ISTH0036: Inhibiting TGF-β2 with “Next Generation” Antisense Oligonucleotides as a New Therapy for Severe Eye Diseases

August 2019
Non-confidential
ISTH0036 Development: Executive Summary

- **Next-generation** antisense oligonucleotide (ASO) **blocking TGF-β2 production**, a major disease driver in ophthalmic indications, like wet AMD and DME
- Novel, first-in-class drug with **excellent PK/PD, safety and efficacy profiles**
- **Target inhibition and multimodal MoA** (anti-permeability, anti-angiogenic, anti-fibrotic, anti-EMT) strongly differentiate ISTH0036 from marketed anti-VEGF drugs Eylea and Lucentis and pipeline drugs
- First in men single-dose Phase 1 study demonstrated **good safety profile**
- Animal data in CNV model demonstrate **similar activity compared to gold-standard** anti-VEGF
- Repeat monkey tox., phase 1 data and EMA/FDA advice received **support ph 2 development** in retinal disease (AMD/DME) and glaucoma surgery
- **Blockbuster potential**: AMD/DME market ~12 bn USD (2018), upside case: dry AMD/PDR/PVR
- **Excellent IP** status and protection in all key markets
- **Orphan Drug status** in the US and EU for Advanced-stage Glaucoma surgery: Fast path to market option
- **Fast, small, cost-efficient Phase 2a signal seeking study** in blockbuster indication wet AMD and in DME in planning (FPI: Q1/2020)
- **Renowned and experienced management team** for development of a leading blockbuster drug
Why Invest in Isarna?

- Clinical Stage Company
- Attractive exit potential with relatively modest investment
- Limited number of current investors
- Lean, flexible company structure managed by experienced team
- Fast time to clinical PoC in blockbuster indications (< 24 months)
- Naïve and pre-treated patients both attractive, commercially viable market opportunity
- Potential for roll-out to other attractive indications such as proliferative DR, dry AMD
- Strong IP position
Capable and Renowned Management Team

- **Chris Huiskamp** - Managing Director, Finance
  - Prev. experience: Sourcia, Assign Group, Medpace, MOL Europe, Maersk Line

- **Marion Munk MD, PhD, FEBO** – Chief Medical Officer,
  - Ass.Prof Ophthalmology Bern / Chicago, Retina and Uveitis Specialist, Managing Director Bern Imaging Reading Center, >150 publications

- **René Rückert, MD, MBA**- Chief Operating Officer
  - Prev. experience: Lead for Global Retina Blockbuster Eylea/Lucentis development at Bayer/Novartis, Consultant, CMO / COO at Ophtha Startups

- **Michel Janicot, PhD** – Head Preclinical Res. & Dev.
  - Prev. experience: JMi ONConsulting, Janssen, Sanofi

- **Eugen Leo, MD PhD MBA** – Clinical Development
  - Prev. experience: LEOConsulting, J&J, Merck-Serono, Micromet
ISTH0036: Development Rationale
Involvement of TGF-β2 in Ocular Disease

TGF-β2 plays a key role in ocular pathology

- **Advanced-stage Glaucoma (POAG*)**

- **Proliferative Vitreoretinopathy**
  - [Connor et al. J Clin Inv 1989]

- **Diabetic Macular Edema and Diabetic Retinopathy**

- **Corneal diseases**

- **“Wet” Age-related macular degeneration**

- **“Dry” Age-related macular degeneration**
  - [Radeke et al. Genome Medicine 2015]
TGF-β2: A Core Driver of Disease Pathophysiology in Neovascular AMD and DME

- **Upregulates VEGF-secretion** from retinal pigment epithelial cells (RPE) and endothelial cells inducing neoangiogenesis
- **Drives Epithelial-to-mesenchymal transformation** of retinal pigment epithelial cells (RPE) and other retinal components, leading to photoreceptor degeneration
- **Promotes Fibrosis** as terminal step of retinal degeneration

Source: https://www.aao.org/topic-detail/diabetic-retinopathy-middle-east

Source: Bright Focus Foundation
TGFβ2 Antisense ISTH0036 Clearly Differentiated From current blockbuster Anti-VEGF Ophthalmic Drugs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Observed/expected effect with ISTH0036</th>
<th>Mechanism described in literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>wet AMD and DME</td>
<td>Potent <strong>anti-angiogenetic/anti-permeability</strong> effect shown in vivo</td>
<td>TGF-β leads to <strong>upregulation of VEGF</strong></td>
</tr>
<tr>
<td></td>
<td>Potent <strong>inhibition of fibrosis</strong></td>
<td><strong>Fibrosis</strong> in retinal diseases well recognized problem – addressing unmet medical need</td>
</tr>
<tr>
<td></td>
<td>Potent <strong>inhibition of epithelial-to mesenchymal transition (EMT)</strong> and <strong>protection of Retinal Pigment Epithelial (RPE) cells</strong> expected</td>
<td>TGF-β drives <strong>EMT</strong> of RPE cells (core disease pathology of AMD)</td>
</tr>
</tbody>
</table>

**Multimodal effects** of ISTH0036 (**anti-permeability/anti-angiogenic, anti-fibrotic, anti-EMT**) provide basis for clinical / strategic differentiation.

**Anticipated superiority** to current anti-VEGF blockbusters **Eylea and Lucentis**
Positioning and Differentiation from Competitors

Competitors

- Main focus on anti-angiogenesis and anti-vascular leakage pathways (VEGF, PDGF, Angiopoietin-2): no late-stage new MoA

- Upcoming new launches / expected approval are again addressing established target and are anti-VEGF drugs (broliciziumab und abicipar)

- Mainly protein drugs (also aptamer and small molecules) that inhibit a released target protein (drug-biodistribution, half-life, target engagement issues)

- Some late stage failures with large and small molecule drugs (likely also caused e.g. by sub-optimal study design in transition from ph2 to ph3,

ISTH0036

- With TGF- β2, Isarna is addressing a target outside of the classical VEGF pathways – clear clinical/strategic differentiation

- ISTH0036 has a multi-modal MoA: On top of anti-angiogenesis/-leakage it also has anti-fibrosis and anti-EMT activity

- ISTH0036 has a very long half-life and long-lasting target engagement

- Antisense therapy targets the mRNA and not protein – so preventing the production of pathogenic cytokine instaed of trying to block already produced/ released factors
ISTH0036: CMC and IP Status
CMC Summary

- **Sufficient Drug Product (DP) available to start Phase 2a program** in at least two indications

- cGMP Drug Substance material was manufactured and released by BioSpring GmbH (Germany)

- The DP is a sterile powder solution for intravitreal injection

- The finished DP is classified as a small-volume parenteral, the dosage form according to EDQM is ‘Powder for solution for injection’

- The excipients (water, hydrochloric acid, sodium hydroxide, nitrogen) used for DP manufacturing meet the compendia requirements of the Ph.Eur. and/or USP

- To date, the temperature conditions for storage and transport of the IMP ISTH0036 is +5°C ± 3°C. Therefore, the IMP should be stored in the refrigerator under controlled conditions
IP Status: Broad Protection and FTO

- Modified TGF-beta oligonucleotide for use in a method of preventing and/or treating an ophthalmic disease (ISTH0036)

- TGF-beta oligonucleotide for use in treatment of ophthalmic diseases (ISTH0036)

- Modified TGF-beta 2 oligonucleotides (cancer, fibrosis, cirrhosis, ophthalmic diseases)

- Modified TGF-beta oligonucleotides (cancer, fibrosis, cirrhosis)

- LNA chemistry: Exclusive License from Santaris/Roche
  - Exclusive IP rights for TGF-β isoforms licensed for all therapeutic indications
  - Isarna retains full ownership of its LNA compounds - no rights to Santaris/Roche
ISTH0036: Preclinical Development
Long-lasting, dose dependent TGFβ2 target downregulation by ISTH0036 IVT in vivo

Pharmacodynamic Profile in Ocular Tissues of Cynomolgus Monkey after IVT Injection

Dose-dependent target TGF-β2 mRNA downregulation in retina

Time-dependent target TGF-β2 mRNA downregulation in retina

Time-dependent TGF-β2 protein downregulation in vitreous humor

Results:
• Significant time- and dose-dependent target engagement (TGF-β2 mRNA downregulation) in the retina upon IVT administration(s) of ISTH 0036
• Significant time- and dose-dependent target suppression (TGF-β2 protein) in vitreous humor
Excellent efficacy in gold-standard / best in class neovascularization (CNV) retina-disease mouse model

**Effect of ISTH0036 and/or Eylea (aflibercept) on CNV formation**

*Fluorescence Angiography (FA) readout on Day 14*

**Method:** Murine CNV model with 3 laser-induced burns on the Bruch’s membrane of C57Bl/6Jrj mouse eyes. ISTH0036 and aflibercept were administered (IVT injection) immediately after CNV induction. The mice were followed for 14 days using in vivo imaging (fluorescein angiography and spectral domain optical coherence tomography (OCT))

**Results:**
- Single intraocular injection of ISTH0036 or aflibercept significantly reduced the presence of CNV lesions
- Non-statistically significant trend for better efficacy with ISTH0036/Eylea combo

**Comparable results to the Standard of Care Eylea (i.e. a 9 Bn USD Blockbuster) in CNV mouse model**
Excellent efficacy in gold-standard / best in class neovascularization (CNV) retina-disease mouse model

Efficacy of ISTH0036 and/or Eylea/aflibercept on vascular leakage

Fluorescence Angiography (FA) readout on Day 14

Results:
- Single intraocular injection of ISTH0036 or aflibercept markedly reduced the presence of CNV lesions, and increased percentage of grade-1 (small) lesions
- Trend for better efficacy with ISTH0036/Eylea combo treatment

Comparable results to the Standard of Care (i.e. a 9 Bn USD Blockbuster) Eylea in CNV mouse model
Excellent efficacy in gold-standard / best in class neovascularization (CNV) retina-disease mouse model

Effect of ISTH0036 and/or Eylea (aflibercept) on OCT morphology

OCT analysis at baseline and post-treatment

0.1-µg ISTH0036

4-µg Eylea

ISTH0036/Eylea combo

Results
• Time-dependent visual effect of both ISTH0036 and aflibercept on CNV lesions (CNV formation and leakage inducing retina thickening and subretinal fluid)

Comparable results to the Standard of Care (i.e. a 9 Bn USD Blockbuster) Eylea in CNV mouse model
Summary of Preclinical Data and Toxicology

- Excellent **tissue uptake** and **sustained target downregulation** (up to 8-16 weeks)

- Potent, **in-vivo proven anti-permeability, anti-angiogenesis, anti-fibrosis** effect in relevant ocular animal models and (evidence-based) **anti-EMT potential**

- **Equipotency to standard of care aflibercept (Eylea)** in-vivo on anti-permeability/-angiogenesis in CNV model with potency of longer treatment effect

- **GLP-Tox studies** completed with **safe administration**

- Available data support further clinical development
ISTH0036: Clinical Development
ISTH0036: Phase I Data

Excellent safety in post-Trabeculectomy/Glaucoma Filtration Surgery
**ISTH-01-111: Phase I dose escalation of ISTH0036**

Advanced stage glaucoma patients undergoing trabeculectomy

**Timelines: 2Q2015 (FPI) – 3Q2016**
- Dose escalation, single IVT* injections
- 12 patients treated
- 4 dose levels (6.75 μg/22.5μg/67.5μg/225 μg with calculated Vitreous(intraocular) peak conc. of 0.3/1.0/3.0/10 μM)
- DLT period 42 days (6 weeks)
- Safety follow-up: 12 weeks
- Prolonged IOP recording: 12 months
- Prolonged safety follow-up: 12 months

**Primary endpoint:** Safety & tolerability

**Secondary endpoints:**
- IOP (at 6 and 12 weeks post surgery)
- Nº of interventions post-trabeculectomy
- Bleb filtering
- Visual field

*IVT: Intravitreal injection
Summary of Phase I Results

- **Excellent tolerability after single injection** with zero drug-related AE

- **Preliminary signs for efficacy** (anti-fibrotic effect) in trabeculectomy setting

- **Full results published**


  First-in-human phase I study of ISTH0036, an antisense oligonucleotide selectively targeting transforming growth factor beta 2 (TGF-β2), in subjects with open-angle glaucoma undergoing glaucoma filtration surgery.

- First in man safety data in combination with **preclinical results** and **completed toxicology** data supportive of ph II development in **major blockbuster retina indications**
ISTH0036: Phase IIa Proposal for Development in Retina Blockbuster Indications „wet“ AMD and DME
Significant Unmet Medical Need in wetAMD and DME

- **Therapeutic effect** of existing anti-VEGF compounds is insufficient
  - Despite >10Bn USD annual sales, limited efficacy: do not improve Visual Acuity (VA) notably in over 30% of all patients in clinically relevant fashion (+5 letters)
  - Major improvement in VA in AMD in only up to 40% of newly diagnosed patients (VA > +15 letters)
  - VEGF-refractory / Suboptimal response to anti-VEGF is a clinically recognized issue

- **No true alternative to anti-VEGF** existing
  - As of today, no anti-VEGF complimentary mode of action drug has been approved or is close to filing/approval
  - New anti-VEGF-compound, brolucizumab, will likely be approved in 2019 showing slightly more potent activity and less frequent dosing claim vs. Aflibercept but won’t alter VEGF refractory patient issue overall

- **No antifibrotic agent** available
  - Fibrosis is distinct issue in wetAMD and several other major retinal disease areas such as advanced diabetic retinopathy

- **No genuine disease-progression preventing agent** existing
  - Epithelial-to-mesenchymal transition of core tissues (e.g. RPE cells) not blocked by existing agents
## ISTH0036: Target Product Profile

<table>
<thead>
<tr>
<th><strong>Product</strong></th>
<th><strong>TGF-β2 locked-nucleic-acid antisense oligonucleotide</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administration Route</strong></td>
<td><strong>Intravitreal injection</strong></td>
</tr>
<tr>
<td><strong>Dosing Frequency</strong></td>
<td><strong>Every other month (Q2M) and potentially less frequent in maintenance therapy</strong></td>
</tr>
</tbody>
</table>
| **Target**            | **TGF-β2-related ophthalmic diseases**  
                        | **Novel therapeutic option independent or in addition to VEGF block** |
| **Effect**            | **Anti-angiogenic/anti-permeable, anti-fibrotic, anti-epithelial-to-mesenchymal (EMT) transition** |
| **Indications**       | **Initial focus: wet AMD and DME**  
                        | **Upward potential: dry AMD, pDR, PVR, Glaucoma** |
| **Initial target popul.** | **1st line treatment-naive and/or 2nd line VEGF-pretreated patients** |
| **Positioning**       | **Monotherapy and/or combo with anti-VEGF drugs**  
                        | **Sole antifibrotic compound** for back of the eye diseases |
| **Pricing**           | **Similar as ranibizumab/afiblercept (~ 2,000USD/ 800€)** |
Proposed Signal-seeking Phase II a Development Strategy

- **Focus on largest retina blockbuster indication**: Safety data of phase I, in-vivo CNV model data and toxicology data support Ph IIa development in wet AMD and DME
- **Two main populations as initial development opportunities**: Treatment-naive patients as largest market and VEGF-pretreated patients
- **Derisked, small signal-seeking studies in minimal phase IIa approach**: Two-segment Ph IIa study with uncontrolled but outcome-rater/patient masked design, allowing for initial identification of ideal target population to start Phase IIb/III dose finding and confirmatory study
- **Robust phase II exploration**: Ph IIa – small-scale demonstration of retinal fluid/CMT reduction (at 6 months, primary endpoint) and VA improvement (secondary endpoint) demonstration of CMT and VA improvement (out to 9mo total FU), with initial exploration of fibrosis and EMT prevention plus validation of injection frequency vs. aflibercept,
- **Filing strategy/Ph III design determination**: Ph IIa explores optimal filing indication, which will be confirmed in Ph IIb part with option to seamless PhIIb/III part to accelerate approval timelines.
- AMD / DME Ph IIa trial synopses available, trial sites identified
# Timelines

<table>
<thead>
<tr>
<th>Program</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1H</td>
<td>2H</td>
<td>1H</td>
</tr>
<tr>
<td>Strategic Milestones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investor Discussion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partnering Discussion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry AMD Planning?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad-board</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industry Talks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTA India/EU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTA Global</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMA/FDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMD Analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DME Global Analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad-board</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Development Indication / Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>wetAMD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial Set-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruit.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Pat naïve Ph2a 6mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3mo F/U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruit.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Pat pretreated Ph2a 6mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3mo F/U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DME</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruit.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Pat naïve Ph2a 6mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3mo F/U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruit.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Pat pretreated Ph2a 6mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3mo F/U</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Phase 2b/3 Pivotal trial 1yr + FU
Ph II a Generating Core Value

- **Efficacy Signal identification** in two major retinal diseases
- Low number of centers in cost-efficient countries, building on existing global academic network and extensive retina drug development expertise of Isarna management team
- Upfront discussion with key players in big-pharma Ophthalmology to streamline study design / outcome expectations and adapting to their needs for possible partnering for late-stage development
- Identification of best ph III / filing population
- **Fast and very cost-efficient path to Phase IIb dose finding/ Ph III pivotal trials**

**Optimized value gain for subsequent financing rounds and / or for major pharma / partnering**
ISTH0036: Positioning and Market Size Estimate
## Positioning with (Conservative) Market Share & Sales Estimates

<table>
<thead>
<tr>
<th>TPP/Target population (AMD/DME)</th>
<th>Filing claim</th>
<th>Eligible patient population*</th>
<th>Estimated market share</th>
<th>Annual sales estimates (mn USD)**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>range</td>
<td>target</td>
<td></td>
</tr>
<tr>
<td>2nd line Combo with anti-VEGF drugs, anti-VEGF-refractory patients</td>
<td>Mean BCVA improvement &gt; 5.0 letters over anti-VEGF drugs alone</td>
<td>12-51% (brolucicubam-, aflibercept-, ranibizumab-refractory), 72-306k pts/y</td>
<td>20% (120k pts/y)</td>
<td>50% (60k pts/y)</td>
</tr>
<tr>
<td>2nd line Mono, anti-VEGF-refractory patients</td>
<td>Non-inferiority to 2nd line anti-VEGF drugs</td>
<td>12-51% (brolucicubam-, aflibercept-, ranibizumab-refractory), 72-306k pts/y</td>
<td>20% (120k pts/y)</td>
<td>30% (36k pts/y)</td>
</tr>
<tr>
<td>1st line Combo, anti-VEGF-treated subgroup</td>
<td>Mean BCVA improvement &gt; 5.0 letters over aflibercept alone</td>
<td>35-40% (aflibercept treated), 210-240k pts/y</td>
<td>35% (210k pts/y)</td>
<td>30% (63k pts/y)</td>
</tr>
<tr>
<td>1st line Combo, all patients</td>
<td>Mean BCVA improvement &gt; 5.0 letters over anti-VEGF drugs alone</td>
<td>90-100%, 540-600k pts/y</td>
<td>95% (570k pts/y)</td>
<td>40% (228k pts/y)</td>
</tr>
<tr>
<td>1st line Mono, all patients</td>
<td>Non-inferiority to anti-VEGF drugs alone</td>
<td>90-100%, 540-600k pts/y</td>
<td>95% (570k pts/y)</td>
<td>25% (143k pts/y)</td>
</tr>
</tbody>
</table>

*Total anti-VEGF-treated patients WW: ~600k
**1.5k/dose x 6 doses = 9k/pt/y
Contact:

Dr. med. René Rückert, MBA
Chief Operating Officer Isarna
rene.ruckert@eyegnos.com

+49-171-20 80 410

www.isarna-therapeutics.com