A MULTICENTRE DOUBLE-BLIND RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND TOLERABILITY OF THREE DOSES OF GS-101-EYE DROPS, AN ANTISENSE OLIGONUCLEOTIDE, VERSUS PLACEBO ON INHIBITION OF CORNEAL NEOVASCULARIZATION, A MAJOR RISK FACTOR OF CORNEAL GRAFT REJECTION

CLINICAL STUDY REPORT OF A FINAL ANALYSIS
Final Version - 7 December 2015
SUMMARY

Name of Sponsor/Company: CTRS	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: GS-101	Volume:	
Name of Active Ingredient: GS-101	Page:	
Title of Study: A MULTICENTRE DOUBLE-BLIND RANDOMIZED STUDY TO INVESTIGATOR THE EFFICACY AND TOLERABILITY OF THREE DOSES OF GS-101 EYE DROPS, AN ANTISENSE OLIGONUCLEOTIDE, VERSUS PLACEBO ON INHIBITION OF CORNEAL NEOVASCULARIZATION, A MAJOR RISK FACTOR OF CORNEAL GRAFT REJECTION.		
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Study centres: University Hospital Zurich, Switzerland (site 1) Inselspital Berne, Switzerland (site 2) University Hospital Erlangen, Germany (site 3) Helios Kliniken Schwerin, Schwerin, Germany (site 4) University Hospital Essen, Germany (site 5) University Hospital Homburg, Saar, Germany (site 6) Hôpital des Quinze-Vingts, Paris, France (site 8) Reading Center and the PI of site 3 moved per September 2011 to University of Cologne, Professor Claus Cursiefen, Director Klinik und Poliklinik für Allgemeine Augenheilkunde, Kerpenerstrasse 62, D-50937 Cologne, Germany		
Publication (reference): Cursiefen C, Bock F, Horn FK, Kruse FE, Seitz B, Borderie V, Früh B, Thiel MA, Wilhelm F, **Geudelin B**, Descohand I, Steuhl KP, Hahn A, Meller D. GS-101 antisense oligonucleotide eye drops inhibit corneal neovascularization: interim results of a randomized phase II trial. Ophthalmology. 2009;116(9):1630-7. At the present stage no other publication is planned.		
Studied period: Date of first enrolment: 12 Jan, 2006 Date of last completed: 9 Dec 2008 (for final analysis)		**Phase of development:** IIb pivotal
Objectives: To determine the optimal dose amongst 3 different concentrations of GS-101 *versus* control (placebo) in order to prevent progression of neovascularization in patients suffering from keratitis or keratouveitis of infections, inflammatory or tramatic origin.		
Methodology: multicentre, double-blind, randomized, comparing 3 concentrations of GS-101 eye drops *versus* control (placebo).		

Number of patients (planned and analyzed):
For the completed study: planned 80 having experienced corneal lesions leading to documented progression of corneal neovascularisation.
For this final analysis: planned 80, enrolled 56; completed analysis: 31 (efficacy) and 56 (safety).

Patient Disposition

	All screened patients N [%]	All randomized/treated patients N(%)	GS-101 N(%)	Placebo N(%)
Screened population	56	-	-	-
Screen failures	0	-	-	-
Patients withdrawn before randomization	0	-	-	-
Randomized ITTpopulation	56	56 (100%)	41 (73.2%)	15 (26.8%)
Randomized patients witdrawn from study	6 (10.7%)	6 (10.7%)	4 (7.1%)	2 (3.6%)
PP population	31 (55.4%)	31 (55.4%)	24 (42.9%)	7 (12.55)
Safety population	56 (100%)	56 (100%)	41 (73.2%)	15 (26.8%)

ITT: Intent-To-Treat; PP: Per Protocol

Diagnosis and main criteria for inclusion:
Adults from either gender, suffering from keratitis or keratouvetitis, with evidence of progression of neovascularization during a period of minimum 2 weeks and maximum 3 months prior to inclusion (as documented by at least 2 photos of the injured cornea).

Test product, dose and mode of administration, batch number : GS-101 as sterile eye drops, 2 drops daily (morning, evening) at 3 different concentrations:

- 0.43 mg/mL (21.5µg/drop) (Group 1)
- 0.86 mg/mL (43µg/drop) (Group 2)
- 1.72 mg/mL (86µg/drop) (Group 3)

Batch number : GNS-002-02-10-05

Duration of treatment : 6 months for the completed study (An interim analysis was performed after 3 months in a subset of 40 patients, see Cursiefen C, Bock F, Horn FK, Kruse FE, Seitz B, Borderie V, Früh B, Thiel MA, Wilhelm F, **Geudelin B,** Descohand I, Steuhl KP, Hahn A, Meller D. GS-101 antisense oligonucleotide eye drops inhibit corneal neovascularization: interim results of a randomized phase II trial. Ophthalmology. 2009;116(9):1630-1637.

Reference therapy, doses and mode of administration, batch number:
Placebo (Vehicle sterile 0.9% NaCl solution), Group 4
Two drops daily (morning/evening)

Criteria for evaluations:
The primary efficacy variable was the progression of corneal neo-vascularization as documented by the photographies.
Analyses by semi-quantitative measurement and computerized morphometry of the photographs of neo-vascularization were performed masked from the technician:.
Secondary variables were:

- Visual acuity after 6 months of treatment (at the end of the study)
- Treatment safety (Local tolerability, Adverse events)

Statistical methods: Progression of corneal neovascularization was analysed as a continuous variable and also as a categorical variable where progression was dichotomized as “increasing” or “regression”. Regression was considered significant if the area of corneal neovascularization measured at baseline was reduced by more than 10% at evaluation time.
Cell area means were compared between doses and placebo with contrasts adjusted for baseline values. Due to small samples and skewed distributions, asymptotic and bootstrap approaches were used.
Cell area (increased *versus* decreased) proportions were compared between four groups with Fisher exact tests and between doses and placebo with Pearson’s chi-square statistics, which are robust with small samples.

Summary:
As per the study protocol, 80 patients were planned to be enrolled into the study. The sponsor performed an interim analysis after the first 40 patients were enrolled (interim analysis report dated 6 Nov 2007). At the time of the interim analysis the sponsor also started a phase III study (EudraCT 2008-005388-33). As this other study was conducted at the same sites, sites enrolled only few patients into GS-101-P2-CG because the physicians preferred their patients be included in the phase III protocol. This phase III study has been completed and demonstrated that GS-101 significantly improved the relative area of corneal neovascularization after 3 months of treatment at a daily dose of 86µg. In this phase III study, however, no statistically significant differences in VA scores were observed between the 2 groups at either time points, i.e. day 30, day 90 or day 180. As a consequence, the Sponsor did not see a rational to continue with the phase II study and decided to close the phase II study as well.

Efficacy Results from the present study GS101-P2-CG:
As the study did not reach the number of patients initially calculated (56 patients included – 31 evaluable), there is a lack of power for the whole analysis. Of the 31 patients, the number of patients was 7 in the placebo group, 8 in the low-dose group, 7 in the intermediate group and 9 in the high dose group.
The progression of corneal neovascularization as a continuous variable was assessed using asymptotic and bootstrap approaches. Only the group receiving 86µg per day (intermediate dose) showed a significant difference *versus* placebo (p=0.04 and p= 0.006) at 3 months and 6 months respectively. The evolution of total neovascularized area in this group is -30.32 ± 23% at 3 months and -50.40 ± 17% at 6 months.
The group receiving 43µg per day (low dose) showed a tendency to arrest progression of neovascularisation (-1.13% and -0,97% at 3 months and 6 months, respectively. The group receiving 172µg per day (high dose) showed no arrest in the progression of neovascularisation at 3 months (+15.90%) but a tendency to regression at 6 months (-18.85%) ; in the latter group, this lack of efficacy at 3 months was due to a lack of response of 2 patients to GS-101, who responded with a delay 3 months later.
A specific analysis was performed in order to evaluate the evolution of the neovascularisation in each group at 1, 3 and 6 months. The group receiving 86µg per day showed a significant regression of neovascularisation at 3 (p=0.014) and 6 months (p=0.0016) *versus* baseline.
The progression of corneal neovascularization as a categorical variable at 3 months was assessed using Fisher exact test to compare all groups and Pearson's chi-square to compare each dose to placeco. Calculation showed that there was a significant statistical difference between all groups (p=0.05). The group receiving 86µg per day showed a significant regression of neovascularization *versus* placebo (p=0.008).
No change of visual acuity was observed.

Safety results:
Eighty six (86) adverse events were reported in 32 patients, most of them unrelated or unlikely related to the study drug.
Sixteen (16) serious adverse events were reported in 13 patients. Thirteen (13) serious adverse events were not related and three (3) serious adverse events were unlikely related to the study drug.

Conclusion:
This multicentre, European, double-blind, randomized study aimed at determining the optimal dose amongst 3 different doses of GS-101 *versus* placebo in order to prevent progression of neovascularization in patients suffering from keratitis or keratouveitis of infectious, inflammatory or traumatic origin.
As the study did not reach the number of patients initially calculated there is a lack of power for the whole analysis.
Regression of corneal neovascularisation was significant in the group receiving 86mg/ml (86µg per day, intermediate dose).
Considering the available data, the study treatments were well tolerated.

Date of report: 7 December 2015