Clinical Trials Update

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25th Annual National MPS Society Family Conference
St. Louis, MO    July 28-30, 2011
Disclosures

• I am a consultant for BioMarin Pharmaceutical, Shire HGT and Zacharon Pharmaceuticals.

• I serve on advisory boards and the speaking bureaus for Genzyme, BioMarin and Shire HGT.

• I am currently the principal investigator for a phase I/II intrathecal enzyme replacement clinical trials for MPS II sponsored by Shire HGT.
## Treatment Options for MPS

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<thead>
<tr>
<th></th>
<th>HSCT</th>
<th>ERT</th>
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<tr>
<td><strong>Somatic</strong></td>
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<td></td>
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<tr>
<td>• MPS I</td>
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<td>Yes</td>
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<tr>
<td>• MPS II</td>
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<td>No</td>
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<tr>
<td>• MPS IIIA</td>
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<td>No</td>
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<tr>
<td>• MPS IIIB</td>
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<td>• MPS IVA</td>
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<td>No</td>
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<tr>
<td>• MPS VI</td>
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<td>• MPS VII</td>
<td>?</td>
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<tr>
<td><strong>CNS</strong></td>
<td></td>
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<tr>
<td><strong>Available</strong></td>
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*Proven clinical benefit

Hematopoietic Stem Cell Transplantation (HSCT)  Enzyme Replacement Therapy (ERT)
ERT for MPS IVA

- A “Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multinational Clinical Study to Evaluate the Efficacy and Safety of 2.0 mg/kg/Week and 2.0 mg/kg/Every Other Week BMN 110 in Patients With Mucopolysaccharidosis IVA (Morquio A Syndrome)” will be starting soon in the US.
## Treatment Options for MPS

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<th>MPS Type</th>
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<tr>
<td>MPS VII</td>
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<td>?</td>
<td>?</td>
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*Proven clinical benefit
Blood-Brain Barrier

- The blood-brain barrier (BBB) is a selective barrier separating the blood from the cells of the central nervous system.
- It occurs along all brain capillaries and consists of tight junctions around the capillaries that do not exist in the normal circulation.
Blood-Brain Barrier (BBB) Function and Properties

- Protects the brain from "foreign substances" in the blood that may injure the brain.
- Protects the brain from hormones and neurotransmitters in the rest of the body.
- Maintains a constant environment for the brain.
- Large molecules, such as enzymes, do not pass through the BBB easily.
Intrathecal (IT) ERT in MPS

• Indications – Central nervous system manifestations and spinal cord compression due to dural thickening.

• Experience - Intrathecal ERT for spinal cord compression in attenuated patients with MPS I and MPS VI has been performed. No major adverse events have been reported related to the IT ERT. Overall clinical impression has been none to moderate improvement in the spinal cord compression symptoms.
Spinal cord compression due to dural thickening

15 year old with Hurler-Scheie syndrome
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• Experience - Intrathecal ERT for spinal cord compression in attenuated patients with MPS I and MPS VI has been performed. No major adverse events have been reported related to the IT ERT. Overall clinical impression has been minimal to mild/moderate improvement in the spinal cord compression symptoms.
Intrathecal ERT in MPS

• IT ERT is being used in conjunction with cord blood transplantation in patients with Hurler syndrome to attempt to prevent the transient neurological decline that occurs after transplantation.

• A clinical trial “A Study of Intrathecal Enzyme Replacement for Cognitive Decline in Mucopolysaccharidosis I” is recruiting patient who are six years and older.

• A phase I/II IT ERT clinical has started in Europe in patients with MPS IIIA.
Rationale for Intrathecal ERT for the Severe Form of MPS II

- The severe form of MPS II is a progressive disorder with both physical and neurological disease.
- IV idursulfase at the recommended dosage is not expected to cross the blood-brain barrier.
- No treatment is available for the neurological disease in MPS II.
- Preclinical data demonstrates that intrathecal enzyme can penetration into brain tissue, is taken up by cells in the CNS and capable of reducing lysosomal storage.
Multiple IT Injections of Idursulfase-IT in Cynomolgus Monkeys via an Intrathecal Drug Delivery Device (IDDD)

- Adult male Cynomolgus monkeys, 5-8 kg, N = 14
- An IDDD catheter was surgically implanted in the lumbar spinal canal
- 5 dosing groups: 0 (Vehicle), 3, 30, 100 or 150 mg idursulfase-IT
- All doses were administered in 1 mL of vehicle
- Each monkey received 3 doses at 1 month intervals
- Animals were sacrificed 24 h after the last dose and tissues and organs were harvested
Multiple IT injections of idursulfase-IT in Cynomolgus Monkeys via an IDDD

Figure 1. I2S Activity in the Brain by Region and Dose
Intrathecal ERT for the severe form of MPS II

- A phase I/II intrathecal ERT clinical trial is now enrolling MPS II patients with the severe form of MPS II to determine the safety and effectiveness of monthly enzyme administered using an implanted intrathecal drug delivery device.
Intrathecal Drug Delivery Device (IDDD)

The IDDD allows for the “intrathecal” injection of iduronate-2-sulfatase directly into the fluid (CSF) surrounding the spinal cord and brain.

**Figure 1:** Portal components and dimensions
A – Septum, B – Outlet tube, C – Suture hole

**Figure 2:** Catheter with guidewire

Images provided courtesy of Smiths Medical MD, Inc., St. Paul, Minnesota, USA
Intrathecal ERT for the severe form of MPS II

- The clinical trial was initially started at the University of North Carolina at Chapel Hill, but a site has now been established in Birmingham, UK.
- The trial is sponsored by Shire HGT.
- To be eligible initially for the study, the MPS II individual had to be between 3 and 8 years of age have some developmental delay, but could not have severe delays based on neurocognitive testing.
Hunter IT ERT Clinical Trial: Study Design for HGT-HIT-045

• Six monthly IT injections of idursulfase-IT via an IDDD with a long-term extension option
• 16 patients with a randomization (3 to 1) to study drug or no-treatment for six months
• Three dose to be evaluated; 10 mg, 30 mg, 100 mg
Hunter IT ERT Clinical Trial: Study Design for HGT-HIT-045

- An intracranial pressure of less than 30 cm of water
- No shunt for hydrocephalus or poorly controlled seizures or medical conditions representing a significant risk for anesthesia or surgery
- At least six months of IV Elaprase without reactions
Hunter IT ERT Clinical Trial: Current Eligibility Requirements

- Males with MPS II between 3-18 years of age

- Cognitive impairment due to Hunter syndrome with an
  - IQ ≤ 77
  or
  - a decline of between 15 and 30 IQ points in the last 3 months to 3 years
Hunter IT ERT Clinical Trial: Study Objectives

• Primary:
  – Safety and tolerability of ascending doses of idursulfase-IT
  – The safety, tolerability, and long term patency of the IDDD

• Secondary:
  – Conc. of idursulfase after single and repeated IT doses in blood
  – Effect of idursulfase-IT on CSF biomarkers
  – Effects of idursulfase-IT on urinary GAG

• Exploratory:
  – Effects of idursulfase-IT on clinical parameters
  – Effects of idursulfase-IT on functional activities of daily living
  – Potential relationships between biomarkers and CNS symptoms
Current Status of the Hunter IT ERT Clinical Trial

- 7 patients have been enrolled to date
- 4 patients have completed 6 months of monthly 10 mg IT injections and are now in the extension study at the same dose
- 1 patient has received 2 doses of 30 mg idursulfase-IT
- 2 patients have been randomized to no-treatment for six months
- 1 no-treatment patient was not eligible for the extension study
Current Status of the Hunter IT ERT Clinical Trial

- To date, the 10 mg idursulfase-IT monthly has been well tolerated.
- The intrathecal drug delivery device has failed and has been re-implanted in 3 out of the 5 patients receiving idursulfase-IT
Thank you for your attention!

Questions?