

A young boy with short brown hair and a hearing aid in his left ear is smiling broadly and pointing towards the camera. He is wearing a white long-sleeved shirt with dark blue horizontal stripes. He is positioned behind a red playground structure, which has a white handle and a red knob visible. The background is a blurred outdoor setting with greenery and a white fence.

Human Genetic Therapies



Operating review HGT



Sylvie Grégoire—President, Human Genetic Therapies

Human Genetic Therapies

Key corporate objectives out to 2015 on track to be achieved.

Two of Shire's key corporate objectives out to 2015 are to become or maintain a number one or number two market position in each of our therapeutic areas, and to generate more than 50% of our sales outside the US. This year's results show, the HGT business unit has already achieved both of these aims and expects to continue to contribute significantly to the achievement of these goals across the whole of Shire out to 2015. However, 2009 was also an important year for us for quite another reason—one which was much more closely related to the special relationships we have with treating physicians and patients, and how we fulfil our responsibilities to them.

Midway through 2009 one of our competitors suddenly had a problem at one of their manufacturing plants, which created an acute and unexpected shortage of their products, which in turn left many patients with limited treatment or no treatment at all. We were asked by the FDA and other authorities to step up and help by doing everything we could to make our treatments, which are currently in development or sold in other countries, available for these vulnerable people, many of whom are dealing with life-threatening conditions.

We brought forward the submission and expected launch of our new Gaucher disease therapy in the US, Canada and the EU, and gave hundreds of patients access to pre-license treatment through pre-approval programs. The same issue of shortage of supply affected the only other Enzyme Replacement Therapy ('ERT') treatment currently available for Fabry disease, and this meant that demand for our own drug, REPLAGAL, increased significantly this year. Again, our priority was to do the right thing for patients, even though there was a cost to us in doing that, both financially and in terms of the extra pressure it put on our manufacturing facilities. We were also able to find ways to supply the drug for free in the US by using treatment or emergency protocols for VPRIV (velaglucerase alfa for Gaucher disease) and REPLAGAL (for Fabry disease).

This has always been a business that has put the needs of patients first, and I'm particularly proud that we were able to show this in action this year, in such a clear and powerful way.

Sylvie Grégoire, President, Human Genetic Therapies

ELAPRASE

Hunter syndrome

Sales in 2009 \$353M

Prevalence
2,000 worldwide.

Product fact
Approved for treatment in 44 countries.

ELAPRASE is the first and only Enzyme Replacement Therapy for Hunter syndrome—a rare, progressive and life-threatening condition that primarily affects boys.

REPLAGAL

Fabry disease

Sales in 2009 \$194M

Prevalence
10,000 worldwide.

Product fact
Approved for treatment in 45 countries.

REPLAGAL replaces the enzyme which is missing or deficient in people suffering from Fabry disease. It's been shown to help improve both kidney function and heart size.

VPRIV

Gaucher disease

Prevalence
10,000 worldwide.

Product fact
Approved in the US on February 26, 2010 and available through pre-approval process around the world.

VPRIV supplements replace beta-glucocerebrosidase, the enzyme that catalyzes the hydrolysis of glucocerebroside, reducing the amount of accumulated glucocerebroside and correcting the pathophysiology of Gaucher disease.

ELAPRASE product sales (\$'M)



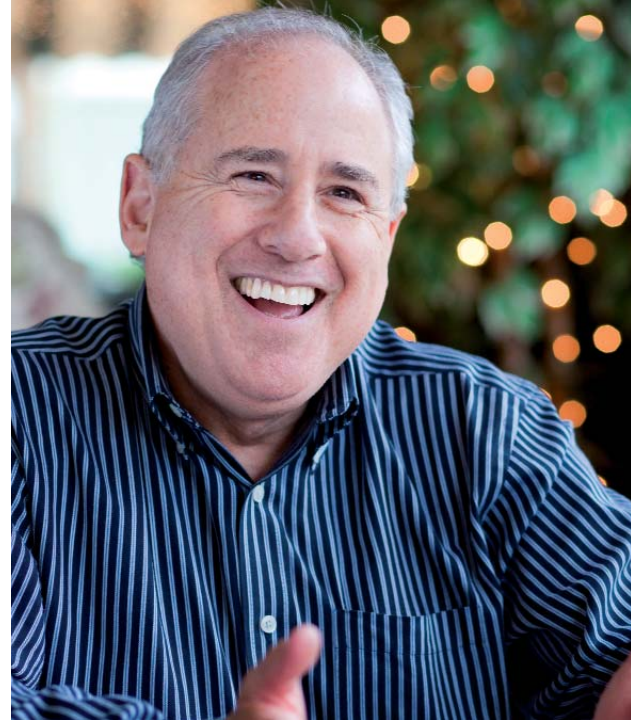
up **16%**

REPLAGAL product sales (\$'M)



up **10%**

Operating review HGT



Human Genetic Therapies

Key achievements in 2009

The most important achievement this year was the way the whole business pulled together to address the unexpected shortfall in market supply in two of HGT's key therapeutic areas. The US regulatory submission and expected launch for the Gaucher disease treatment VPRIV was brought forward ahead of schedule, and this drug received US approval on February 26, 2010, which is great news for the Gaucher patient population. Marketing Authorization Applications have also been made in the EU and Canada, and we expect that the product will be launched in those regions during 2010. It was also made available to patients in many countries across the world through national pre-approval access programs. Acceleration of these plans also meant bringing our own manufacturing plans forward by 18 months.

REPLAGAL was also affected by the same market supply problem, and the US marketing authorization submission was also completed in 2009 to meet this increased demand. The treatment was made available to patients in the US in advance of its formal regulatory approval, to help those affected by the shortage of the competitor's treatment. At the end of the year, a Biologics License Application was submitted for approval in the US. In February 2010, FDA requested additional pharmacokinetic comparability data. As a result, Shire withdrew its December BLA filing, and, at the suggestion of FDA, requested and received Fast Track designation. Shire quickly initiated a rolling BLA submission.

As well as growing sales of key products, HGT also expanded and streamlined its business in 2009. New decision-making forums were established to improve the way the division works and increase efficiency as the business grows internationally. A representative office was opened in Japan, and a lease signed on a new building in Lexington Technology Park. HGT now has 28 offices around the world and continues to set foot in countries where patients require treatments. We also see significant benefit in working with local expertise to improve local understanding and awareness of these diseases.

Portfolio review

HGT has been very adept at developing and streamlining its portfolio in recent years, both in terms of identifying new products and technologies with significant potential, and in deciding when to exit those that have not proved to be as promising as they initially appeared. The objective is to develop our own products internally or identify partnerships through deals balancing the risk and managing development costs through milestone payments.

The leading HGT drugs now being sold in the market are REPLAGAL, ELAPRASE, and FIRAZYR. REPLAGAL is already approved for use in 45 countries around the world. Sales of the Hunter syndrome treatment ELAPRASE continued to grow internationally, and the focus for 2010 will be on Latin America and Eastern Europe. FIRAZYR is now marketed in the five largest European countries, and will soon be launched in a number of new markets, as demand grows for an effective subcutaneous treatment for acute attacks of



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- 1 Lucinda Mickleburgh and daughter Pheobe—REPLAGAL—Fabry disease
 2 Dr Wayne Rosenfeld—VPRIV—Gaucher disease
 3 Di Angelo and Nick Zubia—ELAPRASE—Hunter syndrome

Hereditary Angioedema. FIRAZYR is an innovative treatment and the first new product for this condition in Europe in 30 years. It has also been granted orphan drug protection in the EU until 2018. The aim this year, is to complete Phase 3 trials in the US for this product and file for registration with the FDA in 2010.

The HGT pipeline remains strong, idursulfase has now been administered directly to the Central Nervous System ('CNS') for the first time on a patient with the CNS symptoms of Hunter syndrome. The innovation here was the use of a new intrathecal delivery mechanism, which allows very small quantities of the drug to be injected into the base of the spine where it enters the cerebrospinal fluid for delivery to the brain. If this proves effective, it could open up a number of new opportunities for other products in the HGT pipeline. We plan to extend the use of this innovative device to initiate an ERT trial in Sanfilippo A patients in mid-2010.

A new business development deal was also signed with Santaris Pharma A/S in August 2009. This gives HGT access to another important new technology platform, which will be developed alongside Enzyme Replacement Therapy. This is called Locked Nucleic Acid ('LNA'), and it could make it possible to target genetic diseases that result from excessive quantities of certain proteins, rather than a lack of them, which is what Enzyme Replacement Therapy seeks to correct. The technical name for these diseases is 'autosomal dominant', and many of them are also orphan conditions, which would be treated by the same

specialist physicians and centers of excellence that already use HGT's drugs. The LNA technology is still at an early stage, but if it works it could open up an important new area for the business giving us the lead in new innovative treatments.

New markets

HGT now has a direct presence in 28 countries, and its products are distributed in around 50 countries across the world. New operations will open in Colombia, Poland, Turkey, and Switzerland in 2010.

Focus for 2010

The focus for 2010 will be on international launches for a number of HGT's products, which will leverage the company's existing international commercial infrastructure and R&D expertise. The Switzerland-based office will become an international business center, which will eventually house certain global commercial personnel. The HGT commercial team is already operating on a global scale, and will be the first to move into the new facility when it opens in late 2010.

As Sylvie Grégoire says, "There are some 7,000 orphan diseases affecting around 50 million people worldwide, which means there are still significant new opportunities opening up for HGT, as we exploit our proprietary technologies to develop new therapies, and explore the possibilities for new partnerships and alliances. The key will be to do this in a way that makes the most of the investments we make. It's about collective bravery, and measured risk-taking, which have always been at the heart of HGT's success."