

## **Shire Submits Biologics License Application (BLA) for REPLAGAL<sup>®</sup> with the U.S. Food and Drug Administration (FDA)**

Filing underscores Shire's ongoing commitment to providing U.S. Fabry patients with an alternative treatment option. Company recaps velaglucerase alfa status.

**Cambridge, MA – December 22, 2009** – Shire plc (LSE: SHP, NASDAQ: SHPGY), the global specialty biopharmaceutical company, today announced that it has submitted a BLA with the FDA for REPLAGAL<sup>®</sup> (agalsidase alfa), its enzyme replacement therapy for Fabry disease. REPLAGAL first received marketing authorization in the European Union in 2001, and is approved for the treatment of Fabry disease in 45 countries.

REPLAGAL is currently available to U.S. Fabry patients under an FDA-approved treatment protocol, and the Company is also supporting emergency IND requests. Shire worked closely with the FDA to establish an early access program in response to the ongoing shortage of the currently marketed treatment for Fabry disease in the U.S.

"We continue to deliver on our commitment to the Fabry community by filing a BLA to support long-term access to REPLAGAL in the United States," said Sylvie Grégoire, President of Shire Human Genetic Therapies. "We understand that this has been a difficult time for patients and we remain committed to doing all we can to support the Fabry community during the supply shortage and for the long-term."

Shire expects its REPLAGAL supply to be adequate to meet anticipated global demand.

### **Update on Shire's Potential Gaucher Disease Treatment**

In light of the supply restrictions on one of the commercially available products for Gaucher disease during the past six months, Shire has provided the following update on recent key activities regarding global access to velaglucerase alfa, its enzyme replacement therapy in development for Type 1 Gaucher disease:

- The Company has submitted marketing applications for velaglucerase alfa in the U.S., EU and Canada. In the U.S., the application is being reviewed by the FDA under Priority Review with a PDUFA date of February 28, 2010. The CHMP has granted accelerated review for the EU MAA.
- The FDA recently completed the pre-approval inspections of Shire's Cambridge and Lexington Massachusetts facilities for the manufacturing and testing of velaglucerase alfa. These inspections were an important milestone in the review and approval process for the U.S. NDA for velaglucerase alfa.
- Shire continues to work with U.S. physicians to provide access to velaglucerase alfa under an FDA-approved treatment protocol. In Europe and other countries outside the U.S., patients continue to receive the product through pre-approval access programs.

### **About REPLAGAL® (agalsidase alfa)**

REPLAGAL is a human form of enzyme alpha-galactosidase A (a-Gal A) manufactured in a human cell line by gene activation. REPLAGAL is approved in 45 countries worldwide. REPLAGAL is not currently approved for commercial sale in the U.S.

REPLAGAL is the only human-cell-line-derived form of enzyme replacement therapy (ERT) that is indicated for the long-term treatment of patients with a confirmed diagnosis of Fabry disease ( $\alpha$ -galactosidase A deficiency).

### **About Fabry disease**

Fabry disease is a lysosomal storage disorder (LSD) that interferes with the body's ability to break down a specific fatty substance (globotriaosylceramide or Gb3) which accumulates within the body due to deficiency of a specific enzyme ( $\alpha$ -galactosidase A).

Fabry disease affects both males and females and can present with a number of signs or symptoms of variable degree, such as cardiovascular and/or renal dysfunction, intense or burning pain, heat intolerance, skin lesions, gastrointestinal complaints, hearing loss, and ocular problems.

Lifespan is typically reduced in patients with Fabry disease by approximately 20 years in men and 15 years in women, compared with the general population.<sup>1,2</sup> The principal causes of death are renal failure, cardiomyopathy and cerebrovascular events (e.g. stroke).<sup>3</sup>

Fabry disease affects an estimated 8,000 to 10,000 people worldwide.

### **About Gaucher disease**

Gaucher disease is an autosomal recessive disorder caused by mutations in the GBA gene which results in a deficiency of the lysosomal enzyme beta-glucocerebrosidase. This enzymatic deficiency causes an accumulation of glucocerebroside, primarily in macrophages. In this lysosomal storage disorder (LSD), clinical features are reflective of the distribution of Gaucher cells in the liver, spleen, bone marrow, skeleton, and lungs. The accumulation of glucocerebrosidase in the liver and spleen leads to organomegaly. Bone involvement results in skeletal abnormalities and deformities as well as bone pain crises. Deposits in the bone marrow and splenic sequestration lead to clinically significant anemia and thrombocytopenia.

Gaucher disease is the most prevalent LSD. Gaucher disease has classically been categorized into 3 clinical types. Type 1 is the most common; it is distinguished from Type 2 and Type 3 by the lack of early neurological symptoms. Type 1 Gaucher disease is characterized by variability in signs, symptoms, severity, and progression.

Shire's velaglucerase alfa program included the largest and most comprehensive set of Phase III clinical trials conducted to date for Gaucher disease. Over 100 patients at 24 sites in 10 countries around the world have participated in the clinical studies.

Velaglucerase alfa is made using Shire's proprietary technology, in a human cell line. The enzyme produced has the exact human amino acid sequence and has a human glycosylation pattern.

## **References**

1. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet* 2001;38:769-75.

2. MacDermot KD, Holmes A, Miners AH. Natural history of Fabry disease in affected males and obligate carrier females. *J Inherit Metab Dis* 2001;24 Suppl 2:13-14.

3. Mehta A, Widmer U. Natural history of Fabry disease. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry disease: perspectives from 5 years of FOS. Oxford: Oxford PharmaGenesis Ltd; 2006: p. 183-8.

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**SHIRE PLC**

Shire's strategic goal is to become the leading specialty biopharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on attention deficit hyperactivity disorder (ADHD), human genetic therapies (HGT) and gastrointestinal (GI) diseases as well as opportunities in other therapeutic areas to the extent they arise through acquisitions. Shire's in-licensing, merger and acquisition efforts are focused on products in specialist markets with strong intellectual property protection and global rights. Shire believes that a carefully selected and balanced portfolio of products with strategically aligned and relatively small-scale sales forces will deliver strong results.

For further information on Shire, please visit the Company's website: [www.shire.com](http://www.shire.com).

**"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995**

Statements included herein 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, the Company's results could be materially adversely affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of research, development, approval, reimbursement, manufacturing and commercialization of the Company's Specialty Pharmaceutical and Human Genetic Therapies products, as well as the ability to secure and integrate new products for commercialization and/or development; government regulation of the Company's products; the Company's ability to manufacture its products in sufficient quantities to meet demand; the impact of competitive therapies on the Company's products; the Company's ability to register, maintain and enforce patents and other intellectual property rights relating to its products; the Company's ability to obtain and maintain government and other third-party reimbursement for its products; and other risks and uncertainties detailed from time to time in the Company's filings with the Securities and Exchange Commission.

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