



THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Peter Hillmen, M.B., Ch.B., Ph.D., Neal S. Young, M.D., Jörg Schubert, M.D., Robert A. Brodsky, M.D., Gerard Socié, M.D., Ph.D., Petra Musu, M.D., Ph.D., Alexander Ribi, M.D., Jeffrey Szer, M.B., B.S., Madhoo O. Eshwar, M.D., Ryutaro Nakamura, M.D., Paul Browne, M.B., Antonio M. Buitrago, M.D., Ph.D., Anita Hill, M.B., Ch.B., Hubert Schrezenmeier, M.D., Chieh-Lin Fu, M.D., Jaroslaw Maciejewski, M.D., Ph.D., Scott A. Ballas, Ph.D., Christopher F. Mojsik, M.D., Ph.D., Russell P. Barber, Ph.D., and Lucio Luzzatto, M.D.

ABSTRACT

BACKGROUND
We tested the safety and efficacy of eculizumab, a humanized monoclonal antibody against terminal complement protein C5 that inhibits terminal complement activation, in patients with paroxysmal nocturnal hemoglobinuria (PNH).



FDA U.S. Food and Drug Administration
Protecting and Promoting Your Health

News & Events
FOR IMMEDIATE RELEASE
P07-47
March 16, 2007

FDA Approves First-of-its-Kind Drug to Treat Rare Blood Disorder

The U.S. Food and Drug Administration (FDA) today approved Soliris (eculizumab), the first product for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), a rare type of blood disorder that can lead to disability and premature death. Soliris is classified as an Orphan Drug and is a new molecular entity containing an ingredient not previously marketed in the United States.

"This product is important in that it offers a treatment other than blood transfusion that may help this small population of patients who are often very ill," said Steven Galton, M.D., M.P.H., director, Center for Drug Evaluation and Research, FDA. "This approval is one of multiple examples of how the orphan products program can benefit the public health with urgently needed products that would otherwise not be commercially available."

PNH, which usually develops in adults, is a disease characterized by red blood cells that develop abnormally. Once the abnormal cells are present in the bloodstream, naturally occurring proteins (called the complement system) designed to destroy bacteria and other infection-causing organisms break these cells down. This leads to abnormally depleted red cells and, more importantly, causes anemia. Transfusion levels



EUROPEAN MEDICINES AGENCY
SCIENCE. MEDICINES. HEALTH

22 September 2011
EMA/CHMP/771662/2011
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion¹ (post authorisation)

**Soliris
eculizumab**

On 22 September 2011, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for the medicinal product Soliris. The marketing authorisation holder for this medicinal product is Alexion Europe SAS. They may request a re-examination of the CHMP opinion, provided that they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

The CHMP adopted a new indication as follows:
"Atypical hemolytic uremic syndrome (aHUS)".

Detailed conditions for the use of this product will be described in the updated summary of product characteristics (SPC), which will be published in the revised European public assessment report (EPAR), and will be available in all official European Union languages after the variation to the marketing authorisation has been granted by the European Commission.

For information, the full indication(s) for Soliris will be as follows:
Soliris (eculizumab) is indicated for the treatment of patients with:



THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Enzyme-Replacement Therapy in Life-Threatening Hypophosphatasia

Michael P. Whyte, M.D., Cheryl R. Greenberg, M.D., Nada J. Salzman, M.D., Michael B. Robin, M.D., Ph.D., William H. McAlister, M.D., Deborah Weisbart, M.D., Bradley J. Van Sickle, M.D., Ph.D., Jill H. Simmons, M.D., Terence S. Edgar, M.D., Martin L. Bauer, M.D., Mohammed A. Hamdan, M.D., Nick Bishop, M.D., Richard E. Lutz, M.D., Maïnead McGinn, M.D., Stanley Craig, M.D., Jean N. Moore, M.D., John W. Taylor, D.O., Robert H. Cleveland, M.D., William R. Cranley, M.D., Ruth Lim, M.D., Tom D. Thacher, M.D., Jill E. Mayhew, P.T., Matthew Downs, M.P.H., José Luis Millán, Ph.D., Allison M. Skinner, M.P.H., Philippe Crine, Ph.D., and Hal Landy, M.D.

ABSTRACT

BACKGROUND
Hypophosphatasia results from mutations within the gene for the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). Inorganic pyrophosphate accumulates extracellularly, leading to rickets or osteomalacia. Severely affected babies often die from respiratory insufficiency due to progressive chest deformity or have persistent bone disease. There is no approved medical therapy. ENB-0040 is a bone-targeted,





In 2012 our employees around the world celebrated Alexion's 20th Anniversary. Founded in 1992, Alexion has grown into a global biopharmaceutical company with over 1,500 dedicated colleagues and operations in place to serve patients in nearly 50 countries.

- | | | | |
|----------------------|-----------------------|-----------------------------|-------------------------|
| 1. Barcelona, Spain | 7. Stockholm, Sweden | 13. Toronto, Canada | 19. Smithfield, RI, USA |
| 2. Cheshire, CT, USA | 8. Shanghai, China | 14. Buenos Aires, Argentina | 20. Paris, France |
| 3. Brussels, Belgium | 9. Cambridge, MA, USA | 15. Mexico City, Mexico | 21. Mumbai, India |
| 4. Milan, Italy | 10. Montréal, Canada | 16. Munich, Germany | 22. Sydney, Australia |
| 5. Bogotá, Colombia | 11. Moscow, Russia | 17. Lausanne, Switzerland | |
| 6. Istanbul, Turkey | 12. Tokyo, Japan | 18. Washington, DC, USA | |

Alexion will establish its new world headquarters in New Haven, CT in 2015.

As Alexion continues to grow, our new headquarters will provide a global center for our research initiatives and business operations around the world as we accelerate our efforts to develop and deliver life-transforming therapies for patients suffering with severe and life-threatening ultra-rare disorders.





twenty years of innovation

Alexion Milestones: 1992 – 2012

1992 Alexion commences operations in New Haven, CT

1996 Initial Public Offering on NASDAQ under ticker symbol ALXN

1998 First in-human clinical trial with eculizumab commences

2000 Alexion relocates to new corporate headquarters in Cheshire, CT

2002 Researchers in Leeds, England, commence a pilot study with eculizumab in patients with PNH (paroxysmal nocturnal hemoglobinuria), a severe, life-threatening and ultra-rare hematologic disorder

2004 The *New England Journal of Medicine* publishes positive results from the pilot study with eculizumab in 11 patients with PNH

2004 TRIUMPH, the first pivotal Phase 3 study in patients with PNH, commences

2005 Alexion Europe SAS is established in Paris, France in anticipation of creating access to Soliris® (eculizumab) for patients with PNH in Europe

2006 The *New England Journal of Medicine* publishes strongly positive clinical data from the TRIUMPH PNH study

2007 US FDA approves Soliris as the first and only treatment for patients with PNH

2007 European Commission approves Soliris as the first and only treatment for patients with PNH

2008 Independent physicians in Germany and France first use Soliris as a treatment for patients with atypical hemolytic uremic syndrome (aHUS), a severe, life-threatening and ultra-rare disorder of uncontrolled complement activation

2008 Soliris receives the 2008 Prix Galien USA Award for "Best Biotechnology Product with Broad Implications for Future Biomedical Research"

2009 Soliris receives the Prix Galien France Award for "Drugs for Rare Diseases"

2009 Alexion's Rhode Island Manufacturing Facility receives European Commission approval to supply Soliris

2010 Alexion's Rhode Island Manufacturing Facility receives FDA approval to supply Soliris

2011 US FDA approves Soliris as the first and only treatment for adult and pediatric patients with aHUS

2011 European Commission approves Soliris as the first and only treatment for adult and pediatric patients with aHUS

Today, as the global Alexion team pursues our mission to develop and deliver life-transforming therapies for patients with severe and life-threatening ultra-rare disorders, we continue to:

- Bring Soliris to more patients with PNH in more countries around the world
- Advance the launch of Soliris for patients with aHUS in the US and Europe
- Accelerate development of the most robust research pipeline in our history, with five compounds being investigated in nine severe, ultra-rare disorders
- Build our global organization, now with over 1,500 employees working in Company facilities in 35 countries, to serve more patients worldwide

2012 Accomplishments

January

The first patient with atypical hemolytic uremic syndrome (aHUS) is enrolled in the global aHUS Registry

February

Alexion completes acquisition of Enobia Pharma Corp., including asfotase alfa, an investigational treatment for patients with hypophosphatasia (HPP), an ultra-rare, life-threatening, genetic metabolic disease for which there are no approved treatment options

March

The *New England Journal of Medicine* publishes data from a Phase 2 study of asfotase alfa in patients with HPP; data show 90 percent of patients treated with asfotase alfa achieved substantial skeletal healing at 24 weeks, with improvements in cognitive development and motor and pulmonary function

Data from a Phase 2 study of asfotase alfa in adolescents and adults with HPP presented at the American College of Medical Genetics (ACMG) annual meeting show that all patients who were treated with asfotase alfa had an objective response to therapy as indicated by a reduction in tissue non-specific alkaline phosphatase (TNSALP) substrates. In addition, treated patients showed increase in distance in the six-minute walk test (6MWT)

May

Alexion is added to the S&P 500 Index of leading global companies

June

Researchers present data at the European Hematology Association (EHA) meeting underscoring the critical need for testing patients at high risk for PNH

New data, also presented at EHA, show that the majority of patients with aHUS experienced systemic multi-organ complications prior to treatment, underscoring the risk for sudden and potentially fatal systemic complications of aHUS

Alexion announces plans to relocate its global headquarters to New Haven, CT, US in 2015

September

Forbes ranks Alexion #2 on its annual list of "The World's Most Innovative Companies"

October

Data from an investigator-initiated Phase 2 study of eculizumab (Soliris) in patients with severe relapsing Neuromyelitis Optica (NMO) presented at the American Neurological Association (ANA) annual meeting show eculizumab significantly reduced frequency of attacks in patients

November

Investigators present two-year data at the American Society of Nephrology (ASN) annual meeting showing the long-term benefits of chronic Soliris therapy in patients with aHUS, including continued inhibition of complement-mediated thrombotic microangiopathy (TMA) and improvement in renal function

Final 28-week data from a single-arm eculizumab trial in patients with Shiga-toxin *E. coli*-related hemolytic uremic syndrome (STEC-HUS), also presented at ASN, show a rapid and sustained improvement in TMA and reversal of organ damage with eculizumab treatment

December

Researchers present data at the American Society of Hematology (ASH) annual meeting showing that the significant clinical benefits and long-term safety were sustained over 10 years in PNH patients treated with Soliris

Two-year data demonstrating long-term benefits of chronic Soliris therapy in patients with aHUS are also presented at ASH

Early 2013

Alexion submits a supplemental Biologics License Application (sBLA) to regulatory authorities in Japan for Soliris as a treatment for patients with aHUS

Patient enrollment for a clinical trial of asfotase alfa in HPP begins in Japan

Alexion expands its kidney transplant program to include a third clinical study in transplant patients at elevated risk for delayed graft function (DGF); investigator-initiated study in DGF is under way

Forward-looking statements: This Annual Report contains forward-looking statements, all of which involve certain assumptions, risks, and uncertainties that are beyond Alexion's control and could cause our actual results to differ materially from the statements described. Forward-looking statements involve significant risks and uncertainties, including those more fully described in our Form 10-K contained within this Annual Report and in the most recent periodic reports on Form 10-Q filed by Alexion with the US Securities and Exchange Commission, and actual results may vary materially. Alexion does not undertake any duty to update any forward-looking statements contained in this Annual Report as a result of new information, future events, or otherwise.



“When I was diagnosed with PNH, I was 24 years old, engaged to be married and part of an NCAA championship team in college wrestling. I was devastated when I read that one-third of people with PNH only live for five years from their diagnosis and terrified that I would not be able to have a future with my fiancée. Today, I am taking Soliris, happily married and thrilled to welcome our four-month-old daughter into our lives.”

— Joe E. *Patient with PNH receiving Soliris*

To Our Shareholders:

In 2012, as Alexion celebrated its 20th anniversary as a biotechnology innovator, we again strongly advanced our mission to develop and deliver life-transforming therapies for patients with severe and life-threatening disorders that are also ultra-rare. Our achievements during 2012 spanned our key commercial and clinical growth initiatives:

- In PNH (paroxysmal nocturnal hemoglobinuria) – bringing Soliris® (eculizumab) to more patients with PNH in our core countries of the United States, Western Europe and Japan, as well as to growing numbers of new PNH patients in additional countries
- In aHUS (atypical hemolytic uremic syndrome) – introducing Soliris in the United States as the first and only treatment for patients with aHUS, and preparing for our Soliris launches in aHUS in the major European countries
- Beyond PNH and aHUS – advancing our broad development pipeline, with lead clinical programs now investigating five highly innovative compounds, including eculizumab, as treatments for patients with nine additional severe and life-threatening ultra-rare disorders
- And overall, achieving significant growth across our business while maintaining strong financial discipline to achieve increasing operational leverage

2013: Reaching Milestones Across Our Growth Initiatives

With a global operations platform that now serves patients in nearly 50 countries – and the most robust pipeline of innovative therapeutic candidates in our history – we are on track to reach an unprecedented number of key milestones across our commercial and clinical initiatives in 2013. Our objectives for the year include:

- In our approved indications for Soliris – reaching more patients in countries where commercial operations are already in place, and accelerating our market entries in new countries. In PNH and aHUS alike, our steadfast objective is that every patient who can benefit from Soliris will have access to Soliris

- In our development programs for new indications with eculizumab – advancing our clinical programs in life-threatening, ultra-rare disorders in multiple therapeutic areas, including nephrology, neurology and transplant
- In our development programs with highly innovative therapeutics beyond eculizumab – accelerating the clinical development of asfotase alfa as the first treatment for patients with hypophosphatasia (HPP), and progressing the development of our other highly innovative therapeutics including our cPMP replacement therapy for patients with molybdenum cofactor deficiency (MoCD) type A; ALXN1102/1103, our alternative complement pathway inhibitor; and ALXN1007, a novel anti-inflammatory antibody

Serving More Patients with PNH Worldwide

Even as we drive forward with these wide-ranging growth initiatives, our focus on serving patients with PNH has never been greater – especially since, on a global basis, the majority of PNH patients have not yet received an accurate diagnosis, let alone commenced appropriate treatment. PNH is a debilitating and life-threatening ultra-rare blood disorder characterized by uncontrolled complement activation leading to complement-mediated hemolysis (destruction of red blood cells). Before Soliris, approximately one-third of patients with PNH did not survive more than five years from the time of diagnosis. With the availability of Soliris, the outlook for patients has changed dramatically: In the initial PNH registration trials, 100 percent of patients had an objective response to Soliris, and long-term data published by independent investigators from patients treated with Soliris for up to eight years showed improved survival rates similar to normal healthy individuals matched for their age and gender. In 2012, data presented at the American Society of Hematology (ASH) annual meeting further demonstrated long-term efficacy and safety in PNH patients treated with Soliris over the course of 10 years.

The growing body of data regarding both PNH and the clinical benefits of Soliris is vital for patients. As with many ultra-rare disorders – even those that are severe and for which there is an effective, approved therapy – patients with PNH often suffer

“After months of being misdiagnosed, I was finally told I had aHUS. With this news came a year of debilitating dialysis, extreme nausea and exhaustion, and the loss of vision in one eye due to a retinal blood clot. In 2012, my hematologist started me on Soliris. I am thankful to be able to work again and live like other people my age.”

— Erica S. *Patient with aHUS receiving Soliris*



needlessly because there may be little awareness amongst the medical community of how to recognize or treat their disorder. In 2013, the seventh year of the global introduction of Soliris, we will build on the medical evidence as we continue to expand our PNH disease awareness programs and diagnostic initiatives. Since 2007, these programs have been vital to educating the medical community on which patients are at greatest likelihood of having PNH, the best ways to arrive at an accurate diagnosis, and the most effective treatment options.

In 2012, as in the past, we served substantial numbers of new patients with PNH in each quarter across our longest established territories in the United States, Western Europe and Japan. Importantly, we also began to serve initial patients in Turkey, Brazil and Russia as we implemented disease awareness programs and diagnostic initiatives. In 2013, we will increase our penetration in all countries in which we are currently active. Additionally, we look forward to significant opportunities to serve patients in parts of Latin America, including Argentina, Colombia and Mexico, as well as additional countries including Korea.

Bringing the Unprecedented Hope of Soliris to Initial Patients with aHUS

As we continue our mission to transform the lives of patients with PNH, we have now also begun to transform the lives of patients with aHUS, a chronic, ultra-rare and life-threatening disease in which a genetic deficiency in one or more complement regulatory genes causes chronic uncontrolled complement activation. The lifelong uncontrolled complement activation in aHUS progressively damages vital organs, leading to stroke, heart attack, kidney failure and premature death. Prior to the availability of Soliris for the treatment of aHUS, 65 percent of patients required dialysis, had permanent kidney damage or died within the first year of diagnosis despite receiving plasma exchange or plasma infusion (PE/PI). As in PNH, 100 percent of patients in the aHUS registration trials had an objective response to Soliris.

Following strongly positive results in our prospective clinical trials in aHUS, the FDA and European Commission granted

marketing authorization for Soliris as the first and only approved treatment for patients with aHUS at the end of 2011. Both approvals resulted in strong and broad labels that include pediatric and adult patients with aHUS. In 2012, the first full year in which Soliris was available to patients in the US, we were able to rapidly meet the urgent medical needs of patients presenting with aHUS.

We enter 2013 with a foundation in place for a strong global launch in aHUS. The devastating course of this disorder, together with the life-transforming benefits of Soliris treatment, provides a solid underpinning for rapid diagnosis, reimbursement and treatment of aHUS patients around the world. We are pleased to have built strong support among key opinion leaders who recognize the life-transforming impact that Soliris is having on patients with aHUS. Our efforts are further supported by a growing body of clinical data demonstrating the long-term benefits of Soliris for patients with aHUS. This includes two-year data from the prospective Phase 2 trials that were presented at both the American Society of Nephrology (ASN) and ASH annual meetings in 2012, which showed continued improvement in hematologic and renal function with Soliris. Additionally, an established group of European aHUS clinical experts published a paper supporting Soliris as first-line therapy in patients confirmed to have aHUS.

In the US, a broad range of aHUS patients are being diagnosed and treated with Soliris, including both children and adults, and those with and without a history of receiving plasma exchange. Patients with aHUS are also being treated by multiple specialties and in both hospital and outpatient practice settings. As is also our experience in PNH, we are seeing positive results from our diagnostic initiatives and disease awareness programs for aHUS. For example, an aHUS diagnostic pathway has been introduced to hematologists and nephrologists with positive impact, which we believe will facilitate the more rapid diagnosis of patients with aHUS. Importantly, patients with aHUS in the United States are gaining rapid access to Soliris through broad reimbursement.

Research Pipeline: Lead Programs



In Europe, we are now serving aHUS patients in Germany and initial patients in other countries are also receiving Soliris on a named-patient basis or through local funding authorities. We are also on track to complete the reimbursement processes for aHUS in most of the larger Western European countries and to commence individual country launches during 2013. While our European teams are planning for their individual country launches, we have also recently submitted our supplemental Biologics License Application (sBLA) for aHUS in Japan, an important step for subsequent access to Soliris for Japanese patients. We look forward to serving an increasing number of patients with aHUS around the world throughout 2013 and beyond.

Serving More Patients with More Severe and Ultra-Rare Disorders

Beyond our current commercial initiatives in our approved Soliris indications, we are keenly focused on the need to develop additional highly innovative uses for the breakthrough complement-inhibition technology of eculizumab. We are equally driven by the need to develop new therapeutic agents, both within and beyond complement-mediated diseases.

The expertise we have gained from our experience with Soliris informs all of our pipeline development decisions. We are among the very few companies to have successfully developed and commercialized a high-value ultra-orphan therapy, bringing it through clinical trials and regulatory approval, and then commercializing it successfully in multiple indications around the world on our own. Through this experience, we have learned how to work with regulators to develop approval pathways and trial protocols in disease settings in which there are no clinical precedents. We have also gained valuable experience in enrolling trial sites around the world to recruit patients with the rarest and most severe disorders, as well as in conducting successful disease education programs to significantly raise awareness of a devastating and ultra-rare disorder and the most effective ways to diagnose and treat it.

To best employ these skills on behalf of patients, we now focus only on the most severe and life-threatening

disorders for which there are no approved or effective therapies – disorders that are simultaneously the rarest, in which only very few patients are affected. We now have nine such R&D programs under way, each of which is expected to reach one or more important milestones in 2013.

Investigating the Potential of Eculizumab (Soliris) Beyond PNH and aHUS

Our five lead development programs with eculizumab are focused on severe and ultra-rare complement-mediated disorders beyond PNH and aHUS.

- Shiga-toxin *E. coli*-related hemolytic uremic syndrome (STEC-HUS) is a devastating and life-threatening ultra-rare disease that develops in a subset of patients who become infected with enterohemorrhagic *E. coli* (EHEC). Final 28-week data from our single-arm eculizumab STEC-HUS trial, which was initiated in Germany during the historic EHEC outbreak in mid-2011, were presented at the ASN meeting in November 2012. The data showed that the full clinical study cohort of 198 patients had a rapid and sustained improvement in TMA and reversal of organ damage with eculizumab treatment. Importantly, we are also obtaining and analyzing additional control data from an exploratory matched-control analysis of patients with severe STEC-HUS receiving eculizumab versus other patients who received only best supportive care. The preliminary findings from this analysis showed that eculizumab treatment was associated with consistently higher rates of improvement in renal and neurological function at 8 weeks and 28 weeks, when compared with supportive care only. We believe the additional control data will strengthen our anticipated regulatory submission.
- Kidney Transplant is another area in which complement can play a significant role. We currently have two development programs under way:
 - Acute Humoral Rejection (AHR) – we are currently enrolling patients at elevated risk of AHR, or antibody mediated rejection, in a multinational living-donor kidney transplant trial and a separate multinational deceased-donor kidney transplant trial



“Evie was diagnosed with hypophosphatasia, or HPP, when she was just a few weeks old and we were told that 50% of patients with severe HPP did not survive past one year of age. Needless to say, we were devastated. Fortunately, we were given the opportunity to participate in a clinical trial with asfotase alfa. Today, Evie is still in the trial and enjoys music classes and playing with her sister Lyla.”

— Lindsey E. *Mother of child with HPP*

- Delayed Graft Function (DGF) – we recently expanded our kidney transplant program to include patients at elevated risk for DGF as we sponsored an investigator-initiated study
- Neuromyelitis Optica (NMO) is a devastating, life-threatening, ultra-rare neurological disease in which uncontrolled complement activation causes damage to the spinal cord and optic nerve, leading to paralysis, respiratory failure, blindness and premature death. Positive data from an investigator-initiated Phase 2 single-arm study of eculizumab in patients with severe relapsing NMO presented at the 2012 American Neurological Association annual meeting showed eculizumab significantly reduced frequency of attacks in patients with severe relapsing NMO. Following recent meetings with regulators in the US and Europe, we are accelerating this program and expect to initiate a single multinational registration trial.
- Myasthenia Gravis (MG) is a debilitating and sometimes life-threatening neurological disorder in which uncontrolled complement activation leads to destruction and inflammation at the neuromuscular junction, resulting in severe muscle weakness. Following encouraging results from a Phase 2 study in severe and refractory MG, we have started regulatory discussions and are planning to initiate our next study.

Beyond Eculizumab: Highly Innovative Therapeutics to Treat Ultra-Rare Disorders

Our development programs beyond Soliris are guided by what we know well and do well, applying our proven skills exclusively to patients suffering from severe and life-threatening illnesses in ultra-rare settings. As with our eculizumab programs, we focus only on therapeutic candidates with strong potential to transform patients' lives – not just provide an incremental benefit.

- Asfotase alfa is a highly innovative, late-stage biologic being developed for patients with hypophosphatasia (HPP), an inherited and life-threatening ultra-rare metabolic disorder that leads to progressive damage to multiple vital organs, including destruction and deformity of bones. One-half of

newborn patients with HPP die within one year, and there are no effective treatment options. Clinical trial results from a single-arm study published in the *New England Journal of Medicine* in 2012 showed a dramatic clinical benefit of asfotase alfa and an objective response in 100 percent of study participants. Alexion is currently accelerating the clinical development program for children with HPP, with our objective to file for pediatric registration in the US and Europe. In addition, we are completing the current clinical development program for adults with HPP. Beyond the US and Europe, we have started a registration trial in Japan. During 2012, we also completed an important phase of the process development work in the asfotase alfa manufacturing program to support our clinical studies and eventual commercialization.

- cPMP replacement is an investigational therapy for the treatment of patients with molybdenum cofactor deficiency (MoCD) type A, a severe, ultra-rare and genetic metabolic disorder that is fatal in newborns. Early case studies with cPMP have shown highly encouraging results in individual patients, and we are driven by the potential for cPMP to change the grim outcomes that these infants currently face. We are now planning to initiate the first prospective clinical studies with cPMP.
- ALXN1102/ALXN1103 are the intravenous and subcutaneous versions, respectively, of our novel alternative pathway complement inhibitor, which we are in the early stages of investigating as treatments for severe and ultra-rare inflammatory disorders. We are progressing through our current Phase 1 clinical trial, with the objective to develop subsequent clinical studies with this novel complement inhibitor.
- ALXN1007, a novel anti-inflammatory antibody designed to target severe and ultra-rare inflammatory disorders, is a product of our antibody discovery technologies. We recently completed a single-dose Phase 1 clinical trial in 56 patients and are planning to discuss a multi-dose study with regulators.



From left: Stephen P. Squinto, PhD, *Executive Vice President and Head of Research and Development*; John B. Moriarty, Jr., JD, *Senior Vice President and General Counsel*; Leonard Bell, MD, *Chief Executive Officer*; David L. Hallal, *Executive Vice President and Chief Commercial Officer*; Clare Carmichael, *Senior Vice President and Chief Human Resources Officer*; Vikas Sinha, MBA, CA, CPA, *Executive Vice President and Chief Financial Officer*; Frank Wright, *Senior Vice President and President, Alexion Pharma International Sàrl*.

“Our accomplishments in 2012 position us for continued strong growth in 2013, which we expect will be a pivotal year of milestones across both our commercial operations and development pipeline. Our goal is to continue serving more patients with more disorders worldwide in the decade ahead.”

— Leonard Bell, MD *Chief Executive Officer*

Soliris® Net Product Sales

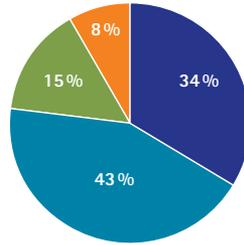
Continued Strong Financial Performance

2012 was another year of sustained growth in revenues and profitability for Alexion. For the full year, we recorded sales of \$1.134 billion, an increase of 45% compared to 2011. By maintaining fiscal discipline as we have grown our global operations to now serve patients in nearly 50 countries, we achieved a 60% increase in non-GAAP net income to \$425.2 million in 2012.

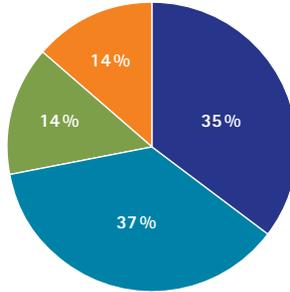
In 2012 we reported robust year-on-year revenue growth across all of our countries. Revenues in the US increased 52% during the year, reflecting continued growth in PNH and the first full year of the aHUS launch. This strong growth in our largest market six years after the initial launch supports the robust long-term growth potential of the Soliris franchise. Revenues in Europe increased 27% on a constant currency basis more than five years following our initial EU approval. Likewise, we achieved strong growth of 40% in our PNH operations in Asia-Pacific, largely related to Japan. The growing momentum of our global expansion is further indicated by the 141% year-on-year growth we experienced across our newer markets. Taken together, the diverse operations that we are building around the world provide us with a foundation for long-term growth in PNH, aHUS and future indications.

Strengthening Our Human Capital and Resources

Today, Alexion has more than 1,500 employees working in Company facilities in 35 countries. We are grateful for the passion and commitment of our talented and dedicated employees as we work together to serve patients with ultra-rare diseases.



2011 \$783,431



2012 \$1,134,114

- United States
- Europe
- Asia-Pacific (primarily Japan)
- Other

In 2012, we welcomed two new leaders to Alexion's executive team: John Moriarty joined Alexion as Senior Vice President and General Counsel, and Frank Wright joined us as Senior Vice President and Head of Alexion Pharma International Sàrl. Both are seasoned executives who will play key roles as we grow our multi-product portfolio in an increasing number of countries.

To support our continued growth, we have also announced the relocation of our global headquarters from Cheshire, CT to New Haven, CT in 2015. Our new headquarters will provide a global center for our research initiatives and business operations around the world to accelerate our efforts to serve more patients with severe and life-threatening ultra-rare disorders.

Looking Ahead in 2013

Our history of innovation since 1992 will serve as the guide for future growth. We are inspired by the number of lives we have been able to transform through the introduction of Soliris for PNH and aHUS, and we will employ our expanding global presence and skills to deliver additional breakthrough therapies for patients with devastating and ultra-rare disorders who currently suffer without hope. We are thankful for all those who make our work possible: our employees, Board of Directors and shareholders, as well as healthcare authorities around the world. Most of all, we thank the patients, families and physicians we serve around the world as we strive to reach new levels of innovation on their behalf.

Leonard Bell, MD
Chief Executive Officer

April 2013

Selected GAAP Financial Results (In thousands, except per share data)

Year Ended December 31,	2012	2011	2010
Net product sales	\$ 1,134,114	\$ 783,431	\$ 540,957
Cost of sales	72,837	93,140	64,437
Operating expenses:			
Research and development	222,732	137,421	98,394
Selling, general and administrative	384,678	308,176	226,766
Acquisition-related costs	22,812	13,486	722
Impairment of intangible asset	26,300	—	—
Amortization of purchased intangible assets	417	382	—
Total operating expenses	656,939	459,465	325,882
Operating income	404,338	230,826	150,638
Other expense	6,772	1,158	1,627
Income before income taxes	397,566	229,668	149,011
Income tax provision	142,744	54,353	51,981
Net income	\$ 254,822	\$ 175,315	\$ 97,030
Earnings per common share — diluted	\$ 1.28	\$ 0.91	\$ 0.52
Shares used in computing earnings per share — diluted	198,501	191,806	186,074

As of December 31,	2012	2011	2010
Consolidated Balance Sheet Data:			
Cash, cash equivalents and marketable securities	\$ 989,501	\$ 540,865	\$ 361,605
Trade accounts receivable, net	295,598	244,288	168,732
Inventories	94,521	81,386	62,165
Property, plant and equipment, net	165,629	165,852	162,240
Goodwill and intangible assets, net	900,323	171,243	44,100
Deferred tax assets	40,040	123,000	174,212
Other assets	127,948	68,117	38,983
Total assets	2,613,560	1,394,751	1,012,037
Accounts payable and accrued expenses	271,275	199,653	123,056
Deferred revenue	31,266	17,905	2,896
Contingent consideration	141,670	18,120	—
Long-term debt	149,000	—	—
Other liabilities	49,499	24,581	26,349
Total liabilities	642,710	260,259	152,301
Total stockholders' equity	1,970,850	1,134,492	859,736
Total liabilities and stockholders' equity	2,613,560	1,394,751	1,012,037

Shareholder Information

Directors

Max Link, PhD^{1,4}

Chairman of the Board

Former Chairman of the Board and CEO, Centerpulse AG

Former CEO, Corange

Former Chairman of the Board and CEO, Sandoz Pharma, Ltd.

Leonard Bell, MD

Chief Executive Officer

William R. Keller^{2,3}

Vice Chairman of Shanghai Association of Foreign Investment Enterprises

Senior Consultant of Shanghai Foreign Investment Development Board

Former General Manager, Roche China Ltd.

Joseph A. Madri, PhD, MD^{2,4}

Professor of Pathology, Yale University School of Medicine

Larry L. Mathis^{1,3}

Former President and CEO, The Methodist Hospital System

R. Douglas Norby^{1,3}

Former Senior Vice President, Chief Financial Officer, Tessera Technologies, Inc.

Alvin S. Parven^{2,3}

President, ASP Associates

Former Vice President, Aetna Health Plans

Andreas Rummelt, PhD^{1,4}

CEO, InterPharmaLink AG

Former Group Head, Quality Assurance and Technical Operations, Novartis

Former Member of Executive Committee, Novartis

Former CEO, Sandoz AG

Ann M. Veneman^{2,3}

Former Executive Director of UNICEF

Former Secretary of US Department of Agriculture

Senior Management

Leonard Bell, MD

Chief Executive Officer

Stephen P. Squinto, PhD

Executive Vice President, Head of Research and Development

Vikas Sinha, MBA, CA, CPA

Executive Vice President, Chief Financial Officer

David L. Hallal

Executive Vice President, Chief Commercial Officer

Clare Carmichael

Senior Vice President, Chief Human Resources Officer

John B. Moriarty, Jr., JD

Senior Vice President, General Counsel

Frank Wright

Senior Vice President, President, Alexion Pharma International Sàrl

Camille L. Bedrosian, MD

Senior Vice President, Chief Medical Officer

Thomas Bock, MD, MBA

Senior Vice President, Global Medical Affairs

M. Stacy Hooks, PhD

Senior Vice President, Technical Operations

Claude Nicaise, MD

Senior Vice President, Strategic Product Development and Global Regulatory Affairs

Heidi L. Wagner, JD

Senior Vice President, Global Government Affairs

Claus Weisemann, PhD

Senior Vice President, Corporate Quality and Compliance

James P. Bilotta, MBA

Vice President, Chief Information Officer

Henric Bjarke

Vice President, Global Metabolic Franchise

Daniel N. Caron, MS

Vice President, Site Operations and Engineering

Sven Ante (Bill) Lundberg, MD

Vice President, Head of Translational Medicine

Margaret M. Olinger, MBA

Vice President, Global Hematology Franchise

Jeremy P. Springhorn, PhD

Vice President, Corporate Strategy and Business Development

Jeroen van Beek, PhD

Vice President, Global Nephrology Franchise

Annual Shareholders Meeting

To be held on May 6, 2013
5:00 p.m.

The Study at Yale
1157 Chapel Street
New Haven, CT 06511
tel 203.503.3900

Other Information

Corporate Headquarters

Alexion Pharmaceuticals, Inc.
352 Knottter Drive
Cheshire, CT 06410
tel 203.272.2596
fax 203.271.8190

Transfer Agent and Registrar

Computershare Trust Company, N.A.
250 Royall Street
Canton, MA 02021

Investor Relations

Rx Communications
445 Park Avenue, 10th Floor
New York, NY 10022
tel 917.322.2569
fax 917.322.2570

Legal Counsel

Ropes & Gray LLP
Boston, MA

Independent Auditors

PricewaterhouseCoopers LLP
Hartford, CT

Trading Symbol

Listing for Alexion Pharmaceuticals, Inc. is found on the NASDAQ stock market under the symbol ALXN.

alexionpharma.com

¹ Member of the Audit Committee

² Member of the Compensation Committee

³ Member of the Nominating and Corporate Governance Committee

⁴ Member of the Pharmaceutical Compliance and Quality Committee

Alexion Pharmaceuticals, Inc.

352 Knotter Drive, Cheshire, CT 06410, USA

Alexion Pharma International Sàrl

Avenue du Tribunal Fédéral 34, 1005, Lausanne, Switzerland

Alexion Pharma G.K.

Ebisu Prime Square Tower, Tokyo 150-0012, Japan

Alexion Pharmaceuticals Australasia Pty Limited

117 Old Pittwater Road, Brookvale NSW Australia, 2100

Alexion Pharma Mexico S de RL de CV

Paseo de los Tamarindos 90 Torre 1 Piso 14, Col. Bosques de la Lomas, CP 05120 D.F. Mexico

www.alexionpharma.com