Innovative Therapies for Retinal Disorders: Developing Disease Modifying Treatments for Diabetic Eye Disease

Company & Investor Presentation – November, 2017
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ThromboGenics
- Novel treatments for retinal disorders, focus on diabetic eye disease

- Front runner in discovery of new science in retina, now focusing on novel therapies for diabetic eye disease
- Progressing multiple (4) late-stage preclinical and clinical pipeline projects targeting novel therapies for Diabetic Retinopathy (DR) and/or Diabetic Macular Edema (DME): ocriplasmin, anti-PLGF, Plasma Kallikrein inhibitor, Integrin Antagonist + undisclosed
- Pioneer of new drug class of pharmacological vitreolysis and 100% owner of JETREA® (ocriplasmin)
  - JETREA® first and only approved pharmacological treatment for sVMA/VMT (approved in +50 countries globally, with nearly 30,000 patients treated in 20 countries)
- +85% owner of Oncurious NV (VIB venture partner):
  - Pediatric Oncology (US clinical trial)
  - 5 Immuno-Oncology projects (pre-clinical) since 09/2017
- 75 - 80 employees globally, HQ in Leuven (BE), US office in Iselin, NJ
- Cash position: € 113.4 m (Q3 FY17)
ThromboGenics value proposition today: the Core

Drug Development
4 Preclinical / Clinical Compounds
Additional in discovery

Disease Modifying Treatments
Tackling Unmet Medical Needs in Diabetic Retinopathy
• THR-409 – ocriplasmin
• THR-317 – anti-PIGF
• THR-149 – plasma kallikrein inh.
• THR-687 – integrin antagonist
  For NPDR/PDR
  with or without DME

• Cash position = >€100 million
• Expected 2018 -20 Newsflow
• Fully funded – 4 yr horizon
ThromboGenics value proposition today: the Core... and more

Drug Development
4 Preclinical / Clinical Compounds
Additional in discovery

Disease Modifying Treatments
Tackling Unmet Medical Needs in Diabetic Retinopathy
- THR-409 – ocriplasmin
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- THR-687 – integrin antagonist
  For NPDR/PDR
  with or without DME

• 100% THR owned
• US is cash neutral (>2016)
• Ex-US in transition from NVS
• Target cash-neutral to contributing

Global BU Commercial

• Cash position = >€100 million
• Expected 2018 -20 Newsflow
• Fully funded – 4 yr horizon

ThromboGenics
Advancing Science, Enhancing Vision

• + 85% THR owned
• Fully funded 3 yr
• VIB leads I/O developments
• BioInvent/NMTRC to lead TB-403 trial

Phy/II TB-403
5 I/O projects (preclinical)
ThromboGenics Regains Global Rights to JETREA® (ocriplasmin)

Leuven, Belgium, 18th September, 2017 – ThromboGenics NV (Euronext Brussels: THR), a biotechnology company developing novel treatments for retinal disorders, with a focus on diabetic eye disease, announced today that it will regain full global rights to JETREA® from Alcon, a Novartis company, based on a mutual agreement that the unique characteristics of JETREA make ThromboGenics a better fit for building a sustainable long-term niche business.

- ThromboGenics and Alcon/Novartis transition commitment for continued JETREA access to customers and patients
- ThromboGenics to receive €53.7 million from Novartis as part of the agreement
- Novartis to invest €10 million in ThromboGenics equity
- ThromboGenics – cash of over €100 million to invest in diabetic eye disease pipeline post Novartis investment
Why diabetic eye disease?
Diabetic retinopathy segment is forecast to grow twice as fast as the overall ophthalmic pharmaceuticals market

- Worldwide sales estimates 2015
  - Ophthalmic pharmaceuticals market*: $19.6 Bio
  - Retinal diseases market**: $7.2 Bio
  - DR & DME segments market: $1.6 Bio

- Worldwide sales forecasts 2023
  - Ophthalmic pharmaceuticals market*: $33.0 Bio
  - Retinal diseases market**: $12.8 Bio
  - DR & DME segments market: $4.2 Bio

** Incl. at least wet AMD, DR/DME, and RVO markets

Abbreviation(s): AMD, age-related macular degeneration; DR, diabetic retinopathy; DME, diabetic macular edema; RVO, retinal vein occlusion; CAGR, compound annual growth rate

Worldwide 2015 415 million people with diabetes
2040 642 million people with diabetes

North America and Caribbean
2015 44.3 million
2040 60.5 million

Europe
2015 59.8 million
2040 71.1 million

Middle East and North Africa
2015 35.4 million
2040 72.1 million

South and Central America
2015 29.6 million
2040 48.8 million

Africa
2015 14.2 million
2040 34.2 million

South East Asia
2015 78.3 million
2040 140.2 million

Western Pacific
2015 153.2 million
2040 214.8 million

* IDF Diabetes Atlas 2015
More than **One in three (!)** people with diabetes will develop diabetic retinopathy

**35.4%**

**NPDR**
Non-proliferative diabetic retinopathy

**PDR**
Proliferative diabetic retinopathy

**with or without DME**
Diabetic macular edema
ThromboGenics is developing **novel therapies for all DR segments**

**ANY DR**

- **NPDR without DME**: 23.6%
- **NPDR with DME**: 4.5%
- **PDR without DME**: 4.2%
- **PDR with DME**: 3.0%

*Any DR is defined as the presence of NPDR, PDR, DME or any combination thereof.*

Abbreviation(s): DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; DME, diabetic macular edema;

Source(s): Yau 2012; Int’l Diabetes Federation and the Fred Hollows Foundation 2015; National Eye Institute 2015
Drug Development Targeting **all DR segments: ‘Multiple Shots on Goal!’**

**Therapeutic action**

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>Inflammation</th>
<th>Edema</th>
<th>Angiogenesis</th>
<th>Fibrosis</th>
<th>Neurodegeneration</th>
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<tbody>
<tr>
<td>THR-409 (ocriplasmin)</td>
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<tr>
<td>THR-317 (anti-PIGF)</td>
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<td>+++</td>
<td>++(+)</td>
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<td>++</td>
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<tr>
<td>THR-687 (integrin antagonist)</td>
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<td>++(2)</td>
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<tr>
<td>THR-149 (plasma kallikrein inhibitor)</td>
<td>+</td>
<td>++++</td>
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</table>

1. prevention blood vessel ingrowth in vitreous (PVD)
2. neo-angiogenesis inhibition + prevention blood vessel ingrowth in vitreous (PVD)

+ = level of therapeutic action
THR-409 : ocriplasmin
THR-409: Inducing a Total PVD with NPDR patients
(Ocriplasmin)

- THR-409 is a disease modifying compound
  - unique mode of action: Posterior vitreous detachment (PVD)

- Phase II CIRCLE study exploring multiple injection regimen
  - Patients: moderately to severe NPDR patients
  - Up to 3 injections of commercial dose / half dose arm
  - Revised protocol – access to broader patient pool

- Potential step-change in the disease management in NPDR:
  - Study will explore progression rates to PDR
  - No other medical products approved for this indication

Ocriplasmin breaks protein bonds to create a Total PVD
THR-409 : Phase II Study Design Overview (TG-MV-015 - CIRCLE)

Treatment population:
- NPDR (stable DME allowed)

n=115 randomised 2:2:1

- THR-409 0,0625 mg
- THR-409 0,125 mg
- Sham

D 0 M 1 M 2 M 3 M 15 M 24

Efficacy Evaluation: PVD

Safety Follow-up
Explore progression to PDR
THR-317 : anti-PIGF (Placental Growth Factor)
Biology background
Diabetic retinopathy (DR) - Current standard of care

Anti-VEGF therapy
- Improvement of visual acuity
- Poor/non responders
- Adverse events: Vessel regression, fibrovascular membranes, neurodegeneration

Clear need for alternative therapies with potential to reduce the risk of treatment-related complications

PIGF (Placental growth factor)
- Member of the VEGF-family
- Signals via binding to VEGFR-1, not to VEGFR-2
- Expressed in many tissues, including the retina (e.g. endothelial cells, glial cells)
- Key molecule in pathological angiogenesis, edema and inflammation

(1) Brownlee et al. 2005 Diabetes 54:1615-25
(2) Agarwal et al. 2014 Pharmacogenomics and Personalized medicine 7: 399-409
(3) Osaadan et al. 2014 Eye 28:510-520
(4) Carmeliet et al. 2001 Nat Med 7:575-83

Source: The Angiogenesis Foundation
THR-317: Placental growth factor (PlGF) is an optimal target to treat more advanced stages in diabetic eye disease

Increasing levels of PlGF correlate with increasing levels of retinal ischemia

Preclinical evidence

Efficacy of PlGF inhibition on different DR hallmarks

- **Neurodegeneration**
  - Akita/PlGF<sup>-/-</sup>
    - Huang et al. 2015
  - Light-induced damage
    - Izawa et al. 2015

- **Inflammation**
  - Mouse CNV
    - Van de Veire et al. 2010, Huang et al. 2011
  - Mouse STZ
    - He et al. 2015

- **Neovascularization/leakage**
  - Mouse CNV and ROP
    - Van de Veire et al. 2010, Huang et al. 2011
  - Mouse STZ and Akita/PlGF<sup>-/-</sup>
    - He et al. 2015, Huang et al. 2015

- **Fibrosis**
  - Mouse CNV
    - Van Bergen T et al. 2016 (in preparation)
THR-317: Phase II Study Overview

Treatment population:
- Anti-VEGF naïve patients
- Anti-VEGF poor responders

n=50

randomised 1:1

THR-317 low dose

THR-317 high dose

SAFETY FOLLOW-UP

DAY 0
DAY 30
DAY 60
DAY 90
DAY 150

EFFICACY EVALUATION
- BCVA
- Retinal Thickness
THR-317: Key take aways

- THR-317 is disease-modifying
  - DME, with potential additional benefit in anti-inflammatory treatment and fibrosis prevention
- Recruiting patients (n=50) in Phase I/IIa
- Only drug in development that targets solely PlGF
- THR-317 offers the potential for two treatment modalities
  - Stand-alone treatment in DME
  - Combination treatment with anti-VEGF
- Sizeable target population
- Phase I/IIa results anticipated Q1 2018
THR-687 : Integrin receptor antagonist
THR-687: integrin inhibition results in potent anti-angiogenic effect

Inhibition of blood vessel sprouting in mouse choroidal explant cultures

THR-687 inhibits spontaneous blood vessel formation at low µM concentrations in vitro
THR-687: Key take aways

- THR-687 is a novel and potent integrin antagonist
- THR-687 has a broad therapeutic potential
  - diabetic retinopathy with and without DME
- NPDR / PDR indication
  - treatment of diabetic retinopathy
  - induction of total posterior vitreous detachment
- Sizeable target population
- Phase I/IIa study to be initiated H1 2018
THR-149: a Plasma kallikrein (PKal) inhibitor
Plasma kallikrein & diabetic macular edema

**Preclinical evidence**
- PKal mediates vascular hyper-permeability, leukostasis, cytokine production, and retinal thickness
- PKal inhibition significantly inhibits retinal vascular leakage in a diabetic mouse model

**Clinical evidence**
- upregulation of intraocular plasma kallikrein contributes to a VEGF independent mechanism
- retinal expression of Bradykinin-1 receptor is increased

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**Vascular injury & initial permeability**

**PLASMA KALLIKREIN**

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<tbody>
<tr>
<td>Bradykinin / bradykinin receptors</td>
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<tr>
<td>Growth factor &amp; cytokine production, vascular hyperpermeability, leukostasis</td>
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<tr>
<td>Diabetic Macular Edema (DME)</td>
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**THR-149**

PKal, plasma kallikrein
Plasma kallikrein and DME patients

- Plasma kallikrein is a key driver in diabetic macular edema
- Potential as a stand-alone treatment and/or treatment in refractory DME patients to current therapy

Adapted: Kita et al. 2015  Diabetes 64:3588–99
THR-149 - A novel, potent and selective PKal inhibitor

- Novel, potent reversible inhibitor of human PKal
  - small constrained peptide, $K_i = 0.36 \text{ nM}$
- Specificity profile showed specificity over 20 human serine proteases
  - no impact on coagulation pathway
- Significant inhibition of bradykinin generation in human vitreous and human plasma
- Significant inhibition of edema in preclinical disease models
- Physical chemical properties fully compatible for slow release formulation
THR-149: Key take aways

- THR-149 is a potent and selective plasma kallikrein inhibitor

- THR-149 is targeting the treatment of diabetic macular edema (DME)
  - impact on disease onset and progression

- THR-149 offers the potential for two treatment modalities
  - stand-alone therapy in diabetic retinopathy with DME
  - refractory DME to current treatment

- Sizeable target population

- Phase I/IIa study to be initiated H1 2018
Diabetic Eye Disease – pipeline / newsflow
Drug Development Targeting all DR segments: ‘Multiple Shots on Goal’ – different mechanisms of action

THR-409 (ocriplasmin)

THR-317 (anti-PIGF)

THR-687 (integrin antagonist)

THR-149 (plasma kallikrein inhibitor)
JETREA®
(ocriplasmin)
Intravitreal Injection, 2.5 mg/mL
JETREA® Commercial Update

- ThromboGenics regained global rights to JETREA® (non-US rights were with Alcon/Novartis until 16/09/2017)
- HY17 reported JETREA® revenue: €2.7m (incl €800k non-US royalties)
- JETREA in the US - break even:
  - Small team, specialized distribution partner, online resources for patient, physician information, including enrollment and reimbursement
- US Launch of new JETREA® ‘Already-Diluted’/ ‘Ready to Use’ formulation imminent
- JETREA® now approved in over 50 countries/ patients treated in 20 countries
- OASIS 2 year follow up data reporting better outcomes than Phase III trial results: confirming positive long-term efficacy and safety data (published in Ophthalmology – AAO Journal)
- Continued ocriplasmin data generation and dissemination: conference and publication plan 2017
Focused on cutting immuno-oncology assets
Recent Highlights

Oncurious acquiring VIB portfolio of 5 next-generation immuno-oncology projects targeting a broad spectrum of cancers

*VIB increases shareholding in Oncurious*

*Add-on to existing activities (clinical trail) in pediatric brain cancers*

*ThromboGenics invests €2.1 million in Oncurious as part of this agreement*

*ThromboGenics now owns +85% of Oncurious*
Oncurious TB-403 Update

- Evaluating TB-403 for medulloblastoma
  - TB-403’s safety has previously been studied in 70 adult cancer patients (Lassen 2012, Martinsson-Niskanen 2011)
  - Compelling data on therapeutic action of TB-403 in medulloblastoma (Harvard)
- Phase I/II a has been initiated – development of TB-403 for medulloblastoma
  - Collaboration agreement has been signed with NMTRC to conduct the Phase I/II trial in the US
- BioInvent International is TB-403 development and business partner (50/50 – development cost and economic benefit)
- European Commission confirmed orphan drug designation for TB-403 for medulloblastoma following a positive opinion issued by the European Medicine Agency (EMA) – January 2017
Summary & key take aways
ThromboGenics
- Novel treatments for retinal disorders, focus on diabetic eye disease

- **Progressing multiple (4) late-stage preclinical and clinical pipeline projects** targeting novel therapies for Diabetic Retinopathy (DR) and/or Diabetic Macular Edema (DME) : ocriplasmin, anti-PLGF, Plasma Kallikrein inhibitor, Integrin Antagonist + undisclosed

- Significant pipeline newsflow over the next 12 months

- **Pioneer of new drug class of pharmacological vitreolysis** and 100% owner of JETREA® (ocriplasmin)
  - JETREA® first and only approved pharmacological treatment for sVMA/VMT (approved in +50 countries globally, with nearly 30,000 patients treated in 20 countries)

- **+85% owner of Oncurious NV** (VIB venture partner): ongoing clinical trial + 5 next gen I/O projects

- Over €100 million in cash to invest in pipeline development

- Welcoming Novartis AG as a shareholder (€10m investment)

- Experienced management team focused on delivering value generating milestones
Thank you for your interest

For questions and information:
Please send your message at IR@thrombogenics.com