Shire’s investigational SHP609, idursulfase-IT, receives FDA Fast Track designation for the treatment of neurocognitive decline associated with Hunter syndrome

Lexington, MA – January 26, 2015 – Shire plc (LSE: SHP, NASDAQ: SHPG) announces that the United States Food and Drug Administration (FDA) has granted Fast Track designation for SHP609 (idursulfase-IT; also known as HGT-2310) for the treatment of neurocognitive decline associated with Hunter syndrome (mucopolysaccharidosis II or MPSII). This investigational formulation of idursulfase has been designed for direct administration into the cerebrospinal fluid via an intrathecal drug delivery device* (IDDD). This formulation is being investigated and developed for use with Shire’s currently approved treatment for Hunter syndrome, ELAPRASE® (idursulfase). ELAPRASE is administered intravenously and does not cross the blood-brain barrier in clinically relevant amounts.

“This is not only the first treatment being investigated to address the significant unmet need of slowing the cognitive decline in MPS II patients, but also the furthest an intrathecal program for enzyme replacement has ever progressed,” said Dr. Philip J. Vickers, Head of Research and Development at Shire. "This Fast Track designation is further recognition of the critical need to develop new, effective therapy options for patients with Hunter syndrome with cognitive impairment."

The FDA's Fast Track program is designed to facilitate the development and expedite the review of drugs that address serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. Fast Track designation provides increased opportunities to interact and meet with FDA, and increases the likelihood of being eligible for priority review if supported by clinical data at the time of BLA.

Shire is currently enrolling patients in its Phase 2/3 pivotal trial (HGT-HIT-094 or AIM-IT), which is a controlled, randomized, open-label, multi-center, assessor-blinded study designed to determine the effect on clinical parameters of neurodevelopmental status of monthly administration of idursulfase IT in pediatric patients with Hunter syndrome and early cognitive impairment who already receive and tolerate therapy with ELAPRASE. An extension study is also planned to assess long-term safety and efficacy.

For further information on the idursulfase IT pivotal trial please go to: https://clinicaltrials.gov/ct2/show/NCT02055118

About Hunter Syndrome
Hunter syndrome is a severely debilitating rare disease that affects 1 in 162,000 total live births, and mainly males. Hunter syndrome is an X-linked disorder caused by a deficiency or absence of the lysosomal enzyme iduronate-2-sulfatase (I2S), which leads to severe clinical complications and early mortality.

* The IDDD used in this trial is investigational in the U.S., but has a CE mark in the EU
About ELAPRASE (idursulfase)
ELAPRASE is an intravenous enzyme replacement therapy (ERT) approved for the treatment of patients with Hunter syndrome in 58 countries worldwide including countries in Asia Pacific, Europe, Latin America and North America. ELAPRASE should only be used in accordance with locally approved prescribing information.

U.S. INDICATION: ELAPRASE
ELAPRASE is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). ELAPRASE has been shown to improve walking capacity in patients 5 years and older.

In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long term clinical outcome; however, treatment with ELAPRASE has reduced spleen volume similarly to that of adults and children 5 years of age and older.

The safety and efficacy of ELAPRASE have not been established in pediatric patients less than 16 months of age.

ELAPRASE IMPORTANT SAFETY INFORMATION

WARNING: RISK OF ANAPHYLAXIS
Life-threatening anaphylactic reactions, presenting as respiratory distress, hypoxia, hypotension, urticaria and/or angioedema of throat or tongue have occurred in some patients during and up to 24 hours after ELAPRASE. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions, and require additional monitoring.

Hypersensitivity Reactions Including Anaphylaxis:
Ensure that personnel administering product are adequately trained in cardiopulmonary resuscitative measures, and have ready access to emergency medical services (EMS). If anaphylactic or other acute reactions occur, immediately discontinue the infusion of ELAPRASE and initiate appropriate medical treatment. Observe patients closely for an appropriate period of time after administration of ELAPRASE, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing reports. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs and symptoms occur. When severe reactions have occurred during clinical trials, subsequent infusions were managed with antihistamine and/or corticosteroids prior to or during infusions, a slower rate of ELAPRASE infusion, and/or early discontinuation of the ELAPRASE infusion.

Risk of Hypersensitivity, Serious Adverse Reactions, and Antibody Development in Hunter Syndrome Patients with Severe Genetic Mutations:
Hunter syndrome patients aged 7 years and younger with complete gene deletion, large gene rearrangement, nonsense, frameshift or splice site mutations experienced a higher incidence of hypersensitivity reactions, serious adverse reactions and anti-idursulfase antibody development.

Risk of Acute Respiratory Complications:
Patients with compromised respiratory function or acute febrile or respiratory illness may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient’s clinical status prior to administration of ELAPRASE and consider delaying the ELAPRASE infusion.

Risk of Acute Cardiorespiratory Failure:
Caution should be exercised when administering ELAPRASE to patients susceptible to fluid overload, or patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated. These patients may be at risk of serious exacerbation of their cardiac or respiratory status during infusions. Appropriate medical support and monitoring measures should be readily available during ELAPRASE infusion, and some patients may require prolonged observation times that should be based on the individual needs of the patient.

**Adverse Reactions:**
In clinical trials, the most frequent serious adverse reactions following ELAPRASE treatment were hypoxic episodes. Other notable serious adverse reactions that occurred in the ELAPRASE-treated patients but not in the placebo-treated patients included one case each of: cardiac arrhythmia, pulmonary embolism, cyanosis, respiratory failure, infection, and arthralgia. The most common adverse reactions occurring in at least three patients (≥9%) aged five years and older were headache, pruritus, musculoskeletal pain, urticaria, diarrhea, and cough. The most common adverse reactions occurring in at least three patients (≥10%) aged seven years and younger were pyrexia, rash, vomiting, and urticaria. In all clinical trials, the most common adverse reactions requiring medical intervention were hypersensitivity reactions, and included rash, urticaria, pruritus, flushing, pyrexia, and headache.

**Immunogenicity:**
In clinical trials in patients 5 years and older, 32 of 63 (51%) patients tested positive for anti-idursulfase IgG antibodies (Ab) at least one time. Of the 32 Ab-positive patients, 23 of 32 (72%) tested positive for Ab at three or more different time points (persistent Ab). The incidence of hypersensitivity reactions was higher in patients who tested positive for Ab than those who tested negative. Thirteen of 32 (41%) Ab-positive patients also tested positive for antibodies that neutralize idursulfase uptake into cells (neutralizing antibodies, NAb) or enzymatic activity at least one time, and 8 (25%) of Ab-positive patients had persistent NAb. There was no clear relationship between the presence of either Ab or NAb and therapeutic response. In the clinical trial in patients 7 years and younger, 19 of 28 (68%) patients treated with ELAPRASE 0.5 mg/kg once weekly tested Ab-positive, with 16 of 19 (84%) having persistent Ab. In addition, 15 of 19 (79%) Ab-positive patients tested positive for NAb, with 14 of 15 (93%) having persistent NAb.

**Postmarketing Experience:**
Late-emergent symptoms and signs of anaphylactic reactions have occurred up to 24 hours after initial treatment and recovery from an initial anaphylactic reaction. In addition, patients experienced repeated anaphylaxis over a two- to four-month period, up to several years after initiating ELAPRASE treatment. Serious adverse reactions that resulted in death included cardiorespiratory arrest, respiratory failure, respiratory distress, cardiac failure, and pneumonia.

Please see the full Prescribing Information, including the Boxed Warning at: [www.elaprase.com](http://www.elaprase.com)

To report SUSPECTED ADVERSE REACTIONS, contact Shire Medical Information at 1-866-888-0660 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

For further information please contact:

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NOTES TO EDITORS

Shire enables people with life-altering conditions to lead better lives.

Our strategy is to focus on developing and marketing innovative specialty medicines to meet significant unmet patient needs.

We focus on providing treatments in Rare Diseases, Neuroscience, Gastrointestinal, and Internal Medicine and we are developing treatments for symptomatic conditions treated by specialist physicians in other targeted therapeutic areas, such as Ophthalmics.

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THE “SAFE HARBOR” STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included in this communication that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire’s results could be materially adversely affected. The risks and uncertainties include, but are not limited to, that:

- Shire’s products may not be a commercial success;
- revenues from ADDERALL XR and INTUNIV are subject to generic erosion;
- the failure to obtain and maintain reimbursement, or an adequate level of reimbursement, by third-party payors in a timely manner for Shire’s products may impact future revenues, financial condition and results of operations;
- Shire conducts its own manufacturing operations for certain of its products and is reliant on third party contract manufacturers to manufacture other products and to provide goods and services. Some of Shire’s products or ingredients are only available from a single approved source for manufacture. Any disruption to the supply chain for any of Shire’s products may result in Shire being unable to continue marketing or developing a product or may result in Shire being unable to do so on a commercially viable basis for some period of time;
- the development, approval and manufacturing of Shire’s products is subject to extensive oversight by various regulatory agencies. Submission of an application for regulatory approval of any of our product candidates, such as our planned submission of a New Drug Application to the FDA for Lifitegrast, may be delayed for any number of reasons and, once submitted, may be subjected to lengthy review and ultimately rejected. Moreover, regulatory approvals or interventions associated with changes to manufacturing sites, ingredients or manufacturing processes could lead to significant delays, increase in operating costs, lost product sales, an interruption of research activities or the delay of new product launches;
- the actions of certain customers could affect Shire’s ability to sell or market products profitably. Fluctuations in buying or distribution patterns by such customers can adversely impact Shire’s revenues, financial condition or results of operations;
- investigations or enforcement action by regulatory authorities or law enforcement agencies relating to Shire’s activities in the highly regulated markets in which it operates may result in significant legal costs and the payment of substantial compensation or fines;
- adverse outcomes in legal matters and other disputes, including Shire’s ability to enforce and defend patents and other intellectual property rights required for its...
business, could have a material adverse effect on Shire’s revenues, financial condition or results of operations;

- Shire faces intense competition for highly qualified personnel from other companies, academic institutions, government entities and other organizations. Shire is undergoing a corporate reorganization and the consequent uncertainty could adversely impact Shire’s ability to attract and/or retain the highly skilled personnel needed for Shire to meet its strategic objectives;

- failure to achieve Shire’s strategic objectives with respect to the acquisition of ViroPharma Incorporated may adversely affect Shire’s financial condition and results of operations;

- Shire’s proposed acquisition of NPS Pharma may not be consummated due to the occurrence of an event, change or other circumstances that gives rise to the termination of the merger agreement;

- a governmental or regulatory approval required for the proposed acquisition of NPS Pharma may not obtained, or may be obtained subject to conditions that are not anticipated, or another condition to the closing of the proposed acquisition may not be satisfied;

- NPS Pharma may be unable to retain and hire key personnel and/or maintain its relationships with customers, suppliers and other business partners pending the consummation of the proposed acquisition by Shire, or NPS Pharma’s business may be disrupted by the proposed acquisition, including increased costs and diversion of management time and resources;

- difficulties in integrating NPS Pharma into Shire may lead to the combined company not being able to realize the expected operating efficiencies, cost savings, revenue enhancements, synergies or other benefits at the time anticipated or at all;

and other risks and uncertainties detailed from time to time in Shire’s or NPS Pharma’s filings with the U.S. Securities and Exchange Commission, including their respective most recent Annual Reports on Form 10-K.