A Phase I First-in-Human single ascending dose study of ISTH0036, a potent and selective antisense oligonucleotide targeting transforming growth factor beta 2 (TGF-β2) for the treatment of primary open-angle glaucoma

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Abstract

Purpose: To study the safety and tolerability and preliminary clinical efficacy of intravitreal ISTH0036 in patients with primary open-angle glaucoma (POAG) undergoing trabeculectomy with Mitomycin C.

Methods: This prospective Phase I trial is performed at three sites. Glaucoma patients scheduled for filtration surgery receive a single intravitreal injection of ISTH0036 at the end of trabeculectomy in escalating total doses of 6.75 µg, 22.5 µg, 67.5 µg or 225 µg, respectively, resulting in calculated intraocular ISTH0036 concentrations in the vitreous humor of 0.3 µM, 1 µM, 3 µM or 10 µM after injection. Outcomes assessed include: type and frequency of adverse events, intraocular pressure (IOP), number of interventions post trabeculectomy, bleb survival, visual acuity and visual field, slit lamp biomicroscopy and optic disc status.

Results: In this ongoing study so far nine patients have been treated (dose level 1 up to dose level 3). For all dose levels tested so far excellent safety and tolerability was confirmed. No treatment associated adverse events, SAE or dose limiting toxicities (DLTs) were observed.

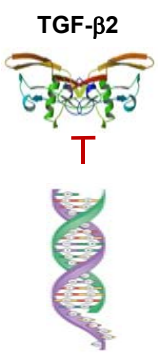
Conclusion: Preliminary results of this First-in-Human trial suggest that intravitreal injection of ISTH0036, a potent and selective antisense oligonucleotide targeting transforming growth factor beta 2 (TGF-β2) is safe and well tolerable.

Compound

ISTH0036 is a fully phosphorothioate 14-mer oligodeoxynucleotide with a 3+3 **LNA***-gapmer pattern selectively targeting TGF-β2 mRNA

5'- **GA**$^{(Me)}$**C**CAGATGCA**GGA** -3'

Inhibition of TGF-β2 as Target for Multi-modal Effects in Ophthalmic Diseases



- One of the most important cytokines involved in the regulation of cell behavior in ocular tissues
- Increased expression is reported in various ocular diseases (glaucoma, AMD, DR, PVR, Pterygium et al.)
- Enhanced gene expression relates to tissue fibrosis, epithelial-mesenchymal transition (EMT), remodeling of extracellular matrix (ECM) and inflammation
- Stimulates vascular endothelial cell proliferation and therefore a role in neovascularization is proposed
- Involved in optic nerve head remodeling and deformation of optic nerve axons

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

Study design – NCT02406833

Primary Objective: To determine the safety and tolerability of ISTH0036

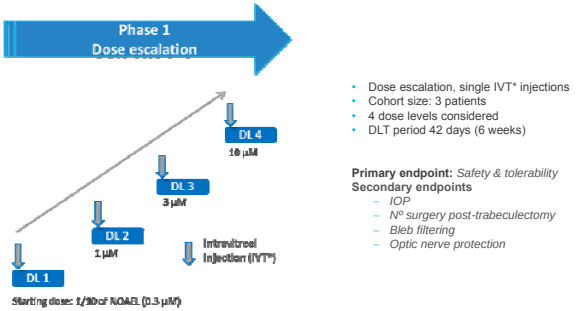
Secondary Objective: To determine preliminary clinical efficacy of ISTH0036

Main Inclusion Criteria:
- Subjects 18-80 years with diagnosis of primary open-angle glaucoma (POAG)
- Subject no longer tolerating or benefitting from topical treatment of glaucoma
- Subject scheduled for trabeculectomy with Mitomycin C (MMC)

Study Design – NCT02406833 (ctd.)

Study Design - ISTH-01-111: Phase I First-in-Human, open-label, dose escalation study in patients with primary open-angle glaucoma (POAG) undergoing trabeculectomy.

- Dose escalation with single doses of ISTH0036 in cohorts of three patients.
- Intravitreal administration of ISTH0036 on day 1 at the end of trabeculectomy, after topical administration of MMC.



- Dose escalation, single IVT* injections
- Cohort size: 3 patients
- 4 dose levels considered
- DLT period 42 days (6 weeks)

Primary endpoint: *Safety & tolerability*
Secondary endpoints
- *IOP*
- *N° surgery post-trabeculectomy*
- *Bleb filtering*
- *Optic nerve protection*

Assessments:

Safety: Continuous assessment of safety parameters; AE reporting according to CTCAE v4.03.; Laboratory parameters at baseline, after 6 and 12 weeks.

Ophthalmic parameters: assessed pre-dose, after 6 and 12 weeks and compared to baseline were intraocular pressure, number of interventions post trabeculectomy, bleb filtering and bleb morphology, visual acuity, visual field, slit lamp biomicroscopy, optic disc status: Heidelberg Retina Tomography (HRT II) and optic disc photograph, electroretinogram (week 6 only).

DLT criteria: All toxicities observed during the 42 days DLT period following the first intravitreal injection that are at least possibly related to ISTH0036 and are ≥ grade 3 or eye disorders ≥ grade 2 or cataract, retinal detachment, retinopathy ≥ grade 1.

Interim Results

Patients and ISTH0036 treatment:
- This interim analysis includes demographic data and safety data of 9 patients treated in the first three cohorts with 6.75 µg, 22.5 µg, and 67.5 µg ISTH0036 equivalent to and approximate drug concentration of 0.3, 1, and 3 µM in the vitreous body.
- The data presented are as of Apr 20, 2016; the study is ongoing.

Table 1: Patient demographics per dose cohort

	Dose Level 1 6.75 µg (0.3 µM) N=3 (100%)	Dose Level 2 22.5 µg (1 µM) N=3 (100%)	Dose Level 3 67.5 µg (3 µM) N=3 (100%)	Total N=9 (100%)
Median age, years (range)	65 (50-77)	63 (46-79)	67 (64-72)	65 (46-79)
Gender				
male, number (%)	1 (33)	2 (67)	2 (67)	5 (56)
female, number (%)	2 (67)	1 (33)	1 (33)	4 (44)
Number of previous ophthalmic interventions	9	2	5	16
Number (%) of patients with interventions				
none	1 (33)	2 (67)	1 (33)	4 (45)
1-3	1 (33)	1 (33)	1 (33)	3 (33)
≥ 4	1 (33)	0 (0)	1 (33)	2 (22)
IOP, mmHG, mean (SD)				
screening	34.7 (16.74)	23.0 (7.79)	15.7 (5.84)	
baseline	28.7 (4.64)	20.7 (4.78)	14.8 (3.52)	

Interim Results

Preliminary Safety and Tolerability of ISTH0036:
- Out of 9 treated patients, 9 completed DLT period (42 days), 6 patients completed end of study assessments (12 weeks).
- No DLT observed.
- 2 SAEs (choroidal effusion, ocular hypertension) were reported in 1 patient; both were assessed as unrelated to ISTH0036 and intravitreal injection and probably related to primary surgery.
- 20 AEs were reported to date
  - No clinical adverse event related to ISTH0036 or intravitreal injection
  - All clinical adverse events related to primary surgery or unrelated
  - 9/10 clinical adverse events related to primary surgery consisted of Grade 1/2 eye disorders, infections and infestations, investigations, immune system disorders, musculoskeletal and connective tissue disorders and vascular disorders.

Table 2: Adverse events per dose cohort

	Dose Level 1 6.75 µg (0.3 µM) N=3	Dose Level 2 22.5 µg (1 µM) N=3	Dose Level 3 67.5 µg (3 µM) N=3	Total N=9
Overall adverse events, n (%)	7 (31.8)	8 (36.4)	7 (31.8)	22 (100)
- Related* to ISH0036	**none**	**none**	**none**	**none**
- Related* to intravitreal injection	**none**	**none**	**none**	**none**
- Related* to primary surgery	**3**	**5**	**4**	**12**
Eye disorders:	3	4	3	10
Eczema eyelids	*1*	*0*	*0*	*1*
*Choroidal effusion***	*1*	*0*	*0*	*1*
Conjunctival hyperaemia	*0*	*1*	*0*	*1*
Corneal erosion	*0*	*1*	*0*	*1*
Corneal oedema	*0*	*1*	*0*	*1*
Lacrimation increased	*0*	*0*	*1*	*1*
Ocular hyperaemia	*0*	*0*	*1*	*1*
Ocular hypertension	*1*	*0*	*0*	*1*
*Ocular hypotension***	*0*	*0*	*1*	*1*
Visual acuity reduced	*0*	*1*	*0*	*1*
Investigations:	0	1	1	2
Intraocular pressure increased	*0*	*0*	*1*	*1*
Intraocular pressure decreased	*0*	*1*	*0*	*1*
- Unrelated*	**4**	**3**	**3**	**10**
Eye disorders: *Corneal erosion*	1	0	1	2
Infections and infestations: *Nasopharyngitis*	1	2	0	3
Investigations: *Intraocular pressure increased*	0	1	0	1
Immune System disorders: *Drug hypersensitivity*	1	0	0	1
Metabolism and nutrition disorders: *Gout*	0	0	1	1
Musculoskeletal and connective tissue disorders: *Muscle spasms*	1	0	0	1
Vascular disorders: *Hypertension*	0	0	1	1

*Reasonable possibility (certain, probable/likely, possible); no reasonable possibility (unlikely-related or unrelated to ISTH0036, intravitreal injection and primary surgery)
** Serious adverse event

Preliminary Course of IOP values:
The mean pre-operative IOP of patients at screening/baseline for dose level 1 and 2 were 34.7/28.7 and 23.0/20.7 mmHg, respectively (SD: 16.74/4.64 and 7.79/4.78). Postoperative values at 6-week FU were 9.8 mmHg (SD: 0.85) and 11.3 mmHg (SD: 5.44), and at 12-week FU 9.7 mmHg (SD: 2.72) and 14.2 mmHg (SD: 5.33).

Full results will be reported upon study completion.

Conclusions

- **ISTH0036 showed excellent tolerability in this First-in-Human study**
- **Intravitreal injection of ISTH0036 is safe and well tolerable**
- **ISTH0036 may represent a promising potential new treatment opportunity for post-trabeculectomy-stage glaucoma and other ocular diseases linked to TGF-β2 such as AMD, diabetic retinopathy and proliferative vitreoretinopathy**

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