SP0878, 2005-005686-11

CLINICAL STUDY REPORT SYNOPSIS

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This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

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Sponsor:

UCB Pharma GmbH

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40789 Monheim

Germany

Official study title:

Confirmatory, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel Groups Study to Assess the Efficacy and Safety of Prostaglandin E1 in Subjects with Dry Age-Related Macular Degeneration

CLINICAL STUDY REPORT SYNOPSIS: SP878

Name of company: UCB Pharma GmbH	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Alprostadil*	**Volume:** Not applicable	
Name of active ingredient: Prostaglandin E_1	**Page:** Not applicable	

Title of study: Confirmatory, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel Groups Study to Assess the Efficacy and Safety of Prostaglandin E_1 in Subjects with Dry Age-Related Macular Degeneration

Investigators: 6 investigators in [redacted]

Study sites: The study was multicenter. 6 study sites enrolled subjects into the study.

Publication (reference): none

Studied period: 3 years and 7 months **First subject enrolled:** 14 Jul 2006 **Last subject completed:** 25 Feb 2010	**Phase of development:** 3

Objective(s): Primary efficacy objective was to show a superior effect of alprostadil compared to placebo on visual acuity in subjects with a dry age-related macular degeneration (AMD) at 3 months after the end of the study drug infusion. Visual acuity was assessed as difference in lines with ETDRS.

Secondary efficacy objectives were:

- The difference in visual acuity between measurements immediately after and at 6 months after the end of study drug infusion and measurements at Baseline
- Progression of the dry AMD
- Development of a wet AMD
- The difference in contrast sensitivity between measurements immediately after and at 3 and 6 months after the end of study drug infusion and measurements at Baseline
- The difference in color vision between measurements immediately after and at 3 and 6 months after the end of study drug infusion and measurements at Baseline

Safety variables were: adverse events, laboratory values, vital signs, physical examination results and ECG at rest.

Methodology: This study was a confirmatory, prospective, randomized, double-blind, placebo-controlled, parallel groups study. Subjects with dry AMD and a visual acuity between 0.2 and 0.7 received 15 infusions of 60µg alprostadil or placebo during a

*Approved as Prostavasin® (this note was added for clarification purposes afterwards)

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Treatment Phase of 3 weeks and were followed-up for a subsequent phase of 6 months.

The study was conducted using a 2-stage group sequential adaptive design.

This clinical study report describes the results from the final analysis which was done after premature stop of the trial due to the results of the interim analysis.

Number of subjects (planned and analyzed): According to the two-stage group sequential test design, the initially planned number of subjects to be included was 60, ie, 30 per treatment arm. The final analysis was based on 36 subjects, 18 per treatment arm.

Diagnosis and main criteria for inclusion:

Subjects had to fulfill the following inclusion criteria:

1. Male and female subjects older than 50 years of age
2. Dry AMD with hard drusen and possibly with beginning geographic atrophy in one eye (if both eyes were affected, the worse eye was defined as the "study-eye"; if the worse eye fulfilled AREDS category 3 or 4, the better eye was defined as the "study-eye")
3. Visual acuity between 0.2 and 0.7 (logMAR) assessed with ETDRS charts
4. Subject was informed and given ample time and opportunity to think about her/his participation and had given her/his written informed consent.
5. Subject was willing and able to comply with all trial requirements for a total of 7 months.

Subjects were not permitted to enroll in the trial if any of the following criteria were met. Criteria applied to the study-eye only unless stated otherwise.

1. Dry AMD AREDS category 3 or 4 in both eyes
2. Wet AMD in at least one eye
3. Detachment of the pigmentary epithelium
4. Glaucoma
5. Diabetic retinopathy
6. Medical history of retinal vein occlusion
7. Uveitis
8. Cataract surgery during the study
9. High myopia (< –6 dpt) with pathological findings of the retina
10. Medical history of any ophthalmic surgery with complications
11. Medical history of cataract surgery without complications within the last 12 weeks
12. Medical history of vitrectomy
13. AREDS medication (vitamin C, beta-carotene, zinc and copper) within the last 2 days
14. Ophthalmologic dietary supplements within the last 2 days
15. Medical history of retinal hemorrhage.

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In addition, internal medical exclusion criteria and general medical exclusion criteria were applied.

Test product, dose(s) and mode of administration, batch number(s): Prostavasin® 20µg ampoules containing 48.2mg dry substance were used. The dry substance consisted of 20µg alprostadil (prostaglandin E_1) in an alphadex inclusion complex and anhydrous lactose. The contents of 3 ampoules were to be dissolved in 100ml of isotonic sodium chloride solution and infused intravenously over 1.5 to 2 hours with an infusion pump.

Batch numbers: [redacted]

Duration of treatment: Alprostadil or placebo was infused once daily in 100 ml sodium chloride solution on every day from Monday to Friday during a Treatment Phase of 3 weeks (=15 infusions).

Reference therapy, dose(s) and mode of administration, batch number(s): Placebo ampoules containing an equivalent amount of dry substance in order to match verum in appearance were used. The dry substance consisted of 47.5mg lactose. The contents of 3 ampoules were to be dissolved in 100 ml of isotonic sodium chloride solution and infused intravenously over 1.5 to 2 hours with an infusion pump.

Batch numbers: [redacted]

Criteria for evaluation:

Efficacy: Visual acuity with and without best possible correction was to be determined with standard ETDRS charts and with laser interference. Differences in visual acuity were assessed as differences in lines on the standard ETDRS charts. The state of the dry AMD and the presence of the wet AMD were determined with binocular ophthalmoscopy and fundus photography as well as with fluorescein angiography. Multifocal electroretinogram was optional. AMD assessments were done with optical coherence tomography. The visual field was determined with perimetry (30-2 program and Goldmann). Contrast sensitivity was determined with the Pelli-Robson test. Color vision was determined with the panel D15 test. Slit lamp examinations were performed and the intraocular pressure was measured by applanation tonometry.

Pharmacokinetics/pharmacodynamics: NA

Safety: Safety was determined by capturing adverse events, measuring standard laboratory parameters (hematology, serum chemistry), recording body height, weight and temperature as well as systolic and diastolic blood pressure plus the pulse rate. ECGs at rest were done.

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Statistical methods:

The primary efficacy endpoint "Difference in visual acuity between measurements at 3 months after the end of study drug infusion and measurements at Baseline, which is assessed as difference in lines with standard ETDRS charts with best possible correction" was tested exploratory, because the study was stopped after the interim analysis.
The primary goal of the study was to test the following null hypothesis pertaining to the equality of the two treatment arms:

H_0: $\mu_{Alprostadil} \leq \mu_{Placebo}$

This was tested against the alternative hypothesis

H_1: $\mu_{Alprostadil} > \mu_{Placebo}$,

where μ denoted the mean differences in visual acuity between measurements at 3 months after the end of study drug infusion minus measurements at baseline as assessed as line difference on the standard ETDRS charts with best possible correction (difference in visual acuity: value of 3 months after the end of study drug infusion - baseline value). The criterion for significance (α) had been set at one-sided $\alpha = 0.025$, which meant that only an effect in the expected direction would be interpreted exploratorily.
P-values were displayed using 4 decimal places and p-values less than 0.0001 as <0.0001.
The last observation carried forward (LOCF) principle was applied in case a subject had terminated prematurely.

Subject disposition:

This study was planned as a confirmatory, double-blind, placebo-controlled study to prove the effect of alprostadil in dry AMD in terms of visual acuity. An interim analysis after 14 subjects per treatment arm showed that the initially calculated sample size of 60 subjects for the final evaluation would need to be increased to 152 subjects to achieve conditional power of 80%. It was decided not to enroll this increased number of subjects, but to stop the study entirely.

After screening 40 subjects, 4 turned out to be screening failures while 36 were randomized (18 to alprostadil, 18 to placebo). One subject from the alprostadil group withdrew consent after receiving 3 infusions. All other subjects completed the study treatment. One subject from the placebo group withdrew between the end of the study treatment and the 1st Follow-Up Visit, so that the 3-Month Follow-Up was performed in 17 alprostadil subjects and 17 placebo subjects. After the 1st Follow-Up, 4 more subjects withdrew from the study so that the 2nd Follow-Up Visit was attended by 14 subjects on alprostadil and 16 subjects on placebo.

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The Safety Set comprised all 36 randomized subjects (18 on alprostadil, 18 on placebo). 3 of these 36 subjects had either no baseline data for the primary efficacy parameter or no post-baseline efficacy results. Therefore, the Full Analysis Set (FAS) following the intention-to-treat principle contained 16 subjects on alprostadil and 17 subjects on placebo. Within the FAS, 7 subjects on alprostadil and 5 subjects on placebo had protocol deviations relevant for safety so that they were excluded from the Per-Protocol Analysis. The Per-Protocol Set (PPS) therefore comprised 9 subjects in the alprostadil group and 12 subjects in the placebo group.

Efficacy results:

Primary efficacy endpoint: The results for the difference in visual acuity between 3 months after the end of the treatment and Baseline are shown in the table below for the FAS and the PPS:

	Alprostadil	Placebo	
Change from Baseline (LOCF)	Mean ± standard deviation (median) [confidence interval]		p-value (one-sided)
Week 16 (FAS)	0.94 ± 1.84 (1.0) [-0.0 ; 1.9] n = 16	0.53 ± 1.66 (0.0) [-0.3 ; 1.4] n = 17	0.1220
Week 16 (PPS)	1.11 ± 1.62 (1.0) [-0.1 ; 2.4] n = 9	0.08 ± 1.24 (0.0) [-0.7 ; 0.9] n = 12	0.0625

In summary, a clear difference between the treatment groups was not proven. However, comparing the FAS results with the PPS results it became obvious that the alprostadil effect increased in the PPS while the placebo effect decreased remarkably, so that a trend for efficacy was identified.

Secondary efficacy endpoints: The difference in visual acuity between 6 months after study end is shown in the table below for the FAS:

	Alprostadil	Placebo
Change from Baseline (LOCF)	Arithmetic mean ± standard deviation (median) [confidence interval]	
Week 29 (FAS)	1.31 ± 1.45 (1.0) [0.5 ; 2.1] n = 16	0.29 ± 2.11 (1.0) [-0.8 ; 1.4] n = 17

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The effect in each group was tested with an exploratory Analysis of Variance-Covariance (ANCOVA) with "treatment" and "center" as factors and "Baseline value" as covariate. The resulting p-values (LS means) were 0.0155 for alprostadil and 0.9510 for placebo.

For all other secondary efficacy parameters, no noteworthy differences were found between the treatment groups.

Pharmacokinetics/pharmacodynamics results: NA

Safety results: 2/18 (11.1%) subjects from the alprostadil group and 6/18 (33.3%) subjects from the placebo group reported a total of 4 vs 9 episodes of treatment-emergent adverse events (TEAEs). The most common type of AE referred to eye disorders with 3 subjects, all from the placebo group, being affected. The events were specified as visual disturbance, vitreous opacities and choroidal neovascularization. All other AEs came from a variety of System Organ Classes with 1 or zero subjects from the alprostadil group being represented in each. No deaths, SAEs other than death or significant AEs were reported. In the alprostadil group, the only AE with a probable or highly probable relation to the study medication was a phlebitis that started and ended on the same day and that had no impact on the subject's further course in the study. The physical examinations, laboratory tests, results for blood pressure and pulse as well as the ECG data revealed no remarkable changes over the study.

Conclusions: In this study with 36 subjects randomized, alprostadil was not proven to be superior to placebo in the treatment of dry AMD based on the primary efficacy variable which was the change in the visual acuity between Baseline and 3 months after the treatment end. However, a trend for efficacy was found when looking at the results of the Per-Protocol Analysis and the magnitude of the treatment effect.

6 months after the treatment, the improvement of the visual acuity in the alprostadil group had increased in comparison to the results after 3 months while a decrease was found for the placebo group for the same parameter during the same time period. It can therefore be concluded that it is worthwhile to continue investigating the benefit of alprostadil in subjects with dry age-related AMD.

The safety results were in line with the known safety profile of alprostadil and did not indicate any considerable risk.

Report date: 29 Oct 2010