DELIVERING INNOVATION
Novel treatments in ophthalmology
Delivering Innovation

Novel treatments in ophthalmology
Spreading Innovation

Summary

Foreword - Dr. Patrik De Haes, CEO
Chapter One - About ThromboGenics
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Dr. Patrik De Haes
Chief Executive Officer

ThromboGenics has started 2015 true to its ambitions, with renewed focus on its core business and a stronger organization. More than ever we’re determined to become a major player in ophthalmology, and we remain dedicated to developing and bringing to market innovative medicines for treatment of vitreoretinal diseases.

Paul Howes
Executive Chairman US

JETREA® is a product with a very bright future in the US.

Dr. Jean Feyen
Head of Pre-Clinical Research

R&D: the key to the future at ThromboGenics.

Dr. Michael Ip
Professor at the Department of Ophthalmology and Visual Sciences of the University of Wisconsin, US

JETREA® could be a first in kind mechanism of action in the treatment of PDR.

Dominique Vanfleteren
Chief Financial Officer

The transitional year 2014 has allowed ThromboGenics to become a stronger company in operational terms. With extensive experience in the biotech sector, the new Chief Financial Officer, Dominique Vanfleteren, will ensure that the company has a solid financial position from which to further evolve.

Dr. Staf Van Reet
Chairman

The Board of Directors of ThromboGenics relies on the experience and diversity of its members’ financial expertise, auditing experience and commercial know-how in the US market. Board Chairman Staf Van Reet notes, “The members play a supervisory role on behalf of the shareholders, but above all they act as a sounding board for the management.”
DETERMINED

CEO Dr. Patrik De Haes

Dear Reader,

ThromboGenics has started 2015 true to its ambitions, with renewed focus on its core business and a stronger organization. More than ever we’re determined to become an important player in ophthalmology, and we remain dedicated to developing and bringing to market new pharmaceutical treatments for diseases of the retina.

For ThromboGenics, 2014 was an eventful year. Together with the Board of Directors, the management studied a range of strategic options before deciding to keep charting an independent course benefiting our company and its stakeholders. That decision produced a number of changes.

Reinforcement in Belgium and in the United States

In Belgium, we welcomed Dominique Vanfleteren to the ThromboGenics management team as new CFO. His main goal is to keep us on a strong financial footing so we can continue realizing our ambitions.

In the United States, the team has also been reinforced to pursue our goal of promoting the commercial success of JETREA®. We are proud to announce the appointment of Paul Howes – former President of Bausch & Lomb, USA – as Executive Chairman of ThromboGenics, Inc. With his wide-ranging commercial experience in ophthalmology, Paul can take the potential of ThromboGenics in the US to a higher level.

Sparking enthusiasm

Our goal in the US is unchanged: to include JETREA® in a changed standard in treating symptomatic vitreomacular adhesion (symptomatic VMA). The retina community is helping us achieve this. Thanks to our efforts in 2014, a rising number of retina specialists are using JETREA® for their patients. They seem highly satisfied with the results and are relating this to their peers. The experiences in patient selection they share with their colleagues are particularly useful, since the chance of complete recovery is much higher when the product is applied to the right target group.

More than ever we are determined to deliver novel vitreo-retinal treatments for patients around the world.
Naturally, in this education process we’re mindful that the US is a “data driven market” so our goal for 2015 is clear: to gather and distribute as much data as possible on the safety and efficacy of JETREA®. To this end we launched several studies in 2014. Ocriplasmin Research to Better Inform Treatment (ORBIT) began in March, with success: 97 centers have signed up to recruit patients for it. Another good example, Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion including Macular Hole (OASIS), is observing 220 patients for 24 months after injection with JETREA®. Its initial topline results have been published in Q1.

ThromboGenics is presenting these studies’ results at conferences and symposia for retina specialists. The first was the American Academy of Ophthalmology meeting in October 2014, where the retina community showed tremendous enthusiasm for JETREA®. Some 500 specialists voted on its safety and 60% were convinced it could be safely used in their patients.

In short, we have every reason to remain positive about the future, both in the US and Europe and in the rest of the world where we’ll continue the roll-out of JETREA® together with Alcon. This makes 2015 the year for our product to secure a firm position outside of the US as well.

New indications
Meanwhile, research into new indications for JETREA® continues at full speed. ThromboGenics has always been an R&D company and will keep investing in it. The focus here is on diabetic retinopathy. Each year, rising numbers of adults contract diabetes worldwide. This can create vulnerability to severe retina diseases, possibly resulting in blindness. One such condition is proliferative diabetic retinopathy: blood vessels that show pathological growth and proliferation in the retina, which can cause the patient to go blind. There is evidence JETREA® can halt this at an early stage, thus stabilizing the disease. As there is currently no treatment having this effect, our product could be of tremendous value for this large group of patients worldwide. The first early-phase studies have started, and we and the retina community eagerly await the initial results.

Oncology spin-out
To keep our R&D fully focused on retina diseases, the Board of Directors decided to divert research on new cancer treatments into a “spin-out construction.” In collaboration with the Flanders Institute for Biotechnology (VIB, Vlaams Instituut voor Biotechnologie), a new company is being created to work solely on R&D of new treatments in pediatric oncology. The initial focus will be the potential of anti-PLGF (placental growth factor) for treating a rare type of brain tumor in children. ThromboGenics will continue to support this work behind the scenes as majority shareholder.

More than meets the eye
One thing is clear: there is more to ThromboGenics than meets the eye. We’re doing much more than outsiders might see at first glance, and the above activities ensure our sustained full engagement. This activity report offers just a peek behind the scenes. We’re proud to show how our team upholds the ThromboGenics way of doing business: as an independent Flemish biotech company successfully developing new products in the laboratory that are then brought to market through our own organization.

Dr. Patrik De Haes, MD
CEO ThromboGenics
Chapter one

About ThromboGenics

Innovative ophthalmic medicines

ThromboGenics is an integrated biopharmaceutical company focused on developing and commercializing innovative ophthalmic medicines for the treatment of vitreo-retinal diseases (back of the eye).

ThromboGenics successfully developed JETREA®, the first and only pharmacological treatment indicated for symptomatic vitreomacular adhesion (symptomatic VMA) and vitreomacular traction (VMT) in the US and Europe, respectively. Symptomatic VMA/VMT is a progressive, sight-threatening condition that can lead to visual distortion, decreased visual acuity, and central blindness. JETREA® offers an earlier and easily administered treatment option that prevents the disease from advancing to the point that a vitrectomy is the only solution.

ThromboGenics’ strong clinical, regulatory and market access capabilities led to the efficient development and approval of its lead drug JETREA®. So far, JETREA® received market approval in 50 countries globally. This novel drug has received positive health technology assessments leading to full reimbursement and coverage in the US, key markets in Europe, and Canada. These highlighted the patient benefits of JETREA®, including its use in earlier treatment of patients with symptomatic VMA. ThromboGenics will draw on this experience in broadening the retinal indications for which JETREA® can be used.

ThromboGenics is strongly committed to research and development on treatments for diabetes-related eye diseases like diabetic retinopathy (DR). It is finalizing plans for a Phase II clinical study to be conducted in the US for developing JETREA® in this area. ThromboGenics is headquartered in Leuven, Belgium, with commercial operations in New Jersey, USA. It employs around 150 people globally (including third-party partners). The company is listed on the NYSE Euronext Brussels exchange under the symbol THR. More information is available at www.thrombogenics.com.
Mission statement
ThromboGenics is dedicated to developing and commercializing new pharmacologic ophthalmic treatments that address important unmet clinical needs. By meeting this goal, ThromboGenics intends to help patients around the world with a new or better treatment for their condition.

The 2014 strategic review has focused the development and commercial activities of the company in the ophthalmologic field, whilst retaining the research capacity to investigate other potential treatments. For that reason, the company has decided to place the asset of the company related to the oncology compound TB-403 in a separate structure set-up with the intention to find external funding and management and ensure that this asset brings value from partnering.

Corporate objectives and strategy

Building an independent global ophthalmology company specialized in vitreo-retinal diseases
ThromboGenics is well-positioned to remain an independent global ophthalmology company developing and commercializing innovative therapies for severe eye diseases with a high unmet medical need.

Driving the sales of JETREA® in the US
The commercial success of JETREA® in the US is key component of its corporate strategy. To meet this goal, ThromboGenics is focusing its sales and marketing on boosting adoption rates in accounts that use JETREA® for treatment of patients with symptomatic VMA. The company aims to raise the number of retina physicians in the US with extensive experience in using JETREA®.

Continuing collection of more real-world data will give physicians a greater understanding of the importance of patient selection. They can thus produce the best possible treatment outcomes with JETREA® and understand the mainly transient adverse events sometimes seen in patients shortly after treatment. As they gain more experience with JETREA® physicians can better identify patients most suitable for treatment with it, yielding improved clinical outcomes. The retina community is driven by peer-to-peer interactions. Increased adoption of JETREA® can be expected as these disseminate positive physician and patient experiences.

Supporting Alcon in developing JETREA® sales outside the US
ThromboGenics continues to help its partner Alcon, working with its parent company Novartis, commercialize JETREA® outside the US. Alcon focuses on building on the strong market access platform established in partnership with ThromboGenics.

In March 2014, JETREA® was approved in Switzerland for treatment of adults with symptomatic vitreomacular traction (VMT). In September, the Spanish Ministry of Health approved reimbursement of JETREA® for treatment of adults with VMT, including when associated with a macular hole of diameter ≤ 400 microns. JETREA® has been put on the Spanish national list of available reimbursed products at the regional and hospital level. There is also good progress in gaining further approvals for JETREA® outside the EU. JETREA® gained its 50th approval globally with the FDA approval in the Philippines in February 2015. Alcon has submitted JETREA® for marketing authorization in several other countries and completed a bridging study in Japan.

The Japanese trial, a randomized, double-blind, multi-center study with patients receiving either ocriplasmin or a sham injection, recruited a total of 168 patients with symptomatic VMA including those associated with macular hole. The results from this study are expected to form part of the regulatory submission that will be made to the Japanese Ministry of Health, Labour and Welfare in 2015 to gain approval to market ocriplasmin in Japan.

Creating further value by supporting the approved indications for JETREA® and developing new indications in the US
Earlier this year, ThromboGenics announced its decision to make prevention of diabetic retinopathy (DR) the next target indication for JETREA®. ThromboGenics is currently completing a tendering process for a CH03 to assist in conducting a Phase II trial with JETREA® in diabetic retinopathy in the US. This study will assess the product’s utility in this greatly underserved patient population. The study is scheduled to start in H1 2015 with the first patient expected to be recruited in H2, 2015.

Progressing its pipeline of earlier stage projects focused on diabetic vitreo-retinal diseases
ThromboGenics seeks greater involvement in earlier-stage projects focused on diabetic eye disease. It will access novel ophthalmic medicines to expand its ophthalmology franchise with a focus on diabetes through its own research, joint development/licensing deals, and possibly acquisitions.

The company’s R&D activities in oncology will be moved to a separate entity. A new company is being formed in partnership with VIB (Flanders Institute for Biotechnology). ThromboGenics will have an equity stake in this new venture focused on pediatric oncology.
THROMBOGENICS highlights 2014–Q1 2015

2014 (Jan)
France’s transparency committee issues positive opinion for reimbursement JeTRea®

2014 (Feb)
ThromboGenics’ Board announces decision to explore strategic options for the company

2014 (Mar)
ThromboGenics awards €3 million IWT Grant to support research new therapeutic for Diabetic Macular Edema

2014 (Apr)
JeTRea® approved in Switzerland for the treatment of VMT

2014 (Jun)
ThromboGenics’ JeTRea® gains first Asian approval in Malaysia

2014 (Aug)
ThromboGenics’ JeTRea® receives positive recommendation from Scottish Medicines Consortium (SMC)

2014 (Sep)
ThromboGenics’ JeTRea® receives reimbursement in Spain

2014 (Oct)
ThromboGenics’ commitment to the US Retina Community highlighted at American Academy of Ophthalmology 2014 Meeting

2014 (Nov)
ThromboGenics provides update on strategic review process - company to remain independent

2015 (Jan)
ThromboGenics appoints Dominique Vanfleteren as new Chief Financial Officer

2015 (Feb)
ThromboGenics’ JeTRea® gains approval in Brazil for the treatment of VMT

2015 (Mar)
JeTRea® gains approval in Argentina and Israel

2015 (Jul)
ThromboGenics appoints Emmanuel Amour as Independent Non-Executive Director

2015 (Aug)
ThromboGenics receives positive CHMP opinion for ready-diluted formulation of JeTRea®

2015 (Sep)
ThromboGenics to present at the J.P. Morgan Annual Healthcare Conference 2015 in San Francisco
CHAPTER TWO

JETREA®

Toward a new standard of care

JETREA® (ocriplasmin) is a truncated form of human plasmin. The drug is indicated for treatment of symptomatic VMA in the US, and for VMT, including when associated with a macular hole of diameter ≤ 400 microns in Europe.

JETREA® is a selective proteolytic enzyme that cleaves fibronectin, laminin and collagen, three major components of the vitreoretinal interface that play a key role in symptomatic VMA/VMT.

JETREA® has been evaluated extensively in the US and Europe, where a multi-center, randomized and double-masked Phase III trial involving 652 patients with symptomatic VMA/VMT was conducted. Both studies met the primary endpoint of symptomatic VMA/VMT resolution at day 28. Of JETREA® patients who achieved resolution of symptomatic VMA/VMT and macular holes by day 28, 72% did so within seven days.

The Phase III program found that 26.3% of patients treated with ocriplasmin saw resolution compared with 10.1% who received a placebo. The program also showed that the drug was well tolerated, with most adverse events being transient and mild.

Patient selection delivers improved patient outcomes

A post-hoc data analysis of the Phase III trials with ocriplasmin showed that criteria such as:
- symptomatic VMA diameter ≤1,500 µm
- absence of an epiretinal membrane
are independently associated with successful symptomatic VMA resolution. Therefore, in clinical practice, many retinal specialists have been using these parameters to guide their patient selection for ocriplasmin injection.
The positive impact of this improved patient selection has been highlighted in a growing number of recent articles. One of these articles provided analysis of data from patients treated at the Cole Eye Institute in Cleveland and other centers. This analysis showed that improved patient selection achieves a treatment success rate of around 50%. This compares with a 26% nonsurgical resolution of symptomatic VMA reported in patients treated with ocipraspin in the drug’s pivotal Phase III studies.

A similar picture was published in a recent paper from retina specialists at the Wills Eye Hospital, Thomas Jefferson University, in Philadelphia. In the paper, they reported a 50% success rate in achieving VMT release in 58 eyes treated with intravitreal ocipraspin. A 27% closure rate was seen in patients with full thickness macular hole. In this study higher rates of success were seen in younger patients with focal VMT and who did not have epiretinal membrane.

**Symptomatic VMA/VMT**

With introduction of JETREA®, for the first time retina physicians have a treatment option for symptomatic VMA (US) or VMT (outside US). If left untreated, this progressive eye disease generally leads to significant visual distortion, deterioration in visual acuity, or even central blindness.

Symptomatic VMA/VMT is caused by traction resulting from a prevalent attachment of the vitreous (jelly-like material in the center of the eye) to the macula at the back of the eye. The macula provides central vision needed for everyday tasks like driving, reading and recognizing faces. Symptomatic VMA/VMT can cause symptoms like distorted or decreased vision. When the disease progresses the traction may eventually result in formation of a hole in the macula (called a macular hole).

**A unique mechanism of action**

Previously, the only treatment option for patients with symptomatic VMA/VMT was surgical separation of the vitreous from the retina, called a vitrectomy. This procedure involves several risks and can lead to complications such as bleeding, pain, post-operative inflammation or irritation. Because of this, it is usually only done when the patient’s vision has deteriorated significantly. This approach is called ‘observation’ or ‘watchful waiting’ until a patient becomes a candidate for surgical treatment and repair of the retina. For many patients this is not a suitable option, as irreversible damage to the retina may have already occurred.

JETREA® is the first pharmacological option for treating symptomatic VMA and VMT. It is administered as an intravitreal injection, a unique mechanism of action. The technique has become routine among retina physicians in recent years and is easy to administer. JETREA® breaks down the protein fibers creating the abnormal traction between vitreous and macula that causes symptomatic VMA/VMT. By dissolving these proteins, JETREA® releases the traction and helps complete the detachment of the vitreous from the macula. If the treatment is successful, the symptomatic VMA/VMT will not recur.

JETREA® allows physicians to treat patients with these symptoms in an earlier stage. Successful treatment can improve patients’ vision and their ability to carry out normal daily activities. It can also stop further progression of this disease.

**Mechanism of action**

Normal Separation (PVD)  
Vitreous remodelling leads to progressive liquefication with age.

Symptomatic VMA  
Incomplete separation can cause vitreomacular adhesion (symptomatic VMA), that results in traction, leading to visual disturbance.

Symptomatic VMA resolved  
Ocriplasmin injected intravitreally acts by weakening the adhesion and separates the vitreous body from the retina, which relieves the traction and resolves the symptoms.

Patient journey US

- Patient experiences vision changes and/or symptoms
- The patient consults a general ophthalmologist/optometrist, who determines the patient is suffering from symptomatic VMA
- The ophthalmologist/optometrist refers the patient to a retina specialist, who discusses the treatment options with the patient
- Observation: as symptomatic VMA is a progressive disease, the condition of the patient can deteriorate till surgery is required. For many patients waiting/observation is not the best option as the symptoms could impact their quality of life.
- Treatment options:
  - Observation
  - JETREA®: JETREA® is the first pharmacological option for treating symptomatic VMA and VMT. It is administered as an intravitreal injection, a unique mechanism of action. By dissolving these proteins, JETREA® releases the traction and helps complete the detachment of the vitreous from the macula. If the treatment is successful, the symptomatic VMA/VMT will not recur.
  - Vitrectomy: before JETREA®, the only treatment option for symptomatic VMA patients was surgical separation of the vitreous from the retina, called a vitrectomy. This procedure entails several risks and can lead to complications like bleeding, pain, post-operative inflammation or irritation. Because of this, it is usually only done when the patient’s vision has deteriorated significantly.
ThromboGenics remains dedicated to developing and bringing to market new pharmacologic treatments for vitreo-retinal diseases.
GLOBAL OVERVIEW
Approval and reimbursement status

Status March 2015: Approved in 51 countries globally.
Approved and reimbursed in 17 countries globally.
**JETREA® IN THE US**

**Driving sales**

ThromboGenics launched JETREA® in the US through its own commercial organization on January 14, 2013. For the first time, retina physicians have a pharmacological treatment option for symptomatic VMA patients. Previously, patients remained largely untreated as their disease had not ‘progressed’ to the point where a vitrectomy (surgery) was deemed appropriate, so they underwent an extended period of observation and disease progression.

In January 2014, a permanent J-Code (J7316) for JETREA® became effective. The J-Code has streamlined the reimbursement process.

ThromboGenics’ management has taken a number of initiatives to ensure that its US organization can meet its goal of making JETREA® the routine earlier treatment for symptomatic VMA patients.

The importance of data in driving the sales of JETREA® has led to ThromboGenics focusing its commercial efforts in the US on Strategic Accounts. This change is designed to increase significantly the number of retina physicians in the US who have detailed knowledge and extensive experience in using JETREA®.

Since the US launch of JETREA®, it has also been clear that as retina physicians treat more patients they become more confident about the patient experience post therapy and as a result feel more comfortable in integrating this novel medicine into the way they manage symptomatic vitreomacular adhesion (symptomatic VMA).

To help more physicians feel comfortable in using this new pharmacological treatment approach, a key focus for the company’s medical education activities during 2014 has been to communicate the message...
that the real world safety profile seen with JETREA® is in line with the product’s approved label in the US. This message has been reinforced to the retina community via a range of conference presentations and published papers including a recent paper from the MIVI-TRUST group, which comprises the lead investigators from the JETREA® Phase III clinical trial program.

This analysis of the safety profile of JETREA® has shown that, in many cases, the short-term adverse effects that a patient experiences post-injection are a reflection of the drug working.

The company continues to help retina specialists better understand the concept of patient selection so they can raise the likelihood of symptom resolution. It is also increasing disease awareness of the treatable population among general ophthalmologists and optometrists.

Focus on strategic accounts

Since the US launch of JETREA® as a treatment option for patients with symptomatic VMA, a number of retina physicians now see it as a valuable clinical alternative to surgery. The company benefits from a number of strategic accounts where JETREA® is already used to deliver consistently good functional outcomes for patients.

ThromboGenics has thus focused more on these accounts to raise the number of retina physicians in the US with extensive experience using JETREA®. As physicians gain more experience with JETREA®, they deliver improved clinical outcomes, in part due to their improved ability to identify patients most suitable for treatment with it.

Positive physician and patient experiences at key accounts, shared with other physicians via peer-to-peer communication, are expected to positively affect the sales of JETREA®.

Patient selection

Through continuing collection of real-world data, physicians can better understand the importance of patient selection. They can thus achieve the best possible treatment outcomes with JETREA® and understand the mainly transient adverse events seen in some patients shortly after treatment.

Recent studies of practical experience have helped identify baseline characteristics predictive for success when treating symptomatic VMA patients with JETREA®. Based on positive ocular features for symptomatic VMA resolution including focal symptomatic VMA, presence of full thickness macular hole (FTMH), and absence of epiretinal membranes (ERM), increased overall symptomatic VMA resolution rates have been reported in postmarketing experience at multiple centers. Optimal patient selection is crucial, and these baseline characteristics will guide retinal physicians in selecting patients who may benefit most from ocriplasmin treatment.
Collecting additional practical clinical data

ThromboGenics continues to generate more real-world data on treatment with JETREÀ®. With this additional real world data, the use of JETREÀ® could be optimized further. This is a key element of ThromboGenics’ strategy to drive the adoption of this novel pharmacological option for the earlier treatment of symptomatic VMA.

**OASIS study**
ThromboGenics is currently conducting the “Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole” (OASIS) study to generate long term data following treatment with ocriplasmin. This sham-controlled double-masked study, which has recruited a total of 220 patients, is designed to assess anatomical and functional outcomes following a single intravitreal injection of ocriplasmin 0.125mg in subjects with symptomatic VMA/VMT including macular hole.

This is an important study in terms of generating real world data with JETREÀ® as the patients in the study are being followed up for a 24-month period post-injection.

The primary endpoint of the study is the proportion of subjects with pharmacological treatment option, we are confident that JETREÀ®’s Phase III clinical program and physician experience during its first year on the market.

Patients will be followed for up to 12 months following a single treatment with JETREÀ®. The ORBIT study is due for completion in mid-2016. The company intends to report data on a regular basis. An interim analysis was presented by the ORBIT Steering Committee, represented by Dr Mathew MacCumber, during the Macula Society Meeting from February 25 – 28, 2015 in Scottsdale, Arizona.

Dr Mathew MacCumber stated, “The interim analysis in the ORBIT study has shown that the safety and efficacy profiles are consistent with the product’s label and the data from the Phase III clinical trials. Further analysis is ongoing to assess these rates compared with the Phase III results. The findings of the interim analysis suggest that ThromboGenics’ medical education activities are beginning to deliver results. A growing number of retina centres are gaining the understanding they need, to select the patients most suited for this novel pharmacological treatment option for symptomatic VMA. With the ORBIT study, and other phase 4 studies ThromboGenics is doing, we will be able to better define the real world safety and efficacy profile of JETREÀ®.”

The next interim data from the ORBIT study will be discussed at the ARVO meeting of early May in Denver, Colorado.

**OZONE study**
In July 2014, ThromboGenics started the “Ocriplasmin Ellipsoid Zone Retrospective Data Collection Study” (OZONE). This is a retrospective patient US study designed to capture more data to characterize the anatomical and symptomatic changes that potentially occur in the six months immediately after treatment with JETREÀ® for symptomatic VMA.

Initial data from this study are expected in the first half of 2015.

**Enhancing symptomatic VMA referrals**
Patients who first notice the symptoms of symptomatic VMA often have their first discussion about their condition with their general ophthalmologist. ThromboGenics has begun implementation of its ID-VMA educational program to train ophthalmologists about symptomatic VMA so that they can better decide when it is appropriate to refer a patient with symptomatic VMA to a specialist retina clinic which has JETREÀ® experience. A number of seminars in this program have already taken place with a total of more than 500 ophthalmologists receiving training from a team of retina specialists.

With greater experience of using JETREÀ® in the specialist retina centers and a growing number of referrals of patients suitable for treatment with this novel pharmacological treatment option, we are confident that JETREÀ®’s adoption will accelerate.
Although ThromboGenics is a biotech company, it is a leader in developing innovative technologies for the vitreo-retinal interface.

Jetrea® IN THE US

Jetrea® is a product with a great future in the US

Executive Chairman Paul G. Howes on ThromboGenics’ business strategy in the US market

Paul Howes had more than 25 years of experience in commercial strategy, product development, sales and marketing in the pharmaceuticals and biotech sectors, including many years in the ophthalmology market, when he joined our Board and started working with the US team of ThromboGenics in August 2014. As Executive Chairman at ThromboGenics, Inc., he focuses on business strategy and commercial execution in the US market. He is bullish on Jetrea® and its future in the US.

“Few companies in biotechnology have taken a product all the way from discovery through to the market on a worldwide basis, with success. Jetrea® is an important and very novel product to treat patients with symptomatic VMA. It offers an additional treatment option, next to observation and vitrectomy. Moreover, Jetrea® also enables an earlier treatment because it is a simple injection as opposed to an operating room procedure, and potentially avoids the need for vitrectomy. This is a great achievement,” Paul Howes says.

In 2014, questions on Jetrea® from our customers focused mainly on the safety profile and how ocriplasmin actually works to treat symptomatic VMA. “In general, if individual specialists need more safety information before embracing any new technology, they are often not all that open to talking about the efficacy of that technology,” Paul Howes explains. “We listened to our customers’ concerns following the initial launch, and began a methodical process to generate the needed data in several discrete studies - OASIS, ORBIT, and OZONE - and we will have much of that data available to us in 2015.” (see page 26 in this report) “Interestingly, since Jetrea® was launched in the US, the real-world experience on the safety front has been very consistent with our product label. With the release of new study information in 2015, we are hoping to pivot over to a more balanced message encompassing both safety and efficacy.”
Real-world data

Clear data are vital to both the understanding of and the perception of JETREA® in ophthalmic medicine. “This is a very data-driven market. The retinal community in the US is relatively small compared to many other medical specialties, with approximately 2,200 practicing retinal specialists across the country. JETREA® came to market with a good Phase III development program, but it did not answer all the questions the community had about both efficacy and safety. There has been a clear need for more data to help explain how the product works, and the clinical setting or patient profile where it is likely to work best.

The number of retinal specialists using JETREA® is expected to grow when more data becomes available. Paul Howes notes: “With more data on safety and efficacy, including some leading-edge ERG (electroretinography) data, our belief is that specialists already comfortable using the drug will use JETREA® for more patients, and those that have been waiting for more data will begin to see opportunities to use it.”

An effective clinical development program that meets the community’s needs is a top priority, and one of ThromboGenics’ main goals in 2015. Giving customers more science and more clinical data will help them evaluate the benefits and risks of JETREA®. “The OASIS study will provide us with a comprehensive overview of the safety profile of JETREA® for as long as two years post-injection. We will work with key opinion leaders to ensure this new data is presented to their peers at major retinal meetings,” Paul Howes explains.

Next target indication

Another leading project for JETREA® in 2015 is initiating work on the next target indication in the US: diabetic retinopathy (DR). “Now that we’re in the market with our first indication, we are ready to commence the next wave of that innovation, the current indication is just the tip of the iceberg,” says Paul Howes.

“This new target indication for JETREA® represents a significant commitment to the retinal community and to the millions of patients with diabetic eye disease”, Paul Howes says. “PDR is a very prevalent condition, much more so than symptomatic VMA/VMT. The consequences of disease progression or delay in treatment are much more serious. There are several million patients in the US with PDR at a severe or very severe stage of the disease. If JETREA® is effective in treating diabetic retinopathy, this would be a major advance for the diabetic population in the US and worldwide. This would be a break-through in retina.”

“JETREA® is a product with a great future that can potentially benefit millions of patients and transform our understanding of various retinal disorders. Although ThromboGenics is a small biotech company, it is a leader in developing innovative technologies for the vitreo-retinal interface, and is poised to make a significant contribution to eye health and vision preservation for many years to come.”
THROMBOGENICS CORPORATE HIGHLIGHTS 2014

JETREA® IN EUROPE AND THE REST OF THE WORLD
Building a market with Alcon

ThromboGenics’ partner Alcon, in conjunction with Novartis, continues to commercialize JETREA® across Europe and Rest of the World (RoW) having achieved positive reimbursements.

Europe

In Europe, JETREA® received approval by the European Medicines Agency (EMA) in March 2013. It was approved for all patients in the European Union for treatment of vitreomacular traction (VMT), including when associated with a macular hole of diameter ≤ 400 microns.

In April 2013 ThromboGenics’ partner Alcon, in conjunction with Novartis, launched the drug in the UK, its first European market. Today JETREA® is available and reimbursed in Austria, Germany, Denmark, Finland, Greece, Ireland, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom, Czech Rep.

Alcon continues to commercialize JETREA® across Europe and is focusing on building on the strong market access platform established in partnership with ThromboGenics. In 2014 good progress was made to bring JETREA® closer to the market in the rest of the world, with first approvals in Asia and South America.

Asia

In April 2014, JETREA® was approved in Malaysia for treatment of adults with VMT, including when associated with a macular hole of diameter ≤ 400 microns. The approval, the first in Asia, was gained following a Priority Review conducted in September 2013. In July 2014, JETREA® was approved in Singapore for the same indication followed by Taiwan in September 2014.

South America

In July 2014, JETREA® was approved in Uruguay, the first country in South America, for treatment of adults with VMT, including when associated with a macular hole of diameter ≤ 400 microns. In October 2014, JETREA® was approved in Chile for the same indication.

Australia

In October 2014, Australia’s Therapeutic Goods Administration (TGA) approved JETREA® for treatment of adults with VMT, including when associated with a macular hole of diameter ≤ 400 microns.

Ukraine

In October 2014, JETREA® was approved in Ukraine for treatment of adults with VMT, including when associated with a macular hole of diameter ≤ 400 microns.

Japan

Alcon has now completed a bridging study in Japan. The Japanese trial, a randomized, double-blind, multi-center study with patients receiving either ocriplasmin or a sham injection, recruited a total of 168 patients with symptomatic VMA including those associated with macular hole. The results from this study are expected to form part of the regulatory submission that will be made to the Japanese Ministry of Health, Labour and Welfare in 2015 to gain approval to market ocriplasmin in Japan.
CHAPTER THREE

RESEARCH AND DEVELOPMENT

Focus on diabetic retinopathy

ThromboGenics’ primary focus is on providing therapeutic benefit for diseases that affect the back of the eye. As a worldwide leader in ophthalmology, ThromboGenics continuously researches drugs that address unmet medical needs. It explicitly focuses on prevention and treatment of diabetic eye diseases like diabetic retinopathy (DR) and diabetic macular edema (DME) that have a very direct impact on the patient’s quality of life.

Diabetic retinopathy is a condition caused by systemic type II diabetes and affects the retina of the eye. “On a microscopic level, pericyte cells surround the blood vessels inside the retina, which cause visible changes in the retina like microaneurysms in the retinal vessels or little infarcts (called “cotton wool spots”). Eventually, new and abnormal blood vessels start to grow on the surface of the retina,” says Dr. Michael Ip, professor at the Department of Ophthalmology and Visual Sciences of the University of Wisconsin, US (see interview on page 42).

The patient with diabetic retinopathy can suffer from two conditions: diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR). “The abnormal blood vessels can start to leak fluid inside the retina, called macular edema. Or new blood vessels start to grow and proliferate on the nerve of the eye and the surface of the retina. Both conditions can eventually cause vision loss,” says Dr. Ip.

With a growing population worldwide suffering from diabetes and current treatment options insufficient, ThromboGenics saw an unmet need and is researching new treatment options for PDR and DME.
Our excellent team will allow us to become a center of expertise for ophthalmology.

Our top-notch research capabilities are our calling card to the outside world

R&D: the key to the future at ThromboGenics

The future of ThromboGenics will be determined in large part by the success of its Research department. In 2014, the company clarified its long-term strategy and reoriented to focus exclusively on ophthalmology. A first-rate team is helping realize these ambitions under the guidance of Jean Feyen, Head of Pre-Clinical Research since 1 April 2014. His outlook: "The 2014 transitional period is successfully behind us and 2015 promises to be a very exciting year."

In 2014 the Senior Management and Board of Directors drafted a clear strategy for the future focused on ophthalmology. This included the Research department. "My first job was to give concrete shape to the renewed focus," explains Jean Feyen. "The team was reorganized so that wherever possible, everyone working in oncology or other research areas could be reassigned to research in ophthalmology. The move ultimately proved successful: we now have a dedicated and productive team with a shared vision. Everyone wants to help work towards achieving the goals we have set for 2015 and for the longer term."

Highly qualified team

Feyen sees the research team as vital to the success of ThromboGenics. "Our excellent team will allow us to become a center of expertise for ophthalmology. We have a reputation, which we intend to maintain, as a top-notch research group in ophthalmology, a preferred partner for collaboration. This is important since we are now concentrating on studying new medicines for diseases related to the retina, but it is not up to us to choose what the potential new research targets will be. Rather, they are determined in collaboration with external partners in the academic and business worlds. Our expertise functions as a calling card that brings us into contact with the partners who can supply us with research targets."
That’s also why developing our own models and tools to support these research activities is a major priority for us. As a company, this kind of knowledge and expertise is a selling point with external partners.”

The research department has the full support of the Senior Management and Board. “In past years ThromboGenics has invested heavily in R&D, and will continue to do so in the future,” notes Feyen.

**New indications for JETREA®**

“In 2014 we invested these resources primarily in new applications for our existing JETREA®, which may be able to reinforce its position as a product,” Feyen is referring to diabetic retinopathy (DR), for which research is underway to determine whether JETREA® can stabilize or prevent it. “We have two types of evidence that JETREA® can inhibit the disease. On the one hand, DR progresses slower in individuals with spontaneously occurring PVD (posterior vitreous detachment, where the vitreous membrane separates from the retina). In addition, a small-scale study has been published in which a natural plasmin, which resembles ocriplasmin, was injected into the eye in a number of patients. The injection induced PVD in them, which inhibited the disease.”

**Data driven**

Moreover, JETREA® has already been used for some time in the treatment of symptomatic VMA/VMT (symptomatic vitreomacular adhesion/vitreomacular traction) in the USA and elsewhere, so it’s logical that the demand for real-world data on its use has grown. ”I can confirm we are talking about a data driven business here. This is not a market you can approach strictly on instinct or through marketing alone. As a pharmaceutical company, ThromboGenics has a responsibility to the medical world. We want to show we’re a serious player that can provide answers for specific questions about the product, and that we’re prepared to openly discuss these answers with the retina specialists.”

That is why in 2014 the company’s Research department launched the PIORVO (Preclinical Investigation of Ocriplasmin Related Vitreoretinal Observations) program. “It involved compiling all the questions we have received from the medical community to date. We created the program to investigate these questions and be able to answer them with conclusive data. The aim is to publish these data in the scientific literature in order to build trust among specialists so they will apply the product to their patients. PIORVO will be a high priority for ThromboGenics in 2015. We hope to have collected the bulk of the data by year’s end.”

**Fascinating year**

“Of course, meanwhile we also have a number of new programs underway in our research into new medicines,” Feyen adds. “The data we compiled on these in 2014 are now being analyzed to determine whether to take the next steps.”

One thing is clear: for the research group at ThromboGenics, 2015 will be quite a fascinating year. “We hope our efforts to further expand the ThromboGenics research portfolio will lead us to innovative new candidate medicines for the treatment of eye disease. We will continue to work hard on partnering with academic groups and other companies: I am confident this will be our pathway to a very exciting future,” concludes Feyen.
Added value for JETREA®: diabetic retinopathy (DR) as next target indication in the US

In August 2014, the company decided on proliferative diabetic retinopathy (PDR) as the next target indication for JETREA® in the US. ThromboGenics intends to play a leading role in preventing PDR.

The latest studies of the Centers for Disease Control and Prevention (CDC) show that a third of the adult population in the US has non-proliferative diabetic retinopathy. A large share of those patients will develop proliferative diabetic retinopathy. Moreover, the number of people in the US suffering from diabetes is still increasing.

Expanding the use of JETREA® beyond symptomatic VMA is part of the company’s strategy to maximize new value-creating opportunities for the drug.

ThromboGenics has initiated a tendering process for a CRO to assist in conducting a Phase II trial with JETREA® in diabetic retinopathy in the US. This study will assess the product’s utility in this significantly underserved patient population.

Diabetic macular edema: research on new treatment options

An estimated 30% of all patients suffering from diabetes for over 20 years are at risk of developing diabetic macular edema (DME). The most common options for treating DME are laser therapy, steroids, anti-VEGF therapy or a combination of these.

ThromboGenics has started research on new treatment options for patients with DME. Its commitment on DME is highlighted by two partnerships. It entered into a collaboration and license agreement with Bicycle Therapeutics to develop and commercialize novel drugs inhibiting a specific target for the treatment of DME. ThromboGenics intends to develop therapeutics based on Bicycle’s bicyclic peptides, which can inhibit a target involved in vascular permeability. A selective inhibition of this target would offer a new approach with the potential for better treatment of DME. ThromboGenics and Bicycle will collaborate on the preclinical development of these inhibitors. ThromboGenics has an exclusive license from Bicycle Therapeutics to undertake clinical development and commercialization of identified drug candidates.
As part of the company’s standalone strategy, ThromboGenics decided in August 2014 to spin off ThromboGenics will have the exclusive license on a novel protein. In exchange, Eleven Biotherapeutics to use its AMP-Rx protein design technology to create a new therapeutic with improved pharmaceutical and therapeutic benefits. ThromboGenics will have the exclusive license to all future developments and commercialization of this novel protein. In exchange, Eleven Biotherapeutics will receive an undisclosed upfront payment and is eligible to receive undisclosed payments for development, regulatory and sales milestones, and as royalties on potential future sales commensurate with industry standards.

Oncology: research and development in spinoff

As part of the company’s standalone strategy, ThromboGenics decided in August 2014 to spin off Oncology research activities. A new company is being formed in partnership with VIB (Flanders Institute for Biotechnology). ThromboGenics will have an equity stake in this new venture focusing on paediatric oncology.

Interview

Dr. Michael Ip, Professor at the ophthalmology department of University of Wisconsin, US

Dr. Michael Ip, professor at the ophthalmology department of University of Wisconsin, is an expert in the diagnosis and treatment of vitreoretinal diseases. For over 15 years he has been involved with clinical investigations for diabetic retinopathy, both proliferative diabetic retinopathy and macular edema. He is watching the R&D evolutions in diabetic retinopathy closely. “The concept of what ThromboGenics is trying to achieve is extremely promising,” he states.

Diabetic retinopathy is increasing in prevalence in the US. “Almost a third of the adult population in the US are suffering from diabetes and a substantial proportion of these – hundreds of thousands – will develop proliferative diabetic retinopathy,” he says. “Their number is going up every year; all these people will be confronted with vision loss if they are not treated adequately. Any investigation into how we can ameliorate the complications of this disease is most welcome,” says Dr. Ip.

Promising concept

In the last ten to fifteen years there have been extensive investigations regarding diabetic retinopathy and macular edema, but there has been a lack of significant clinical study of proliferative diabetic retinopathy (PDR). Currently pharmaceutical companies are looking at prevention and treatment of PDR. Dr. Ip is following this closely. “The concept of ThromboGenics with JETREA® is extremely promising,” he says.

In PDR, changes occur in the vitreoretinal interface. Where the vitreous gel contacts the retina the vascular vessels grow and cause pathology. If you can separate the vitreous gel safely from the retina, that will likely have a highly protective effect on the progression of proliferative diabetic retinopathy or diabetic retinopathy in general. When we now perform vitreoretinal surgery, the main goal is to identify the vitreous gel in the eye and separate it from the surface of the retina. This is very difficult to achieve; it’s what makes this surgery so challenging.”

To detach the vitreous from the retina, which Dr. Ip calls “a unique mechanism,” is how JETREA® achieves its clinical effect. “The treatment with JETREA® (ocriplasmin) is different from any other pharmacologic agent we have used before. It can induce a posterior vitreous detachment and separate the vitreous from the retina. This is an enzymatic process: ocriplasmin causes an enzymatic lysis of the interface between the vitreous gel and the retina. It weakens the junction so that posterior vitreous detachment can occur: if this can be achieved in an earlier stage of the disease it might halt the progression of diabetic retinopathy and prevent patients from developing PDR and vision loss. It’s first in class that we use something like that in the eye.”

Imperfect therapies

The current therapies for PDR are imperfect and complex. One way to treat it is intravitreal laser photocoagulation. Dr. Ip explains: “At a certain level of PDR the patient’s retina becomes very ischemic, lacking oxygen. The eye reacts and tries to become less ischemic by growing new blood vessels in response to the release of vascular endothelial growth factor (VEGF). The problem with these blood vessels is that they are all abnormal: they break, bleed, contract and cause retinal detachment. With intravitreal laser photocoagulation much of the peripheral retina is destroyed. Consequently, we can down regulate the production of vascular endothelial growth factor, which causes regression of the blood vessels that are already in the eye. This way we can attempt to halt the visual loss. It is an effective, but imperfect treatment because there is much destruction of the peripheral retina. It also has many side effects like night vision difficulties, loss of peripheral vision field, problems with color vision, or even acute complications as serious choroidal detachments. It does not even always work: many patients still go on to develop vitreous hemorrhages and retinal detachments and suffer vision loss.”

More recent research has involved the study of anti-VEGF injections on diabetic retinopathy. “Various groups have shown that the retina can regress with the eye injections, but the therapy is quite intensive – many injections are needed in the first two years – and its long-term effectiveness has yet to be proven. It would be helpful to have a more convenient treatment, with fewer side effects and greater convenience. If we could find something like that, it would be extremely valuable to our patients and to the ophthalmology community as a whole.”

First in kind mechanism of action

A drug that can treat and prevent progression of PDR is therefore eagerly awaited. “In the US, the ophthalmology community has really appreciated the efforts ThromboGenics has made to develop new treatments for retinal diseases. JETREA® is a first in kind mechanism of action. I applied the company for persisting in the investigation. The mechanism of action makes sense, there is a market for this, and there is an unmet medical need. I think the study really should move forward, it should be welcomed with open arms by the ophthalmology community.”

What is diabetic retinopathy?

Diabetic retinopathy is a condition that occurs because of diabetes and affects the retina, the back part of the eye. It is a prevalent disease in the US. “On a microscopic level, several cells surrounding the blood vessels inside the retina are attenuated, causing visible changes in the retina such as microaneurysms and/or infarcts (called ‘cotton wool spots’). Eventually new and abnormal blood vessels start to grow on the surface of the retina,” says Dr. Ip.

The patient with diabetic retinopathy can suffer from two conditions: diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR). The abnormal blood vessels can start to leak fluid inside the retina, called macular edema. Or new blood vessels start to grow and proliferate on the nerve of the eye and the surface of the retina. Both conditions can eventually cause vision loss,” says Dr. Ip.

Interview Dr. Michael Ip, Professor at the ophthalmology department of University of Wisconsin, US

“JETREA® could be a first in kind mechanism of action in the treatment of PDR”
CHAPTER FOUR

OUR ORGANIZATION

The people behind the success of ThromboGenics

Organizational changes

The company’s standalone strategy has led to organizational changes focusing on the optimal level of resources for commercializing JETREA® in the US and further clinical development of this novel drug in the US. The medical affairs, market access, and pre-clinical research activities in Europe have been significantly reduced. Following these changes ThromboGenics has around 150 employees per 31st December 2014 from 192 at the end of 2013. (incl third party partners)

Europe

Several market access and medical affairs positions in Europe associated with supporting ThromboGenics’ non-US / RoW Alcon partnership are being phased out as the tasks are assumed by Alcon. R&D was reorganized based on a project portfolio review. ThromboGenics’ Irish branch was closed in October 2014, holding on to a representative office only.

United States

A new commercial business structure has been implemented in the United States with a focused field team, while creating a new team of Strategic Account Managers. The US organization was strengthened with strong commercial profiles to bolster business and support commercialization of JETREA® in the US. During 2014, a series of operational improvements have been undertaken at ThromboGenics, Inc. These changes have been made in order to have more effective marketing and sales efforts as well as higher service and education levels in key accounts, a new US Head of Commercial and a team of experienced product managers have been hired.
Executive Committee

Dr. Patrik De Haes – Chief Executive Officer
Dr. Patrik De Haes has over 25 years of experience in the global healthcare industry, in product development, marketing and general management. Before joining ThromboGenics as CEO in 2008, he was head of Roche’s Global Insulin Infusion business. Before that Patrik was President and CEO of Di energetic Medical Systems Inc, a medical device company based in Minneapolis, USA. He also led the global development and commercialization of the first biotech product at Sandoz Pharma (now Novartis) in Switzerland. Patrik holds a degree in Medicine from the University of Leuven.

Dominique Vanfleteren – Chief Financial Officer
In January 2015, ThromboGenics appointed Dominique Vanfleteren as its new Chief Financial Officer (CFO). Dominique has over 25 years of experience in senior finance, operational, control and reporting roles in quoted international biopharmaceutical companies. Before joining ThromboGenics, Dominique spent 12 years at UCB, a global biopharmaceutical company, where he held a number of international managerial finance positions, the latest being CFO of UCB's Asia Pacific Operations, operating from Brussels and Shanghai. Prior to joining UCB, Dominique worked for GSK for 16 years. He held a number of senior finance positions in Brussels and London, the latest as Finance Director of GSK’s Diversified Healthcare Services Europe.

The full ThromboGenics Executive Committee gathers a wealth of Big Pharma experience and includes people with backgrounds in international experience in research, clinical development, commercialization and financing.

The members of the ThromboGenics Executive Committee are Dr. Andy De Deene, Dr. Patrik De Haes, Paul G.Howes, Dr. Jean Feyen, Ed Kessig, David Pearson, Claude Sander, Laurence Raemdonck and Dominique Vanfleteren.

At the same time, the Medical Affairs team has been strengthened by increasing the number of clinical and scientific doctorate level associates.

Ed Kessig was appointed US Head of Commercial, and member of the ThromboGenics Executive Committee. Ed builds on a rich commercial experience across a broad range of therapeutic categories and markets. He gained most of his commercial experience at Elan Pharmaceuticals, INOTherapeutics and Auxilium Pharmaceuticals. Before joining ThromboGenics, Ed was Senior Vice President of Sales at Auxilium.

Another key initiative is the appointment of Nanaimo Bioventures LLC, represented by Paul G. Howes to the newly created position of the Executive Chairman of ThromboGenics. Paul brings to ThromboGenics over 30 years of commercial strategy and sales and marketing experience, much of it in ophthalmology. He also joined the ThromboGenics NY’s Board of Directors.

You have been the new Chief Financial Officer at ThromboGenics since the beginning of 2015. What does your job within the organization mostly entail and what is your main focus at the company?
Dominique Vanfleteren: “At ThromboGenics a CFO has many responsibilities, ranging from the entire organization of accounting, internal reporting, controlling, treasury and taxes to keeping the Board of Directors informed as defined by the rules of corporate governance. In addition extremely important is maintaining relations with various stakeholders such as our shareholders and investors.”

2014 was a transitional year for ThromboGenics. In your view, has the company successfully emerged from the process?
The transitional year enabled the company to critically review its strategy. We have all seen the results, with the great advantage that ThromboGenics now has a good basis on which to move ahead.”
For your job, what do you expect the year 2015 will bring?

“A year in which our financial department will grow from an already strong team to a genuine business partnership within the ThromboGenics organization. And by business partnership I mean making the necessary resources available to our R&D and sales departments in order to generate return on investment.”

What are the major goals for ThromboGenics in 2015?

“Strategically, to become an important player in ophthalmology and a specialist in diseases of the retina. In terms of R&D, to expand our research portfolio, and on the commercial side, to ensure that eye specialists select the right patients for JETREA®. Keeping in mind that we will need to spend our cash wisely.”

How do you see the future of ThromboGenics on the longer term?

“Successful – by further realizing the potential of JETREA® and expanding the franchise but also through focusing on ophthalmology. There is a huge potential given the growing numbers of patients with diabetes related eye conditions. The company has the benefit of outstanding expertise and is set to single-handedly bring a unique molecule to the US market in a very short time span. This is absolutely unique for a Belgian biotech company.”

You have a wealth of experience working for publicly listed companies in the biopharma sector. How would you describe the position of ThromboGenics within this sector?

“The company is transitioning towards a fully-fledged biopharmaceutical profile. ThromboGenics has all the qualities of a large biotech firm, yet its small scale allows it to react quickly and efficiently and to take targeted decisions. Given the cash to do so, ThromboGenics has what it takes to make a mark in its field.”

Board of Directors

The year 2014 brought changes to the Board of Directors. Sadly, the company had to say goodbye to Jean-Luc Dehaene, who passed away at the age of 73. “The contribution of Jean-Luc Dehaene to the company and the Board of Directors was priceless. He had expertise in several different domains and was able to assess any situation in the right way. As a person he is irreplaceable,” says Staf Van Reet, Chairman of the Board of Directors of ThromboGenics (see interview on page 50).

Appointment of Paul G. Howes

Paul Howes, Executive Chairman of ThromboGenics, Inc. also joined the ThromboGenics NV’s Board of Directors. “We are delighted to welcome Paul Howes to the Board of Directors. He has very broad commercial experience in ophthalmology and will be the link between the US organization and the Board of Directors of ThromboGenics”, says Staf Van Reet, Chairman of the Board of Directors.

Paul Howes was previously President & CEO of Inotek Pharmaceuticals, where he is still an independent Board director. Before that he was President of the Americas Region for Bausch & Lomb, during which he led a major expansion of the US pharmaceutical business and a highly successful turnaround of the US cataract surgical business. Prior to joining Bausch & Lomb in 2003, Paul spent 16 years in various senior management roles at Merck & Co., Inc. Paul is a graduate of Harvard College and earned his MBA from York University in Toronto, Canada. He currently serves as the Chairman of the Board of Prevent Blindness America.

Appointment of Emmanuèle Attout

In January 2015, ThromboGenics’ Board of Directors nominated Emmanuèle Attout as its new Independent non-executive director. Ms. Attout also joins the company’s Audit Committee. Commenting on her appointment, Ms. Attout said: “I am very pleased to be joining the ThromboGenics Board. I have been impressed by the clear strategy the company has outlined to build a profitable business focused on providing innovative medicines for the treatment of a number of important vitreo-retinal diseases and I am looking forward to contributing to its successful execution.”

“We are delighted to welcome Emmanuèle to the ThromboGenics’ Board as a non-executive director. Her broad business and financial experience will be extremely valuable to our Board and Audit Committee as we work to execute the standalone strategy we announced in mid-2014,” says Chairman Staf Van Reet.
The Board’s hands-on approach strengthens trust

The Board was closely involved in exploring strategic options implemented by the ThromboGenics management. "Of course, management takes the initiative and makes the budgetary and conceptual proposals. Our role is to subject all this to a critical evaluation, to ask questions and offer suggestions," says Chairman Van Reet. "Our contribution is geared to orientation and adjustment of specific ideas to arrive at a consensus. As the Board we unanimously support the chosen strategy. Our role is now chiefly overseeing the implementation of this course of action."

Intrinsic value

Of course, this goal will depend partly on the further commercial growth of JETREA. "Here too we fully support the strategy, and as the Board we want to provide the necessary support," Van Reet confirms. "It’s clear that ThromboGenics needs to take a more creative approach than the Big Pharma companies, with their larger budgets and more staff. That’s why we’re focusing even more attention on scientific and clinical communication about the product. We will continue to demonstrate its value and that its adverse effects are controllable and temporary. In addition, we’ll now be approaching a smaller group of clinicians, specifically those specialists we feel will be able to publish the best results. After all, we believe clinicians who can effectively interpret and apply the product will have the best chances of success. They have the potential to become excellent ambassadors to convince the broader medical world of our product’s value."

Meanwhile, worldwide JETREA is receiving more approvals and its use is spreading. "The new approvals we obtained in 2014, in a rising number of countries, show the product’s unquestionable intrinsic value. We assume the potential of JETREA will lead to increased sales and greater success on the market."

Trust

The Board’s hands-on approach strengthens trust by shareholders, who have shown understanding for the sometimes difficult decisions the company has had to make in the past year. "In 2014 we reconsolidated our position to be able to fully commit to planning our longer-term activities. Both the organization and budgets were adjusted to expected revenues in the coming years. These are not easy decisions, but they are a part of good governance. They will lead to continuity and growth for the company, not only in sales of JETREA but also in new projects launched to position ThromboGenics worldwide as a leading player in ophthalmology."

The Board fully supports research into the next indication for JETREA: proliferative diabetic retinopathy (PDR). "This once again emphasizes our faith in the product’s potential, even beyond its original indication. ThromboGenics needs to continue to innovate and grow. That is why we unanimously decided to invest in this area as well."

New members

The past year has seen a number of shifts within the Board following the quite unexpected death of Jean-Luc Dehaene. "Of course it was a severe blow for the company and the Board," notes Van Reet. "Anyone would acknowledge he was an absolutely unique figure who contributed significantly to the Board. He had wide-ranging experience, extensive knowledge and meaningful insights into running companies. He was someone who always knew how to correctly assess a situation. It has never been our ambition to try to replace him as a person. In the past year we have once again stayed true to our goal of developing the strongest and most diverse Board possible."

Another new member, Emmanuèle Attout, recently joined the Board as an independent Non-Executive Director. "Through many years of experience at PwC, one of the world’s largest audit firms, she has acquired tremendous insight into the rules of corporate governance. For that reason alone she’s an important asset to the Board. In a company like ThromboGenics the governance rules are not only highly complex, they also demand close monitoring. During her career at PwC Emmanuèle Attout has also seen how international companies evolve and operate and she can contribute her knowledge in this area," adds Van Reet.

"The appointment of these experts gives the Board experienced team members who can support the renewed focus on ophthalmology. The transitional year 2014 has allowed our organization to grow stronger and given it a clear goal and confidence in the future of ThromboGenics, both in the shorter and longer term," Van Reet concludes.

The Board of Directors unanimously supports the chosen strategy

"The Board of Directors unanimously supports the chosen strategy."

Dr. Staf Van Reet, Board Chairman

The Board of Directors of ThromboGenics relies on the experience and diversity of its members’ financial expertise, auditing experience and commercial know-how in the US market. Board Chairman Staf Van Reet notes, "The members play a supervisory role on behalf of the shareholders, but above all they act as a sounding board for the management."
Shareholders information

Key information for investors

Listing

ThromboGenics is listed on the Eurolist by Euronext Brussels under the symbol THR. Since 2009 it has been listed on the NEXT 150 Index, made up of mid to large capitalization stocks on the Euronext exchange.

Investor relations

Our investor relations policy includes:

- Providing reliable, accurate, and valuable information in a timely manner to help shareholders make informed decisions
- Full transparency
- Operating within the company’s policies and adhering to the relevant security laws and regulations
- Strengthening our dialogue with the investment community
- Providing access to the senior management team
Shareholding structure

On December 31, 2013, ThromboGenics had 36,094,349 outstanding shares and 766,500 outstanding warrants.

The free float amounts to 81.8%. The shareholding structure can be summarized as follows:

- Public: 80.4%
- Thomas Clay: 7.7%
- Biggar Ltd: 5.9%
- Norges Bank: 3.03%
- Landon Clay: 3.0%

Paying agent services

KBC Bank acts as the company’s paying agent. The paying agent will not charge shareholders with respect to payments of dividends, the exercise of subscription rights and other events concerning ThromboGenics’ shares.

Financial calendar

<table>
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<tr>
<th>Date</th>
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<tbody>
<tr>
<td>Thu, March 12, 2015</td>
<td>Full Year Results 2014</td>
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<tr>
<td>Thu, May 5, 2015</td>
<td>General Shareholders Meeting 2015</td>
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<tr>
<td>Thu, May 21, 2015</td>
<td>Business Update Q1 2015</td>
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<tr>
<td>Wed, August 26, 2015</td>
<td>Half Year Results 2015</td>
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<tr>
<td>Thu, November 5, 2015</td>
<td>Business Update Q3 2015</td>
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Glossary

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<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMD</td>
<td>Age-related Macular Degeneration</td>
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<tr>
<td>Anti-PIGF</td>
<td>Anti-Placental growth factor</td>
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<tr>
<td>BLA</td>
<td>Biological license application</td>
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<tr>
<td>CADTH</td>
<td>Canadian Agency for Drugs and Technologies in Health</td>
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<td>CDC</td>
<td>Centers for Disease control and prevention</td>
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<td>CIO</td>
<td>Chief Information Officer</td>
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<td>CEPS</td>
<td>Economic Committee of European Pharmaceutical Societies</td>
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<td>Chief Medical Officer</td>
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<td>CMVR</td>
<td>Canadian Medical Research Council</td>
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<td>CRO</td>
<td>Clinical research organization</td>
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<td>DME</td>
<td>Diabetic Macular Edema</td>
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<td>EMA</td>
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<td>Food and Drug Administration</td>
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Component Highlights 2014

Contact details

5756

ShankholdeRs Information