Corporate Overview

Dr. Philippe Calais
Chief Executive Officer

October 2015
Executive Summary

Advancing innovative TGF-β isoform-specific therapies into the clinic

- Leader in deciphering TGF-β biology & role in disease pathophysiology
- Proprietary research platform for selection of TGF-β isoform-selective ASOs
- Exploit key roles of TGF-β isoforms in ophthalmology, fibrosis & oncology to target unmet medical needs for major & orphan diseases
- Strategic partnerships with Santaris/Roche & Sanofi Trabedersen (1st gen. ASO) asset sale to Autotelic
- Agile, semi virtual private Dutch B.V. with US & German affiliates

ASO: AntiSense Oligonucleotide
TGF-β: Clinical Development Opportunities
Selection of high ‘probability-of-success’ diseases

**OPHTHALMOLOGY**
- Glaucoma*
- Diabetic retinopathy
- Proliferative vitreoretinopathy
- Age-related macular degeneration
- Secondary cataract (PCO)
- Corneal diseases (pterygium, keratoconus)

**ONCOLOGY**
- Pancreatic cancer
- Lung cancer
- Renal cancer
- Hepatocellular
- RPPP-based patient selection

**CARDIOVASCULAR**
- Coronary bypass remodeling

**FIBROSIS/CIRRHOSIS**
- Kidney fibrosis*
- Idiopathic pulmonary fibrosis*
- Liver cirrhosis
- Osteogenesis imperfecta
- Primary biliary cirrhosis
- Scleroderma
- Other

**CNS DISEASE**
- Alzheimer’s disease
- Parkinson’s disease

* Selected lead indications
Isarna’s Platform Core Differentiating Feature

TGF-β isoform involvement varies according to disease

OPHTHALMOLOGY

TGF-β2

TGF-β1

ONCOLOGY

TGF-β2

TGF-β1

TGF-β3

FIBROSIS

TGF-β1

TGF-β2

Tailored treatments for 3 therapeutic areas
## Isarna’s Pipeline

<table>
<thead>
<tr>
<th>Program</th>
<th>Research</th>
<th>Preclinical Development</th>
<th>Phase 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ophthalmology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β2</td>
<td></td>
<td></td>
<td>ISTH0036</td>
</tr>
<tr>
<td><strong>Fibrosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β1</td>
<td></td>
<td></td>
<td>ISTH1106</td>
</tr>
<tr>
<td><strong>Oncology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β2</td>
<td></td>
<td></td>
<td>ISTH0047</td>
</tr>
<tr>
<td>TGF-β1</td>
<td></td>
<td></td>
<td>ISTH1047</td>
</tr>
<tr>
<td>TGF-β + immune mod.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPPP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RPPP: Responder Patient Profiling Program
TGF-β Inhibitors Common Preclinical Properties

- **Potent & selective** ASOs with improved drug-like properties vs 1\textsuperscript{st}-gen. ASOs
- **Efficient target engagement:** mRNA, protein & downstream pathways

![Graph showing TGF-β1 mRNA Downregulation (%) vs TGF-β2 mRNA Downregulation (%)](image)

- **Biphasic PK profile** in biological matrices upon systemic/local injection
- **Pronounced & long-lasting distribution** in organs/tissues
- **Long-lasting target engagement** in selected organs/tissues
**ISTH0036 Product Rationale in Advanced Glaucoma**

**Predominant cytokine**
Aqueous & vitreous humor, neuronal retina & retinal pigmented epithelium

**Elevated levels in primary open angle glaucoma**

**TGF-β2**
core physiopathologic factor in glaucoma

**TM function impairment & IOP increase**
TGF-β2 dependent EMT

**Direct optic nerve damaging**

**Post trabeculectomy scarring, fibrosis & bleb closure**
Core driver

---

TM: Trabecular Meshwork  
IOP: IntraOcular Pressure  
EMT: Epithelial Mesenchymal Transition
Glaucoma – High Unmet Medical Need
2nd leading cause for blindness in the world

Optic nerve damage related disease
- Results in visual field loss
- Increased IOP based upon trabecular meshwork alterations

- 10% unresponsive to topical treatment require surgery to control disease
- Filtration surgery: last resort standard procedure
- 1st filtration surgery failure rate: up to 33% (6mth to 1y)
- Repeat surgeries blindness

Glaucoma prevalence, in M
ISTH0036 - Mechanism of Action

Disease modifier in glaucoma pathophysiology

**Pharmacology:** TGF-β2 ASO with potent, selective, sequence- & dose-dependent downregulation of TGF-β2 mRNA & protein

**Administration:** Intravitreal injection every 2 months for 12 months

**MoA**

3-directional properties resulting from TGF-β2 inhibition:

1. Prevention of further IOP rise through anti-scarring effect
2. Optic nerve head neuroprotection
3. Trabecular meshwork protection via antifibrotic effect

See TGF-β isoform common preclinical properties (slide 6)
ISTH0036 Summary of Preclinical Properties

Increase bleb size & survival*

Bleb area collagen deposition reduction*

Antifibrotic & anti-angiogenic effect**

* Mouse glaucoma filtration surgery model  ** Mouse choroidal neovascularization model
ISTH0036 - Clinical Development Strategy
Expand target indications post GFS Phase I

ISTH0036
GFS Phase I

GFS (ODD)
Phase II/III

Diabetic retinopathy
Phase II/III

Wet AMD
Phase II/III

Proliferative vitreoretinopathy & secondary cataract
Phase II/III

Disease driver:
- IOP
- Bleb scarring
- Nerve damage
- Proliferative fibrotic reaction
- Pathophysiology
- Proliferative fibrotic reaction
- Epithelial cell proliferation

GFS: Glaucoma Filtration Surgery
ODD: Orphan Drug Designation
TGF-β: Key Driver Role in Fibrotic Disorders

TGF-β1 isoform dominance in fibrosis pathogenesis

- Strong scientific evidence for clinically potent pro-fibrotic effect
- Associated with activity of other cytokines e.g. IL-7, TNF, ...
- Recognized key role in TGF-β driven epithelial-mesenchymal transition
- Epithelial cell activation / proliferation / differentiation promotion & collagen-producing myofibroblasts → fibrous connective tissue synthesis

Proinflammatory and profibrotic mediators in the initiation and maintenance of fibrosis
Summary of Preclinical Package & Evidence*

- Pronounced anti-fibrotic effects (ophthalmology program)
- Preliminary evidence of anti-fibrotic effect; ISTH0047 as prototype:
  - Common features described previously
  - Pharmacology efficacy studies underway in PF & KF models
  - IND/CTA-enabling toxicology program & manufacturing to be completed

* Upon systemic administration

PF: pulmonary fibrosis
KF: kidney fibrosis
Status of Isarna’s Fibrosis Program

**Target severe & life-threatening diseases**
- Prioritize high unmet medical needs indications: KF & IPF (ODD)
- Expand: liver cirrhosis, osteogenesis imperfecta (ODD)

**Development strategy going forward**
- Single agent or combination with complementary therapeutic agent
- Complete IND-ready preclinical package for KF & IPF

**Establish partnership or strategic alliance**
- Optimize & accelerate pipeline development

* Pending financing

**ISTH1106**
TGF-β1 targeting compound

*KF: Kidney Fibrosis  IPF: Idiopathic Pulmonary Fibrosis*
Oncology
TGF-β Role in Immuno-Oncology

Target TGF-β pathway-addicted tumors

- Established role in tumor microenvironment
- Peritumoral immunosuppression is a key driver for tumor growth & metastasis
- Variable predominance & cross talk of TGF-β1, β2 & potentially β3 isoforms
- TGF-β2 directed therapy: 1st clinical evidence of potent antitumor activity (NSCLC phase III study with belagenpumateucel-L, ASCO 2014)

Immuno-oncology modalities

- Combine immune checkpoint inhibitors (e.g. PD-1, PD-1L, CTLA-4) with TGF-β inhibitors
- Combination of immune check point inhibitor CTLA-4 with TGF-β inhibitor enhances efficacy in in melanoma model (ASCO 2014)
- Combine cancer vaccines with TGF-β inhibitors
Summary of Preclinical Package & Evidence*

- Established PoC: Evidence of anti-tumor activity \textit{in vivo}

- Specific therapeutic effect on lung metastasis
  No effect on ‘primary’ tumors (not shown)

- Anti-metastasis potential in lung metastasis mouse models of RCC & breast cancer

- Common features described previously
- Established \textbf{tolerance} and \textbf{manufacturing} completed for ISTH0047**
- Results presented at AACR 2013/2014 & ASCO 2014

* Upon systemic administration
** ISTH0047: previously ASPH_0047
Responder Patient Profile Program (RPPP)

Patient selection based on TGF-β tumor expression

- Establish “Personalized Medicine” treatment based on TGF-β isoform expression with specificity to Isarna isoform treatment
- Develop companion diagnostic

For example: TGF-β2 signature in TCGA GBM

Level 1: Detection of TGF-β isoform mRNAs &/or proteins by ISH or qRT-PCR, or IHC, respectively, in tumor biopsies

Level 2: TGF-β isoforms and downstream pathways detection

Level 3: TGF-β isoform specific ‘activated pathways gene expression signature’ from tumor biopsies

Companion diagnostic
Isarna’s Strategy in Oncology

**Rationale**
- Target TGF-β pathway-addicted tumors
- Select patients with high TGF-β expression

**Pipeline development***
- ISTH1047: ongoing preclinical dev.
- TGF-β2: select new lead compound
- Explore TGF-β1/β2 combination
- Test dual modality combinations (e.g. check point inhibitors, vaccines)
- ODD: mesothelioma, pancreatic cancer

**Establish partnership/ strategic alliance**
- Accelerate pipeline development

**ISTH0047 (TGF-β2) & ISTH1047 (TGF-β1)**

* Pending financing
Corporate Information
Experienced Management Team Supported by Top Tier Advisors

Management

Philippe Calais, CEO: Pharm.D, PhD; ICI, Roche, Neurochem, Ambrilia, Univalor
Michel Janicot: Head, Preclinical Research and Development, PhD; Janssen, Sanofi
Eugen Leo: Head, Clinical Development, MD, PhD, MBA; Janssen, Merck-Serono, Micromet

Strong Scientific Advisory Board (SAB) leadership

Ophthalmology
Alon Harris, PhD, Indiana U., US
David Spalton, MD, London Clinic Eye Centre, UK
Walter Stark, MD, Johns Hopkins Hospital, US
Rohit Varma, MD, U. of Southern California, US
Michael Wormstone, PhD, U. of East Anglia, UK

Oncology
Rosemary Akhurst, PhD, UCSF, San Francisco, USA
Ugur Sahin, MD, TVZ, TRON, Mainz, Germany
Josep Tabernero, MD, VHIO, Barcelona, Spain
Michael Weller, MD, U. Hospital Zurich, Switzerland
Isarna Corporate History Overview

- Corporate restart
- Began new LNA-ASO isoform specific program
- Acquired exclusive rights to LNA (Roche) for TGF-β
- Expanded pipeline to 3 therapeutic areas
- Established Sanofi CMO partnership

1998 - 2013

Trabedersen glioma Phase III termination

2H 2012 ------------------- end 2014

- Complete IND for fibrosis & oncology
- Validating partnership

2015 +

Trabedersen asset sale
- Steps towards public listing