TOLERABILITY DATA FOR SHIRE’S CUVITRU ACCEPTED FOR ORAL PRESENTATION AT THE AMERICAN COLLEGE OF ALLERGY, ASTHMA & IMMUNOLOGY ANNUAL MEETING

Data reveals key findings on the tolerability of CUVITRU [Immune Globulin Subcutaneous (Human), 20% Solution] for patients, regardless of treatment infusion volume and rates

Lexington, Mass. – November 12, 2016 Shire plc (LSE: SHP, NASDAQ: SHPG) will present additional data supporting the tolerability of CUVITRU [Immune Globulin Subcutaneous (Human), 20% Solution] in patients two years of age and older with primary immunodeficiency (PI) diseases in North America at the 2016 Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology in San Francisco. The presentation will highlight key findings on established tolerability of CUVITRU for PI patients who received CUVITRU in the Phase II/III North American clinical trial. Of note, increased infusion volumes and rates were not associated with an increase in causally-related local adverse reactions, and infusions were well-tolerated during onboarding and throughout the study.

“As the latest treatment to be added to Shire’s industry-leading IG portfolio, CUVITRU exemplifies our commitment to reducing the burden of PI for patients living with this challenging, often debilitating condition,” said Philip J. Vickers, Ph.D., Head of Research and Development, Shire. “As a customizable therapy, CUVITRU offers patients and physicians multiple options to tailor their IG treatment to fit their needs and preferences, such as varying the volume/site, the dosing frequency, and infusion rate.”

PI is a group of more than 300 genetic disorders in which part of the body’s immune system is missing or functions improperly, in some cases making it more difficult to fight off infections.\(^1\,^2\) PI affects six million people worldwide, of which approximately 250,000 reside in the U.S.\(^3\,^4\) Most people with PI have abnormally low or nonexistent IG levels, and may benefit from IG replacement treatment to help the body prevent infections. Since it only offers temporary protection, many people with PI require IG replacement treatment throughout their lives.\(^5\)

“AACAI’s annual meeting is a welcome opportunity for the immunology community to learn more about the benefits CUVITRU can offer patients with PI looking to take control of their IG treatment,” said Sudhir Gupta, MD, PH.D., MACP, Chief of Basic and Clinical Immunology, and Director, Programs in Primary Immunodeficiency and Aging, at University of California, Irvine. “The data reinforces that patients can work with their physician to individualize their dosage and administration schedule, allowing for greater flexibility and control within their normal daily routine.”

As demonstrated in the clinical trials, CUVITRU offers patients the ability to infuse up to 60 mL (12 grams) per site and up to 60 mL per hour per site, as tolerated, allowing for fewer infusion sites and shorter infusion durations compared to other conventional subcutaneous IG treatments. The data to be presented at AACAI offers additional evidence that patients achieved the increased rate and volume, without compromising tolerability. Approximately 72% of patients in the clinical trial achieved the maximum infusion rate of 60 mL per hour per site, occurring after a median time of 3 infusions with no association between infusion rate and causally related local adverse event (AE) rates. Importantly, 99.8% infusions of CUVITRU were completed without a rate reduction, interruption, or discontinuation indicating the infusions were well tolerated. In addition, 75% of infusions delivered a volume of 30 mL per site or greater, with no association
between volume per site and causally-related local AEs. The full clinical trial results can be found in *Journal of Clinical Immunology*.

CUVITRU is the latest product in Shire's industry-leading IG portfolio. The U.S. Food and Drug Administration approved CUVITRU in September 2016. Shire also received successful completion of a decentralized procedure to support CUVITRU approval by 17 authorities in Europe in June 2016. The company expects to initiate additional global regulatory submissions for CUVITRU in late 2016 and 2017.

For more information on CUVITRU, please visit [www.cuvitru.com](http://www.cuvitru.com).

**About Primary Immunodeficiency**

Primary immunodeficiencies (PI) are a group of more than 300 disorders in which part of the body's immune system is missing or does not function properly. Normally, the immune system protects the body from pathogenic microorganisms like bacteria, viruses, and fungi, which can cause infectious diseases. When any part of a person's immune system is absent or dysfunctional, the individuals are susceptible to infections, and it may take longer to recover from infections. When a defect in the immune system is inherited and genetically determined, it is called primary immune deficiency.

**About CUVITRU [Immune Globulin Subcutaneous (Human), 20% Solution]**

CUVITRU is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Solution indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older.

CUVITRU is for subcutaneous infusion only.

**Detailed Important Risk Information**

**BOXED WARNING: THROMBOSIS**

Thrombosis may occur with immune globulin products, including CUVITRU. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors.

For patients at risk of thrombosis, administer CUVITRU at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.

**CONTRAINDICATIONS**

CUVITRU is contraindicated in patients who have had an anaphylactic or severe systemic hypersensitivity reaction to the subcutaneous administration of human immune globulin and in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity to human immune globulin treatment.

**WARNINGS and PRECAUTIONS**

**Hypersensitivity:** Severe hypersensitivity reactions may occur, even in patients who have tolerated previous treatment with human immune globulin. IgA-deficient patients with antibodies to IgA are at greater risk of developing potentially severe hypersensitivity and anaphylactic reactions.
Renal Dysfunction/Failure: Monitor renal function and urine output and consider lower, more frequent dosing in patients who are at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure.

Thrombosis: Monitor for signs and symptoms of thrombosis and assess blood viscosity for those at risk for hyperviscosity.

Aseptic Meningitis Syndrome (AMS): Monitor for clinical signs and symptoms of AMS.

Hemolysis: Monitor for clinical signs and symptoms of hemolysis and delayed hemolytic anemia.

Transfusion-Related Acute Lung Injury (TRALI): Monitor for pulmonary adverse reactions associated with TRALI.

Transmittable Infectious Agents: Because CUVITRU is made from human plasma, it may carry a risk of transmitting infectious agents, such as viruses and other pathogens. No confirmed cases of transmission of viral diseases or variant Creutzfeldt-Jakob disease (vCJD) have been associated with CUVITRU.

Interference with Laboratory Tests: False positive serological test results, with the potential for misleading interpretation, may occur as the result of passively transferred antibodies.

ADVERSE REACTIONS
The most common adverse reactions observed in clinical trials in ≥ 5% of patients were: local adverse reactions, systemic adverse reactions including headache, nausea, fatigue, diarrhea, and vomiting.

Please see Full Prescribing Information, including Boxed Warning regarding Thrombosis, available at: http://www.shirecontent.com/PI/PDFS/Cuvitru_USA_ENG.pdf.

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References


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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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Forward-Looking Statements

Statements included herein that are not historical facts, including without limitation statements concerning future strategy, plans, objectives, expectations and intentions, the anticipated timing of clinical trials and approvals for, and the commercial potential of, inline or pipeline products 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, the following:

- Shire’s products may not be a commercial success;
- increased pricing pressures and limits on patient access as a result of governmental regulations and market developments may affect Shire’s 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 manufacture of Shire’s products is subject to extensive oversight by various regulatory agencies. Regulatory approvals or interventions associated with changes to manufacturing sites, ingredients or manufacturing processes could lead to significant delays, an increase in operating costs, lost product sales, an interruption of research activities or the delay of new product launches;
- certain of Shire’s therapies involve lengthy and complex processes, which may prevent Shire from timely responding to market forces and effectively managing its production capacity;
- Shire has a portfolio of products in various stages of research and development. The successful development of these products is highly uncertain and requires significant expenditures and time, and there is no guarantee that these products will receive regulatory approval;
- 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 affect Shire’s revenues, financial conditions or results of operations;
- Shire’s products and product candidates face substantial competition in the product markets in which it operates, including competition from generics;
adverse outcomes in legal matters, tax audits 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 the combined company’s revenues, financial condition or results
of operations;
• inability to successfully compete for highly qualified personnel from other companies and
organizations;
• failure to achieve the strategic objectives with respect to Shire’s acquisition of NPS
Pharmaceuticals, Inc., Dyax Corp. (“Dyax”) or Baxalta Inc. (“Baxalta”) may adversely affect Shire’s
financial condition and results of operations;
• Shire’s growth strategy depends in part upon its ability to expand its product portfolio through
external collaborations, which, if unsuccessful, may adversely affect the development and sale of
its products;
• a slowdown of global economic growth, or economic instability of countries in which Shire does
business, as well as changes in foreign currency exchange rates and interest rates, that adversely
impact the availability and cost of credit and customer purchasing and payment patterns, including
the collectability of customer accounts receivable;
• failure of a marketed product to work effectively or if such a product is the cause of adverse side
effects could result in damage to the Shire’s reputation, the withdrawal of the product and legal
action against Shire;
• 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;
• Shire is dependent on information technology and its systems and infrastructure face certain risks,
including from service disruptions, the loss of sensitive or confidential information, cyber-attacks
and other security breaches or data leakages that could have a material adverse effect on Shire’s
revenues, financial condition or results of operations;
• Shire incurred substantial additional indebtedness to finance the Baxalta acquisition, which may
decrease its business flexibility and increase borrowing costs;
• difficulties in integrating Dyax or Baxalta 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 filings with the Securities and Exchange
Commission, including those risks outlined in “ITEM 1A: Risk Factors” in Shire’s Quarterly Report on Form
10-Q for the quarter ended June 30, 2016.

All forward-looking statements attributable to us or any person acting on our behalf are expressly qualified
in their entirety by this cautionary statement. Readers are cautioned not to place undue reliance on these
forward-looking statements that speak only as of the date hereof. Except to the extent otherwise required
by applicable law, we do not undertake any obligation to update or revise forward-looking statements,
whether as a result of new information, future events or otherwise.