Developing Novel Disease Modifying Treatments for Diabetic Eye Disease

Company & Investor Presentation – May, 2017
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Today’s Agenda

- ThromboGenics at a glance
- Why diabetic eye disease?
- Clinical candidates – THR-409 & THR-317 - in Phase II development
- Pre-clinical candidates – THR-687 & THR-149 - progressing to Phase I/II studies
- Oncurious – progress with TB-403 – Phase I/IIa recruiting patients
- JETREA status
- Newsflow
- Key take away
ThromboGenics
- Pioneering treatments for back of the eye (retina) disease, diabetic eye disease

- Back of the eye disease (retina), focus on disease modifying treatments for diabetic eye disease

- 4 novel treatments under development in Diabetic Macular Edema and/or Diabetic Retinopathy (DR):
  2 clinical trials recruiting patients/ 2 clinical trials preparing for initiation

- Pioneered new drug class of pharmacological vitreolysis with JETREA®:
  - JETREA® approved in over 50 countries (27,000+ patients treated to date)
  - Basis of expertise in ophthalmology/ retina

- Oncology asset spun out into Oncurious NV (ThromboGenics + VIB) / Phase I/II recruiting in US

- Listed on Euronext Brussels (IPO 2006 : THR)

- 75 - 80 employees globally

- HQ in Leuven (BE), US office in Iselin, NJ
2016/ 2017: continue transition and execute clinical trial plans

- Re-focused activities and resources on drug development for the treatment of diabetic eye disease
- Unveiled innovative pipeline of drug candidates targeting diabetic retinopathy (DR) and diabetic macular edema (DME)
  - 4 novel disease modifying molecules that together address all segments of the DR market
- Progressed clinical development of THR-409 and THR-317 – both drug candidates in Phase II studies
- Significant progress with THR-687 and THR-149 – clinical development expected to start YE 2017/ early 2018
- Achieved key commercial goal of reaching operational break even for JETREA business in the US
- Progressing recruitment of patients in Oncurious Phase I/IIa evaluating TB-403 for medulloblastoma
- Healthy cash position (€ 73.5 m) and strict cash management: available cash plus JETREA® royalty income to fund ongoing and planned development activities for foreseeable future
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

Compound Annual Growth Rate 2015-2023

- 6.8%
- 9.3%
- 16.1%

** 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

ThromboGenics
Advancing Science, Enhancing Vision.
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

**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* 35.4%

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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>THR-409</strong> (ocriplasmin)</td>
<td></td>
<td></td>
<td>+++(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>THR-317</strong> (anti-PIGF)</td>
<td>++</td>
<td>+++</td>
<td>+ + (+)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>THR-687</strong> (integrin antagonist)</td>
<td>++</td>
<td>++</td>
<td>+++(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>THR-149</strong> (plasma kallikrein inhibitor)</td>
<td>+</td>
<td>++++</td>
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</tbody>
</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
  - A unique mode of action: Posterior vitreous detachment (PVD)

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

- A sizeable and growing target population
  - Moderately to severe NPDR patients

- Phase II CIRCLE study exploring multiple injection regimen
  - (up to 3 injections)
  - Half dose arm
  - Revised protocol – access to broader patient pool
THR-409 : Phase II Study Design Overview (TG-MV-015 - CIRCLE)

Treatment population:
- NPDR (stable DME allowed)

n=115 randomised 2:2:1

D0 -> THR-409 0,0625 mg

M1 -> THR-409 0,125 mg

M2 -> Sham

M3 -> SAFETY FOLLOW-UP

M15 -> EFFICACY EVALUATION: PVD

M24 -> 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 ¹
- Poor/non responders ²
- Adverse events: Vessel regression, fibrovascular membranes, neurodegeneration ³

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

PIGF (Placental growth factor) ⁴
- 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
THR-317: Placental growth factor (PIGF) is an optimal target to treat more advanced stages in diabetic eye disease

Increasing levels of PIGF correlate with increasing levels of retinal ischemia

Preclinical evidence

Efficacy of PlGF inhibition on different DR hallmarks

- **Neurodegeneration**
  - Akita/PI GF\(^{-/-}\)
    - 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/PI GF\(^{-/-}\)
    - He et al. 2015, Huang et al. 2015

- **Fibrosis**
  - Mouse CNV
    - Van Bergen T et al. 2016 (in preparation)
Anti-PIGF and Inflammation
Mouse CNV – leukocyte infiltration

- Anti-PIGF Ab inhibits inflammation in CNV model, comparable to aflibercept (2.4 µg/eye)
- Equimolar dosing (3.1 µg/eye) of anti-VEGFR-2 Ab showed no effect
Anti-PIGF and Fibrosis
Mouse CNV – collagen deposition

- Anti-PIGF Ab inhibits collagen deposition in CNV model
- Equimolar dosing of aflibercept (2.4 µg/eye) or anti-VEGFR-2 Ab (3.1 µg/eye) showed no effect
**Anti-PIGF and neurodegeneration**

*Swiss mouse - Survival and apoptosis of ganglion cells*

- Neutralization of PIGF did not trigger a neurodegenerative response
- Anti-VEGFR-2 Ab reduced retinal ganglion cell density due to an increase in cell apoptosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival</th>
<th>Apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PIGF Ab (25 mg/kg, IP)</td>
<td>+14%</td>
<td>+10%</td>
</tr>
<tr>
<td>Anti-VEGFR2 Ab (25 mg/kg, IP)</td>
<td>-32%</td>
<td>+58%</td>
</tr>
</tbody>
</table>

**Legend:**
- IgG
- anti-PIGF Ab
- anti-VEGFR-2 Ab

Mean ± SEM (N=6), * p<0.05; *** p<0.001
Anti-PIGF and neurodegeneration

*Mouse STZ – neurodegeneration*

- Anti-PIGF Ab does not significantly alter retinal ganglion cell density in mouse STZ model
- Anti-VEGFR-2 Ab reduce number of retinal ganglion cell by 20%
Anti-PIGF and Pericyte coverage
Mouse CNV – pericyte coverage

- Anti-PIGF Ab stimulate pericyte coverage in CNV model, compared to no protective effect of an anti-VEGFR-2 Ab

<table>
<thead>
<tr>
<th>% Improvement of pericyte coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PIGF Ab</td>
</tr>
<tr>
<td>anti-VEGFR-2 Ab</td>
</tr>
</tbody>
</table>
THR-317: Phase II Study Overview

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

randomised 1:1

n=50

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

- THR-317 offers the potential for two treatment modalities
  - Stand-alone treatment in DME
  - Combination treatment with any anti-VEGF

- Only drug in development that targets solely PlGF

- Sizeable target population

- Phase I/IIa results anticipated Q1 2018
THR-687 : Integrin receptor antagonist
THR-687 Rationale: differential effects of inhibiting VEGF and integrin
Integrin antagonism provides multiple points of attack to treat diabetic retinopathy

Angiogenesis cycle
endothelial cell migration, proliferation, differentiation and maturation

Integrin antagonism treats disease root cause (vascularization) with multiple points of attack

Adapted: Boyer 2014 The Ophthalmologist 38-40
THR-687: potent inhibitor of multiple integrin receptors
THR-687 targets integrin receptors involved in angiogenesis and permeability

<table>
<thead>
<tr>
<th>Integrin</th>
<th>Integrin receptor class</th>
<th>THR-687 IC(_{50}) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha_\text{v}\beta_3)</td>
<td>RGD binding</td>
<td>4.4 ± 2.7</td>
</tr>
<tr>
<td>(\alpha_\text{v}\beta_5)</td>
<td>RGD binding</td>
<td>1.3 ± 0.5</td>
</tr>
<tr>
<td>(\alpha_5\beta_1)</td>
<td>RGD binding</td>
<td>6.8 ± 3.2</td>
</tr>
<tr>
<td>(\alpha_{2\text{b}}\beta_3)</td>
<td>RGD binding</td>
<td>105 ± 26</td>
</tr>
<tr>
<td>(\alpha_2\beta_1)</td>
<td>Collagen binding</td>
<td>121,000 ± 25,000</td>
</tr>
<tr>
<td>(\alpha_3\beta_1)</td>
<td>Laminin binding</td>
<td>&gt; 5,000000</td>
</tr>
</tbody>
</table>

THR-687 is a high affinity pan RGD integrin 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 \textit{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

- Clinical Proof of Concept study
  - start phase I/IIa anticipated end 2017
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
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, Ki = 0.36 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
Inhibition of plasma kallikrein results in strong anti-edema effect

IC$_{50}$ = 115 ± 60 nM

INHIBITION OF BRADYKININ FORMATION RESULTS IN SIGNIFICANT REDUCTION IN EDEMA
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

- Phase I study to be initiated Q1 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

- Achieved break even in the US
  - JETREA® in the US is available with smaller team and a well-oiled specialized distribution channel
  - Online resources for patient, physician information, including enrollment and reimbursement

- OASIS 2 year follow up data reporting better outcomes than Phase III trial results: efficacy and safety (published in Ophthalmology – AAO Journal)

- JETREA® now approved in over 50 countries

- Continued ocriplasmin data generation and dissemination: conference and publication plan 2017
  - ARVO, ASRS, EURETINA, AAO – paper and poster presentations / advisory board meetings

- Preparing launch of new JETREA® ‘Ready to Use’ formulation
Developing TB-403 for pediatric cancers
Oncurious 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 development and financing partner of Oncurious for TB-403
- 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 today:
disease modifying treatments for diabetic eye disease + upside potential

Diabetic Eye Disease
Disease Modifying Treatments
Tackling Unmet Medical Needs in Diabetic Retinopathy

THR-409 – ocriplasmin – Phase II
THR-317 – anti-PIGF – Phase II
THR-687 – integrin antagonist
THR-149 – plasma kallikrein inhibitor

For NPDR/PDR
with or without DME

€ 73.3 million in cash
+ royalties and other revenues

ONCURIOUS
TB-403 for medulloblastoma
Phase I/IIa

+ Third party investment
Self-sustaining

JETREA US
Commercial
Cash neutral

Self-sustaining
2016/ 2017 – Continue transition and execute clinical trial plans

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Thank you for your interest

For questions and information:
Please send us a message via IR@thrombogenics.com