

# Summary

#### **Clinical Development Timeline**

#### Phase I

The first time the safety of a new drug candidate is evaluated in humans

#### Phase II

The first time the new drug candidate is evaluated in people suffering from the disease for which it is being developed as a treatment.

#### Phase III

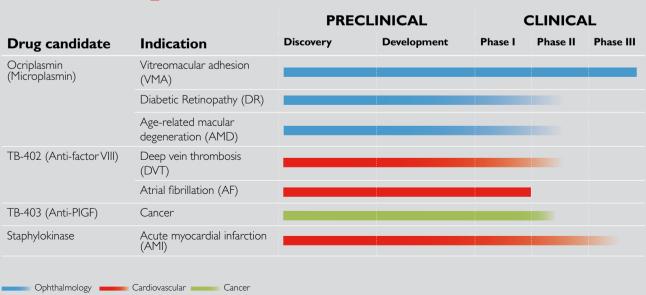
A larger clinical evaluation of the new drug candidate in patients suffering from the disease the drug is designed to treat. Phase III clinical trials provide the data needed to make a regulatory submission for the new drug to be approved.

#### **US and European filings**

Manufacturers intending to commercialize a biologic in the US submit a biologic license application (BLA) to the FDA before commercialization. A BLA provides the information needed to gain marketing approval of a new biological drug such as ocriplasmin (microplasmin). In Europe, manufacturers submit a marketing authorization application (MAA) for their new biological drug to the European Medicines Agency (EMA).

ThromboGenics is one of Europe's most successful biotechnology companies. In recent years the company has made significant progress towards the goal of becoming a transforming force in ophthalmic medicine and innovative biopharmaceuticals. This success, combined with the potential of its lead product, ocriplasmin, has enabled the company to deliver significant returns to shareholders since its IPO in mid-2006.

## Clinical Pipeline Chart



## ADOUT Throbe Consider to

"ThromboGenics is on track to become a strong and profitable biopharmaceutical company, with a focus on innovative ophthalmic medicines."

Patrik De Haes, CEO



## Working To Transform The Retinal Disease Landscape

ThromboGenics NV is a fast-growing biopharmaceutical company specializing in innovative treatments for eye disease, vascular disease and cancer. Positive Phase III data for its lead product ocriplasmin, for the treatment of retinal diseases, has put ThromboGenics firmly on track to becoming a strong, profitable and self-sustaining business. ThromboGenics is confident that by successfully commercializing ocriplasmin, it will achieve its corporate goals and deliver significant value for patients, physicians and shareholders.

ThromboGenics is rapidly advancing its corporate strategy, especially now that it has demonstrated ocriplasmin's potential to transform the treatment of symptomatic vitreomacular adhesion (sVMA).

#### What is sVMA?

As part of the normal aging process, the vitreous (the central gel part of the eye) separates from the retina (back of the eye). This separation is called "posterior vitreous detachment" (PVD). However, if the separation is not complete, areas of focal attachment or vitreomacular adhesion (VMA) can occur. The incomplete

separation of the vitreous from the retina is called anomalous or pathologic PVD.

VMA occurring as a result of anomalous PVD can create pulling forces, or "traction," on the retinal surface. This occurs because the vitreous forms an abnormally strong adhesion to the surface of the macula (the center of the retina responsible for central vision).

When VMA leads to symptoms such as visual impairment and metamorphopsia (distorted vision), it is called symptomatic vitreomacular adhesion (sVMA).

VMA can lead to the development of sight-threatening complications, such as VMT (Vitreomacular Traction) syndrome, macular puckers and macular holes. Traction caused as a result of the adhesion leads to a hole in the macula. Macular puckers and macular holes can also lead to distorted vision, a loss of visual acuity and/ or blindness.

There is also evidence that VMA is associated with several common retinal disorders that can potentially cause blindness, including age-related macular degeneration (AMD), diabetic retinopathy (DR), and diabetic macular edema (DME).

Today, the standard of care in the treatment of sVMA is either observation (watch and wait) or a vitrectomy, a surgical procedure that induces PVD by removing the vitreous gel, thus releasing the VMA. During a vitrectomy, the surgeon uses specialized instruments to remove the vitreous. Although the surgery is efficient at removing the vitreous, vitrectomy is an operative procedure that carries potential risks to the patients' eyes, including bleeding, retinal tears, retinal detachments, infection and cataract progression.

#### Ocriplasmin - a Novel Treatment Option

Ocriplasmin is a proteolytic enzyme that dissolves the protein glue that links the vitreous to the retina. It is administered via an intravitreal injection. This novel treatment option could be a paradigm shift in the treatment of sVMA and restore patients' vision.

The results from the pivotal Phase III MIVI-TRUST (Microplasmin Intravitreous Injection – Traction Release Without Surgical Treatment) program announced during 2010 confirmed ocriplasmin's potential as an important new pharmacological





treatment for a range of retinal conditions.

The two Phase III trials (TG-MV-006 and TG-MV-007) in the program were remarkably consistent, confirming the overall benefits of ocriplasmin. The two trials met their primary endpoint demonstrating that nearly 30% of patients treated with ocriplasmin achieved resolution of VMA compared with 10% of patients on placebo. The results were highly statistically significant.

Ocriplasmin also met the secondary endpoints: Pharmacological closure of full-thickness macular hole (FTMH) and inducing total PVD. The pooled results showed that ocriplasmin closed the FTMH in 40% of patients, induced total PVD in 13% and improved visual acuity and visual function. Ocriplasmin was generally safe and well tolerated.

ThromboGenics expects to file US and European regulatory submissions for ocriplasmin during the second half of 2011. When approved, ocriplasmin will address a significant unmet medical need in a growing population in both the US and Europe and will provide patients with access to this novel pharmacological treatment for sVMA.

The company is already building an experienced team to prepare for the launch of ocriplasmin. During 2010, ThromboGenics secured a long-term commercial supply agreement for the active substance with MSD Biologics (UK), part of the Merck BioManufacturing Network.

### **ThromboGenics Funded** for Success

Outside ophthalmology, ThromboGenics has two other clinical programs that broaden its pipeline and provide additional potential funding sources. ThromboGenics expects further income from its strategic alliance with Roche for its novel anticancer antibody TB-403 (anti-PIGF). Roche started a Phase Ib study with TB-403 in combination with sorafanib (Bayer's Nexavar<sup>®</sup>) in hepatocellular carcinoma (HCC, liver cancer).

The strategic deal with Roche is potentially worth up to €500 million, and ThromboGenics will receive double-digit royalties after commercialization.

ThromboGenics, which discovered TB-403, receives 60% of the revenue from this deal under the terms agreed with co-development partner BioInvent

International, which receives the remaining 40% of the revenue. TB-403 completed a Phase I study in patients with advanced cancer in 2009.

ThromboGenics is also developingTB-402 (anti-Factor VIII), a novel, long-acting anticoagulant for the prevention of thrombosis after orthopaedic surgery and for atrial fibrillation. Phase II data demonstrated superior antithrombotic activity and comparable safety to the standard treatment enoxaparin (sanofi-aventis' Lovenox®).

The Phase II data suggest that TB-402 could play an important role in the post-surgical treatment of venous thromboembolism (VTE) because of its comparable safety profile and simple dosing regime. Its novel mode of action is expected to reduce the risk of undesirable bleeding events, even at high doses, and the need for patient monitoring.

ThromboGenics is based in Leuven, Belgium, and employs around 80 people globally. It is listed on Eurolist by NYSE Euronext under the symbol THR.

# Delivening Our Key Strategic Objectives

#### CLINICAL

#### 9 Feb. 2010

Ophthalmology, the prestigious Journal of the American Academy of Ophthalmology, publishes a paper covering the positive Phase II results of ocriplasmin, ThromboGenics' lead product. The trial evaluated the product's safety and efficacy in helping to separate the vitreous from the retina, a process used to treat retinal disorders. The journal highlights that ocriplasmin could be a potential breakthrough for sVMA.

#### 20 Apr. 2010

ThromboGenics announces that ocriplasmin met its primary endpoint in the first MIVI-TRUST Phase III trial (TG-MV-006) evaluating ocriplasmin for the treatment of sVMA. The primary endpoint was pharmacological resolution of focal VMA one month after a single injection of ocriplasmin.

#### 6 May 2010

ThromboGenics and **BioInvent** International announce positive Phase II data for TB-402, a novel, long-acting anticoagulant for deep vein thrombosis (DVT) prophylaxis. TB-402 demonstrated superior antithrombotic activity and comparable safety to the standard treatment enoxaparin. The recombinant human monoclonal antibody which partially inhibits Factor VIII could become part of standard post-surgical anticoagulant therapy.

#### 7 Iun. 2010

data from the first MIVI-TRUST Phase III trial (TG-MV-006), showing that a single injection of ocriplasmin cured over 40% of patients with full thickness macular hole, a condition that can lead to serious visual impairment, including central blindness, if left untreated.

#### I Sept. 2010

ThromboGenics announces further ThromboGenics announces that ocriplasmin met its primary endpoint in the second MIVI-TRUST Phase III trial (TG-MV-007), confirming the positive data from TG-MV-006. Results also showed that ocriplasmin improved visual acuity and visual function of patients without the need for surgery.

#### 5 Nov. 2010

Co-development partner Roche announces plans to start a Phase lb/ II trial with ThromboGenics/BioInvent's novel anticancer antibody TB-403 in combination with Avastin<sup>®</sup> in patients with glioblastoma multiforme during the first quarter of 2011.

#### CORPORATE

#### 17 May 2010

ThromboGenics and **BioInvent** receive a €10 million milestone payment from Roche following the initiation of an imaging study of TB-403. Roche will continue to fund further research activities undertaken by ThromboGenics and BioInvent related to this novel humanized monoclonal antibody.

#### 30 Sept. 2010

ThromboGenics signs a 10-year commercial supply deal with MSD Biologics (UK) for the production of ocriplasmin. MSD Biologics, a contract manufacturing organization with specific expertise in microbial-derived biologics, has been producing ocriplasmin for ThromboGenics' clinical develop- 5 Nov. 2010 ment program since 2007.

#### 14 Oct. 2010

Independent market research by MedPanel, on behalf of the investment bank leffries International Ltd, confirmed that ocriplasmin could be an important first pharmacological treatment for sVMA. A survey of 50 vitreoretinal specialists in the US found that a significant proportion was aware of ocriplasmin and would be willing to use it for a wide range of retinal disorders.

team to prepare for the com-The company has appointed Ram placed 2,944,523 new shares with ocriplasmin, Paul de Nijs Head of sional investors and institutional Head of Medical Ophthalmology.

#### 3 Dec. 2010

ThromboGenics builds its senior ThromboGenics successfully raises €56 million through a primercial launch of ocriplasmin, vate placement. The Company Palanki Head of US Marketing for domestic and international profes-Market Access, and Aniz Girach investors in the US, putting it in a strong financial position for the start of 2011.

#### 2011 - ThromboGenics -**Bringing Ocriplasmin to Market**

In the next year, we expect to make significant progress in preparing for the commercialization of ocriplasmin - a major step towards our goal of building a strong and profitable company focused on novel ophthalmic medicines. We plan to file US and European regulatory submissions for ocriplasmin in the second half of 2011.

## Thrombogenics Is Well Positioned For Success

"The positive results from our Phase III MIVI-TRUST program showing that ocriplasmin has the potential to be an important new pharmacological treatment for a range of potentially blinding retinal diseases has validated our ambition to become a transforming force in ophthalmic medicine."

Steve Pakola, CMO







## A Crucial Year In Sight

#### Dear Shareholder,

ThromboGenics is positioned for success following our numerous clinical and financial achievements in 2010. **2010 marked a pivotal year** in ThromboGenics' development as we announced positive Phase III results for our lead product, **ocriplasmin**. Ocriplasmin is a novel treatment that could transform the way retinal disorders are treated. In addition, we are fortunate to receive continued support from investors who believe in and share our vision. As we enter another critical year in ThromboGenics' growth, we will continue to drive our strategy to become a successful, profitable and self-sustaining company focused on cutting-edge ophthalmic medicines.

Our strong cash position at the start of 2010 enabled us to deliver our key objectives for the year. Our future success is largely dependent on ocriplasmin. In 2010, Thrombo Genics demonstrated the significant clinical benefits of ocriplasmin to the retinal and investment community. The positive Phase III data that we had anticipated from the MIVI-TRUST program reaffirms our commitment and determination to developing an innovative ophthalmology portfolio around this exciting new medicine.

Ocriplasmin has the potential to offer a completely new pharmacological approach to the treatment of sight-threatening retinal disorders. We are currently preparing to file ocriplasmin as a pharmacological treatment for patients with impaired vision due to symptomatic vitreomacular adhesion (sVMA). When approved, ocriplasmin would be the first pharmacological treatment for sVMA to reach the market.

VMA is a pathology that leads to many serious retinal diseases. There is a clear need for new, minimally invasive approaches for these retinal diseases that affect a significant number of people that do not have an available treatment today.

We remain confident in the **potential commercial success** of this product that looks well positioned to meet a significant unmet medical need. The ophthalmic market is one of the fastest growing specialty therapeutic sectors within the pharmaceutical market, with limited competition in many sub-sectors. In the case of sVMA, there are no approved products and very few new agents in early development.

In April, we announced positive data from the first pivotal Phase III MIVI-TRUST trial (TG-MV-006). The trial met its primary endpoint of pharmacological resolution of focal VMA one month after a single injection of ocriplasmin. In September, we reported that the second MIVI-TRUST trial (TG-MV-007) had also met its primary endpoint, confirming the results of the first study. The MIVI-TRUST program is the largest interventional clinical program ever performed to specifically evaluate the pharmacological treatment of sVMA. The program comprised two trials involving 652 patients in total. In addition to meeting its primary endpoints, a single injection of ocriplasmin was shown to close full thickness macular holes in around 40% of patients. It induced total PVD, improved VA and visual function, and was generally safe and well tolerated.

These exciting Phase III data received a positive response from retinal specialists after being presented at key conferences in Europe and North America in 2010. Key opinion leaders will present the MIVI-TRUST Phase III pooled data at a number of conferences during 2011 to continue raising awareness of ocriplasmin among retinal specialists.

We plan to file the US and European regulatory submissions for ocriplasmin in the second half of 2011.

ThromboGenics intends to commercialize this novel medicine through its own field force and has started building an experienced multidisciplinary launch team.

In parallel with our success with ocriplasmin, we have continued to advance our other key clinical programs as planned. Our novel antibody TB-402 (anti-factor VIII), a long-acting anticoagulant for deep vein thrombosis after knee surgery, has shown positive results in a 316-patient Phase II trial. TB-402 demonstrated superior antithrombotic activity and comparable safety to the standard treatment enoxaparin. The recombinant human monoclonal antibody could become part of a standard post-surgical treatment to prevent venous thromboembolism (VTE), given that it is easier to use and as a result would improve patient compliance.

ThromboGenics along with our partner BioInvent International, received a €10 million milestone payment after co-development partner Roche started its first clinical study for our novel anticancer antibody TB-403 (anti-PIGF). TB-403, a humanized monoclonal antibody, represents a potentially promising cancer therapy. TB-403 has a novel mechanism of action based on its ability to selectively block the formation of the new blood vessels required for tumor growth.

ThromboGenics finished a very successful year by raising €56 million from both European and US investors in an over-subscribed private placement. We plan to use our strong financial position to fund the activities needed to ensure the successful launch of ocriplasmin and to drive our commercial strategy over the next few years. The successful fundraising is further testimony to the confidence our shareholders place in ThromboGenics' exciting product pipeline and management's ability to successfully execute our ophthalmic-focused strategy.

ThromboGenics **faces an exciting and demanding year ahead** as we prepare for the regulatory filings of ocriplasmin, a key step in our plans to commercialize and bring this novel medicine to patients. We also intend to continue progressing our other exciting clinical programs so they can be brought to market as quickly as possible. By successfully delivering on these goals we expect to continue to deliver significant value for our shareholders.

With the combination of the **right people, resources and determination**, the ThromboGenics team ensures that we will remain on track to becoming a self-sustaining and profitable company focused on ophthalmics. On behalf of the management, I wish to thank you all for your support and continued interest in ThromboGenics and I look forward to sharing our future success with you.

**Dr. Patrik De Haes,**Chief Executive Officer of Thrombo Genics

## Ocriplasmin In Action

Due to its novel mode of action, ocriplasmin could offer retinal specialists a pharmacological approach for the treatment of a range of retinal diseases.

Ocriplasmin is a proteolytic enzyme that dissolves the protein glue that links the vitreous to the retina. It is administered via an intravitreal injection. Positive Phase III results have been reported on ocriplasmin from the MIVI-TRUST

program evaluating the pharmacological treatment of sVMA. This is a condition where the vitreous (the central gel part of the eye) has an abnormally strong adhesion to the surface of the back of the eye (the retina) and causes visual impairment.

Ocriplasmin represents a potential breakthrough because it offers a minimally invasive pharmacological treatment

option for a condition that is typically only treated when the visual impairment warrants surgical intervention.

ThromboGenics believes that an intravitreal injection with ocriplasmin could transform the way retinal diseases are treated by providing a potential pharmacological option for a range of retinal conditions that can lead to blindness.

Vitreous remodelling leads to progressive liquefaction with age<sup>1</sup>











**Normal Separation (PVD)** 

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





Ocriplasmin injected intravitreally acts by weakening and breaking the protein fibers that are causing the adhesion and separates the vitreous body from the retina, which relieves the traction and resolves the symptoms





I. Bishop. Prog Retinal Eye Res. 2000; 19:323-344.

## Ocriplasmin - Set To Meet A Significant Unmet Need In The Ophthalmic Market

#### **The Ophthalmology Market**

ThromboGenics is focusing on the unmet medical needs of an attractive and growing market for ophthalmic medicines. The positive dynamics of this market are due to the increasing prevalence of eye disorders. This is the result of a growing elderly population and shifting lifestyles as more people develop diseases such as diabetes, which are associated with an increased risk of eye disease.

In 2009, the global market for ophthalmic pharmaceuticals was thought to be worth approximately \$14 billion, with much of the recent growth driven by the introduction of therapies for wet age-related macular degeneration (AMD) such as Lucentis® (Genetech).

Encouragingly, from ThromboGenics' point of view, developments in the market have shown that despite its recent growth, there remains a clear need for

new ophthalmic medicines that can lead to improved treatment outcomes. Retinal specialists have traditionally been early adopters of innovative medications, and with the experience they have gained with intravitreal injection of AMD medications, ocriplasmin is likely to experience a rapid uptake. The combination of unmet medical need, a first-in-class therapy and a prescribing community that is receptive bodes well for the significant commercial success of ocriplasmin.









#### Ocriplasmin Positive Phase III Clinical Results in Patients with sVMA

In 2010, ThromboGenics delivered positive results from its Phase III MIVI-TRUST program evaluating ocriplasmin for the pharmacological treatment of sVMA. The MIVI-TRUST program is the largest interventional clinical program ever performed to specifically evaluate the pharmacological treatment of sVMA.

The Phase III program showed that ocriplasmin was able to resolve sVMA in close to 30% of patients. The program also showed that it was able to cure 40% of patients with macular hole pharmacologically.

### About Symptomatic Vitreomacular Adhesion

As part of the normal aging process, the vitreous (the central gel part of the eye) separates from the retina (back of the eye). This separation is called "posterior vitreous detachment" (PVD). However, if the separation is not complete, areas of focal attachment or vitreomacular adhesion (VMA) can occur. The incomplete separation of the vitreous from the retina is called anomalous or pathologic PVD.

VMA occurring as a result of anomalous PVD can create pulling forces, or "traction," on the retinal surface. This occurs because vitreous forms an abnormally strong adhesion to the surface of the macula (the center of the retina responsible for central vision).

When VMA leads to symptoms such as visual impairment and metamorphopsia (distorted vision), it is called symptomatic vitreomacular adhesion (sVMA).

VMA can lead to the development of sightthreatening complications, such as VMT syndrome, macular puckers and macular holes, each of which can also lead to distorted vision, a loss of visual acuity and/or blindness.

There is evidence that VMA is associated with several common eye disorders that can potentially cause blindness, including age-related macular degeneration (AMD), diabetic retinopathy (DR), and diabetic macular edema (DME).

The diagnosis of sVMA has improved significantly in recent years due to the advent of optical coherence tomography (OCT). The use of OCT makes it easy for the treating physician to clearly see the degree of adhesion between the vitreous and retina.

Prior to OCT, the diagnosis of VMA was difficult and was usually made by excluding other potential causes of the patient's impaired vision.

The improved ability to diagnose VMA using OCT has led to the discovery that VMA is implicated in many other retinal disorders.

## Treating sVMA – Surgery is Currently the Only Option

Today, the standard of care in the treatment of sVMA is either observation (watch and wait) or a vitrectomy, a surgical procedure that induces PVD by removing the vitreous gel, thus releasing the VMA. During a vitrectomy, the surgeon uses specialized instruments to remove the vitreous.

Although the surgery is efficient at removing the vitreous, vitrectomy is an operative procedure that potential carries risks to the patients' eyes, including bleeding, retinal tears, retinal detachments, infection and cataract progression.

## OCT: Improving The Diagnosis Of VMA

Vitreomacular adhesion (VMA) is becoming a more easily recognisable condition due to the use of Optical Coherence Tomography (OCT), a new type of imaging technology. Improvements in OCT technology have revolutionized the way specialists in the ophthalmology field are able to identify VMA. OCT has allowed for faster and much easier diagnosis of back of the eye conditions such as VMA and is the technique used in ThromboGenics' Phase III trial program for ocriplasmin, MIVI-TRUST.

OCT is used for taking cross-sectional pictures of the retina. It is used to diagnose and follow treatment in certain

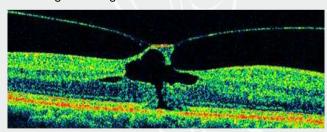
eye conditions, such as vitreomacular adhesion (VMA), age-related macular degeneration, diabetic macular edema and other diseases affecting the macula.

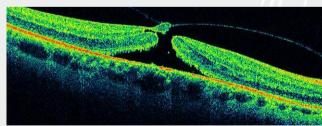
OCT is in effect 'optical ultrasound' that is able to generate cross-sectional images by capturing the pattern of the light scattering generated from within tissue of interest. OCT is being increasingly used by the medical community because it provides much higher resolution images than other imaging modalities such as MRI or ultrasound.

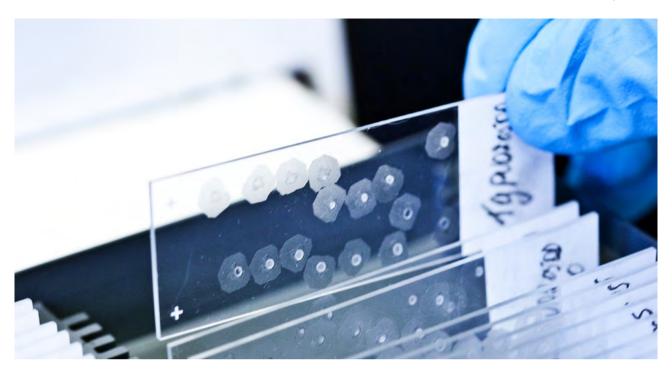
OCT is a non-invasive imaging test which allows doctors to look at each of the ten layers in the retina. As a result of OCT, the doctor is able to measure the thickness of each layer to aid in the early detection and diagnosis of retinal diseases and conditions such as vitreo-macular adhesion, age-related macular degeneration, macular swelling, macular holes, cystoid macular edema, central serous retinopathy and optic nerve damage.

OCT has a number of other advantages including its ability to deliver instant real-time high resolution images of tissue. There is no need for patients to undergo any preparation prior to the OCT procedure. OCT also uses infrared light and does not use harmful ionizing radiation, meaning that the equipment can be safely located anywhere.

OCT images showing vitreomacular traction and macular hole







The growing number of patients with retinal disorders led to approximately 250,000-300,000 vitrectomies per year being performed in the US, and about 850,000 globally. Given the growing prevalence of retinal disorders, it is likely that the number of vitrectomies carried out worldwide will increase.

#### Ocriplasmin - Potentially the First Pharmacological Treatment Option for sVMA

Data from both Phase II and Phase III clinical trials have consistently shown that ocriplasmin is able to resolve VMA in close to 30% of patients. Given these results, ocriplasmin could potentially represent a breakthrough in the way sight-threatening retinal diseases are treated.

In its Phase III clinical trial program, ThromboGenics has shown that the patients who achieved a resolution of their VMA also saw an improvement in their vision.

#### Positive Pivotal Phase III Trial Results with Ocriplasmin (MIVI-TRUST)

A key corporate highlight for Thrombo Genics in 2010 was the successful conclusion of the Phase III clinical trial program with ocriplasmin. The program involved two clinical trials, one conducted in the US (TG-MV-006 trial), and the other was performed in the US and in Europe (TG-MV-007 trial).

The MIVI-TRUST trials, both of which were multi-center, randomized, placebo-controlled and double-masked, evaluated

 $125\mu g$  of ocriplasmin versus placebo in the intravitreal treatment of patients with focal VMA.

The positive pooled results from both trials were delivered in just 20 months from the first patient being recruited. The successful management of this study led to the ThromboGenics team being short-listed for the Clinical Research Team of the Year at the 2010 Scrip Awards.

The successful Phase III MIVI-TRUST program showed that ocriplasmin:

- Successfully resolved sVMA in 30% of patients
- Closed FTMH without the need for surgery in 40% of patients
- Improved the vision of patients
- Was generally safe and well tolerated

Both the TG-MV-006 and TG-MV-007 trials met the primary endpoint, achieving a statistically significant improvement in the resolution of VMA. The pooled results from the MIVI-TRUST program showed that 26.4% of the 465 ocriplasmin-treated patients achieved resolution of their VMA at 28 days, compared with just 10.2% of the 182 patients who received a placebo injection. This was a highly statistically significant result (p=0.000002).

The MIVI-TRUST pooled results also highlighted ocriplasmin's impressive effect in patients diagnosed with FTMH.

In this group, 40.6% of the 106 patients had a closure of their FTMH at 28 days following a single 125 $\mu$ g injection of ocriplasmin. This compares with 10.6% of the 47 patients in the placebo group. This was again a highly statistically significant result (p=0.00015). The closure of their FTMH led to ocriplasmin-treated patients experiencing a significant improvement in visual acuity (VA) compared with baseline.

Importantly the Phase III program showed that patients who benefited from ocriplasmin also saw their vision improve. The pooled VA data from the Phase III program showed that at the end of the six-month study period,

23.7% of the ocriplasmin-treated patients had achieved at least a 10-letter (2 lines) improvement in VA without the need for vitrectomy. This compares with only 11.2% of the patients who received a placebo injection (p=0.0002). Within the ocriplasmin-treated population, 9.7% of patients achieved a 15-letter (3 lines) VA improvement without need for vitrectomy, compared with just 3.7% of the placebo patients (p=0.01). In addition, ocriplasmin-treated patients showed an improved visual function when compared with placebo, based on the VFO-25 (the National Eye Institute Visual Functioning Questionnaire) results.

The pooled results also confirmed that ocriplasmin was generally safe and well tolerated. There was no evidence of an increased risk of retinal tear or detachment.

### **Evaluating Ocriplasmin in Other VMA-Implicated Indications**

Data indicate that VMA is implicated in other retinal disorders such as DME, DR and exudative (wet) AMD, and leads to a worse prognosis for these patients<sup>1</sup>. Ocriplasmin is currently in Phase II for DR and AMD.

DR is a common complication of diabetes, involving damage to blood vessels in the retina, partly due to elevated blood

sugar levels. It is a major cause of visual loss and the leading cause of blindness in patients aged 20-60. Around 18 million Americans are diagnosed diabetics and an estimated 4.1 million Americans have DR<sup>2</sup>.

DR is currently treated with laser photocoagulation (LP) to seal the blood vessels in the retina. For patients who do not respond to LP, vitrectomy is currently the most widely used treatment option.

Vitreomacular separation could be beneficial in the treatment of diabetic macular edema (DME). A study published in *Ophthalmology* found that separating the vitreous from the retina could promote the spontaneous resolution of DME and consequently improve visual acuity<sup>3</sup>.

Previous studies have shown that the adhesion between the vitreous and retina tends to be much stronger in advanced-stage DME patients. This finding has been made in patients undergoing vitrectomy to resolve their condition<sup>4</sup>.

This level of adhesion makes it more challenging to achieve a total PVD in patients with advanced DME, as opposed to earlier-stage DR. PVD has been shown to be associated with a decreased rate of neovascularization and DME<sup>5</sup>.

<sup>&</sup>quot;Posterior vitreous detachment and neovascularization in diabetic retinopathy", Akiba J, Arzabe CW, Trempe CL., Ophthalmology, 1990;97, (7):889-91.

<sup>&</sup>quot;Posterior Vitreomacular Adhesion: A Potential Risk Factor for Exudative Age-Related Macular Degeneration?", Krebs I, Brannath W, Glittenberg C, Zeiler F, Sebag J, Binder S. American Journal of Ophthalmology, 2007, Nov; 144(5):741-746. Epub 2007 Sep 20.

<sup>&</sup>quot;The role of abnormal vitreomacular adhesion in age-related macular degeneration: spectral optical coherence tomography and surgical results", Mojana F, Cheng L, Bartsch DU, Silva GA, Kozak I, Nigam N, Freeman WR. American Journal of Ophthalmology, 2008 Aug;146(2):218-227. Epub 2008 Jun 6.

<sup>&</sup>lt;sup>2</sup> CDC (Centres for Diseases Control and Prevention), 2009

<sup>&</sup>lt;sup>3</sup> "Association Between the Short-Term Natural History of Diabetic Macular Edema and the Vitreomacular Relationship in Type II Diabetes Mellitus," Hikichi T, Fujio N, Akiba J, Takahashi M, Yoshida A, Ophthalmology, 1997; 104 (3): 473-8

<sup>4 &</sup>quot;Vitrectomy for persistent diffuse diabetic macular edema," Stolba U, Binder S, Gruber D, et al. American Journal of Ophthalmology 2005; 140: 295-301

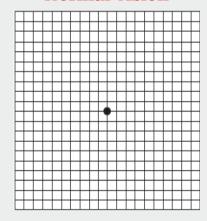
<sup>&</sup>lt;sup>5</sup> "Short-Term Natural History of Diabetic Macular Edema," Ophthalmology 1997



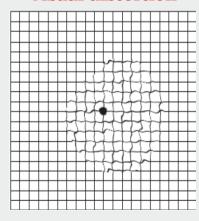
## Symptomatic Vitreomacular Adhesion Is A Significant Clinical Problem

- Visual distortion, loss in visual acuity, central blindness
- > Poor visual function

#### **Normal vision**



#### **Visual distortion**



**Central blindness** 



## Complications Of Focal VMA: Visual Distortion And Central Blindness

As part of the normal aging process, the vitreous (the central gel part of the eye) separates from the retina (back of the eye). This separation is called "posterior vitreous detachment" (PVD). However, if the separation is not complete, areas of focal attachment or vitreomacular adhesion (VMA) can occur

The incomplete separation of the vitreous from the retina is called anomalous or pathologic PVD. VMA occurring as a result of anomalous PVD can create pulling forces, or "traction," on the retinal surface. This occurs because the vitreous forms an abnormally strong adhesion to the surface of the macula (the center of the retina responsible for central vision). When VMA leads to symptoms such as visual impairment and metamorphopsia (distorted vision), it is called sympvitreomacular adhesion tomatic (sVMA).

VMA can lead to the development of sight-threatening complications, such as VMT (Vitreomacular Trac-

tion) syndrome, macular puckers and macular holes. Traction caused as a result of the adhesion leads to a hole in the macula. Macular puckers and macular holes can also lead to distorted vision, a loss of visual acuity and/or blindness.

There is also evidence that VMA is associated with several common retinal disorders that can potentially cause blindness, including age-related macular degeneration (AMD), diabetic retinopathy (DR), and diabetic macular ederna (DME).

treatment of sVMA is either observation (watch and wait) or a vitrectomy, a surgical procedure that induces PVD by removing the vitreous gel, thus releasing the VMA. During a vitrectomy, the surgeon uses specialized instruments to remove the vitreous and replace it with a saline solution. Although the surgery is efficient at removing the vitreous, vitrectomy is an operative procedure that carries potential

risks to the patients' eyes, including bleeding, retinal tears, retinal detachments, infection and cataract progression.

Ocriplasmin is a proteolytic enzyme that dissolves the protein glue that links the vitreous to the retina. It is administered via an intravitreal injection commonly administered in a doctor's office. This novel treatment option could be a paradigm shift in the treatment of sVMA and restore patients' vision. The results from the pivotal Phase III MIVI-TRUST (Microplasmin Intravitreous Injection - Traction Release Without Surgical Treatment) program announced during 2010 confirmed ocriplasmin's potential as an important new pharmacological treatment for a range of retinal conditions. The two Phase III trials (TG-MV-006 and TG-MV-007) in the program were remarkably consistent, confirming the overall benefits of ocriplasmin. The two trials met their primary endpoint demonstrating that nearly 30% of patients treated with ocriplasmin

#### **DME Phase II Trial**

In October 2009, ThromboGenics announced the results of a Phase IIa trial, evaluating ocriplasmin for the treatment of diabetic macular edema (MIVI II DME). The trial was designed to be the initial step in evaluating ocriplasmin in patients with diabetes, a group which is more prone to eye disease, and specifically DR.

MIVI II DME was a Phase IIa, randomized, double-masked, sham-injection-controlled, dose-ascending clinical trial evaluating the safety and initial efficacy of intravitreal ocriplasmin for the treatment of patients with diabetic macular edema, a form of diabetic retinopathy. The trial recruited 51 patients across Europe.

The efficacy endpoint of the study was ocriplasmin's ability to separate the vitreous from the retina. Patients enrolled in this trial had advanced DME, as evidenced by prior laser treatment in 76% of the ocriplasmin-treated patients.

The Phase IIa study showed that within three days after ocriplasmin injection, a total separation of the vitreous from the retina was achieved in two out of 15 patients treated with the highest 125  $\mu$ g dose. Encouragingly, by day 28, two additional patients, out of 15, in the 75  $\mu$ g dose group had also seen the same outcome.

The results of this trial are encouraging, as they show that ocriplasmin is able to pharmacologically induce the release of VMA in some DME patients, a population with severe adhesion<sup>6</sup>. These results suggest that further studies are warranted in diabetic patients (less severe patients).

## VMA and Age-Related Macular Degeneration

Growing evidence suggests that VMA may play an important role in the progression of exudative AMD (also referred to as wet AMD).

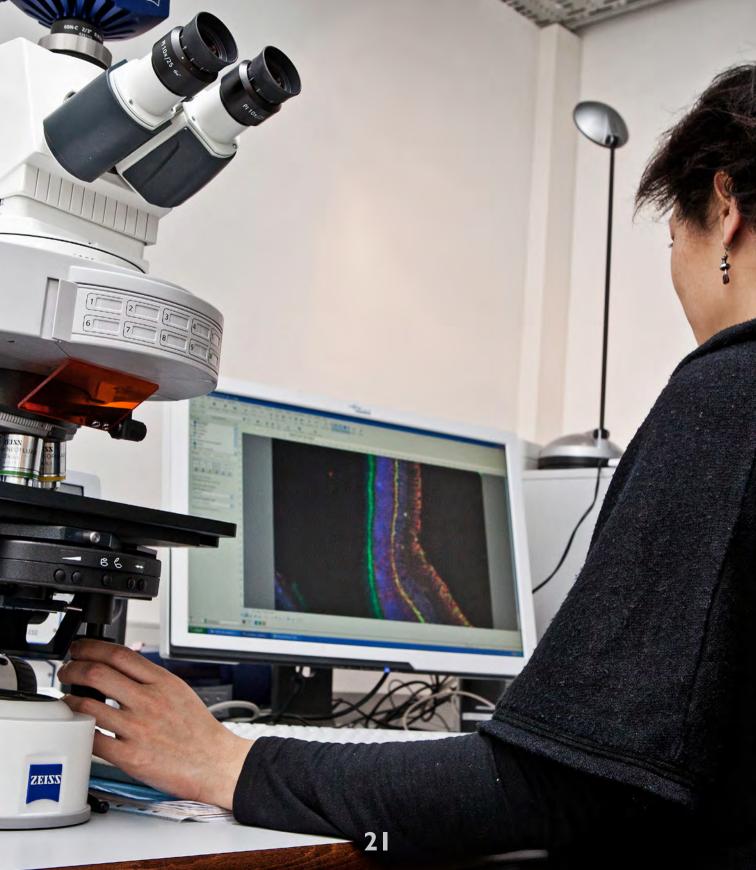
AMD is the most common cause of vision loss in patients aged 50 or older. AMD is a leading cause of severe visual impairment in western countries, affecting more than 10 million people worldwide. Exudative AMD is an advanced form of the disease; around 90% of severe AMD cases are exudative<sup>7</sup>. It occurs when abnormal blood vessels behind the retina start to grow under the macula. These blood vessels are often fragile and can leak blood and fluid below the macula, damaging the photoreceptors and causing vision loss.

Exudative AMD is mainly treated with anti-VEGF (vascular endothelial growth factor) drugs such as Lucentis®, which block the activity of vascular endothelial growth factor (VEGF).



<sup>&</sup>lt;sup>6</sup> "Optical coherence tomography assessment of the vitreoretinal relationship in diabetic macular edema," Gaucher D, Tadayoni R, Erginay A, Haouchine B, Gaudric A, Massin P, Am J Ophthalmology 2005 May; 139 (5):807-13

<sup>7 &</sup>quot;HTRAI Variants in Exudative Age-Related Macular Degeneration and Interactions with Smoking and CFH," Pancy O S Tam, Tsz Kin Ng, David T L Liu, Wai Man Chan, Sylvia W Y Chiang, Li Jia Cheng, Andrew DeWan, Josephine Hoh, Dennis S C Lam, Chi Pui Pang, Investigative Ophthalmology & Visual Science 2008, 49 (6), 2357-2365





This stops the growth and leakage of the abnormal blood vessels implicated in the disease. However, anti-VEGFs are a chronic treatment and therefore need to be given indefinitely. This means that patients require many injections over a prolonged period to prevent the re-growth of the abnormal blood vessels.

## Ocriplasmin in Phase II for AMD

ThromboGenics started a first Phase II trial with ocriplasmin for the treatment of exudative AMD in December 2009. Recent publications have demonstrated that approximately one third of AMD patients

have focal VMA and that this adhesion occurs in the same location as the wet AMD pathology<sup>8</sup>.

The MIVI 5 (Microplasmin for IntraVitreous Injection) Phase II, randomized, double-blind, sham-controlled trial is evaluating ocriplasmin intravitreal injection (125  $\mu$ g) for the treatment of focal VMA in patients with exudative AMD. The trial expects to enrol approximately 100 patients at up to 30 centres across Europe and the US. The primary endpoint of the trial is the pharmacological resolution of VMA, defined as the separation of the vitreous from the retina by 28 days. This will be assessed by an independent Central Reading Center

based on OCT images. Additional measures of efficacy and safety will also be assessed over a one-year follow-up period.

The study is close to completing patient recruitment, with the results expected in mid-2012 following a one-year follow-up period post-treatment.

## Realizing Ocriplasmin's Commercial Potential

ThromboGenics' successful development of ocriplasmin is significant because it could address a high unmet medical need within the ophthalmic market. The Company intends to commercialize ocriplasmin itself to capitalize on its significant

<sup>8</sup> Robison CD et al, 2009; Mojana J et al, 2008; Krebs I et al, 2007

market potential. This key strategic decision has been made based on a number of important factors:

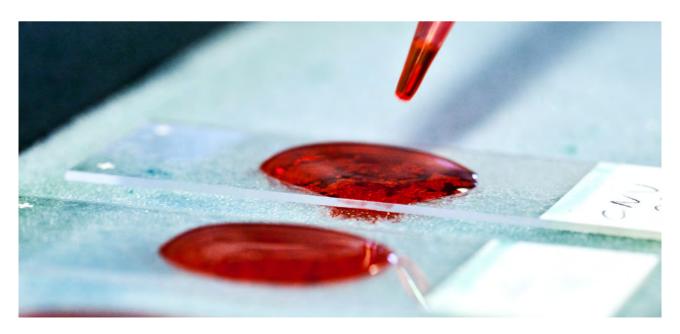
- The field force and marketing investment needed to access retinal specialists in the major markets, the target audience for ocriplasmin, is of a size that ThromboGenics feels comfortable funding;
- The clinical data generated with ocriplasmin has clearly shown that it has the potential to become an important new pharmacological treatment option initially for important retinal diseases such as sVMA and macular holes:
- It will provide us with a very strong base from which to broaden our ophthalmic business by in-licensing further products to generate additional shareholder value.

The decision also reflects our increasing confidence in the commercial potential of ocriplasmin. The Phase III clinical results that we generated last year have shown us that ocriplasmin has a number of characteristics that we believe will appeal to the retinal specialist community.

The interest in ocriplasmin from retinal specialists has been clear from the response to the Phase III results that have been presented at a number of international ophthalmology conferences.

This interest has also been confirmed by independent market research conducted by MedPanel on behalf of Jefferies, an investment bank. This survey of 50 retinal specialists showed that most of them were aware of ocriplasmin and that based on the Phase III MIVI-TRUST data would consider using it.

The current level of awareness in this key target audience, as well as further presentations of ocriplasmin Phase III data at key retinal conferences in 2011, augurs well for the potential uptake of the drug upon regulatory approval. ThromboGenics is currently expanding the commercial team in anticipation of the product's launch. This team is working on the detailed plans and pre-launch activities to ensure that we are well positioned to ensure that we can deliver ocriplasmin's significant commercial potential.



## Beyond Ocriplasmin – Our Antibody Pipeline Provides Significant Upside

ThromboGenics is making good progress with its other key clinical programs: TB-402, a novel long-acting anticoagulant, and TB-403, a novel cancer agent outlicensed to Roche. The company believes that it will continue to generate significant shareholder value and further funding from both of these novel antibody drug candidates.

#### TB-402 – Novel Properties Boost the Anticoagulant Market

TB-402 offers an exciting opportunity for ThromboGenics to generate attractive returns from the anticoagulant market. It is a novel recombinant human monoclonal antibody that partially inhibits Factor VIII, a key component of the coagulation cascade.

TB-402 has several advantages over many currently available treatments. Clinical and pre-clinical studies have already shown that TB-402 has novel properties that make it an attractive option for the prevention of

important coagulation disorders, including VTE, post-surgery and atrial fibrillation.

Its novel mode of action is expected to reduce the risk of undesirable bleeding events, even at high doses, as well as the need for patient monitoring. These are the two main drawbacks associated with current anticoagulant therapy.

#### The Anti-Coagulant Market – The Need for Innovative Products

The global anti-coagulant market is currently estimated at around \$6 billion per annum. Injectable heparin-based products and the oral drug warfarin are currently the mainstay of treatment; however, there are a number of disadvantages with both these therapies.

Lovenox®, a low molecular weight product, dominates the heparin market, generating sales of €2.8 billion in 2010. However, Lovenox® has drawbacks, including the requirement for daily injection, a regimen that can be painful and time-consuming from a patient's perspective. It can, on occasion, also cause spontaneous bleeding events.

Warfarin is the most frequently prescribed oral anti-coagulant. It is a very low priced product and its annual sales are approximately \$500 million. However, warfarin therapy is associated with significant problems. It has numerous interactions with food and other drugs which can result in unpredictable dosage response. Consequently, patients receiving warfarin require continuous monitoring to ensure that they do not experience unwanted bleeding events. This process is very costly and inconvenient. Moreover, warfarin has numerous side effects, of which severe haemorrhage is the most significant.











These significant problems with warfarin have led many companies to invest in developing new improved oral anti-coagulants. However, these newer agents also have problems, such as the need for frequent dosing and the fact that the effects are irreversible. Despite these drawbacks market analysts expect a number of these new oral agents to achieve sales of well over \$1 billion, demonstrating the need for innovation in the anticoagulant market.

Although TB-402 will most likely reach the market after the introduction of the new oral anticoagulant agents, its clinical benefits suggest that it could gain an important share of the anticoagulant market.

TB-402's long-acting properties offer additional advantages by ensuring safe and reversible anticoagulation for up to one month with a single dose. The reduced dosing regimen also could help improve patient compliance in the elderly population, the major users of anticoagulant therapy. In addition, in the hospital setting it could significantly reduce the nursing time and associated costs of using low molecular weight heparin-based products.

Despite the competitive nature of the anticoagulant sector, the clinical and market evidence behind TB-402, including its novel mode of action, make it well positioned for commercial success.

#### TB-402 – A Simple Likely Approach for VTE

As a long-acting agent lasting for several weeks, TB-402 could be given as a single dose to prevent the development of VTE in patients undergoing surgery. This would be an attractive option for patients and physicians, as all current anticoagulant treatment options require daily treatment for up to several weeks. Importantly, the effects of TB-402 are reversible, making it easy for patients who have received the antibody to undergo further surgery quickly when needed.

In May 2010, ThromboGenics reported positive data from a 315-patient open-label Phase II trial investigating TB-402 for the prevention of VTE following total knee-replacement surgery.VTE comprises both deep vein thrombosis (DVT) and pulmonary embolism (PE).

In this study TB-402 demonstrated superior antithrombotic activity and comparable safety to the standard treatment Lovenox®, a low molecular weight heparin, marketed by sanofi-aventis.

The TB-402 Phase II trial was an active (enoxaparin)-controlled, dose-escalating, multicenter; prospective, randomised, open-label study evaluating TB-402 for the prophylaxis of VTE after knee surgery. The study assessed three different doses of TB-402 (0.3, 0.6 and 1.2 mg/kg) each given as a single intravenous bolus injection post-knee-replacement surgery, across 30 centers mainly in Europe. The objective of the study was to assess the safety and efficacy of the three escalating doses of TB-402.

#### **VTE a Major Public Health Issue**

DVT occurs when a blood clot forms in a deep vein, most commonly in the lower leg. DVT is deemed a major public health issue, as highlighted by a 2008 "Call to Action" by the US Surgeon General. It is estimated that DVT or PE affects more than 350,000 individuals in the US alone.

Moreover, DVT and PE together may be responsible for more than 100,000 deaths in the US each year<sup>9</sup>.

Patients undergoing hip replacement or knee surgery are particularly at risk of developing DVT; therefore all patients are treated with anticoagulants prophylactically to reduce the risks of blood clots. As a result, the market opportunity for TB-402 is large and growing. If current trends persist, it is estimated that 1.4 million patients will undergo knee replacements and 600,000 patients hip replacements in the US by 2015<sup>10</sup>.

#### **TB-402 - Atrial Fibrillation**

Atrial fibrillation (AF) is another area where TB-402 could generate significant revenues. AF is a heart arrhythmia caused by the upper chambers of the heart beating irregularly. This can result in the formation of blood clots when blood is not pumped from the heart effectively. These clots have the potential to cause a stroke if they break off and travel to the arteries supplying the brain. AF is becoming increasingly frequent in elderly patients and affects around seven million people in Europe and the US. Given TB-402's novel anticoagulant properties, it could be an important treatment for stroke prevention in AF.

ThromboGenics believes that TB-402 could be a significant entrant into the anticoagulant therapy market, based on its novel therapeutic profile. The Company intends to out-license the late-stage de-

velopment and commercialization of this antibody to a larger biopharmaceutical partner.

## TB-403 – Roche Invests in Clinical Development

ThromboGenics' novel anticancer agent TB-403 (anti-PIGF) has generated much excitement since it was the subject of a major strategic alliance deal with Roche in June 2008.TB-403 shows great promise in advancing the treatment of cancer:

TB-403, a humanized monoclonal anti-PIGF antibody (placental growth factor), has been shown to selectively inhibit the formation of the new blood vessels (anti-angiogenesis) needed to support the growth of cancer tissue.

TB-403 is considered a potential breakthrough in cancer therapy due to its novel mode of action. Scientists have been aware of the benefits of angiogenesis inhibitors on reducing tumour size. However, the development for angiogenesis inhibitors for the treatment of cancer has generally been limited by the fact that these drugs inhibit the growth of new blood vessels in both cancerous and healthy tissue. As a result, their therapeutic potential is hampered by unwanted severe side effects, TB-403, on the other hand, has been shown to inhibit the growth of new blood vessels in cancer tissue, but without compromising healthy tissue.

The potential benefits offered by TB-403 have been widely acknowledged. In November 2009, ThromboGenics and

BioInvent won "Licensing Deal of the Year" at the Scrip Awards. This prestigious award, which rewards excellence in the biopharmaceutical and clinical research industries, acknowledged the achievement of both companies in forming this mutually strategic and value-adding licensing deal.

The strategic alliance with Roche, worth up to €500 million, provides ThromboGenics with greater financial stability and validates the potential of TB-403. ThromboGenics and its partner BioInvent have received €65 million in upfront and milestone payments to date, with potential for an additional €435 million in milestones as well as double-digit royalties on future product sales. In addition Roche has assumed responsibility for all future development costs for TB-403. ThromboGenics, which discovered TB-403, receives 60% and BioInvent 40% of all revenue from the Roche deal.

#### TB-403 to Move into Phase II

In May 2010, ThromboGenics and BioInvent received a €10 million milestone payment from Roche. This payment was triggered by the start of a clinical study by Roche.

Roche started a Phase Ib study with TB-403 in combination with Nexavar<sup>®</sup> in patients with hepatocellular carcinoma. The trial, which will recruit 60-70 patients, is evaluating the safety, pharmacokinetics and pharmacodynamics of this potential combination treatment. The first part will consist of a dose-finding study in combina-

<sup>9 &</sup>quot;The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism," September 15, 2008, pl.

<sup>10 &</sup>quot;Changes in Surgical Loads and Economic Burden of Hip and Knee Replacements in the US: 1997-2004," Sunny Kim, Arthritis & Rheumatism (Arthritis Care & Research), April 15, 2008; 59:4, pp. 481-488.

tion with Nexavar®, the only current treatment for this cancer. The second part will evaluate Nexavar® alone versus Nexavar® plus TB-403.

TB-403 completed a Phase I study in November 2009 in patients with advanced solid tumours. The results showed that TB-403 was well tolerated with no reported dose limiting toxicity. In the same month, the data were presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Boston, US.

The multi-center, dose escalation study, conducted in 23 patients, was designed to determine the maximum tolerated dose of TB-403 and to evaluate safety and tolerability in patients with advanced solid tumours. TB-403 was shown to be well tolerated, and no dose-limiting toxicity was observed with doses up to 10 mg/kg weekly and 30 mg/kg every three weeks. In the patient population with advanced solid tumours, stable disease was observed in six of 23 patients. In the case of the two patients who were treated with 5 mg/kg TB-403 weekly, their disease was stable for approximately 12 months.

#### **Staphylokinase**

Staphylokinase, a thrombolytic agent developed by ThromboGenics, has successfully completed Phase II clinical trials.

Staphylokinase could be used in cardiovascular disease to dissolve blood clots, which are responsible for causing an acute myocardial infarction (AMI), or heart attack. This thrombolytic agent with a similar efficacy to tPA and a lower price could be of substantial importance in advancing the standard of care of patients receiving thrombolytic therapy.

#### **Partnership on THR-100**

ThromboGenics entered into a license agreement with Bharat Biotech International Limited (India) in December 2006. The terms of the agreement cover the manufacturing, clinical development and commercialization. Under the terms of the agreement ThromboGenics will receive double-digit royalties on net sales and Bharat Biotech will assume responsibility for all future costs.

#### **Partnership on THR-174**

Data from preclinical studies suggest that this second generation staphylokinase may have potential to provide an even better efficacy and safety profile and, most importantly, reduced immunogenic response compared to earlier versions of staphylokinase, as well as to some other earlier established thrombolytics such as streptokinase. This means that THR-174 could potentially be administered to patients more than once, allowing treatment of subsequent cardiac events and improving quality of care.

ThromboGenics has completed a license agreement with Rhein Minapharm (Egypt) for the production, clinical development and commercialization of THR-174 in the Middle East, Africa and other countries. In return for granting this license, ThromboGenics will receive upfront and milestone payments, and will earn doubledigit royalties on net sales while Rhein Minapharm will assume responsibility for all future costs.



## R&D – Developing Further Innovative Products For The Market

ThromboGenics has evolved into a successful biotech company with a pipeline of novel new biological drugs for the treatment of eye diseases, cardiovascular disease and cancer. Our success is based on innovative R&D, creating and sharing know-how and our ability to transform our ideas into value-generating, novel treatments that target significant unmet medical needs.

The success of this approach was clearly demonstrated in 2010 when our ophthalmic, anti-coagulant and cancer programs all achieved important clinical milestones. ThromboGenics' validation of its lead product ocriplasmin, for retinal diseases, in pivotal Phase III studies has strengthened its strategy to become as a leading ophthalmics company. Moreover, ThromboGenics' other clinical programs with ocriplasmin and the advancement of its anticancer and anticoagulant antibodies have shown that it has the depth and knowledge to develop a portfolio of innovative products that target areas of high unmet need.

From the outset, ThromboGenics has established a very strong network of potential partners and stakeholders globally. This strategy has allowed us to access the truly innovative science and technology that we need to generate significant value for our shareholders. In Belgium, we have sourced products that are now part of our clinical development pipeline from leading research centers, the University of Leuven, and the Flanders Institute for Biotechnology (VIB).

We seek the right partnerships to advance our corporate goals. Internationally, ThromboGenics has developed collaborations with companies in Europe, the US, India and the Middle East to progress our pipeline. We recently secured a long-term supply agreement with our partner in the UK to ensure our commercial needs for ocriplasmin. In addition, we have formed key contacts with retinal specialists in US and key European countries to expand the potential use of ocriplasmin globally.

ThromboGenics remains committed to building its portfolio of innovative medicines based on the knowledge of our collaborators and the skill of our staff. These insights will allow us to build upon our successes, introduce new products, and derive further value in a range of therapy areas.

Since our move to new premises in the Bio-Incubator, we have continued to increase our capabilities in research. At present we employ over 30 people in our pre-clinical research activities with a broad range of relevant R&D skills.

We are confident that these investments will generate further exciting novel products for our development pipeline. These products will enhance our growth potential and enable us to continue to deliver medicines that are of great value to both patients and physicians.



## ThromboGenics

Team

"ThromboGenics' team's diverse skill set will be critical in achieving the Company's ambition to become a leading player in ophthalmic medicines. The team's positive, determined and enthusiastic attitude is what makes ThromboGenics a great place to work."

Laurence Raemdonck, Head of HR

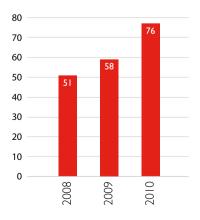


## Preparing For Successful Launch Of Ocriplasmin And Beyond

ThromboGenics' remarkable business and clinical success in 2010 reflects the hard work and dedication of its employees.

The Company's total global headcount grew to 76 at the end of 2010. The majority of employees are based in ThromboGenics' headquarters in Leuven, Belgium. Although ThromboGenics is increasing the number of staff located in New York and Dublin, with six in each office. The team is highly qualified, with

#### **Global Headcount Evolution**



70% of its employees holding a Master's degree, and extremely diverse, with members from nine different countries.

ThromboGenics' relocation to the Bio-Incubator Park in Leuven, Belgium, in 2009, has enabled it to hire more staff and develop expertise in key areas. In 2010 alone, ThromboGenics recruited 24 new staff in areas such as regulatory affairs, quality assurance, chemistry manufacturing and controls, marketing and pharmacovigilance, as we prepare to file ocriplasmin in the US and Europe. It is crucial that ThromboGenics has expertise in these areas in order to ensure the successful commercialization of ocriplasmin for the treatment of retinal diseases.

A third of the new staff joined R&D, highlighting the importance we place on innovation. In addition, we made appointments in finance and clinical operations. The recruitment of highly skilled people reinforces our objective of building a profitable, integrated and self-sustaining business that will deliver value to all of

our stakeholders. We are committed to creating a truly innovative working environment and pride ourselves in having established a flat organization where employees feel empowered to make decisions. ThromboGenics has continued to improve internal collaborations across key departments and to implement decisions quickly, a vital component for achieving our planned goals for ocriplasmin and our other clinical programs.

We are building our senior team to support the commercialization of ocriplasmin, following positive data from our Phase III MIVI-TRUST clinical program. The Company has appointed a Head of Marketing in the US, Global Head of Market Access and Global Head of Medical Ophthalmology to drive the commercialization of ocriplasmin.

We face an exciting time in 2011, as we move closer towards bringing ocriplasmin to the market and advancing our other programs. We plan to continue strengthening the organization with the right



people with the right attitude and the right mix of skills as we are convinced that this is the foundation for us achieving our strategic goals.

ThromboGenics recognizes the challenges and opportunities impacting its business environment. Our people are driven by the feeling their work is connected to corporate strategy and has a real impact. They are energized by challenges and the Company ensures they have the resources and support they require to succeed in their roles. We not only reward success,

but also seek to develop our staff personally and professionally.

ThromboGenics' values and clear strategy, coupled with the drive and enthusiasm of our experienced management team, have enabled us to recruit the best people to advance the Company's strategy. As we enter 2011, we expect the commitment of our employees to deliver against their key objectives as ThromboGenics strives towards becoming a leader in cutting-edge medicines for treating eye diseases.

#### The Board of Directors

ThromboGenics' board of directors consists of highly experienced people from a range of disciplines across the Life Sciences industry. The executive members are Patrik De Haes, Chief Executive Officer, and Chris Buyse, Chief Financial Officer. The non-executive board members, not employed by the Company, are: Désiré Collen, Chairman and founder of ThromboGenics; Landon T. Clay, Manager Member of East Hill Advisors, LLCC and partner of East Hill University Spinout Funds; Jean-Luc Dehaene, former prime minister of Belgium and Vice Chairman of the European Convention; Luc Philips, Member of Executive Committee and CFO of KBC Group NV; and Staf van Reet, Chairman of ActoGeniX, a clinical stage biopharmaceutical company.

#### **The Management Team**

The eight-member management team has considerable experience in research, clinical development, commercialization and financing: Patrik De Haes, Chief Executive Officer, Chris Buyse, Chief Financial Officer, Stuart Laermer, Chief Business Development Officer, Steve Pakola, Chief Medical Officer, Jean Marie Stassen, Head of Pre-Clinical/R&D, Phil Challis, Head of Chemistry, Manufacturing and Controls, Andy De Deene, Head of Program Management, and Laurence Raemdonck, Head of Human Resources. The management team also makes up the Executive Committee. It is responsible for the vision and strategy of the Company, and convenes on a regular basis to plan and oversee the implementation of Thrombo Genics' policies.



#### **Patrik De Haes**

#### Chief Executive Officer

Patrik De Haes has over 20 years of experience in the global healthcare industry, covering product development, marketing and general management. Before joining ThromboGenics, Patrik was Head of Roche's Global Insulin Infusion business. He was President and CEO of Disetronic Medical Systems Inc, a leading insulin infusion therapy 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.

#### **Chris Buyse**

#### Chief Financial Officer

Chris Buyse's experience in international company finance and running and establishing best financial practice spans more than 20 years. Previously, as CFO of the Belgian biotechnology company CropDesign, he coordinated its acquisition by BASF in early 2007. Chris has also been Finance Director of WorldCom/MCI Benelux, a European subsidiary of one of the world's largest telecom companies, and CFO and interim CEO of Keyware Technologies. He has also held financial positions at Spector Photo Group, Suez Lyonnaise des Eaux and Unilever: Chris holds a Masters Degree in Economics from the University of Antwerp and an MBA from the Vlerick School in Ghent.

#### **Stuart Laermer**

#### Chief Business Development Officer\*

Stuart Laermer manages ThromboGenics' business development, and has more than 20 years of global experience in the commercialization of novel technologies. He was formerly Vice President, Business Development at Synthon Chiragenics and Physiome Sciences, where he was a founding member of the management team. He has also been Director Business Development at F. Hoffmann-La Roche AG and Director Biotechnology & Specialty Products at Fisher Scientific. Stuart has an MSc in Chemical Engineering from Columbia University and an MBA from New York University.

#### Steve Pakola

#### Chief Medical Officer\*

Steve Pakola is a licensed physician with extensive clinical trial experience, including 12 years in pharma/biotech clinical development. Steve was formerly Associate Director, Cardiovascular Clinical Research, at Boehringer Ingelheim Pharmaceuticals. In this role, he was the global medical lead for its lipid-lowering development program and the US medical lead for the direct-thrombin-inhibitor development program. Before Boehringer Ingelheim, he held senior clinical development positions at Quintiles Cardiovascular Therapeutics and Organon, Inc. Steve received his MD degree from the University of Pennsylvania.

#### Jean Marie Stassen

#### Head of Pre-Clinical/R&D

lean Marie Stassen is a medical scientist with over 20 years of research and drug development experience. He is responsible for developing ThromboGenics' preclinical programs and was co-founder and member of the board of FlandersBio. He joined ThromboGenics in 2001 from Boehringer Ingelheim Pharma, Germany, where he was a research project leader for the cardiovascular therapeutic area, e.g. Pradaxa™ (dabigatran). As a preclinical expert, he was heavily involved in the European registration of the thrombolytic TNKase™ (Tenecteplase). He was formerly managing Director of Thromb-X NV. Together with Désiré Collen, Jean Marie characterized tPA and staphylokinase. He is author and co-author of more than 100 papers in peerreviewed journals, and more than 250 patents and patent applications. Jean Marie holds his PhD in Medical Sciences from the University of Umeå, Sweden.

#### **Phil Challis**

#### Head of Chemistry, Manufacturing and Controls

Phil Challis has over 20 years of experience in biologics' product development and brings valuable experience in developing ThromboGenics' manufacturing strategy. He previously worked in a management role at UCB Pharma and has managed manufacturing programs for early and late-stage clinical trials and commercialization. Phil has held key product development positions at Lonza Biologics and Celltech. Phil holds a Bachelors degree in Biological Sciences from the University of Plymouth.

<sup>\*</sup> Located in the US

#### **Andy De Deene**

#### Head of Program Management

Andy De Deene has extensive experience in drug development, including clinical development, pharmacovigilance and medical affairs. He previously worked as both Manager and Director for the Janssen Research Foundation and XCellentis in Belgium. Andy holds an MD from the University of Ghent, trained as a dermatologist at the University of Cologne, and obtained an executive MBA from Vlerick Management School.

#### Laurence Raemdonck

#### Head of Human Resources

Laurence Raemdonck joined ThromboGenics as HR Manager in 2007. Laurence was previously employed in the telecom sector at Verizon Business. She has responsibility for all areas related to human resources, such as recruitment, compensation, performance management, training and development, and organizational design and development. This involves working closely with her HR colleagues and line managers across the business and at different levels of the organization. As Head of HR, she is an advocate for both the Company and its people. She has a Masters Degree in Germanic Philology and a degree in Human Resources.





Phil Challis, Andy De Deene, Laurence Raemdonck, Chris Buyse, Patrik De Haes and Jean Marie Stassen



Left to right:

Steve Pakola, Stuart Laermer and Patrik De Haes

## Glossary

**AF** Atrial Fibrillation

**AMD** Age-Related Macular Degeneration

AMI Acute Myocardial Infarction

Anti-PIGF Anti-Placental Growth Factor

**BLA** Biological License Application

**DME** Diabetic Macular Edema

DR Diabetic RetinopathyDVT Deep Vein Thrombosis

**EMA** European Medicines Agency

FTMH Full-Thickness Macular Hole

HCC HepatoCellular Carinoma

LP Laser Photocoagulation

MAA Marketing Authorization Application

Metamorphopsia Distorted vision

MIVI Microplasmin (ocriplasmin)

Intravitreous Injection

MIVI II DME Microplasmin (ocriplasmin)

for the treatment of Diabetic

Macular Edema

**MIVI-TRUST** Microplasmin Intravitreous

Injection – Traction Release Without Surgical Treatment

**Ocriplasmin** Formerly known as microplasmin

**OCT** Optical Coherence Tomography

**PE** Pulmonary Embolism

PIGF Placental Growth Factor
PVD Posterior Vitreous Detachment

Total for the odds Betagninion

**VA** Visual Acuity

ςVMΔ

**VEGF** Vascular Endothelial Growth Factor

Symptomatic Vitreomacular Adhesion

**VFQ-25** Visual Functioning Questionnaire

**VIB** Flanders Institute for Biotechnology

**VMA** VitreoMacular Adhesion

**VMT syndrome** Vitreomacular Traction syndrome

VTE Venous Thrombo Embolism

## Information For Shareholders

#### Listing

The Company's shares are listed on NYSE Euronext under the ticker symbol THR.

#### **Financial Calendar**

Business Update H1: 12 May 2011
HalfYear Results 2010: 24 August 2011
Business Update H2: 3 November 2011

#### **Registered Office**

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Belgium

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#### **Paying Agent Services**

KBC Bank is acting as 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.

#### **Investor Relations Contact**

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#### **Forward Looking Statements**

Certain statements in this document may be considered "forward-looking". Such forward-looking statements are based on current expectations, and, accordingly, entail and are influenced by various risks and uncertainties. The Company therefore cannot provide any assurance that such forward-looking statements will materialize and does not assume an obligation to update or revise any forward-looking statement, whether as a result of new information, future events or any other reason Additional information concerning risks and uncertainties affecting the business and other factors that could cause actual results to differ materially from any forward-looking statement is contained in the Financial Section of the Company's Annual Report.

## **ThromboGenics**

#### Headquarter

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