incur costs due to lost work days. Travel including air, ground transportation, hotel and modest food costs will be reimbursed by the study.

20. Consent Process

Informed consent will be obtained by study investigators in a private area, such as a small conference room, office, or consultation room. Subjects will be given the informed consent document to read ahead of time in their preferred language. They will be allowed at least two days to read this consent in advance of the informed consent signing. Investigators will follow SOP: Informed Consent Process for Research (HRP-090) when obtaining informed consent for this

research. Translators will be provided for the informed consent process if the subject's preferred language is not English. Subjects or their guardians will be asked about their willingness to continue with the study at each visit.

Children under the age of 18 years may participate in the study. Permission will be obtained from both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. A legal guardian with documentation of this status may provide permission for the child to participate in the study. Children under age 18 years but at least 12 years of age will be asked to assent to the study using a separate, child assent form.

Minor subjects will be re-consented upon reaching 18 years of age to demonstrate their willingness to continue in the study.

If the subject cannot read, an impartial witness will be present during the entire consent discussion to attest that the information in the consent form and any other information provided was accurately explained to, and apparently understood by, the subject, and that consent is freely given.
The witness may be a family member or friend. The witness may not be a person involved in the design, conduct, or reporting of the research study.
After the explanation of the study, the principal investigator will make an assessment as to whether the subject/representative understands the information provided. He/she will assure that the subject does not feel pressured by time or other factors to make a decision. He/she will assure that the subject understands that there is a voluntary choice to make and that the subject is capable of making and communicating an informed choice. If these assurances cannot be made, the investigator will determine that the subject is incapable of consent, and the subject will not enter the study.

Special provision for subjects who are adults incapable of consent: This is a protocol that is designed to study patients with cognitive impairment and it is also a treatment protocol with potential to benefit subjects with cognitive impairment. Thus, there is an ethical conflict between providing the opportunity of possible treatment to a special population, and protecting their rights to decline treatment.

The following additional safeguards and consent procedure will be undertaken before allowing an adult incapable of consent to participate in this research:

1. An appropriate surrogate per California law will be identified.

2. The investigator will describe the research to the participant (to the extent compatible with the subject's understanding) and indicate the intent to obtain surrogate consent. This will be documented.

3. If the research participant expresses resistance or dissent to being in the research or to the use of the surrogate consent by word or gesture, she will be excluded from the research study.

4. The surrogate will complete a “Self-Certification of Surrogate Decision Makers for Potential Subject’s Participation in University of California Research” (Appendix E). It certifies that the surrogate knows the subject very well and believes that they can carry out her preferences.

5. If the subject and the surrogate agree to participation in the study, then the surrogate will sign the informed consent form and the subject will sign the assent form.

6. If the cognitive ability of the subject changes, then the subject will be re-evaluated for decision-making capacity and will be consented if she gains the ability to consent.

21. Process to Document Consent in Writing

We will follow SOP: Written Documentation of Consent (HRP-091) to obtain documentation of informed consent.

22. Vulnerable Populations

The study will enroll children. Pregnant women are excluded from participation, due to uncertainty over harm to the fetus. Prisoners will not be enrolled, due to inability to travel for study visits. Adults unable to consent will be allowed to enroll if the above safeguards are followed.

23. Drugs or Devices

23.1 Investigational Product

Recombinant human α-L-iduronidase (rhIDU) is a polypeptide with an apparent molecular weight of 82,000 Daltons. It is supplied in 5.0 mL Type I glass tubing vials each containing 5.0 mL of the investigational product. The vial is sealed with a siliconized, grey stopper and capped with an aluminum tamper evident crimp top. Recombinant human α-L-iduronidase is FDA-approved for intravenous use in humans (Aldurazyme®, BioMarin Pharmaceutical Inc., Novato, California).

The solution in each vial contains a nominal laronidase concentration of 0.58 mg/mL and a pH of approximately 5.5. The extractable volume of 5.0 mL from each vial provides 2.9 mg laronidase, 43.9 mg sodium chloride, 63.5 mg sodium phosphate monobasic monohydrate, 10.7 mg sodium phosphate dibasic heptahydrate, and 0.05 mg polysorbate 80. Aldurazyme does not contain preservatives; vials are for single use only and stored in a refrigerator at 4˚C. The final product is a solution that is clear to slightly opalescent, and colorless to pale yellow.

For administration to subjects, Aldurazyme® will be diluted with between 6 mL to 8 mL of Elliotts B® Solution (Ben Venue Laboratories, Inc., Bedford, Ohio). Elliotts B® solution is a buffered intrathecal electrolyte/dextrose injection developed as a diluent for intrathecal chemotherapy. Its composition is roughly similar to human cerebrospinal fluid in pH, electrolyte composition, glucose content, and osmolarity. It is FDA-approved in the United States for intrathecal

use in humans. In areas where Elliotts B® is not available, an equivalent solution may be made by a pharmacist. This solution would be prepared from sterile component solutions to be equivalent in sodium, chloride, potassium, dextrose, bicarbonate, pH, and osmolarity to Elliotts B® solution.

23.2 Packaging and Labeling

The Aldurazyme vials will be obtained from a commercial source. The labeling in commercial territories will be as approved by that territorial regulatory authority.

Drug will be stored and dispensed by the investigational pharmacy service at each site.

24 Multi-Site Human Research

This is a multi-site study. All sites will have the most current version of the protocol, consent document, and HIPAA authorization. All required approvals will be obtained at each site (including approval by the site's HSC of record) prior to site initiation. All modifications will be communicated to sites, and approved (including approval by the site's HSC of record) before the modification is implemented. All engaged participating sites will safeguard data as required by local information security policies. All local site investigators will be monitored at six month intervals by study personnel to ensure that they conduct the study appropriately. All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Study sites will be informed of substantial study problems including unexpected serious adverse events, problems with the investigational product, subject withdrawal or the closure of the study within 24 hours of the investigator's first knowledge of the event. Interim results will be communicated to study sites on an annual basis.

25 Community-Based Participatory Research

Not applicable.

26 Sharing of Results with Subjects

Sharing of interim results with subjects or their physicians is not planned. Exceptions include adverse events or test results that require medical attention or medical care in order to prevent further harm to the subject.

APPENDIX A

Mini-Mental State Exam, modified slightly for children (Ouvrier et. al. 1993)

Orientation		Score	Points
1. What is the	year?	____	1
	season?	____	1
	date?	____	1
	day?	____	1
	month?	____	1
2. Where are we?	Country	____	1
	State or territory	____	1
	Town or city	____	1
	Hospital or suburb	____	1
	Floor or address	____	1
Registration			
3.	Name three objects, taking one second to say each. Then ask the patient all three after you have said them. (Tree, clock, boat). Give one point for each correct answer. Repeat the answers until patient learns all three.		3
Attention and Calculation			
4.	Serial sevens. Give one point for each correct answer. Stop after five answers		5
5.	Spell WORLD backwards		5
Recall			
6.	Ask for names of three objects learned in Q.3. Give one point for each correct answer		3
Language			
7.	Point to a pencil and a watch. Have the patient name them as you point		2
8.	Have the patient repeat "No ifs, ands or buts"		1
9.	Have the patient follow a three-stage command. "Take a piece of paper in your right hand. Fold the paper in half. Put the paper on the floor"		3
10.	Have the patient read and obey the following: "CLOSE YOUR EYES". (Write it in large letters).		1
11.	Have the patient write a sentence of his or her choice. (The sentence should contain a subject and an object, and should make sense. Ignore spelling errors when scoring).		1
12.	Have the patient copy the design printed below. (Give one point if all sides and angles are preserved and if the intersecting sides form diamond shape).		1
	Total		35

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APPENDIX B

Functional Independence Measure Score

Each area of functioning is evaluated and scored by the subject on a 7 point scale. Scores of 6 or 7 are considered “Independent,” and 5 or below considered “Dependent.”

7 = Complete independence. The activity is typically performed safely, without modification, assistive devices or aids, and within reasonable time.

6 = Modified independence. The activity requires an assistive device and/or more than reasonable time and/or is not performed safely.

5 = Supervision or setup. No physical assistance is needed, but cuing, coaxing, or setup is required.

4 = Minimal contact assistance. Subject requires no more than touching and expends 75% or more of the effort required in the activity.

3 = Moderate assistance. Subject requires more than touching and expends 50-75% of the effort required in the activity.

2 = Maximal assistance. Subject expends 25-50% of the effort required in the activity.

1 = Total assistance. Subject expends 0-25% of the effort required in the activity.

Areas of functioning addressed:

- Self-care -- Eating, grooming, bathing, dressing-upper body, dressing-lower body, and toileting are evaluated on the 7-point scale
- Sphincter control -- Bladder and bowel management are each rated on the 7-point scale.
- Mobility -- Transfer to bed, chair, or wheelchair, transfer to toilet, and transfer to tub or shower are graded on the scale.
- Locomotion -- Walking/wheelchair and stairs

A total FIM score is assigned. A score of 1 is entered if the subject is not testable in that area. The score will be an integer from 13 to 91.

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APPENDIX C

MRI of brain: Scoring system

Abnormal signal intensity:

Lesions will be estimated as to size (3 dimensions) and number, and will be divided by location into basal ganglia, white matter, and cortex. Signal changes observed on T2 images will be graded on a scale from 0-3, where 0 is absent, 1 is patchy and confined to the periventricular area, 2 is patchy but in other white matter areas as well as periventricular, and 3 is diffuse.

Enlargement of perivascular space:

Enlargement of the perivascular space will be classified in five brain regions: periventricular and subcortical white matter, corpus callosum, basal ganglia, thalami, and brainstem. These regions will be scored for enlargement on a scale from 0-3, where 0 is no enlargement, 1 is < 3mm enlargement, 2 is between 3 and 8 mm enlargement, and 3 is > 8 mm of enlargement.

Other findings, such as brain atrophy and megacisterna magna will be graded on a scale from 0-3, with 0 as absent, 1 as mild, 2 as moderate, and 3 as severe. Additional abnormalities will also be noted.

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APPENDIX D

Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964 and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975 35th World Medical Assembly, Venice, Italy, October 1983, 41st World Medical Assembly, Hong Kong, September 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996

I. Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, “The Health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act only in the patient’s interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.”

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is

purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

II. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the Investigator and the Sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case a physician who is not engaged in the investigation and who is completely independent of this official relationship should obtain the informed consent.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

13. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

III. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure if, in his or her judgement, it offers hope of saving life and re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best-proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge only to the extent that its potential diagnostic or therapeutic value of the patient justifies medical research.

IV. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subject should be a volunteer - either a healthy person or patient for whom the experimental design is not related to the patient's illness.

3. The Investigator or the investigating team should discontinue the research if, in his/her judgement, it may be harmful to the individual if continued.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

Protection of Human Subjects (21 CFR Part 50)

Informed consent must be obtained from every patient before he or she enters a study. It must be given freely and not under duress. Consent must be documented by use of a consent form that has been approved by the IRB and signed by the patient or the patient's legally authorized representative. The Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent, his or her signature should also be included. Non-English-speaking patients must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given to the patient signing it. Another copy must be kept in the Investigator's files and made available to Sponsor and FDA representatives upon request. If, for any reason, patient risk increases as the study progresses, the patient must sign a revised consent form that has been approved by the IRB. Before the study begins, a sample of the consent form must be provided to the Sponsor. The FDA may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all patients.

Only in the case of a life-threatening incident may a study drug be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the Investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB within five working days. In this situation, the Investigator may not administer any subsequent study drug to that patient until informed consent and IRB approval are obtained.

A. BASIC ELEMENTS OF INFORMED CONSENT

Every consent form must include the following eight elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;
- A description of any reasonably foreseeable risks or discomforts to the patient;
- A description of any benefits to the patient or to others that may be reasonably expected from the research;
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the patient;
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA and Sponsor representatives may inspect the records;
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available or a statement describing where further information may be obtained;
- An explanation of whom to contact for answers to pertinent questions about the research and the patient's rights, and whom to contact in the event of a research-related injury; and,
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.

B. ADDITIONAL ELEMENTS OF INFORMED CONSENT

When appropriate, one or more of the following elements of information shall also be included in the consent form:

A statement that the particular treatment or procedure may involve risks to the patient (or to the embryo or fetus, if the patient is or may become pregnant) which are currently unforeseeable;.

Anticipated circumstances under which the Investigator without regard to the patient's consent may terminate the patient's participation;

Any additional costs the patient might incur from participation in the research;

The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient;

A statement that significant new findings developed during the course of the research that might affect the patient's willingness to continue participation will be provided to the patient; and,

The approximate number of patients involved in the study.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

Informed consent allows the patient to fully understand his or her participation and serves to protect the Investigator and Sponsor from potential negligence claims. A fully informed patient is the best protection against such claims.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent is legally effective. Some states, such as California and Oregon, require further action on the Investigator's part concerning subject consent.

APPENDIX E

Self-Certification of Surrogate Decision Makers for Potential Subject's Participation in University of California Research

Self-certification of Surrogate Decision Makers for Potential Subject's Participation in University of California Research

Section 1:
I am willing to serve as a surrogate decision maker for _____
(Potential Subject)

to participate in _____
(Title of research project and IRB #)

research conducted by _____
(Principal Investigator)

Section 2:

Category of Potential Surrogate	**Check (√) the category that best describes your relationship to the potential subject:**	**For the cateaories listed above yours, provide the name(s) of other relatives. *example, if you are the adult son or daughter of the potential subject, provi the names of adults, if any, who are be described by categories 1-4 only)***
1. Agent named in the potential subject's advanced health care directive.	☐	1.
2. Conservator or guardian of the potential subject, with authority to make health care decisions for the potential subject	☐	2.
3. Spouse of the potential subject.	☐	3.
4. Domestic partner of the potential subject	☐	4.
5. Adult son or daughter of the potential subject	☐	5.
6. Custodial parent of the potential subject	☐	6.
7. Adult brother or sister of the potential subject	☐	7.
8. Adult grandchild of the potential subject	☐	8.
9. Adult whose relationship to the potential subject does not fall within one of the above listed categories and is best described as: _____ (Example: cousin, aunt, etc.)	☐	9.

Section 3:
The following section information must be completed only for surrogate consent to participate in research in non-emergency settings:
*(Check the statement which **best** describes the basis of your knowledge of the potential subject)*

_____ I live with the potential subject and have done so for _____ years.

_____ I have discussed participation in research with the potential subject and believe that I can carry out his/her preferences.

_____ Other (please describe): _____

Section 4:
Potential Surrogate's Contact Information:

Name: _____
Address: _____
_____
Home Phone: ( ) _____
Work Phone: ( ) _____
Cell Phone: ( ) _____
E-mail: _____

_____ __/__/____ _____ __/__/____
Signature of Potential Surrogate Date Signature of Witness Date

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