

Sharp focus High impact



We've long believed we have a unique opportunity to champion underserved patient communities by placing them at the center of all we do. 2016 was a standout year as Shire became the global leader in rare diseases — a position we are determined to build on as we go forward.



Year in review

February

Shire partner, Shionogi, submits New Drug Application in Japan for ADHD treatment for children

30th Anniversary with innovative global program to benefit children with Rare Diseases

January

Completion of acquisition of Dyax

Shire moves up 10 positions on the Global 100 Sustainability Index



Dyax Corp.

A game changing year

2016 was a transformational year for Shire. We took a big step forward in serving people with rare diseases with the acquisition of Baxalta, which added three new therapeutic areas including category leadership in hematology and immunology and a growing franchise in oncology. As a result of the acquisition and strong performance across our combined portfolio, we achieved record revenue of \$11.4 billion, almost double 2015's \$6.4 billion.

Since successfully navigating and finalizing the Baxalta acquisition, we are ahead of plan on the massive task of integration and delivering promised synergies. We are now approximately 24,000 people strong and are bringing our products to patients in over 100 countries.

We also completed the \$6 billion acquisition of Dyax to expand our industry-leading portfolio in Hereditary Angioedema ("HAE") and we in-licensed from Pfizer a very promising candidate for Crohn's disease and ulcerative colitis.

Our employees did an outstanding job staying focused and delivering for patients during a time of significant change. In 2016, we also launched truly innovative products to address high unmet medical needs.

- The launch of XIIDRA, the only prescription eye drop approved in the U.S. for the treatment of signs and symptoms of dry eye disease, was another big success. We had an exceptional new drug launch, demonstrating our strength in commercial excellence and capturing 19 percent of market share within four months. This marks an outstanding entry into ophthalmics and we aim to further build a leadership position in this therapeutic area.
- We launched CUVITRU™ in the U.S., a convenient at-home, subcutaneous treatment for primary immunodeficiency. Convenience is important to our patients and their families because many of our medicines are given as infusions or injections, through various devices and delivery methods.
- Outside the U.S., we gained EU Marketing Authorization of ONIVYDE® for the treatment of metastatic adenocarcinoma of the pancreas in adult patients who have had gemcitabine-based therapy. ONIVYDE is the first and only approved treatment option for this patient population.

These new therapies exemplify our commitment to new-to-class, potentially best-in-class, or novel treatments for rare diseases.

All in all, 2016 was a standout year where we achieved our goal of becoming the leading biotech company focused on rare diseases. Today, 75 percent of our pipeline and 65 percent of our sales are in rare diseases.

A unique need — and model — for biotech innovation

Rare diseases, most of which are genetic and are present throughout a person's entire life, pose a significant medical and economic burden for patients, communities and healthcare systems. There are more than 7,000 known rare diseases impacting 350 million people worldwide. Millions more have specialized conditions. What these figures do not reflect are the untold number of mothers, fathers, friends and family who watch a loved one struggle with health challenges that, in many cases, cannot be adequately addressed today. Nearly 50 percent of the time these loved ones are children.

What's more, delays to diagnosis are commonly experienced by patients with rare diseases, and can lead to serious consequences for their health, as well as the wider healthcare system.

May

Positive CHMP opinion in Europe for REVESTIVE® (Teduglutide) for pediatric patients with Short Bowel Syndrome

Campaign to support international Mucopolysaccharidosis ("MPS") awareness day

June

Top-line results for Phase 2 trial of SHP607 in extremely premature infants

Positive topline results of SHP465 efficacy and safety study in adults with ADHD

Shire and Kamada announce FDA approval of expanded label for self-infusion of GLASSIA® for the treatment of emphysema due to severe AAT deficiency

Launch of 2016 excellence in ADHD patient group awards

April

Submits NDA to FDA for new formulation of VYVANSE® (lisdexamfetamine dimesylate) CII as chewable tablets

Positive results of SHP465 safety and efficacy study in children and adolescents with ADHD

Baxalta

June

License SHP647 from Pfizer, adding to established and leading gastrointestinal portfolio

FDA breakthrough therapy designation for SHP621 and SHP625, investigational products for rare gastrointestinal conditions

Completion of decentralized procedure in Europe for immunoglobulin treatment CUVITRU

Completion of combination with Baxalta creating the global leader in Rare Diseases

These facts are what drive our unique model for biotech innovation. It is a mix of internal knowledge, capabilities and research, combined with collaborations with external partners, and supplemented by business development and M&A. We are very flexible in our approach, combining internal and external to create the best routes to innovation.

At the same time, we are extremely focused on growing and leading in our chosen therapeutic areas. We see our patient communities as key partners in innovation. Close, long-term relationships with patients, their doctors and caregivers make all the difference in finding solutions for the challenges of their often-lifetime conditions. We have also significantly expanded our support services in helping patient's gain access to and stay on our medicines.

An exciting late-stage clinical portfolio

Our pipeline has transformed in recent years, and now includes compounds with potential rare disease indications at all stages of development. Most of the products are new-to-class, potentially best-in-class or novel. We have 17 Phase 3 programs and most are expected to launch by the end of 2020, if approved. These include:

- SHP465, the first new treatment in almost a decade for Attention Deficit Hyperactivity Disorder ("ADHD").
- SHP621, recently granted breakthrough therapy designation by the U.S. FDA for eosinophilic esophagitis, a serious, chronic rare disease.

- SHP643, recently granted breakthrough therapy designation by the U.S. FDA for hereditary angioedema ("HAE"). If we are able to replicate the clinical data we saw in earlier trials and if SHP643 is approved, we believe this product has the potential to be an advancement in the way HAE patients are treated, offer significant benefit to patients, and serve as a key growth driver for Shire's business.
- SHP607, our treatment for neonatal complications, has had positive Phase 2 results and is now going into Phase 3, with the potential to significantly impact the health of premature infants.

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We want to be known for our focus on underserved patient communities and our ability to be a high growth company that is run very efficiently, and has a laser focus on innovation in a select area of rare diseases.
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With approximately 40 programs in the clinic and about 20 in the later stages of development, we now have the deepest, and most innovative, pipeline in our 30-year history.

A commitment to doing the right thing

Our employees lead the way in ensuring we have a positive impact on society. In addition to their day-to-day focus on patients and a commitment to doing the right thing at work, they are also involved in our communities. In 2016, approximately 6,500 employees participated in our Global Day of Service in 150 locations around the world. Together, they donated over 25,000 hours of their time. This was for one event. We know our people and teams are dedicated to helping others throughout the year and also to using our resources in a responsible way. In fact, the company has received awards and recognition for our responsibility efforts and I encourage you to read on in this report to learn more.

It is an honor to work alongside our talented and dedicated employees and I'm thrilled that Shire is a place where people like to work, where we not only attract the best at all levels but also invest in their ongoing education and development. We saw a surge in job applications in 2016, also mirroring the greater recognition we have gained in our industry as a biotech leader.

Building on our leading position

We have a strong track record of excellent commercial execution and delivering on short and medium-term financial promises

Gail Fosler,
appointed as Non-Executive Director in June



July

SHP626 (Volixibat) receives FDA Fast Track designation for an investigational treatment for adults who have Nonalcoholic Steatohepatitis ("NASH") with liver fibrosis

ADYNOVATE phase 3 efficacy and safety data in children to be showcased during International Congress of the World Federation of Hemophilia

August

First prescription eye drop, XIIDRA launched (lifitegrast ophthalmic solution) 5 percent is now available in the U.S.

VONVENDI®, the first and only recombinant treatment for adults affected by von Willebrand disease, launches in the U.S.

FDA approval of ADYNOVATE® with BAXJECT III reconstitution system

Albert Stroucken,
appointed as Non-Executive Director in June



July

Launch of pediatric indication for immunodeficiency treatment HYQVIA® in Europe

FDA approves XIIDRA (lifitegrast ophthalmic solution) 5 percent — The only treatment indicated for the signs and symptoms of Dry Eye Disease

Extension of market authorization in Europe for REVESTIVE (teduglutide) for the treatment of pediatric patients with Short Bowel Syndrome ("SBS")

September

Shire closes public offering of \$12.1 billion senior notes

U.S. FDA approval of CUVITRU™ [immune globulin subcutaneous (human), 20 percent solution] treatment for Primary Immunodeficiency

to our shareholders. We like to set stretch goals and the integration of Baxalta has not distracted us from this focus.

As we grow, we want to retain the touch and feel of a small biotech so we have the benefits both of scale and agility. It's about very simple, very flat and rapid decision-making. We support this through innovation and operational excellence, through the interplay between our key strategic centers in Zug, Boston and Dublin, and through our In-line, Pipeline and Corporate Committees.

Speed matters, especially to the patients who are waiting for treatments, and that's why we've built a fast-paced, entrepreneurial, international culture where we give people freedom and opportunity to excel while also setting a high bar for being ethical and responsible.

Our teams will continue to support people with rare diseases through every step of their journey. This includes targeted diagnostic approaches to help improve the pathway to diagnosis, assistance programs for those with limited financial resources and personalized life-long programs that support on-going treatment and enhance quality of life. We also remain committed to working alongside partners, doctors, patient advocacy organizations, governments and payers to deliver value and meaningful outcomes that help ease the long-term economic burden of these diseases for patients, communities and healthcare systems.

While each rare disease community is small on its own; together they make one



It has been a banner year for us and we were pleased to see our performance honored by our peers when Shire was named Scrip's Pharma Company of the Year in 2016.



large rare disease population in need of solutions. Shire is in a leading position to provide these solutions on a global scale, enabling more patients and families around the world to live their lives to the fullest.

Thank you for your continued support.



Flemming Ornskov, MD, MPH
Chief Executive Officer

October

Granted EU marketing authorization of ONIVYDE®, in combination with 5-fluorouracil ("5-FU") and leucovorin ("LV"), for the treatment of Metastatic Adenocarcinoma of the Pancreas in adult patients who have progressed following gemcitabine-based therapy

November

Shire to establish rare disease innovation hub in Cambridge, Mass.

CUVITRU launches in the U.S. for Primary Immunodeficiency

2016 Global day of service

Investor day showcases strength of rare disease pipeline and commercial portfolio

October

Update to VYVANSE® (lisdexamfetamine dimesylate) U.S. labeling to include new longer-term maintenance of efficacy data in adults with moderate to severe Binge Eating Disorder

Patent trial and appeal board upholds the validity of LIALDA® patent

December

Shire named "Pharma Company of the Year" by Scrip