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Title:	Randomized, double masked; active controlled, crossover phase III Equivalence study of dorzolamide 2% eye drops solution in subjects with open angle glaucoma or ocular hypertension	
Study codes: SCO 5449		
Date of draft report: March 03, 2010		
Principal Investigators:	Prof. Dr. Norbert Pfeiffer	
Investigators:	Dr. Katrin Lorenz	
Study centre:	Department of Ophthalmology Johannes Gutenberg-University Mainz Langenbeckstr. 1 55131 Mainz, Germany	
CRO:	Scope Life Sciences GmbH Frohbösestraße 12-14 22525 Hamburg Germany	
Time of clinical part:	15.05.2009 (first screening examination) - 29.01.2010 (end-of-follow up in the last patient)	Clinical Phase: III
Indication	Open Angle Glaucoma and Ocular Hypertension	
Primary objective:	To assess the equivalence of topically administered Dorzolamide 2% Eye Drops Solution (test formulation) compared to Trusopt® Eye Drops Solution (reference formulation) in lowering intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.	
Secondary objectives:	To assess the safety and tolerability of repeated topical administration of Dorzolamide 2% eye drops solution in patients with open angle glaucoma or ocular hypertension.	
Study design:	Prospective, monocentric, double-blind, randomized, active-controlled, crossover study	
Patients:	planned for completion: 32 enrolled and randomized: 35 drop-outs: 2 data set for safety analysis: 34 completed all periods per protocol: 32	
Diagnosis and main inclusion and exclusion criteria:	**<u>Main inclusion criteria:</u>** Patients meeting all of the following criteria will be considered for enrolment to the trial: • Male or female patients of any race aged 18 years or older • A clinical diagnosis of open angle glaucoma, pseudoexfoliation or	

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	pigment dispersion glaucoma, or ocular hypertension in one or both eyes • IOP controllable on one drug treatment in the study eye in a way that assures clinical stability of vision and the optic nerve throughout the study • Baseline IOP between 18 and 32 mmHg in the study eye (in eyes not included in the study IOP must have been controllable on no pharmacological treatment or on the study medicine only) • Best corrected visual acuity of 20/200 or better in the study eye **<u>Main exclusion criteria</u>:** Patients presenting 1 of the following criteria will not be enrolled in the trial: • Chronic or recurrent inflammatory eye disease • Ocular trauma within the past six months • Current ocular infection, i.e. conjunctivitis or keratitis • Any abnormality preventing reliable applanation tonometry • Intraocular surgery or laser treatment within the past three months • Inability to discontinue contact lens wear during the study • Use of any systemic medication that would affect IOP with less than a 1-month stable dosing regimen before the screening visit • Patient is allergic to sulfonamides • Severe renal dysfunction or hyperchloraemic acidosis	
Drug 1: **TEST** **(treatment a)**	name: substance: strength: dosage form: mode/route: company responsible for manufacturing the product: batch size: batch number: manufacturing date:	Dorzolamide 2% eye drops solution Dorzolamide hydrochloride 20 mg/ml eye drops topical Rompharm Company SRL, Romania 25 L 004 01/2009
Drug 2: **REFERENCE** **(treatment b)**	name: substance: strength : dosage form: mode/route: company responsible for manufacturing the product: batch number: expiry date: batch number: expiry date:	Trusopt® eye drops solution (2%) Dorzolamide hydrochloride 20 mg/ml eye drops topical Chibret Pharmazeutische GmbH, Germany 0841700 09/2009 0893570 12/2010

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Treatment: Two treatments were investigated in this study. One drop t.i.d. of either test or reference product were applied for 28 (± 5) days (at 8:00, 15:00, 22:00) in the study eye	
Efficacy measurement:	Intraocular pressure (IOP) will be determined on each visit (1, 2, 3, and 4) by means of applanation tonometry at the following time points: 8:00, 12:00, 16:00 (±1h)
Primary endpoint	The primary efficacy parameter will be the difference in mean diurnal IOP from visit 1 (baseline) to visit 2 and from visit 3 (baseline) to visit 4: $\delta IOP_{av} = IOP_{av\ baseline} - IOP_{av\ dorzolamide}$
Secondary endpoints	The secondary efficacy parameter will be the difference in mean diurnal IOPs at each individual time point: $\delta IOP(t) = IOP(t)_{baseline} - IOP(t)_{dorzolamide}$
Statistical analysis	Primary analysis variable: Comparison of average diurnal change of IOP of TEST and REFERENCE $\delta IOP_{av\ TEST} - \delta IOP_{av\ REFERENCE}$ Secondary analysis variables: Comparison of the change of IOP of TEST and REFERENCE at discrete time points $\delta IOP(t)_{TEST} - \delta IOP(t)_{REFERENCE}$

Results:

The primary efficacy parameter was the difference in mean diurnal IOP from visit 1 (baseline) to visit 2 and from visit 3 (baseline) to visit 4 ($\delta IOP_{av} = IOP_{av\ baseline} - IOP_{av\ dorzolamide}$). Using the ANOVA-model anticipated in the statistical analysis plan, the 90% confidence interval for the primary endpoint the δIOP_{av} difference (-0.53 mmHg [-1.58 mmHg – 0.52 mmHg]) appeared fail to miss the acceptance range for equivalence of +/- 1.5 mmHg.

There were minor methodological complications concerning the estimation of the primary efficacy parameter. The $\delta IOP_{av} = IOP_{av\ baseline} - IOP_{av\ dorzolamide}$ revealed a higher intrasubject variability than anticipated. There were multiple reasons for the higher variability observed in this study.

The evaluation of the compliance of the patients was based on self-reports of the patients. The actual amounts of really used study medication showed, however, a large inter- and intrasubject variability. This variability was due to the difficulties related to the self-administration of the study medication.

Another reason for the higher variability of the IOP depressing effects could have been the fact that different investigators had determined the IOP within a patient at different visits.

A third and quantifiable source of variation was the pre-medication baseline IOP. The criterion for the baseline IOP in patients to be included was set to 18 - 32 mmHg in the study eye, i.e. the eye with the higher baseline IOP. There were several patients showing an IOP ≥18 mmHg in visit 1 only in one or two of totally six measurements. In 25% of the patients the averaged baseline IOP was ≤18 mmHg.

The impact of the baseline IOP on the response to the study medication was investigated in an analysis of covariance (ANCOVA). If the pre-medication baseline (in visit 1 and 3, respectively) is introduced as a covariate into the ANOVA-model, the intrasubject variability is reduced from +/- 2.48 mmHg without covariate to +/- 2.11 mmHg.

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The pre-medication baseline IOP was the sole significant ($P<0.01$) source of variation.

Under the ANCOVA model, the 90% confidence interval for the average change of the IOP becomes -0.27 mmHg [-1.17 mmHg – 0.64 mmHg] and is included by the acceptance range -1.5 mmHg to +1.5 mmHg stipulated in the study protocol. The same is true for the changes of the IOP at discrete time points, which now all meet the acceptance range.

The precision of the study thus was substantially improved by the ANCOVA. These results suggest equivalence for the formulations under test with respect to the extent of the depression of the IOP.

Safety:

Altogether 53 adverse events were observed during the study, in 30 of these events was the relationship assessed as suspected (related, probably related or possibly related) to the study drugs: 15 events after the administration of test medication and 15 events after reference treatment. 8 AEs were classified as *unlikely* and 15 as *not* related to the study drug.

There were 3 serious adverse events with no relationship to the study medication.

Four AEs led to a drop out of one patient. One Patient withdrew his consent due to SAE.

No relevant differences in incidence or pattern of AEs were found between the two treatments investigated.

No significant changes in vital signs or in clinical laboratory variables were detected. No safety affecting results were found in the ophthalmologic examinations and the Ocular Symptoms Questionnaires.

The observed eye-tolerability of both treatments was good, no relevant difference between the treatments was found.

The study medication was well tolerated, without relevant differences in safety profiles of the two treatments investigated.

Summary Statistics for the Average IOP – Study Eye

PD-Variable	Stat	T	R	T-R
Baseline IOP_{av}	N	32	32	32
[mmHg]	MEAN	20.01	20.35	-0.34
	STD	3.04	3.11	2.51
	MIN	14.67	16.00	-6.33
	MEDIAN	19.67	19.58	0.00
	MAX	27.33	27.50	5.33
IOP_{av}	MEAN	17.83	17.65	0.19
[mmHg]	STD	3.55	2.82	3.03
	MIN	13.67	13.00	-5.00
	MEDIAN	17.33	17.83	0.58
	MAX	28.00	24.00	9.50

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Summary Statistics for the Average IOP – Study Eye

PD-Variable	Stat	T	R	T-R
δIOP_{av}	MEAN	2.17	2.70	-0.53
[mmHg]	STD	2.36	2.76	3.45
	MIN	-2.67	-2.67	-8.83
	MEDIAN	2.33	3.00	-0.08
	MAX	6.67	8.50	4.83

T: Test, R: Reference; Note: the signs of the baseline corrected effects are positive (the larger the value the larger the desired effect).

Change in IOP - 90% Confidence Intervals ANOVA

PD-Variable	Point Estimator T-R	Lower Confidence Limit	Upper Confidence Limit
δIOP_{av} [mmHg]	**-0.53**	**-1.58**	**0.52**
δIOP 8:00 [mmHg]	-0.69	-1.97	0.60
δIOP 12:00 [mmHg]	0.08	-1.19	1.35
δIOP 16:00 [mmHg]	-0.98	-2.33	0.36

T: Test, R: Reference; Note: the signs of the baseline corrected effects are positive (the larger the value the larger the desired effect), the negative sign means inferiority

Change in IOP - 90% Confidence Intervals - ANCOVA (covariate = baseline)

PD-Variable	Point Estimator T-R	Lower Confidence Limit	Upper Confidence Limit
δIOP_{av} [mmHg]	**-0.27**	**-1.17**	**0.64**
δIOP 8:00 [mmHg]	-0.46	-1.42	0.50
δIOP 12:00 [mmHg]	0.07	-1.04	1.17
δIOP 16:00 [mmHg]	-0.34	-1.49	0.81

T: Test, R: Reference; Note: the signs of the baseline corrected effects are positive (the larger the value the larger the desired effect), the negative sign means inferiority

Dependence of the Expected IOP Decrease (δIOP_{av}) on the pre-Medication Baseline IOP

Baseline IOP_{av} [mmHg]	δIOP_{av} [mmHg] under T	δIOP_{av} [mmHg] under R
18.00	0.643	0.912
20.18 *)	2.303	2.572
22.00	3.693	3.962

T: Test, R: Reference; note: the signs of the baseline corrected effects are positive (the larger the value the larger the desired effect); *) average baseline IOP for T and R found in the study.