Press Release

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Shire's Investigational Subcutaneous C1 esterase inhibitor (C1 INH [Human]) Liquid for Injection (SHP616) Significantly Reduces Hereditary Angioedema Monthly Attack Rate Versus Placebo in a Phase 3 Pivotal Trial

- *Median HAE attack reduction of 79% from Day 0 and 85% from Day 14*
- *38% of patients HAE attack free while receiving SHP616*

Lexington, MA – September 11, 2017 – Shire plc (LSE: SHP, NASDAQ: SHPG), the global leader in rare diseases, announces positive topline Phase 3 results for the SAHARA™ study, a global, multi-center, randomized, double-blind, placebo-controlled, partial crossover trial that evaluated the efficacy and safety of subcutaneously administered C1 esterase inhibitor [human] Liquid for Injection, also referred to as SHP616 Liquid, versus placebo over two 14-week treatment periods in patients 12 years of age or older with symptomatic Hereditary Angioedema (HAE). SHP616 is an investigational treatment administered subcutaneously, being evaluated for the prevention of angioedema attacks in patients with HAE—a rare genetic disease characterized by recurrent swelling of extremities, gastrointestinal tract, and upper airways.

"Patients want and deserve options when it comes to their treatment for HAE," said Dr. William Lumry, Clinical professor of Internal Medicine at Southwestern Medical School, Dallas, Texas. "These results are clinically significant, meaningful and relevant to HAE patients whose needs are currently not met today."

This study met its primary endpoint and all key secondary endpoints. The fixed 2000 IU dose, administered every three to four days as a single 4mL subcutaneous injection, led to a statistically significant and clinically meaningful reduction of 2.32 (95% CI: 1.74 – 2.89, $p < 0.0001$) attacks/month in the mean HAE attack rate (primary endpoint) compared to placebo. In a commonly reported measure of effectiveness, SHP616 Liquid yielded a median HAE attack rate reduction of 79% from Day 0 (entire treatment period) or 85% from Day 14 (after reaching steady state) compared to placebo. A total of 78% of patients' experienced 50% or greater reduction in HAE attack rate (key secondary) compared to placebo, and 38% of patients were attack free during their SHP616 Liquid treatment period, compared to 9% during the placebo period. The 75 patients randomized in this study were required to have at least two HAE attacks per month in the three consecutive months prior to screening, and were representative of the full HAE disease spectrum (88% Type 1 HAE; 12% Type 2 HAE; mean of 11.9 attacks three months prior to screening; 51% had a history of prior use of long term prophylaxis). The study was completed by 77% of patients in the crossover sequences and 87% in the active-only sequence.

No treatment-related serious adverse events or deaths were reported. In the crossover sequences, the most common adverse events were viral upper respiratory tract infection (5.3% placebo vs. 12.5% SHP616 Liquid), upper respiratory tract infection (7.0% placebo vs. 12.5% SHP616 Liquid) and headache (10.5% placebo vs. 10.7% SHP616 Liquid). There were no venous thromboembolic events and no anti-C1 INH antibodies were detected.

“In developing medicines for HAE patients over the last decade, we know that treating physicians and patients suffering from HAE look for efficacious, safe and convenient treatment and prevention options, and we continue to strive to meet as many of these needs as possible through continued innovation.” said Howard Mayer, M.D., ad interim Head of Research and Development, Shire. "We are very pleased with the strong results of this study, which demonstrated efficacy with a low volume dosing regimen, and what it potentially could mean for the global HAE community, if approved.”

HAE is a rare, genetic disorder estimated to affect about 1 in 10,000 to 1 in 50,000 people worldwide. The condition results in recurrent, localized edema (swelling). The areas of the body most commonly affected are the extremities, gastrointestinal tract, and upper airways. The swelling can be debilitating and painful, potentially impacting both work and education for people living with HAE. Swelling of the throat can be life-threatening due to asphyxiation.

About the SAHARA™ Study
The SAHARA™ study is a global, multi-center, randomized, double-blind, placebo-controlled, two-period, three-sequence, partial crossover study, that allowed an evaluation of efficacy and safety of subcutaneously administered C1 esterase inhibitor [human] Liquid for Injection, also referred to as SHP616 Liquid, versus placebo, for prevention of HAE attacks. Patients meeting eligibility criteria were enrolled into one of three treatment sequences after being stratified by baseline C1 INH LTP (two cross-over sequences of 14 weeks duration, with SHP616 followed by placebo or vice versa; and the third sequence with administration of SHP616 consecutively for 28 weeks). To fully evaluate the efficacy of 2000 IU of SHP616 Liquid alone, additional C1 INH was prohibited, and Firazyr® (icatibant) was used to treat acute angioedema attacks, in patients ≥ 18 years.

Shire’s Commitment to Hereditary Angioedema (HAE)
Shire is a dedicated, long-term partner to the HAE community with nearly a decade of clinical and real-world experience supporting patients. We believe each patient deserves a right-fit approach to treatment, and our existing portfolio of products currently includes three distinct therapy options. We are committed to serial innovation and rely on our expertise to help fulfill unmet treatment needs for patients with HAE. Beyond our focus on developing novel treatments, we provide specialized services and support offerings that help meet the needs of the HAE community. Learn more at shire.com.

Indication
FIRAZYR is a medicine used to treat acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older.

Important Safety Information
Laryngeal attacks can become life threatening. **If you have an HAE attack of the throat (laryngeal attack)**, inject FIRAZYR and then go to the nearest hospital emergency room right away.
The most common side effects of FIRAZYR include:

- redness, bruising, swelling, warmth, burning, itching, irritation, hives, numbness, pressure, or pain at the injection site
- fever
- too much of an enzyme called transaminase in your blood
- dizziness
- nausea
- headache
- rash

These are not all of the possible side effects of FIRAZYR. Tell your healthcare provider if you have any side effect that bothers you or that does not go away. You are encouraged to report

negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Tell your healthcare provider if you have any other medical conditions, if you are breastfeeding or plan to breastfeed, or if you are pregnant or planning to become pregnant. FIRAZYR has not been evaluated in pregnant or nursing women. You and your healthcare provider will decide if FIRAZYR is right for you.

If your symptoms continue or come back, you may repeat your FIRAZYR injection at least 6 hours apart. Do not use more than 3 doses of FIRAZYR in a 24-hour period.

Tiredness, drowsiness, and dizziness have been reported following the use of FIRAZYR. If this occurs, do not drive a car, use machinery, or do anything that needs you to be alert.

For additional safety information, click here for Prescribing Information, including Patient Information, and discuss with your doctor.

For further information please contact:

Media Relations

Elizabeth Kalina	ekalina@shire.com	+1 781 482 2713
Gwen Fisher	gfisher@shire.com	+1 781 482 9649

Investor Relations

Ian Karp	ikarp@shire.com	+1 781 482 9018
Robert Coates	rcoates@shire.com	+44 1256 894874

NOTES TO EDITORS

About Shire

Shire is the leading global biotechnology company focused on serving people with rare diseases and other highly specialized conditions. We strive to develop best-in-class products, many of which are available in more than 100 countries, across core therapeutic areas including Hematology, Immunology, Neuroscience, Ophthalmics, Lysosomal Storage Disorders, Gastrointestinal / Internal Medicine / Endocrine and Hereditary Angioedema; and a growing franchise in Oncology.

Our employees come to work every day with a shared mission: to develop and deliver breakthrough therapies for the hundreds of millions of people in the world affected by rare diseases and other high-need conditions, and who lack effective therapies to live their lives to the fullest.

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