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To be as brave as the people we help.

Philip J. Vickers, Ph.D.
Global Head of Research & Development

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Ms. Barbara Wedehase
Executive Director, National MPS Society
PO Box 14686
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Dear Barbara,

I am reaching out to you to provide you and the members of the National MPS Society a comprehensive update on the current status of the development of Shire's SHP-609 program for MPS II patients with cognitive impairment. A similar update is being sent to the Canadian and UK MPS Societies.

As you are aware, Shire is investigating the use of idursulfase that has been formulated for direct administration into the cerebrospinal fluid. It is intended that the drug will be administered directly into the central nervous system (CNS) via an implanted intrathecal drug delivery device (IDDD). The development plan for the SHP-609 program has been designed for earliest possible registration with the goal of enabling broad access to patients with MPS II who have cognitive impairment. After working closely with the FDA and EMA over a period of more than a year, we are happy to say that we have reached agreement on the design of a controlled pivotal clinical trial that we hope will help establish safety and efficacy of idursulfase administered intrathecally (known as idursulfase-IT) via an IDDD. This agreement enables us to implement a single pivotal trial that, if successful, should be acceptable to both FDA and EMA for registration purposes. Additionally, I would like to note that in the US, the SHP-609 program will have to be filed and, if approved, regulated as a drug-device combination – which will require that Shire demonstrate the safety and efficacy of both the drug and the device in order to secure regulatory approval.

Long-term administration of intrathecal enzyme replacement therapy (ERT) is an unprecedented approach to delivery of the deficient enzyme directly to the CNS in order to bypass the blood brain barrier. Evidence for intrathecal administration of drugs comes from experience in administration of analgesic medications and chemotherapy, albeit for typically a more limited duration of time than the rare diseases being evaluated by Shire. Several methods have been evaluated for delivery of medications to the CNS such as IDDD, intracerebroventricular administration and lumbar puncture. Shire selected the IDDD for the investigational studies as we hope in the long term that the device may represent a less invasive way to deliver treatment to the CNS. This is especially important as many of the diseases for which we are developing therapies primarily affect young children and necessitate chronic treatment. The implantation of an IDDD is a neurosurgical procedure conducted under general anesthesia.

As part of our ambitious development plan, we are working to accumulate a robust package of pre-clinical and clinical evidence to submit to regulatory authorities. At this time however, the safety and efficacy of idursulfase-IT for patients with MPS II and cognitive impairment have not yet been established in clinical studies. As you are aware, we have completed a 16-patient Phase I/II clinical trial (HGT-HIT-045) where 12 patients received investigational drug. Fifteen out of the 16 patients subsequently enrolled in an ongoing extension study. At this time, we only have data in a limited number of patients enrolled in the Phase I/II clinical trial and its extension. Furthermore, and very importantly, the risks of long term administration of idursulfase-IT, including the risks of developing neutralizing antibodies, or the risk of infection associated with the monthly access to the cerebrospinal fluid, in a larger cohort of MPS II patients are yet unknown.

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Additionally, based on the experience in HGT-HIT-045 and its extension and our completed Phase I/II trial in Sanfilippo A (HGT-SAN-055), there were many challenges with the development of a satisfactory IDDD for these patients. The first device used in the trials showed an unacceptable level of device failures.

Since then, Shire has partnered with another device manufacturer to develop an IDDD which has certain features that we hope will prevent some of the device complications seen in the earlier clinical trials. Regulatory approval has been secured in the EU for introduction of the new device in clinical trials, and we have recently begun implantation of the new device in patients enrolled in our intrathecal clinical trials in Europe. We are conducting additional studies and working closely with the FDA to get approval to introduce the IDDD in clinical trials in the US. However, at this time, the device is on Partial Clinical Hold in the US pending the provision of additional device data for review by the FDA. We also have a limited supply of the IDDD, and we will need to test the performance of the device in this patient population in a controlled clinical trial before it can ultimately be approved. It is possible that further testing and additional device modifications may be needed based on the experience in the clinical trials.

Following agreement with the FDA and EMA on the clinical trial design, as noted above, we recently initiated the pivotal Phase II/III clinical trial HGT-HIT-094, known as AIM-IT. This study is a controlled, randomized, two-arm, multi-center, international, assessor-blinded study designed to assess the safety, tolerability and efficacy of 10 mg of idursulfase-IT administered once per month over a period of 12 months via an IDDD in MPS II patients 3-18 years of age who demonstrate early cognitive impairment. Shire expects to enroll up to 42 male patients in the AIM-IT study. There will be a 2:1 (active: no treatment) randomization where 28 patients randomized to the treatment arm will receive idursulfase-IT while patients randomized to the no treatment arm will not receive idursufase-IT. Included in AIM-IT is a sub-study enrolling patients under the age of 3 years all of whom will receive idursulfase-IT. All patients in the trial will continue to receive weekly intravenous idursulfase therapy. The primary objective of AIM-IT is to determine the effect of the treatment regimen in pediatric patients with MPS II and early cognitive impairment on the General Conceptual Ability (GCA) score as measured by the Differential Ability Scales (DAS-II). The key secondary objective of AIM-IT is to determine the effect of the treatment regimen in pediatric patients with MPS II and early cognitive impairment on the Adaptive Behavior Composite (ABC) score as measured by the Vineland Adaptive Behavior Scales (VABS-II).

We are planning to conduct this clinical trial in the United States, United Kingdom, Spain, Mexico, Argentina, Columbia and Canada. These countries were specifically selected as the primary endpoint of the study the DAS-II is validated only in English and Spanish. The trial is currently open for enrollment in the United Kingdom, Spain and the US. Although the device introduction in the clinical trials in the US is currently on hold as noted above, we have received approval to enroll up to 9 eligible patients in the US prior to the lifting of the Partial Clinical Hold. These patients, if randomized to treatment, would receive investigational idursulfase-IT via monthly lumbar puncture until such time as the IDDD is available for introduction in clinical trials in the US. Currently, one site is open for enrollment and the others are expected to follow in coming weeks.

We want to assure the members of the National MPS Society that we are working very hard to speed the development of idursulfase-IT as much as possible. These efforts include the successful negotiation for a single trial with both the FDA and EMA; the opening of additional sites; and working closely with the FDA to allow a limited number of US patients to enroll in the trial prior to the lifting of the Partial Clinical Hold with respect to the IDDD. We are focusing our efforts on collecting the necessary safety and efficacy data as expeditiously as possible.

We have as you know, received a number of requests for compassionate/early access to idursulfase-IT. We are deeply sympathetic to the situation of these families. However, in view of the extremely limited safety and efficacy data generated so far in the clinical trials, the introduction of a new IDDD and the unknown, long-term potential for drug-related immunogenicity, we do not have sufficient information to make a benefit-risk assessment that could support providing wider access at this time. Doing so at this stage in development may jeopardize a successful and timely conduct and conclusion of the AIM-IT trial, which will include a no-treatment arm to assess whether intrathecal idursulfase demonstrates evidence of efficacy. Ensuring patient safety and generating data with the goal of providing a safe and effective treatment to the wider MPS II community are

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our highest priorities for this program. Shire is considering the conduct of a supplementary study once the AIM-IT study has completed, if there is sufficient evidence establishing the safety and efficacy of idursulfase-IT and the new device. We hope this could occur in the second half of 2016; however, this timing is subject to the successful enrollment and completion of the AIM-IT trial and therefore could be even later. Additional information about Shire's position on compassionate use is available on our website at the following link: http://www.shire.com/shireplc/en/about/policies/compassionate-use.

Again, I would like to re-emphasize that Shire's goal is to have an approved product and device available to all MPS II patients around the world as soon as possible. We are focusing our efforts on our clinical trials in the hopes of generating the evidence that administration of idursulfase-IT and the new IDDD are safe and efficacious in this patient population.

We would like to continue our close partnership with the National MPS Society, and we hope that we may count on its members to support the AIM-IT trial. As this program progresses, we propose to have a teleconference with you and other MPS Societies such as the Canadian MPS Society and International MPS Network, on a regular basis so that we can update you on the ongoing development efforts.

We will be reaching out to you in the coming days to schedule a follow up teleconference to discuss further and answer any questions. We look forward to working closely with you and the members of the National MPS Society.

Kind regards,

Philip J. Vickers, Ph.D.
Global Head of Research and Development
Shire